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► **To cite this version:**

Yuting Ma, Guido Kroemer. The cancer-immune dialogue in the context of stress. *Nature Reviews Immunology*, 2023, 24 (4), pp.264-281. 10.1038/s41577-023-00949-8 . hal-04605997

**HAL Id: hal-04605997**

**<https://hal.science/hal-04605997v1>**

Submitted on 9 Jun 2024

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# **The cancer-immune dialogue in the context of stress**

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17 **Abstract**

18  
19 Although there is little direct evidence supporting that stress affects cancer incidence,  
20 it does influence the evolution, dissemination and therapeutic outcomes of neoplasia,  
21 as shown in human epidemiological analyses and mouse models. The experience of and  
22 response to physiological and psychological stressors can trigger neurological and  
23 endocrine alterations, which subsequently influence malignant (stem) cells, stromal  
24 cells, and immune cells in the tumour microenvironment, as well as systemic factors in  
25 the tumour macroenvironment. Importantly, stress-induced neuroendocrine changes  
26 that can regulate immune responses have been gradually uncovered. A number of  
27 stress-associated immunomodulatory molecules (here termed SAIMs) can reshape  
28 natural or therapy-induced anti-tumour responses by engaging their corresponding  
29 receptors on immune cells. Moreover, stress can cause systemic or local metabolic  
30 reprogramming and change the composition of the gastrointestinal microbiota which  
31 can indirectly modulate anti-tumour immunity. Here, we explore the complex  
32 circuitries that link stress to perturbations in the cancer-immune dialogue and their  
33 implications for therapeutic approaches to cancer.

34  
35

## 36 Introduction

37  
38 Historically, Western culture has been wedded to the idea that body and mind are  
39 separate, often antinomic entities. Despite the rise of ‘psychosomatic medicine’ during  
40 the 20<sup>th</sup> century, only recently has it been considered that mental and physical health  
41 may be inseparable<sup>1</sup> and that psychiatric diseases have a pathophysiological substratum  
42 that reaches beyond the central nervous system<sup>2</sup>.

43  
44 Likewise, until a few decades ago, cancer was thought to be a cell-autonomous disease  
45 in which genetic and epigenetic instability drives cells to premalignancy (dysplasia,  
46 metaplasia) and then to overt neoplasia. Although it was known that non-transformed  
47 cells contribute to tumour progression, for instance by providing trophic support via  
48 angiogenesis<sup>3</sup>, it was only relatively recently discovered that cancer can only arise in  
49 the context of failing immunosurveillance and that efficient anticancer therapies rely  
50 on the (re)activation of anticancer immune responses<sup>4</sup>. Moreover, emerging evidence  
51 also supports the existence of bidirectional regulatory networks between the immune  
52 and neuroendocrine systems<sup>5-7</sup>. Discoveries in this field will help to elucidate the  
53 molecular basis of body-mind dialogues in the context of cancer immunosurveillance.

54  
55 Both the immune and neuroendocrine systems are ubiquitous, with cell types that are  
56 part of these systems widely distributed over the body. Consequently, effector  
57 molecules produced by both systems can reach any compartment of the body<sup>8,9</sup>. As a  
58 result, it is tempting to assume that neuroendocrine effectors and immunological factors  
59 might engage in a crosstalk that has evolved to maintain tissue homeostasis and to  
60 minimize or avoid the manifestation of diseases<sup>5,10</sup>. Indeed, most leukocytes are in close  
61 proximity to sympathetic and/or parasympathetic nerve endings in lymphoid organs<sup>6,11-  
62 13</sup>. Nerve fibres in the spleen and lymph nodes can modulate immune responses such as  
63 antibody production and inflammation<sup>7,14,15</sup>. Conversely, manipulation of components  
64 of the immune system has been shown to perturb neurobiological and behavioural  
65 features in animal models<sup>16,17</sup>.

66  
67 Importantly, tumours are generally infiltrated by distinct leukocyte subpopulations<sup>18</sup>  
68 and they are sometimes innervated or surrounded by nerve fibres<sup>19</sup>. In mouse prostate  
69 tumour xenografts, sympathetic and parasympathetic nerve fibres were reported to  
70 promote tumour development and dissemination, respectively<sup>20</sup>. The pro-tumoral  
71 effects of sympathetic adrenergic nerve fibres were partially attributed to metabolic  
72 shifts in endothelial cells that drive local angiogenesis<sup>21</sup>. High densities of adrenergic  
73 and cholinergic nerves also correlated with poor clinical outcomes in patients with  
74 prostate cancer<sup>20</sup>. Conversely, genetically induced stimulation of parasympathetic  
75 cholinergic nerve fibres in rodent models of breast cancer effectively blocked tumour  
76 outgrowth by downregulating the expression of immune checkpoint molecules<sup>22</sup>.  
77 Although the communication between nerves and immune cells in tumours is starting  
78 to be explored<sup>22,23</sup>, it remains unknown whether stress may influence local neural  
79 remodelling and immune regulation in the tumour microenvironment (TME).

80  
81 Certain environmental and lifestyle factors (such as sunbathing, smoking) have been  
82 associated with an increased risk of cancer, as they can lead to genomic damage or  
83 instability<sup>24</sup>. In mice, there is also evidence that chronic stress can accelerate  
84 tumorigenesis<sup>25,26</sup>. However, epidemiological studies failed to provide convincing  
85 evidence that objective stressors (such as adverse life events like the death of a spouse,

86 divorce, or illness) and subjective stress (such as depression or anxiety) increase cancer  
87 susceptibility in humans<sup>27-29</sup>. This contrasts with the observation that stress-related  
88 conditions such as post-traumatic stress disorder (PTSD) or anxiety show a significant  
89 association with obesogenic processes and an elevated risk of autoimmunity<sup>30,31</sup>. The  
90 discrepancy between the observations in humans and mice may reflect inter-species  
91 differences, the oversimplification and artificiality of mouse models of stress and  
92 tumorigenesis, the vast heterogeneity of human cancer, as well as the low reliability of  
93 mental status evaluation in retrospective studies. It is also noteworthy that the  
94 vulnerability to stress may vary significantly between different individuals and is  
95 affected by variations in genetic risk factors<sup>32</sup>, neuroanatomic features<sup>33</sup>, and metabolic  
96 patterns<sup>34</sup>.

97  
98 In this Review, we examine how stress affects anticancer immune responses. We  
99 summarize evidence showing how stress-evoked neuroendocrine factors (including  
100 steroid hormones, neurotransmitters, and neuropeptides) reshape local and systemic  
101 immune responses by engaging corresponding receptors on immune cells. We refer to  
102 these as stress-associated immunomodulatory molecules (SAIMs). We also depict an  
103 interplay between the nervous system, systemic metabolism and the gastrointestinal  
104 microbiota upon stress, as well as their effect on the cancer-immune crosstalk (**Fig. 1**).  
105 Based on existing evidence and emerging mechanistic insights, we share our vision of  
106 novel immunotherapeutic targets and approaches to treat cancer.

## 107 108 **[H1] Links between stress and cancer**

109  
110 Understanding the connection between stress and cancer is particularly important as  
111 anxiety and depression are highly prevalent in patients with cancer<sup>35</sup>. Cancer diagnosis  
112 and treatment may cause symptoms that meet the full clinical criteria of PTSD in up to  
113 ~20% of total cases and can lead to long-term alterations in neuroendocrine  
114 circuitries<sup>36,37</sup>. Surgery-related stress has been shown to cause an excess release of  
115 catecholamines and prostaglandins perioperatively in patients with cancer, which can  
116 promote metastatic progression<sup>38</sup>. Despite the lack of proof that stress causes cancer in  
117 humans, there is convincing epidemiological evidence that objective stressors and self-  
118 evaluated psychological distress correlate with negative cancer outcomes (progression,  
119 metastasis, recurrence, therapeutic failure, and increased mortality)<sup>39-43</sup>. Adverse life  
120 circumstances in general have been closely associated with a skewing towards  
121 proinflammatory responses and can dampen antiviral activity in circulating leukocytes.  
122 These changes have largely been attributed to glucocorticoid-related pathways and the  
123 activation of the adrenergic system<sup>44,45</sup>. Moreover, gene signatures indicative of the  
124 activity of the glucocorticoid, adrenergic, dopaminergic, serotonergic, and muscarinic  
125 systems have been closely correlated with unfavourable outcomes in patients with  
126 prostate cancer<sup>46</sup>.

127  
128 The adverse impact of stress on cancer outcomes has been replicated in mouse models,  
129 allowing to establish causality and to explore the underlying mechanisms. Repeated  
130 restraint, male domination, or unpredictable chronic mild stress (UCMS) are  
131 established procedures to induce stress in rodents (**Supplemental Box 1**). These have  
132 been shown to cause behavioural, psychological, and biological changes that promote  
133 tumour development, metastatic dissemination, and therapeutic failure in mice<sup>47-52</sup>.  
134 Moreover, mice held in standard housing conditions are already stressed and alleviating

135 stress by shifting them from the hypothermic to thermoneutral conditions or placing  
136 them in an ‘enriched’ environment can significantly reduce tumour growth<sup>53,54</sup>.

137

138 To dissect how stress can influence cancer incidence, evolution, and therapeutic  
139 outcomes, the direct effects of neuroendocrine factors on cancer cells and stromal  
140 elements have been explored. An abundant literature suggests that stress-induced  
141 glucocorticoids and catecholamines can directly regulate cell death and enhance the  
142 proliferation, therapeutic resistance, stemness traits, and dissemination of tumour cells  
143 in mouse models<sup>25,55-62</sup> (**Box 1**). Also, these factors can reshape the tumour stroma by  
144 promoting angiogenesis, lymphogenesis, axonogenesis, and extracellular matrix  
145 formation<sup>47,49,63-67</sup> (**Box 2**). Here, we focus on stress-induced neuroendocrine effectors,  
146 and their direct and indirect effects on immune cells and anti-cancer responses.

147

## 148 **[H1] The neuroendocrine response to stress**

149

### 150 *[H2] Stress-induced neuroendocrine factors*

151

152 The biosynthesis and secretion of neuroendocrine factors are crucial for stress-induced  
153 neuro-endocrine-immune interplay. The sympathetic adrenal-medullary (SAM) and  
154 hypothalamic-pituitary-adrenal (HPA) axes constitute two major arms of  
155 neuroendocrine responses to stress. They generate the paradigmatic ‘stress hormones’,  
156 catecholamines and glucocorticoids, respectively. A close-to-immediate reaction to  
157 stress activates the SAM axis, stimulating the production of catecholamines (notably  
158 dopamine, noradrenaline (norepinephrine), and adrenaline (epinephrine)) by  
159 chromaffin cells of the adrenal medulla and postganglionic fibres of the sympathetic  
160 nervous system<sup>68,69</sup>. Surges of adrenaline and noradrenaline can activate  $\alpha$ - or  $\beta$ -  
161 adrenergic receptors (ARs), which subsequently trigger phospholipase C (PLC)-protein  
162 kinase C (PKC) signalling or the cyclic adenosine monophosphate (cAMP)-protein  
163 kinase A (PKA) pathway<sup>70,71</sup>. Following an instant, but transient, response via the SAM  
164 axis, a slightly delayed activation of the HPA axis initiates the cascade-like biosynthesis  
165 of corticotropin-releasing hormone (CRH) by hypothalamic neurons,  
166 adrenocorticotrophic hormone (ACTH) by the hypophysis, and finally glucocorticoids  
167 (cortisol in humans or corticosterone in rodents) by the adrenal gland<sup>72</sup>. Elevated  
168 circulating glucocorticoids can activate the ubiquitously expressed nuclear receptor  
169 NR3C1 (also called glucocorticoid receptor, GR), which engages glucocorticoid  
170 response elements and initiates transcriptomic reprogramming<sup>73</sup>. Alternatively, they  
171 can engage a high-affinity membrane receptor G-protein coupled receptor 97  
172 (GPR97)<sup>74</sup> on leukocytes, which modulates the development and inflammatory  
173 response of immune cells<sup>75,76</sup>.

174

175 Stress can stimulate the production of other neuroendocrine factors in the central  
176 nervous system. For example, serotonergic neurons in the dorsal raphe nucleus can  
177 convert L-tryptophan to serotonin (5-HT), which attenuates stress by engaging multiple  
178 postsynaptic 5-HT receptors<sup>77</sup>. Cholinergic neurons in the nucleus basalis of Meynert  
179 can synthesize acetylcholine (ACh), which mediates the parasympathetic “rest and  
180 digest” response by activating muscarinic or nicotinic ACh receptors<sup>78,79</sup>. The  
181 inhibitory neurotransmitter gamma-aminobutyric acid (GABA) is mainly generated by  
182 amygdala GABAergic interneurons, which binds to ionotropic or metabotropic GABA  
183 receptors<sup>80,81</sup> and counterbalances the excitatory neurotransmitter glutamate.  
184 Histaminergic neurons in hypothalamic tuberomammillary nucleus can convert L-

185 histidine to histamine, which can be detected by G protein-coupled histamine  
186 receptors<sup>82,83</sup>. Endogenous opioid neuropeptides (known as endorphins, enkephalins,  
187 dynorphins) are synthesized by opioidergic neurons in the limbic and paralimbic  
188 regions of the brain and the spinal cord, which bind to  $\mu$ ,  $\delta$ , or  $\kappa$  opioid receptors<sup>84-86</sup>.  
189 The above-mentioned receptors have been identified not only on neurons, but also on a  
190 diverse array of immune cells<sup>87</sup>.

191

192 It is noteworthy that a complex regulatory network exists within each individual stress-  
193 responsive module (such as the negative and positive feedback circuits in the HPA  
194 axis<sup>88</sup>) and among different neuroendocrine elements (as exemplified by the interplay  
195 between the SAM and HPA axes<sup>68</sup>, as well as that between serotonergic neurons and  
196 the HPA axis<sup>89</sup>). Mounting evidence suggests that the sources of neuroendocrine factors  
197 are not limited to the central nervous system and endocrine glands. They can be also  
198 produced locally in peripheral tissues by sympathetic or parasympathetic nerves<sup>7,9,14,15</sup>,  
199 specialized endocrine cells<sup>90,91</sup>, epithelial cells<sup>92</sup>, immune cells<sup>14,93</sup>, and even gut  
200 microbiota<sup>94</sup> (**Box 3**). However, how stress may influence the locoregional secretion of  
201 neuroendocrine factors and their clearance is yet to be explored.

202

## 203 *[H2] Neuroendocrine changes in tumours*

204

205 In mouse xenograft models, sustained adrenergic signalling favours axonogenesis by  
206 stimulating tumour cells to produce brain-derived neurotrophic factor (BDNF)<sup>67</sup>. In  
207 return, tumour innervation affects malignant growth and dissemination via locally  
208 released neurotransmitters<sup>19,95</sup>. In mouse breast cancer models, noradrenaline released  
209 locally from sympathetic nerve terminals, rather than mildly elevated systemic  
210 adrenalin or noradrenaline, is likely to drive stress-induced tumour progression and  
211 metastasis<sup>96</sup>. Emerging evidence from mouse models of pancreatic cancer suggest that  
212 the sympathetic and sensory nervous systems mainly foster tumour progression,  
213 whereas the parasympathetic nervous system appears to inhibit tumour growth.  
214 Neurotransmitters that account for these regulatory effects include catecholamines,  
215 substance P, and acetylcholine<sup>97,98</sup>. Accordingly, sympathectomy of the prostate gland  
216 or genetic or pharmacological blockade of ARs can reduce BDNF secretion, inhibit  
217 tumour innervation and prolong survival of tumour-bearing mice<sup>20,99</sup>. Indeed, a high  
218 density of sympathetic and parasympathetic nerve fibres in tumours and adjacent tissues,  
219 as well as elevated levels of intra-tumoral BDNF and noradrenaline, have been  
220 associated with poor clinical outcome in patients with cancer<sup>20,67</sup>. The parasympathetic  
221 system and vagal nerves seem to be endowed with anti-tumour properties, since low  
222 heart-rate variability (indicating reduced vagal activities) and vagotomy correlate with  
223 increased cancer risk or unfavourable clinical outcomes, presumably due to  
224 acetylcholine-mediated regulation of the cancer immune contexture<sup>100-102</sup>.

225

## 226 **[H1] Immune regulation by SAIMs**

227

228 The cellular, molecular and anatomic basis for the neuroendocrine modulation of local  
229 and systemic immunity are starting to be investigated in rodent models<sup>103</sup>. So far, most  
230 of this work (often in the context of infection) has focussed on glucocorticoids and  
231 catecholamines. These paradigmatic SAIMs exhibit both immunosuppressive or  
232 immunostimulatory function, depending on their target cells, the duration and intensity  
233 of stress, the type of immune response, and the timing of stress relative to the course of  
234 immune response<sup>104-107</sup>. For example, in the context of viral infection, a glucocorticoid

235 surge induced by repeated restraint was shown to reduce the levels of CD8<sup>+</sup> dendritic  
236 cells (DCs) and downregulate their cross-presentation capabilities, thereby weakening  
237 the priming of antigen-specific cytotoxic T lymphocytes (CTLs) in mice<sup>108</sup>. In a mouse  
238 model of moderate stress upon dietary restriction, glucocorticoid-induced upregulation  
239 of chemokine receptor CXCR4 on memory CD8<sup>+</sup> T cells facilitated their homing to the  
240 bone marrow<sup>109</sup>. This stress-induced preconditioning can enhance immune responses to  
241 a secondary bacterial infection<sup>109</sup>. Indeed, the immunoregulatory effect of  
242 glucocorticoid is highly cell type-specific despite the ubiquitous expression of GR<sup>110</sup>.  
243 This can be explained by the diversified transcriptional output and post-translational  
244 modifications of GR in different cell types<sup>73</sup>.

245  
246 Both acute and chronic stress can affect the normal physiology of the dopaminergic  
247 system (such as dopamine metabolism, transmission, turnover, and innervation)<sup>111</sup> and  
248 trigger dopamine release<sup>112,113</sup>. By engaging different subtypes of metabotropic G  
249 protein-coupled dopamine receptors, it can stimulate the homing of naive CD8<sup>+</sup> T  
250 cells<sup>114</sup>, inhibit NK cell expansion and IFN $\gamma$  production<sup>115</sup>, and alleviate the activation  
251 of the NLRP3 inflammasome<sup>116</sup>. Surges of noradrenaline can rapidly boost antigen  
252 capture by DCs via  $\alpha$ 2-AR-mediated PI3K and ERK1/2 signalling upon acute  
253 stress<sup>117</sup>. However, stimulating  $\beta$ 2-AR on LPS-treated DCs leads to preferential  
254 secretion of IL-23 over IL-12p70, therefore augmenting T<sub>H</sub>17 response and reducing  
255 T<sub>H</sub>1 response of CD4<sup>+</sup> T cells<sup>118</sup>.  $\beta$ 2-adrenergic stimulation through catecholamines  
256 can also enhance the suppressive function of regulatory T (T<sub>reg</sub>) cells by upregulating  
257 the expression of cytotoxic T-lymphocyte associated protein 4 (CTLA4)<sup>119</sup>.  
258 Chemogenetic activation of the sympathetic nervous system or administration of AR  
259 agonists can mimic stress conditions in mice. These procedures induce  
260 vasoconstriction, reduce local blood flow and cause abrupt hypoxia, thus  
261 compromising T cell motility and immune responses<sup>120</sup>. In response to acrophobic  
262 stress, the noradrenergic signal from splenic sympathetic nerves was shown to  
263 stimulate choline acetyltransferase (ChAT)-expressing T cells, which subsequently  
264 activated acetylcholine-responding B cells via the  $\alpha$ 9 nicotinic receptor and enhanced  
265 their production of antibodies in response to immunization<sup>14</sup>. In all the examples  
266 above, the immunomodulatory effects of neuroendocrine factors can be determined by  
267 the profile and density of their corresponding receptors on different types of immune  
268 cells<sup>87,121</sup>.

## 269 270 **[H1] SAIMs reshape tumour immune contexture**

271  
272 The presence of various leukocyte subpopulations in the TME can reflect either  
273 ongoing immunosurveillance or, on the contrary, tumour-promoting inflammation and  
274 immunosuppression. The density, composition, organization, and functional state of  
275 leukocyte infiltrates, the so-called 'immune contexture', has a decisive impact on  
276 cancer evolution and responses to cancer immunotherapy<sup>18</sup>. Emerging evidence  
277 demonstrates that stress can modulate local and systemic tumour immunosurveillance.  
278 For example, repeated restraint was reported to increase the susceptibility of mice to  
279 UV-induced squamous cell carcinoma and this correlated with elevated levels of  
280 circulating and tumour-infiltrating T<sub>reg</sub> cells, as well as defective IFN $\gamma$  production by T  
281 cells in the skin<sup>50</sup>. Also, high levels of stress have been associated with impaired NK  
282 cell function in patients with ovarian and breast cancer<sup>122,123</sup>. Hence, SAIMs and their  
283 detection by immune cells play a central role in stress-induced immunological changes  
284 in individuals with cancer.



285

286 [H2] Glucocorticoids

287

288 Although pharmacologic doses of synthetic glucocorticoids are clearly anti-  
289 inflammatory and immunosuppressive, stress-induced elevation of endogenous  
290 glucocorticoids can either inhibit or potentiate immune responses, depending on the  
291 dose, timing, and duration of glucocorticoid secretion, target cells and downstream  
292 transcriptional changes<sup>105</sup> (Fig. 2). In rodents with metastatic tumours, surgery-induced  
293 stress or sustained exposure to a wet cage dramatically reduced the immune-stimulatory  
294 effects of a TLR9 agonist CpG-C, whereas blocking GR and ARs with antagonists  
295 enhanced the tumoricidal activity of NK cells and favoured long-term survival<sup>124</sup>. In  
296 mice under stress from repeated social defeat, the efficacy of chemotherapies, cancer  
297 vaccines, and immune checkpoint blockade against primary or transplanted tumours  
298 was largely compromised<sup>52</sup>. This stress preconditioning durably elevated the  
299 glucocorticoid tonus but decreased the levels of circulating noradrenaline and 5-HT.  
300 Mechanistically, stress-induced glucocorticoid surge and GR-mediated transactivation  
301 of the transcriptional regulator TSC22D3 impaired type I IFN responses and the antigen  
302 presentation machinery in tumour-infiltrating DCs, leading to T cell dysfunction and  
303 therapeutic failure<sup>52</sup>. Administration of clinically-relevant doses of synthetic  
304 glucocorticoids (without causing a reduction in thymic cellularity) or transgenic  
305 overexpression of *Tsc22d3* in DCs was sufficient to abolish the efficacy of  
306 chemotherapy and prophylactic tumour vaccines in non-stressed mice, whereas  
307 systemic administration of the GR antagonist mifepristone or conditional deletion of  
308 *Tsc22d3* in DCs rendered mice refractory to stress-induced immunosuppression<sup>52</sup>.  
309 Indeed, mifepristone showed both therapeutic benefits (by reducing tumour  
310 progression) and palliative effects (by alleviating pain and increasing the expectancy  
311 and quality of life) in patients with benign, malignant, or even metastatic tumours<sup>125-  
312 127</sup>. It is noteworthy that antidepressants, such as serotonin/noradrenaline reuptake  
313 inhibitors, can reduce the severity of major depression without affecting the survival of  
314 patients with cancer<sup>128,129</sup>.

315

316 Within the TME, cells of the monocyte-macrophage lineage can also produce  
317 glucocorticoids, which cause CD8<sup>+</sup> T cell dysfunction by engaging GR and  
318 upregulating the transcription factor TCF1. This in situ glucocorticoid secretion has  
319 been associated with immunotherapeutic failure in both preclinical models of  
320 melanoma and in patients with melanoma<sup>130</sup>. In patients with lung cancer, single-cell  
321 RNA sequencing revealed a positive correlation between *TSC22D3* expression by  
322 tumour-infiltrating DCs and its expression by peripheral blood mononuclear cells  
323 (PBMCs). Moreover, circulating cortisol levels were found to be positively correlated  
324 with *TSC22D3* expression by PBMCs, as well as the mood state of patients with  
325 colorectal or lung cancer<sup>52,131</sup>. High expression of *TSC22D3* has also been identified as  
326 a negative prognostic marker in patients with colorectal, lung, or gastric cancer<sup>52</sup>.  
327 Indeed, patients with non-small cell lung cancer who received corticosteroids had poor  
328 responses to PD1/PD-L1 blockade<sup>132</sup>. It remains unclear whether this was due to  
329 corticosteroid-mediated immune suppression, or simply because patients with cancer at  
330 advanced stages are more likely to receive high-doses of the corticosteroid prednisone  
331 as a palliative treatment. Although glucocorticoids can abrogate the immunotherapeutic  
332 control of peripheral tumours, they do not seem to affect the efficacy of PD1-targeted  
333 checkpoint therapy for intracranial gliomas in mice, perhaps because of its unique  
334 immune-privileged TME<sup>133</sup>. In mouse models of mesothelioma, glucocorticoids were

335 found to promote lymphodepletion in the blood, but not in the TME. This may explain  
336 their modest but significant negative impact on the therapeutic benefits of weakly  
337 efficacious chemoimmunotherapy<sup>134</sup>. Nevertheless, glucocorticoid treatment did not  
338 cause noticeable inhibition in the therapeutic control of mesothelioma in mice treated  
339 with highly efficacious cancer therapies<sup>134</sup>. Therefore, the impact of glucocorticoids on  
340 tumour immunosurveillance and therapeutic outcomes can be determined by their local  
341 production and accessibility in the TME, the anatomic location of tumours, and the  
342 immunogenic properties of cancer therapies (Fig. 2).

343

#### 344 [H2] Catecholamines

345

346 Although catecholamines can be immunostimulatory under some circumstances<sup>135,136</sup>,  
347 they are generally viewed as immunosuppressive<sup>116,137,138</sup>. Aversive stimuli can  
348 promote mesolimbic dopamine release in mice and humans<sup>112,113,139</sup>, whereas long-term  
349 exposure to psychosocial adversity may dampen the dopaminergic activity<sup>140</sup>. In the  
350 context of malignancy, stress response associated with disease progression may be  
351 reflected in significantly elevated levels of plasma dopamine. Increased circulating  
352 dopamine in patients with lung cancer is sufficient to inhibit the proliferation and  
353 cytotoxicity of T cells via dopamine receptor D1 (DRD1)<sup>141</sup>. In a mouse model of  
354 melanoma, dopamine also exhibited immunosuppressive properties. Genetic or  
355 pharmacologic inhibition of DRD3 can boost tumour antigen cross-presentation by DCs  
356 and augment CTL responses<sup>142</sup>. Nevertheless, the beneficial effects of dopamine  
357 signalling on anti-tumour immunity have been demonstrated. For example, in a mouse  
358 model of lung cancer, liganded DRD2 on myeloid-derived suppressor cells (MDSCs)  
359 decreased their tumour infiltration<sup>143</sup>. By acting on D1-like receptors, dopamine can  
360 also attenuate nitric oxide (NO) production by GR1<sup>+</sup>CD115<sup>+</sup> monocytic MDSCs and  
361 reverse local immunosuppression in mouse models of lung cancer and melanoma<sup>144</sup>.

362

363 The immunosuppressive effect of adrenergic signalling in lymphocytes has been well  
364 documented. It can rapidly and robustly boost the expression of the orphan nuclear  
365 receptor subfamily NR4A<sup>145</sup>, among which NR4A1 is a key mediator of T cell  
366 dysfunction<sup>146</sup>. High expression of NR4A1 represses the transcription of several  
367 effector molecules, whereas genetic deletion of *Nr4a1* in mice boosts immune  
368 responses against tumours<sup>146</sup>. Catecholamines are very efficient at inhibiting the  
369 priming of anti-tumour CD8<sup>+</sup> T cell responses, which may be explained by the fact that  
370 naïve T cells express comparatively high levels of  $\beta$ 2-ARs<sup>147</sup>. In a mouse model of B-  
371 cell lymphoma, chronic stimulation with the non-selective  $\beta$ -AR agonist isoprenaline  
372 largely abolished the efficacy of a tumour vaccine targeting NKT cells and  
373 immunotherapies targeting costimulatory or coinhibitory molecules. This was found to  
374 be largely due to a selective reduction in CD8<sup>+</sup>T cell responses<sup>148</sup>. Further studies  
375 showed that sustained  $\beta$ -AR signalling in CD8<sup>+</sup> T cells dampened their metabolic  
376 adaptation upon activation, leading to impaired glucose uptake, glycolysis, and  
377 mitochondrial function<sup>149</sup>. Stress-induced catecholamine surges also favour myeloid  
378 cell-mediated immunosuppression. In mouse models of breast cancer,  $\beta$ 2-adrenergic  
379 signalling was reported to promote the M2 polarization of macrophages<sup>150</sup> and their  
380 infiltration in the primary tumour parenchyma to accelerate metastatic dissemination<sup>151</sup>.  
381 It also supports the accumulation of MDSCs in the TME and upregulates the expression  
382 of arginase-1 and PD-L1<sup>152</sup>. In stressed mice with prostate tumours and patients with  
383 prostate cancer and depressive symptoms, noradrenaline-stimulated production of

384 neuropeptide Y (NPY) was found to correlate with an increased density of CD68<sup>+</sup>  
385 tumour-associated macrophages (TAMs) and local immunosuppression<sup>153</sup> (**Fig. 3**).

386

387 The genetic deletion or pharmaceutical inhibition of  $\beta$ 2-AR (with ICI118.551 or  
388 propranolol), but not the blockade of  $\beta$ 1-ARs (with metoprolol)<sup>154</sup>, enhanced the  
389 efficacy of anti-PD1 therapy in mouse models of melanoma and breast cancer<sup>154,155</sup>.  
390 Similarly, blocking adrenergic stress or  $\beta$ 2-AR significantly improved the abscopal  
391 effect of ionizing radiation therapy by augmenting anti-tumour immunity in mice with  
392 melanoma, breast cancer, or colon cancer<sup>156</sup>.  $\beta$ 2-AR blockade and local injection of  
393 TLR2 ligands can increase the efficacy of a tumour antigen-loaded DC vaccine in a  
394 mouse model of thymoma<sup>157</sup>. Recent clinical studies prove the concept that  
395 pharmacological blockade of  $\beta$ -ARs may offer therapeutic benefit to patients with  
396 cancer. In a triple-blind placebo-controlled clinical trial for patients with breast cancer,  
397 preoperative administration of the nonselective  $\beta$ -AR inhibitor propranolol reduced  
398 biomarkers associated with invasive potential, increased gene transcription indicative  
399 of M1-polarized macrophages, type 1 and type 2 conventional DCs, and boosted the  
400 intra-tumoral accumulation of CD68<sup>+</sup> TAMs and CTLs<sup>158</sup>. In another randomized  
401 placebo-controlled phase II clinical trial for patients with breast cancer, perioperative  
402 inhibition of  $\beta$ -ARs (with propranolol) and cyclooxygenase-2 (COX-2, with etodolac)  
403 substantially inhibited the expression of EMT-related genes and reduced the activity of  
404 pro-metastatic and proinflammatory transcription factors<sup>159</sup>. This combination therapy  
405 also enhanced the production of IL-12, IFN $\gamma$  and CD11a (a NK activation marker),  
406 suppressed the secretion of IL-6 and C-reactive protein, and attenuated the mobilization  
407 of CD16<sup>-</sup> monocytes<sup>159</sup>. In a prospective study without randomization, blinding, or a  
408 placebo control, the off-label use of propranolol at the time of cancer diagnosis  
409 appeared to lower the risk of disease recurrence in patients with melanoma<sup>160</sup>. In a  
410 retrospective clinical study of patients with metastatic melanoma, pan  $\beta$ -AR  
411 antagonists, rather than  $\beta$ 1-AR selective blockers, seemed to prolong overall survival  
412 following immunotherapy with IL-2 plus CTLA4- and/or PD1-targeted checkpoint  
413 therapy<sup>161</sup>. Future studies may explore predictive biomarkers, optimize therapeutic  
414 regimens, and develop combinatory approaches to utilize  $\beta$ -AR antagonists in cancer  
415 treatment.

416

#### 417 [H2] Other SAIMs

418

419 The impact of other SAIMs on cancer immunosurveillance has been gradually  
420 explored. For example, acute restraint stress was reported to induce tumour immune  
421 evasion by increasing the plasma levels of the neuropeptide kisspeptin and the  
422 expression of its receptor GPR54 in splenic and tumour-infiltrating T cells. Here,  
423 kisspeptin-GPR54 was shown to activate NR4A1 via ERK5 signalling and contribute  
424 to T cell dysfunction and exhaustion<sup>162</sup>. Endogenous cannabinoids (such as anandamide  
425 and 2-arachidonoylglycerol) are actively involved in stress adaptation and regulation of  
426 the HPA axis<sup>163</sup>. It was recently discovered that the anandamide can impair the function  
427 of tumour-specific T cells through cannabinoid receptor 2 (CB2R), and high levels of  
428 plasma anandamide correlated with poor overall survival in patients with cancer<sup>164</sup>.

429

430 In response to persistent stress, the stress-relieving activities of the parasympathetic  
431 system, vagal responses, and ACh production are often suppressed<sup>165</sup>. Interestingly,  
432 these responses are positively associated with anti-cancer immune responses, which

433 may open up new therapeutic approaches. For example, the parasympathetic  
434 neurostimulation with genetic approaches reduced the expression of PD1 and FOXP3  
435 on T cells, thereby stimulating IFN $\gamma$  production and inhibiting the progression of breast  
436 cancer in mice<sup>22</sup>. These effects can be counteracted with pirenzepine, an antagonist of  
437 cholinergic receptor muscarinic 1, indicating that agonists of this receptor might be  
438 beneficial for cancer treatment<sup>22</sup>. Reportedly, synthetic agonists of  $\alpha$ 7-AChR display  
439 anti-inflammatory, antiproliferative and tumour suppressive properties in both mice and  
440 humans<sup>100</sup>. Nicotine (an agonist of nicotinic AChRs) can upregulate the expression  
441 of costimulatory molecules, adhesion molecules, chemokine receptors on DCs, hence  
442 facilitating the priming of CTLs and augmenting the preventive and therapeutic effects  
443 of DC-based anticancer vaccines<sup>166</sup>. Moreover, subdiaphragmatic electrical stimulation  
444 designed to increase the vagal tonus in mice also upregulated the secretion of trefoil  
445 factor 2 (TFF2) by splenic memory T cells. TFF2 can activate the chemokine receptor  
446 CXCR4 and suppress cyclin D1-dependent expansion of MDSCs, and it was shown to  
447 reduce the carcinogenic potential of azomethane/dextran sodium sulfate in mouse  
448 models of inflammatory colorectal cancer<sup>167</sup> (**Fig. 4**). Consequently, in addition to  
449 inhibiting the adrenergic/sympathetic system, the stimulation of the  
450 cholinergic/parasympathetic system might provide novel therapeutic opportunities  
451 against cancer. It remains to be investigated whether a combination of cholinergic  
452 activation and adrenergic inhibition might yield superior tumour control by local  
453 immune infiltrates.

454

## 455 **[H1] SAIMs affect the tumour macroenvironment**

456

457 In addition to the direct regulatory effects on immune cells, SAIMs can induce  
458 metabolic reprogramming of immune cells and other cells within the TME and  
459 throughout the body<sup>17,168-172</sup>. Moreover, stress often disrupts the brain-gut axis, leading  
460 to intestinal permeabilization, microbial dysbiosis, overt inflammation, and the  
461 exposure of microbial components and metabolites<sup>173</sup>. These stress-induced changes in  
462 the tumour macroenvironment often cause immune dysregulation and systemic  
463 aberrations in anti-tumour immune responses (**Fig. 1**).

464

### 465 ***[H2] SAIM-induced metabolic reprogramming***

466

467 Stress can alter the metabolic patterns in the brain<sup>168,169</sup>, in peripheral organs (such as  
468 the liver and the adipose tissue)<sup>170,171</sup>, as well as in circulating and tissue-resident  
469 immune cells<sup>17</sup>. A growing body of evidence suggests that metabolic status and  
470 fluctuations of metabolites are critical determinants of the viability, differentiation,  
471 activation, and function of immune cells<sup>174</sup>, which can be mechanistically explained by  
472 energy supply, macromolecule synthesis, signal transduction, and post-translational  
473 modifications<sup>175</sup>.

474

475 Stress-induced glucocorticoids and catecholamines can potently mobilize glucose and  
476 lipids into the circulation, which support increased demands of energy and biomaterials  
477 of the body<sup>176,177</sup>. Accumulating evidence substantiates that SAIMs are closely involved  
478 in the metabolic shifts in immune cells, which further influence their responses to  
479 tumours. In mouse models of breast cancer, the  $\beta$ 2-AR stress pathway was found to  
480 dictate the immunosuppressive function of MDSCs and TAMs by causing a series of  
481 metabolic changes<sup>178,179</sup>. It augments oxidative phosphorylation, fatty acid oxidation,  
482 and arachidonic acid cycle (to generate an immunosuppressive metabolite

483 prostaglandin E2 (PGE2) but reduces glycolysis in tumour-infiltrating MDSCs<sup>178</sup>. The  
484 immunosuppressive effect of  $\beta$ 2-AR signalling in TAMs can be strengthened by  
485 inflammatory mediators, mainly through elevating the COX-2/PGE2 system<sup>179</sup>. Since  
486 metabolic cues can shape T cell fate and effector functions, stress-induced metabolic  
487 changes, such as mitochondrial dysfunction and insufficient energy supply, may lead  
488 to immune suppression and tumour escape<sup>180,181</sup>. In mouse models of melanoma and  
489 colon cancer, chronic stress was found to dampen T-cell glycolysis and oxidative  
490 phosphorylation via  $\beta$ 2-AR signalling, thus causing T cell exhaustion in the TME<sup>182</sup>. In  
491 a mouse model of sarcoma, the administration of corticosteroids decreased the  
492 frequency of low-affinity memory T cells (but not their high-affinity counterparts) by  
493 suppressing fatty acid metabolism, leading to a compromised efficacy of immune  
494 checkpoint blockade<sup>183</sup>. Chronic stress-induced adrenaline was reported to upregulate  
495 lactate dehydrogenase A (LDHA) and enhance glycolysis in mouse and human  
496 mammary tumours<sup>61</sup>. The upregulation of LDHA and elevated levels of lactic acid in  
497 the TME favoured immune escape and correlated with poor survival in patients with  
498 melanoma and in mouse models of melanoma<sup>184</sup>. This can be linked to the reduced  
499 expression of nuclear factor of activated T cells (NFAT, a key regulator of T-cell  
500 function) and hampered production of IFN $\gamma$  in T cells and NK cells<sup>184</sup>. In response to  
501 SAIMs such as glucocorticoids, catecholamines, and 5-HT, neutrophils can rapidly  
502 release the inflammatory cytokines S100A8 and S100A9<sup>185</sup>, which are known to  
503 mediate immune evasion in cancer<sup>186</sup>. Stress-activated neutrophils also generate  
504 oxidized lipids and promote the recurrence of dormant lung and ovarian cancer in mice  
505 by stimulating the fibroblast growth factor pathway<sup>185</sup>. Overall, these findings  
506 demonstrate that metabolic changes induced by SAIMs, both on the systemic and on  
507 the cellular level, have a negative effect on immune responses against cancer.

508

## 509 *[H2] Stress-induced protein modifications*

510

511 Metabolic reprogramming can modulate immune responses by generating bioactive  
512 metabolites that facilitate the post-translational modifications (PTMs) of proteins<sup>187</sup>.  
513 Several studies showed that stress-induced catecholamines can enhance glycolysis and  
514 lactate production<sup>61,188</sup>. In mouse models of lung cancer and melanoma, the  
515 accumulation of exogenous or endogenous lactate in TAMs has been validated<sup>189</sup>. This  
516 is consistent with a high level of lactylation of histone lysine residues in TAMs, which  
517 contributes to their epigenetic switch to the M2-polarized state<sup>189</sup>.

518

519 The immunoregulatory potential of other metabolite-dependent post-translational  
520 modifications have been documented<sup>187</sup>, but discoveries regarding their association  
521 with stress and SAIMs have just begun to emerge. The addition of O-linked  $\beta$ -N-  
522 acetylglucosamine (O-GlcNAc) to serine or threonine residues of target proteins is  
523 mediated by O-GlcNAc transferase<sup>190</sup>. O-GlcNAcylation can promote the development,  
524 differentiation, and activation of T and B cells, support the activation of neutrophils,  
525 regulate the inflammatory responses of macrophages, and impede the cytotoxicity of  
526 NK cells<sup>190</sup>. It is noteworthy that stress-induced release of cortisol and catecholamines  
527 often cause hyperglycemia and immune dysregulation<sup>191,192</sup>. Hyperglycemia was  
528 reported to augment O-GlcNAcylation in TAMs, which favours their M2-like  
529 polarization and supports the immune evasion of colorectal cancer in mice and  
530 humans<sup>172</sup>. The covalent attachment of palmitic acid to cysteine residues of target  
531 proteins is mainly catalysed by zinc finger DHHC domain-containing (ZDHHC)  
532 palmitoyl acyltransferases<sup>193</sup>. These enzymes are expressed in a region- and cell-type

533 specific pattern in the mouse brain<sup>194</sup>, and chronic exposure to restraint stress can  
534 significantly alter the synaptic palmitoyl-proteome<sup>195</sup>. Interestingly, ZDHHC3-  
535 mediated palmitoylation can stabilize PD-L1 by blocking its ubiquitination and  
536 degradation<sup>196</sup>. Pharmacological inhibition or genetic silencing of ZDHHC3 can  
537 decrease PD-L1 expression on tumour cells and enhance anti-tumour T-cell  
538 immunity<sup>196</sup>. Therefore, stress-induced fluctuations of metabolites and PTMs may  
539 enable a fine-tuning of immune responses against cancer.

540

## 541 **[H2] Stress-induced microbial alterations**

542

543 Microbial communities in the gut have been recognized as key regulators of the  
544 bidirectional interaction between the enteric and the central nervous system<sup>197</sup>. By  
545 generating various metabolic and neurochemical factors and regulating the production  
546 of inflammatory cytokines, they can build up connections between intestinal events and  
547 emotional and cognitive responses in the brain<sup>198</sup>. It is noteworthy that stress-induced  
548 proinflammatory cytokines and neuroendocrine factors (such as catecholamines,  
549 histamine, 5-HT, and CRH) can disrupt the gut-brain axis, cause a leaky gut, and  
550 ultimately lead to microbial imbalance<sup>173,199,200</sup>. Indeed, faecal samples harvested from  
551 patients with major depressive disorder contain more *Enterobacteriaceae* and *Allistipes*,  
552 but less *Faecalibacterium*<sup>201,202</sup>, as compared to those from healthy individuals. In the  
553 GI tract of patients with generalized anxiety disorder, the prevalence of  
554 *Faecalibacterium*, *Eubacterium rectale*, *Lachnospira*, *Butyricoccus*, and *Sutterella*  
555 were significantly reduced<sup>202</sup>.

556

557 A balanced microbiota is vital for immune homeostasis, whereas stress-induced  
558 dysbiosis often leads to immune dysregulation<sup>2,203</sup>. In a mouse model of inflammatory  
559 bowel disease, chronic stress can induce GI dysbiosis and augment local inflammation  
560 in the colonic lamina propria, thus facilitating the development of colitis<sup>204</sup>. GI  
561 dysbiosis allows bacteria to invade the mucosal barriers and migrate into lymphoid  
562 nodes<sup>205</sup> and other tissues<sup>206</sup>, leading to the exposure of pathogen-associated molecular  
563 patterns (PAMPs)<sup>203</sup> to the immune system. Thus, bacterial DNA, lipopolysaccharide,  
564 double-stranded RNA, polysaccharide A, peptidoglycan motifs, and bacterial cell wall-  
565 derived muramyl dipeptide can modulate local and systemic immune responses by  
566 engaging corresponding pattern recognition receptors on immune cells<sup>207,208</sup>. Moreover,  
567 microbial and tumour-associated antigens may share cross-reactive T cell epitopes<sup>209,210</sup>,  
568 and microbial peptides were reported to boost anti-tumour immunity via antigenic  
569 mimicry<sup>211</sup>. Importantly, probiotic supplementation with *Bifidobacterium longum*,  
570 *Lactobacillus farciminis*, and *Lactobacillus helveticus* can help to re-establish a  
571 balanced microflora, attenuate stress-induced neuroendocrine circuits, diminish  
572 intestinal permeability, and alleviate inflammation in patients with endotoxemia<sup>212,213</sup>.  
573 Dysbiosis of the microflora has been shown to compromise anticancer immunity and  
574 the therapeutic benefits of cancer immunotherapy<sup>214-216</sup>. Conversely, a high abundance  
575 of commensal bacteria and probiotics is associated with efficient immunotherapeutic  
576 responses in patients with melanoma<sup>216</sup>, supporting the idea that bacteria that promote  
577 general health also promote anticancer immunity<sup>217</sup>.

578

579 GI microflora-derived metabolites also exhibit immunoregulatory properties<sup>218,219</sup>.  
580 Notably, indole metabolites, tryptophan derivatives, secondary bile acids, and short-  
581 chain fatty acids (SCFAs) from the microbiota can modulate local or systemic immune  
582 responses by engaging pregnane X receptor (PXR), aryl hydrocarbon receptor (AhR),

583 farnesoid X receptor (FXR), Takeda G protein-coupled receptor 5 (TGR5), and orphan  
584 G protein coupled receptors (GPR41 and GPR43), respectively<sup>220</sup>. In the context of  
585 cancer, the activation of these receptors on immune cells or tumour cells often leads to  
586 immunosuppression. For example, TGR5 signalling in TAMs can promote their M2-  
587 polarization, which subsequently hamper CTL response against mouse lung cancer<sup>221</sup>.  
588 High expression of FXR in mouse lung cancer cells also creates an immunosuppressive  
589 microenvironment and causes CTL inactivation and exhaustion<sup>222</sup>. AhR signalling in  
590 mouse oral squamous cell carcinoma can upregulate the expression of immune  
591 checkpoints, whereas genetic deletion of AhR triggers long-lasting anti-tumour  
592 immunity and facilitates tumour regression<sup>223</sup>. Stress-associated enteric dysbiosis can  
593 reduce the abundance of SCFA-producing bacteria in patients with generalized anxiety  
594 disorder<sup>202</sup>. In mice, it was shown that SCFAs contribute to the development of CD8<sup>+</sup>  
595 memory T cells<sup>224</sup>. Of note, in patients with solid tumours, the outcome of PD1-targeted  
596 immune checkpoint inhibitors correlated with the abundance of SCFAs<sup>225,226</sup>.  
597 Altogether, stress-induced metabolic changes in the gut microbiota may have  
598 oncoimmunological impacts, which lack in-depth exploration and merit further  
599 investigation.

600

601 Microbiome-associated biosynthesis of neuroactive factors in the gut and their impact  
602 on tumour immunosurveillance are being gradually unravelled. Intestinal flora-derived  
603 SCFAs can promote 5-HT production by enterochromaffin cells in the gut  
604 epithelium<sup>213</sup>, and indigenous spore-forming bacteria have been identified as important  
605 modulators of this process<sup>212</sup>. Indeed, gut 5-HT accounts for a substantial proportion of  
606 the total pool of 5-HT in the body<sup>212</sup>. Depletion of 5-HT cargo or inhibition of 5-HT  
607 release can enhance the accumulation and effector function of the CD8<sup>+</sup> T cells,  
608 decrease PD-L1 expression, and delay the outgrowth of pancreatic and colorectal  
609 tumours in mice<sup>227</sup>. Dysbiosis and stress-related disorders can be alleviated by some  
610 probiotics, which promote the generation of neurotransmitters (such as  
611 endocannabinoids produced by *Lactobacillus casei* DG<sup>94</sup>) or influence the expression  
612 of their receptors (such as *Lactobacillus rhamnosus*-dependent regulation of GABA  
613 receptors in the brain via the vagus nerve<sup>228</sup>). By engaging CB1R or CB2R on immune  
614 cells, cannabinoids can reshape the immune landscape of the TME to positively or  
615 negatively regulate tumour growth<sup>229</sup>. In mouse models of lung and colon cancer,  
616 GABA signalling can promote local immunosuppression by excluding T cells from the  
617 TME<sup>230</sup> and eliciting IL-10-producing anti-inflammatory TAMs<sup>231</sup>. It was reported that  
618 *Staphylococcus pseudintermedius* can generate dopamine and 5-HT<sup>232</sup>, while  
619 *Firmicutes* (such as *Clostridium sporogenes* and *Ruminococcus gnavus*) can  
620 decarboxylate tryptophan to produce  $\beta$ -arylamine neurotransmitter tryptamine<sup>233</sup>. The  
621 opportunistic pathogen *Enterococcus faecalis* can generate tyramine (the invertebrate  
622 equivalent of noradrenaline<sup>234</sup>) via tyrosine decarboxylases<sup>235</sup>. Accumulated tyramine  
623 can engage trace amine-associated receptors (TAARs) and induce the release of  
624 catecholamine stores from nerve terminals in porcines<sup>236</sup>. Altogether, we speculate that  
625 targeting stress-induced dysbiosis, metabolic or neuroendocrine changes, and related  
626 immunological abnormalities may provide novel therapeutic strategies to improve  
627 tumour immunosurveillance in individuals under unresolved stress.

628

## 629 **Conclusion and perspective**

630

631 As discussed above, psychosocial stress affects cancer immunosurveillance. The  
632 regulatory network underpinning these interactions is composed of central or peripheral

633 SAIMs, metabolic changes and bioactive metabolites, dysbiosis and specific microbial  
634 components, as well as different cell types that either generate or respond to these  
635 factors. There are various known and yet unknown receptors or sensors of SAIMs, and  
636 many of the downstream signalling pathways that affect transcriptomic profiles,  
637 metabolomic patterns, and PTMs are yet to be elucidated. The disentanglement of this  
638 ecosystem has barely begun. Progress in the area will require interdisciplinary  
639 collaborations among scientists working across diverse areas, such as neurology,  
640 psychology, psychiatry, oncology, immunology, endocrinology, metabolism, and  
641 microbiology. Moreover, a scaling up of spatially and temporally resolved ‘omics’  
642 approaches as well as the development of reductionist in vitro and in vivo models will  
643 be necessary, using single cell- and spatially-resolved transcriptomics, proteomics and  
644 metabolomics, live-cell or live-tissue imaging, organoid and 3D culturing,  
645 microfluidics and other biophysical methods. Such models will need to reconstruct the  
646 complexity of neoplasia by regarding tumours as organized assemblies of different cell  
647 types that closely communicate with sympathetic, parasympathetic, and sensory nerve  
648 terminations, as well as the microbiota both in the GI tract and in the tumour.

649

650 However, it should be noted that cancer directly affects the neuroendocrine and immune  
651 systems as well. This is due to the usually traumatic experience of cancer diagnosis,  
652 often invasive operations, and major side effects of treatments, but it also concerns the  
653 pathophysiology of the disease itself. Thus, advanced cancer with its corollaries (such  
654 as pain, inflammation, cachexia) is usually coupled to the ‘sickness response’,  
655 involving a radical rewiring of neuroendocrine circuitries, metabolic switches from  
656 anabolism to catabolism, as well as behavioural alterations (insomnia, social isolation)  
657 and immune abnormalities<sup>10</sup>. This stereotyped response activates an immune-  
658 neuroendocrine feedback loop, in which inflammatory mediators produced in  
659 peripheral tissues can reach specific areas in the hypothalamus to induce similar  
660 changes as those induced by stress.

661

662 Since neurotransmitters and stress hormones can exhibit different local and systemic  
663 effects, pharmacological intervention targeting the synthesis of catecholamines or  
664 cortisol steroidogenesis are not feasible to treat stress-related disorders due to their  
665 excessive side effects. In contrast, specific antagonists of subclasses of ARs are in  
666 medical use and are generally well tolerated<sup>237</sup>. Although it appears obvious that, given  
667 their immunosuppressive effects, synthetic glucocorticoids should be avoided for the  
668 routine management of patients with cancer, it is certainly premature to broadly  
669 recommend GR antagonists for cancer treatment. Ongoing clinical trials are testing the  
670 anti-cancer potential of the GR antagonist mifepristone as monotherapy or in  
671 combination with chemotherapy or immunotherapy for breast cancer<sup>125,126</sup>. A similar  
672 caveat may apply to surgical, electrical, or pharmacological sympathectomy and  
673 parasympathetic stimulation. Given the importance of these systems in homeostatic  
674 regulation, clinical trials need to be carefully planned to avoid deleterious side effects  
675 for such neuroendocrine interventions. Strictly localized approaches (such as intra-  
676 tumoral manipulations of SAIM receptors with antagonists or agonists, sympathetic  
677 denervation, or parasympathetic stimulation), used alone or combined with  
678 immunotherapies, may be feasible strategies to elicit anti-tumour immunity with an  
679 abscopal effect on metastases<sup>238</sup>. Traditional approaches of stress management and  
680 psychotropic medications have been put into use for a long time. However, their impact  
681 on tumour control and antitumour immune response needs further investigation (**Box**  
682 **4**).



683

684 Here we have aimed to condense limited knowledge on physiological and psychological  
685 stress, neuronal/endocrine circuitries, and immuno-oncology into a coherent paradigm  
686 involving SAIMs that affect the cancer-immune crosstalk. Rewired metabolic  
687 roadmaps, metabolite-mediated cell-cell communication, and microbial dynamics are  
688 also emerging as crucial modulators of behavioural patterns and the cancer-immune  
689 dialogue<sup>239,240</sup>. Although this endeavour already appears very ambitious, it might  
690 underestimate the impact of other so-far unknown factors. Hence, future research needs  
691 to address these ever-expanding complexities to understand the inseparable link  
692 between mind and body.

693

## 694 **Acknowledgements**

695

696 Y.M. is supported by Science and Technology Innovation 2030 Major Project  
697 (STI2030-Major Projects 2022ZD0205700), Natural Science Foundation of China  
698 (NSFC grant No. 81972701), CAMS Innovation Fund for Medical Sciences (CIFMS;  
699 2021-I2M-1-074, 2022-I2M-2-004), National special support plan for high-level talents,  
700 Suzhou Municipal Key Laboratory (SZS2023005), and Innovative and Entrepreneurial  
701 Team Program (Jiangsu Province). G.K. is supported by the Ligue contre le Cancer  
702 (équipe labellisée); Agence National de la Recherche (ANR)–Projets blancs; AMMICA  
703 US23/CNRS UMS3655; Association pour la recherche sur le cancer (ARC);  
704 Cancéropôle Ile-de-France; Fondation pour la Recherche Médicale (FRM); Equipex  
705 Onco-Pheno-Screen; European Joint Programme on Rare Diseases; the European  
706 Union Horizon 2020 Projects Oncobiome and Crimson; Institut National du Cancer  
707 (INCa); Institut Universitaire de France; LabEx Immuno-Oncology (ANR-18-IDEX-  
708 0001); High-end Foreign Expert Program in China (GDW20171100085); the RHU  
709 Immunolife; Seerave Foundation; SIRIC Stratified Oncology Cell DNA Repair and  
710 Tumor Immune Elimination (SOCRATE); and SIRIC Cancer Research and  
711 Personalized Medicine (CARPEM).

712

## 713 **References**

714

- 715 1 Braslow, J. T. & Marder, S. R. History of Psychopharmacology. *Annu Rev Clin Psychol* **15**, 25-  
716 50, doi:10.1146/annurev-clinpsy-050718-095514 (2019).
- 717 2 Cruz-Pereira, J. S. *et al.* Depression's Unholy Trinity: Dysregulated Stress, Immunity, and the  
718 Microbiome. *Annu Rev Psychol* **71**, 49-78, doi:10.1146/annurev-psych-122216-011613 (2020).
- 719 3 Hanahan, D. & Weinberg, R. A. The hallmarks of cancer. *Cell* **100**, 57-70, doi:10.1016/s0092-  
720 8674(00)81683-9 (2000).
- 721 This review elegantly summarizes current knowledge about the links among depression pathogenesis,  
722 immunity and microbiome, as well as possible therapeutic interventions.
- 723 4 Hanahan, D. & Weinberg, R. A. Hallmarks of cancer: the next generation. *Cell* **144**, 646-674,  
724 doi:10.1016/j.cell.2011.02.013 (2011).
- 725 5 Veiga-Fernandes, H. & Artis, D. Neuronal-immune system cross-talk in homeostasis. *Science*  
726 **359**, 1465-1466, doi:10.1126/science.aap9598 (2018).
- 727 6 Godinho-Silva, C., Cardoso, F. & Veiga-Fernandes, H. Neuro-Immune Cell Units: A New  
728 Paradigm in Physiology. *Annu Rev Immunol* **37**, 19-46, doi:10.1146/annurev-immunol-042718-  
729 041812 (2019).
- 730 7 Huang, S. *et al.* Lymph nodes are innervated by a unique population of sensory neurons with  
731 immunomodulatory potential. *Cell* **184**, 441-459 e425, doi:10.1016/j.cell.2020.11.028 (2021).
- 732 This study discovered that lymph node-innervating sensory neurons can interact with several predicted  
733 cell types and change their transcriptome. And the unexpected sensory neuro-immune circuit  
734 exhibits the capacity to monitor the inflammatory state in the lymph node.
- 735 8 Kabata, H. & Artis, D. Neuro-immune crosstalk and allergic inflammation. *J Clin Invest* **130**,

736 1475-1482, doi:10.1172/JCI124609 (2019).

737 9 Chen, C.-S., Barnoud, C. & Scheiermann, C. Peripheral neurotransmitters in the immune system.  
738 *Current Opinion in Physiology* **19**, 73-79, doi:<https://doi.org/10.1016/j.cophys.2020.09.009>  
739 (2021).

740 10 Wang, A., Luan, H. H. & Medzhitov, R. An evolutionary perspective on immunometabolism.  
741 *Science* **363**, doi:10.1126/science.aar3932 (2019).

742 11 Guyot, M. *et al.* Apical splenic nerve electrical stimulation discloses an anti-inflammatory  
743 pathway relying on adrenergic and nicotinic receptors in myeloid cells. *Brain Behav Immun* **80**,  
744 238-246, doi:10.1016/j.bbi.2019.03.015 (2019).

745 12 Al-Shalan, H. A. M., Hu, D., Nicholls, P. K., Greene, W. K. & Ma, B. Immunofluorescent  
746 characterization of innervation and nerve-immune cell neighborhood in mouse thymus. *Cell*  
747 *Tissue Res* **378**, 239-254, doi:10.1007/s00441-019-03052-4 (2019).

748 13 Jung, W. C., Levesque, J. P. & Ruitenbergh, M. J. It takes nerve to fight back: The significance  
749 of neural innervation of the bone marrow and spleen for immune function. *Semin Cell Dev Biol*  
750 **61**, 60-70, doi:10.1016/j.semdb.2016.08.010 (2017).

751 14 Zhang, X. *et al.* Brain control of humoral immune responses amenable to behavioural  
752 modulation. *Nature* **581**, 204-208, doi:10.1038/s41586-020-2235-7 (2020).

753 This well-designed study identifies a specific brain–spleen neural connection in mice that enhances  
754 humoral responses in response to an elevated platform regimen.

755 15 Rosas-Ballina, M. *et al.* Splenic nerve is required for cholinergic antiinflammatory pathway  
756 control of TNF in endotoxemia. *Proc Natl Acad Sci U S A* **105**, 11008-11013,  
757 doi:10.1073/pnas.0803237105 (2008).

758 16 Miyajima, M. *et al.* Metabolic shift induced by systemic activation of T cells in PD-1-deficient  
759 mice perturbs brain monoamines and emotional behavior. *Nat Immunol* **18**, 1342-1352,  
760 doi:10.1038/ni.3867 (2017).

761 This paper reveals how a key immune checkpoint molecule PD-1 is involved in regulating systemic  
762 metabolism, the biosynthesis of neurotransmitters, and behaviours.

763 17 Fan, K. Q. *et al.* Stress-Induced Metabolic Disorder in Peripheral CD4(+) T Cells Leads to  
764 Anxiety-like Behavior. *Cell* **179**, 864-879 e819, doi:10.1016/j.cell.2019.10.001 (2019).

765 This interesting study suggests that stress-induced abnormal mitochondrial fission and purine synthesis  
766 in CD4<sup>+</sup>T cells influence oligodendrocytes in the amygdala, which is a prerequisite for the onset  
767 of anxiety.

768 18 Fridman, W. H., Zitvogel, L., Sautes-Fridman, C. & Kroemer, G. The immune contexture in  
769 cancer prognosis and treatment. *Nat Rev Clin Oncol* **14**, 717-734,  
770 doi:10.1038/nrclinonc.2017.101 (2017).

771 19 Faulkner, S., Jobling, P., March, B., Jiang, C. C. & Hondermarck, H. Tumor Neurobiology and  
772 the War of Nerves in Cancer. *Cancer Discov* **9**, 702-710, doi:10.1158/2159-8290.CD-18-1398  
773 (2019).

774 This comprehensive review summarizes recent progresses that deal with the potential link between  
775 tumour-induced innervation with in the TME and cancer initiation, progression, and metastasis.

776 20 Magnon, C. *et al.* Autonomic nerve development contributes to prostate cancer progression.  
777 *Science* **341**, 1236361, doi:10.1126/science.1236361 (2013).

778 21 Zahalka, A. H. *et al.* Adrenergic nerves activate an angio-metabolic switch in prostate cancer.  
779 *Science* **358**, 321-326, doi:10.1126/science.aah5072 (2017).

780 22 Kamiya, A. *et al.* Genetic manipulation of autonomic nerve fiber innervation and activity and  
781 its effect on breast cancer progression. *Nat Neurosci* **22**, 1289-1305, doi:10.1038/s41593-019-  
782 0430-3 (2019).

783 23 Cervantes-Villagrana, R. D., Albores-Garcia, D., Cervantes-Villagrana, A. R. & Garcia-Acevez,  
784 S. J. Tumor-induced neurogenesis and immune evasion as targets of innovative anti-cancer  
785 therapies. *Signal Transduct Target Ther* **5**, 99, doi:10.1038/s41392-020-0205-z (2020).

786 24 Wei, E. K., Wolin, K. Y. & Colditz, G. A. Time course of risk factors in cancer etiology and  
787 progression. *J Clin Oncol* **28**, 4052-4057, doi:10.1200/JCO.2009.26.9324 (2010).

788 25 Feng, Z. *et al.* Chronic restraint stress attenuates p53 function and promotes tumorigenesis. *Proc*  
789 *Natl Acad Sci U S A* **109**, 7013-7018, doi:10.1073/pnas.1203930109 (2012).

790 26 Jang, H. J., Boo, H. J., Lee, H. J., Min, H. Y. & Lee, H. Y. Chronic Stress Facilitates Lung  
791 Tumorigenesis by Promoting Exocytosis of IGF2 in Lung Epithelial Cells. *Cancer Res* **76**,  
792 6607-6619, doi:10.1158/0008-5472.CAN-16-0990 (2016).

793 27 Schoemaker, M. J. *et al.* Psychological stress, adverse life events and breast cancer incidence:  
794 a cohort investigation in 106,000 women in the United Kingdom. *Breast Cancer Res* **18**, 72,  
795 doi:10.1186/s13058-016-0733-1 (2016).

- 796 28 Wang, Y. H. *et al.* Depression and anxiety in relation to cancer incidence and mortality: a  
797 systematic review and meta-analysis of cohort studies. *Mol Psychiatry* **25**, 1487-1499,  
798 doi:10.1038/s41380-019-0595-x (2020).
- 799 A systematic review and meta-analysis containing 51 eligible cohort studies involving 2,611,907  
800 participants, which tested the association between “anxiety and depression” and the risk of  
801 cancer incidence, cancer-specific mortality, and all-cause mortality in cancer patients.
- 802 29 Butow, P. *et al.* Does stress increase risk of breast cancer? A 15-year prospective study.  
803 *Psychooncology* **27**, 1908-1914, doi:10.1002/pon.4740 (2018).
- 804 30 Tomiyama, A. J. Stress and Obesity. *Annu Rev Psychol* **70**, 703-718, doi:10.1146/annurev-  
805 psych-010418-102936 (2019).
- 806 31 Song, H. *et al.* Association of Stress-Related Disorders With Subsequent Autoimmune Disease.  
807 *JAMA* **319**, 2388-2400, doi:10.1001/jama.2018.7028 (2018).
- 808 32 Buchanan, T. W. & Lovallo, W. R. The role of genetics in stress effects on health and addiction.  
809 *Curr Opin Psychol* **27**, 72-76, doi:10.1016/j.copsyc.2018.09.005 (2019).
- 810 33 Anacker, C. *et al.* Neuroanatomic Differences Associated With Stress Susceptibility and  
811 Resilience. *Biol Psychiatry* **79**, 840-849, doi:10.1016/j.biopsych.2015.08.009 (2016).
- 812 34 Misiewicz, Z. *et al.* Multi-omics analysis identifies mitochondrial pathways associated with  
813 anxiety-related behavior. *PLoS Genet* **15**, e1008358, doi:10.1371/journal.pgen.1008358 (2019).
- 814 35 Mitchell, A. J. *et al.* Prevalence of depression, anxiety, and adjustment disorder in oncological,  
815 haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies.  
816 *Lancet Oncol* **12**, 160-174, doi:10.1016/S1470-2045(11)70002-X (2011).
- 817 36 Cordova, M. J., Riba, M. B. & Spiegel, D. Post-traumatic stress disorder and cancer. *Lancet*  
818 *Psychiatry* **4**, 330-338, doi:10.1016/S2215-0366(17)30014-7 (2017).
- 819 37 Mehnert, A. & Koch, U. Prevalence of acute and post-traumatic stress disorder and comorbid  
820 mental disorders in breast cancer patients during primary cancer care: a prospective study.  
821 *Psychooncology* **16**, 181-188, doi:10.1002/pon.1057 (2007).
- 822 38 Horowitz, M., Neeman, E., Sharon, E. & Ben-Eliyahu, S. Exploiting the critical perioperative  
823 period to improve long-term cancer outcomes. *Nat Rev Clin Oncol* **12**, 213-226,  
824 doi:10.1038/nrclinonc.2014.224 (2015).
- 825 39 Batty, G. D., Russ, T. C., Stamatakis, E. & Kivimaki, M. Psychological distress in relation to  
826 site specific cancer mortality: pooling of unpublished data from 16 prospective cohort studies.  
827 *BMJ* **356**, j108, doi:10.1136/bmj.j108 (2017).
- 828 40 Palesh, O. *et al.* Stress history and breast cancer recurrence. *J Psychosom Res* **63**, 233-239,  
829 doi:10.1016/j.jpsychores.2007.05.012 (2007).
- 830 41 Wang, X. *et al.* Prognostic value of depression and anxiety on breast cancer recurrence and  
831 mortality: a systematic review and meta-analysis of 282,203 patients. *Mol Psychiatry* **25**, 3186-  
832 3197, doi:10.1038/s41380-020-00865-6 (2020).
- 833 42 Moreno-Smith, M., Lutgendorf, S. K. & Sood, A. K. Impact of stress on cancer metastasis.  
834 *Future Oncol* **6**, 1863-1881, doi:10.2217/fon.10.142 (2010).
- 835 43 Chida, Y., Hamer, M., Wardle, J. & Steptoe, A. Do stress-related psychosocial factors contribute  
836 to cancer incidence and survival? *Nat Clin Pract Oncol* **5**, 466-475, doi:10.1038/nponc1134  
837 (2008).
- 838 44 Powell, N. D. *et al.* Social stress up-regulates inflammatory gene expression in the leukocyte  
839 transcriptome via beta-adrenergic induction of myelopoiesis. *Proc Natl Acad Sci U S A* **110**,  
840 16574-16579, doi:10.1073/pnas.1310655110 (2013).
- 841 45 Irwin, M. R. & Cole, S. W. Reciprocal regulation of the neural and innate immune systems. *Nat*  
842 *Rev Immunol* **11**, 625-632, doi:10.1038/nri3042 (2011).
- 843 46 Lu, D. *et al.* Stress-Related Signaling Pathways in Lethal and Nonlethal Prostate Cancer. *Clin*  
844 *Cancer Res* **22**, 765-772, doi:10.1158/1078-0432.CCR-15-0101 (2016).
- 845 47 Thaker, P. H. *et al.* Chronic stress promotes tumor growth and angiogenesis in a mouse model  
846 of ovarian carcinoma. *Nat Med* **12**, 939-944, doi:10.1038/nm1447 (2006).
- 847 48 Zhang, X. *et al.* Chronic stress promotes gastric cancer progression and metastasis: an essential  
848 role for ADRB2. *Cell Death Dis* **10**, 788, doi:10.1038/s41419-019-2030-2 (2019).
- 849 49 Le, C. P. *et al.* Chronic stress in mice remodels lymph vasculature to promote tumour cell  
850 dissemination. *Nat Commun* **7**, 10634, doi:10.1038/ncomms10634 (2016).
- 851 50 Saul, A. N. *et al.* Chronic stress and susceptibility to skin cancer. *J Natl Cancer Inst* **97**, 1760-  
852 1767, doi:10.1093/jnci/dji401 (2005).
- 853 51 Ben-Eliyahu, S., Page, G. G., Yirmiya, R. & Shakhar, G. Evidence that stress and surgical  
854 interventions promote tumor development by suppressing natural killer cell activity. *Int J*  
855 *Cancer* **80**, 880-888, doi:10.1002/(sici)1097-0215(19990315)80:6<880::aid-ijc14>3.0.co;2-y

856 (1999).

857 52 Yang, H. *et al.* Stress-glucocorticoid-TSC22D3 axis compromises therapy-induced antitumor  
858 immunity. *Nat Med* **25**, 1428-1441, doi:10.1038/s41591-019-0566-4 (2019).

859 This study provides strong evidence that psychological stress compromises the efficacy of immune-  
860 dependent cancer therapies, by elevating the endogenous glucocorticoid tonus and stimulating  
861 TSC22D3 expression in tumour-infiltrating DC.

862 53 Kokolus, K. M. *et al.* Baseline tumor growth and immune control in laboratory mice are  
863 significantly influenced by subthermoneutral housing temperature. *Proc Natl Acad Sci U S A*  
864 **110**, 20176-20181, doi:10.1073/pnas.1304291110 (2013).

865 54 Cao, L. *et al.* Environmental and genetic activation of a brain-adipocyte BDNF/leptin axis  
866 causes cancer remission and inhibition. *Cell* **142**, 52-64, doi:10.1016/j.cell.2010.05.029 (2010).

867 55 He, L. *et al.* Glucocorticoid Receptor Signaling Activates TEAD4 to Promote Breast Cancer  
868 Progression. *Cancer Res* **79**, 4399-4411, doi:10.1158/0008-5472.CAN-19-0012 (2019).

869 56 Obradovic, M. M. S. *et al.* Glucocorticoids promote breast cancer metastasis. *Nature* **567**, 540-  
870 544, doi:10.1038/s41586-019-1019-4 (2019).

871 57 Melhem, A. *et al.* Administration of glucocorticoids to ovarian cancer patients is associated with  
872 expression of the anti-apoptotic genes SGK1 and MKP1/DUSP1 in ovarian tissues. *Clin Cancer*  
873 *Res* **15**, 3196-3204, doi:10.1158/1078-0432.CCR-08-2131 (2009).

874 58 Petrella, A. *et al.* Dexamethasone inhibits TRAIL-induced apoptosis of thyroid cancer cells via  
875 Bcl-xL induction. *Eur J Cancer* **42**, 3287-3293, doi:10.1016/j.ejca.2006.07.018 (2006).

876 59 Sorrentino, G. *et al.* Glucocorticoid receptor signalling activates YAP in breast cancer. *Nat*  
877 *Commun* **8**, 14073, doi:10.1038/ncomms14073 (2017).

878 60 Flaherty, R. L. *et al.* Glucocorticoids induce production of reactive oxygen species/reactive  
879 nitrogen species and DNA damage through an iNOS mediated pathway in breast cancer. *Breast*  
880 *Cancer Res* **19**, 35, doi:10.1186/s13058-017-0823-8 (2017).

881 61 Cui, B. *et al.* Stress-induced epinephrine enhances lactate dehydrogenase A and promotes breast  
882 cancer stem-like cells. *J Clin Invest* **129**, 1030-1046, doi:10.1172/JCI121685 (2019).

883 62 Sastry, K. S. *et al.* Epinephrine protects cancer cells from apoptosis via activation of cAMP-  
884 dependent protein kinase and BAD phosphorylation. *J Biol Chem* **282**, 14094-14100,  
885 doi:10.1074/jbc.M611370200 (2007).

886 63 Nagaraja, A. S. *et al.* Adrenergic-mediated increases in INHBA drive CAF phenotype and  
887 collagens. *JCI Insight* **2**, doi:10.1172/jci.insight.93076 (2017).

888 64 Yang, E. V. *et al.* Norepinephrine up-regulates the expression of vascular endothelial growth  
889 factor, matrix metalloproteinase (MMP)-2, and MMP-9 in nasopharyngeal carcinoma tumor  
890 cells. *Cancer Res* **66**, 10357-10364, doi:10.1158/0008-5472.CAN-06-2496 (2006).

891 65 Sood, A. K. *et al.* Stress hormone-mediated invasion of ovarian cancer cells. *Clin Cancer Res*  
892 **12**, 369-375, doi:10.1158/1078-0432.CCR-05-1698 (2006).

893 66 Kilpatrick, L. E. *et al.* Complex Formation between VEGFR2 and the beta2-Adrenoceptor. *Cell*  
894 *Chem Biol* **26**, 830-841 e839, doi:10.1016/j.chembiol.2019.02.014 (2019).

895 67 Allen, J. K. *et al.* Sustained Adrenergic Signaling Promotes Intratumoral Innervation through  
896 BDNF Induction. *Cancer Res* **78**, 3233-3242, doi:10.1158/0008-5472.CAN-16-1701 (2018).

897 68 Ulrich-Lai, Y. M. & Herman, J. P. Neural regulation of endocrine and autonomic stress  
898 responses. *Nat Rev Neurosci* **10**, 397-409, doi:10.1038/nrn2647 (2009).

899 69 Picard, M. *et al.* Mitochondrial functions modulate neuroendocrine, metabolic, inflammatory,  
900 and transcriptional responses to acute psychological stress. *Proc Natl Acad Sci U S A* **112**,  
901 E6614-6623, doi:10.1073/pnas.1515733112 (2015).

902 70 Cole, S. W. & Sood, A. K. Molecular pathways: beta-adrenergic signaling in cancer. *Clin Cancer*  
903 *Res* **18**, 1201-1206, doi:10.1158/1078-0432.CCR-11-0641 (2012).

904 71 Wu, D., Katz, A., Lee, C. H. & Simon, M. I. Activation of phospholipase C by alpha 1-  
905 adrenergic receptors is mediated by the alpha subunits of Gq family. *J Biol Chem* **267**, 25798-  
906 25802 (1992).

907 72 Wick, G., Hu, Y., Schwarz, S. & Kroemer, G. Immunoendocrine communication via the  
908 hypothalamo-pituitary-adrenal axis in autoimmune diseases. *Endocr Rev* **14**, 539-563,  
909 doi:10.1210/edrv-14-5-539 (1993).

910 73 Weikum, E. R., Knuesel, M. T., Ortlund, E. A. & Yamamoto, K. R. Glucocorticoid receptor  
911 control of transcription: precision and plasticity via allosterity. *Nat Rev Mol Cell Biol* **18**, 159-  
912 174, doi:10.1038/nrm.2016.152 (2017).

913 74 Ping, Y. Q. *et al.* Structures of the glucocorticoid-bound adhesion receptor GPR97-Go complex.  
914 *Nature* **589**, 620-626, doi:10.1038/s41586-020-03083-w (2021).

915 75 Wang, J. J. *et al.* Gpr97 is essential for the follicular versus marginal zone B-lymphocyte fate

916 decision. *Cell Death Dis* **4**, e853, doi:10.1038/cddis.2013.346 (2013).

917 76 Chu, T. Y. *et al.* GPR97 triggers inflammatory processes in human neutrophils via a  
918 macromolecular complex upstream of PAR2 activation. *Nat Commun* **13**, 6385,  
919 doi:10.1038/s41467-022-34083-1 (2022).

920 77 Graeff, F. G., Guimaraes, F. S., De Andrade, T. G. & Deakin, J. F. Role of 5-HT in stress, anxiety,  
921 and depression. *Pharmacol Biochem Behav* **54**, 129-141, doi:10.1016/0091-3057(95)02135-3  
922 (1996).

923 78 Mineur, Y. S. *et al.* Cholinergic signaling in the hippocampus regulates social stress resilience  
924 and anxiety- and depression-like behavior. *Proc Natl Acad Sci U S A* **110**, 3573-3578,  
925 doi:10.1073/pnas.1219731110 (2013).

926 79 Picciotto, M. R., Higley, M. J. & Mineur, Y. S. Acetylcholine as a neuromodulator: cholinergic  
927 signaling shapes nervous system function and behavior. *Neuron* **76**, 116-129,  
928 doi:10.1016/j.neuron.2012.08.036 (2012).

929 80 Lydiard, R. B. The role of GABA in anxiety disorders. *J Clin Psychiatry* **64 Suppl 3**, 21-27  
930 (2003).

931 81 Nuss, P. Anxiety disorders and GABA neurotransmission: a disturbance of modulation.  
932 *Neuropsychiatr Dis Treat* **11**, 165-175, doi:10.2147/NDT.S58841 (2015).

933 82 Panula, P. & Nuutinen, S. The histaminergic network in the brain: basic organization and role  
934 in disease. *Nat Rev Neurosci* **14**, 472-487, doi:10.1038/nrn3526 (2013).

935 83 de Almeida, D. O., Ferreira, H. S., Pereira, L. B. & Fregoneze, J. B. Hypertensive response to  
936 stress: the role of histaminergic H1 and H2 receptors in the medial amygdala. *Physiol Behav*  
937 **144**, 95-102, doi:10.1016/j.physbeh.2015.03.009 (2015).

938 84 Bali, A., Randhawa, P. K. & Jaggi, A. S. Stress and opioids: role of opioids in modulating stress-  
939 related behavior and effect of stress on morphine conditioned place preference. *Neurosci*  
940 *Biobehav Rev* **51**, 138-150, doi:10.1016/j.neubiorev.2014.12.018 (2015).

941 85 Valentino, R. J. & Van Bockstaele, E. Endogenous Opioids: The Downside of Opposing Stress.  
942 *Neurobiol Stress* **1**, 23-32, doi:10.1016/j.ynstr.2014.09.006 (2015).

943 86 Pecina, M. *et al.* Endogenous opioid system dysregulation in depression: implications for new  
944 therapeutic approaches. *Mol Psychiatry* **24**, 576-587, doi:10.1038/s41380-018-0117-2 (2019).

945 87 Oshaghi, M., Kourosh-Arabi, M. & Roozbehkia, M. Role of neurotransmitters in immune-  
946 mediated inflammatory disorders: a crosstalk between the nervous and immune systems. *Neurol*  
947 *Sci* **44**, 99-113, doi:10.1007/s10072-022-06413-0 (2023).

948 88 Herman, J. P. *et al.* Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response.  
949 *Compr Physiol* **6**, 603-621, doi:10.1002/cphy.c150015 (2016).

950 89 Lanfumey, L., Mongeau, R., Cohen-Salmon, C. & Hamon, M. Corticosteroid-serotonin  
951 interactions in the neurobiological mechanisms of stress-related disorders. *Neurosci Biobehav*  
952 *Rev* **32**, 1174-1184, doi:10.1016/j.neubiorev.2008.04.006 (2008).

953 90 Sui, P. *et al.* Pulmonary neuroendocrine cells amplify allergic asthma responses. *Science* **360**,  
954 doi:10.1126/science.aan8546 (2018).

955 91 Bellono, N. W. *et al.* Enterochromaffin Cells Are Gut Chemosensors that Couple to Sensory  
956 Neural Pathways. *Cell* **170**, 185-198 e116, doi:10.1016/j.cell.2017.05.034 (2017).

957 92 Sidler, D. *et al.* Colon cancer cells produce immunoregulatory glucocorticoids. *Oncogene* **30**,  
958 2411-2419, doi:10.1038/onc.2010.629 (2011).

959 93 Honke, N. *et al.* Endogenously produced catecholamines improve the regulatory function of  
960 TLR9-activated B cells. *PLoS Biol* **20**, e3001513, doi:10.1371/journal.pbio.3001513 (2022).

961 94 Guida, F. *et al.* Antibiotic-induced microbiota perturbation causes gut endocannabinoidome  
962 changes, hippocampal neuroglial reorganization and depression in mice. *Brain Behav Immun*  
963 **67**, 230-245, doi:10.1016/j.bbi.2017.09.001 (2018).

964 95 Monje, M. *et al.* Roadmap for the Emerging Field of Cancer Neuroscience. *Cell* **181**, 219-222,  
965 doi:10.1016/j.cell.2020.03.034 (2020).

966 96 Walker, A. K. *et al.* Circulating epinephrine is not required for chronic stress to enhance  
967 metastasis. *Psychoneuroendocrinology* **99**, 191-195, doi:10.1016/j.psyneuen.2018.09.012  
968 (2019).

969 97 Renz, B. W. *et al.* beta2 Adrenergic-Neurotrophin Feedforward Loop Promotes Pancreatic  
970 Cancer. *Cancer Cell* **33**, 75-90 e77, doi:10.1016/j.ccell.2017.11.007 (2018).

971 98 Renz, B. W. *et al.* Cholinergic Signaling via Muscarinic Receptors Directly and Indirectly  
972 Suppresses Pancreatic Tumorigenesis and Cancer Stemness. *Cancer Discov* **8**, 1458-1473,  
973 doi:10.1158/2159-8290.CD-18-0046 (2018).

974 99 Renz, B. W. *et al.* beta2 Adrenergic-Neurotrophin Feedforward Loop Promotes Pancreatic  
975 Cancer. *Cancer Cell* **34**, 863-867, doi:10.1016/j.ccell.2018.10.010 (2018).

976 100 Reijmen, E., Vannucci, L., De Couck, M., De Greve, J. & Gidron, Y. Therapeutic potential of  
977 the vagus nerve in cancer. *Immunol Lett* **202**, 38-43, doi:10.1016/j.imlet.2018.07.006 (2018).

978 101 De Couck, M., Caers, R., Spiegel, D. & Gidron, Y. The Role of the Vagus Nerve in Cancer  
979 Prognosis: A Systematic and a Comprehensive Review. *J Oncol* **2018**, 1236787,  
980 doi:10.1155/2018/1236787 (2018).

981 102 Husby, A., Wohlfahrt, J. & Melbye, M. Vasectomy and Prostate Cancer Risk: A 38-Year  
982 Nationwide Cohort Study. *J Natl Cancer Inst* **112**, 71-77, doi:10.1093/jnci/djz099 (2020).

983 103 Webster, J. I., Tonelli, L. & Sternberg, E. M. Neuroendocrine regulation of immunity. *Annu Rev*  
984 *Immunol* **20**, 125-163, doi:10.1146/annurev.immunol.20.082401.104914 (2002).

985 104 Taves, M. D. & Ashwell, J. D. Glucocorticoids in T cell development, differentiation and  
986 function. *Nat Rev Immunol*, doi:10.1038/s41577-020-00464-0 (2020).

987 105 Cain, D. W. & Cidlowski, J. A. Immune regulation by glucocorticoids. *Nat Rev Immunol* **17**,  
988 233-247, doi:10.1038/nri.2017.1 (2017).

989 106 Dhabhar, F. S. & McEwen, B. S. Enhancing versus suppressive effects of stress hormones on  
990 skin immune function. *Proc Natl Acad Sci U S A* **96**, 1059-1064, doi:10.1073/pnas.96.3.1059  
991 (1999).

992 107 Sharma, D. & Farrar, J. D. Adrenergic regulation of immune cell function and inflammation.  
993 *Semin Immunopathol* **42**, 709-717, doi:10.1007/s00281-020-00829-6 (2020).

994 108 Hunzeker, J. T. *et al.* A marked reduction in priming of cytotoxic CD8<sup>+</sup> T cells mediated by  
995 stress-induced glucocorticoids involves multiple deficiencies in cross-presentation by dendritic  
996 cells. *J Immunol* **186**, 183-194, doi:10.4049/jimmunol.1001737 (2011).

997 109 Collins, N. *et al.* The Bone Marrow Protects and Optimizes Immunological Memory during  
998 Dietary Restriction. *Cell* **178**, 1088-1101 e1015, doi:10.1016/j.cell.2019.07.049 (2019).

999 110 Franco, L. M. *et al.* Immune regulation by glucocorticoids can be linked to cell type-dependent  
1000 transcriptional responses. *J Exp Med* **216**, 384-406, doi:10.1084/jem.20180595 (2019).

1001 111 Pani, L., Porcella, A. & Gessa, G. L. The role of stress in the pathophysiology of the  
1002 dopaminergic system. *Mol Psychiatry* **5**, 14-21, doi:10.1038/sj.mp.4000589 (2000).

1003 112 Soliman, A. *et al.* Stress-induced dopamine release in humans at risk of psychosis: a  
1004 [<sup>11</sup>C]raclopride PET study. *Neuropsychopharmacology* **33**, 2033-2041,  
1005 doi:10.1038/sj.npp.1301597 (2008).

1006 113 Pruessner, J. C., Champagne, F., Meaney, M. J. & Dagher, A. Dopamine release in response to  
1007 a psychological stress in humans and its relationship to early life maternal care: a positron  
1008 emission tomography study using [<sup>11</sup>C]raclopride. *J Neurosci* **24**, 2825-2831,  
1009 doi:10.1523/JNEUROSCI.3422-03.2004 (2004).

1010 114 Watanabe, Y. *et al.* Dopamine selectively induces migration and homing of naive CD8<sup>+</sup> T cells  
1011 via dopamine receptor D3. *J Immunol* **176**, 848-856, doi:10.4049/jimmunol.176.2.848 (2006).

1012 115 Mikulak, J. *et al.* Dopamine inhibits the effector functions of activated NK cells via the  
1013 upregulation of the D5 receptor. *J Immunol* **193**, 2792-2800, doi:10.4049/jimmunol.1401114  
1014 (2014).

1015 116 Yan, Y. *et al.* Dopamine controls systemic inflammation through inhibition of NLRP3  
1016 inflammasome. *Cell* **160**, 62-73, doi:10.1016/j.cell.2014.11.047 (2015).

1017 117 Yanagawa, Y., Matsumoto, M. & Togashi, H. Enhanced dendritic cell antigen uptake via alpha2  
1018 adrenoceptor-mediated PI3K activation following brief exposure to noradrenaline. *J Immunol*  
1019 **185**, 5762-5768, doi:10.4049/jimmunol.1001899 (2010).

1020 118 Takenaka, M. C. *et al.* Norepinephrine Controls Effector T Cell Differentiation through beta2-  
1021 Adrenergic Receptor-Mediated Inhibition of NF-kappaB and AP-1 in Dendritic Cells. *J*  
1022 *Immunol* **196**, 637-644, doi:10.4049/jimmunol.1501206 (2016).

1023 119 Guerreschi, M. G. *et al.* Beta2-adrenergic receptor signaling in CD4<sup>+</sup> Foxp3<sup>+</sup> regulatory T cells  
1024 enhances their suppressive function in a PKA-dependent manner. *Eur J Immunol* **43**, 1001-1012,  
1025 doi:10.1002/eji.201243005 (2013).

1026 120 Devi, S. *et al.* Adrenergic regulation of the vasculature impairs leukocyte interstitial migration  
1027 and suppresses immune responses. *Immunity* **54**, 1219-1230 e1217,  
1028 doi:10.1016/j.immuni.2021.03.025 (2021).

1029 121 Schiller, M., Ben-Shaanan, T. L. & Rolls, A. Neuronal regulation of immunity: why, how and  
1030 where? *Nat Rev Immunol* **21**, 20-36, doi:10.1038/s41577-020-0387-1 (2021).

1031 122 Lutgendorf, S. K. *et al.* Social support, psychological distress, and natural killer cell activity in  
1032 ovarian cancer. *J Clin Oncol* **23**, 7105-7113, doi:10.1200/JCO.2005.10.015 (2005).

1033 123 Varker, K. A. *et al.* Impaired natural killer cell lysis in breast cancer patients with high levels of  
1034 psychological stress is associated with altered expression of killer immunoglobulin-like receptors.  
1035 *J Surg Res* **139**, 36-44, doi:10.1016/j.jss.2006.08.037 (2007).

1036 124 Levi, B. *et al.* Stress impairs the efficacy of immune stimulation by CpG-C: Potential  
1037 neuroendocrine mediating mechanisms and significance to tumor metastasis and the  
1038 perioperative period. *Brain Behav Immun* **56**, 209-220, doi:10.1016/j.bbi.2016.02.025 (2016).

1039 125 Koide, S. S. Mifepristone. Auxiliary therapeutic use in cancer and related disorders. *J Reprod*  
1040 *Med* **43**, 551-560 (1998).

1041 126 Check, J. H., Dix, E., Cohen, R., Check, D. & Wilson, C. Efficacy of the progesterone receptor  
1042 antagonist mifepristone for palliative therapy of patients with a variety of advanced cancer types.  
1043 *Anticancer Res* **30**, 623-628 (2010).

1044 127 Check, J. H., Check, D., Wilson, C. & Lofberg, P. Long-term High-quality Survival with Single-  
1045 agent Mifepristone Treatment Despite Advanced Cancer. *Anticancer Res* **36**, 6511-6513,  
1046 doi:10.21873/anticancer.11251 (2016).

1047 128 Cronin-Fenton, D. *et al.* Concurrent new drug prescriptions and prognosis of early breast cancer:  
1048 studies using the Danish Breast Cancer Group clinical database. *Acta Oncol* **57**, 120-128,  
1049 doi:10.1080/0284186X.2017.1407040 (2018).

1050 This study identifies a particular myeloid cell population in the TME that produces endogenous  
1051 glucocorticoid to induce dysfunctional CD8<sup>+</sup>T cells and failure of cancer immunotherapy.

1052 129 Mulick, A. *et al.* Is improvement in comorbid major depression associated with longer survival  
1053 in people with cancer? A long-term follow-up of participants in the SMaRT Oncology-2 and 3  
1054 trials. *J Psychosom Res* **116**, 106-112, doi:10.1016/j.jpsychores.2018.11.008 (2019).

1055 130 Acharya, N. *et al.* Endogenous Glucocorticoid Signaling Regulates CD8(+) T Cell  
1056 Differentiation and Development of Dysfunction in the Tumor Microenvironment. *Immunity* **53**,  
1057 658-671 e656, doi:10.1016/j.immuni.2020.08.005 (2020).

1058 131 Yi, L. & Zheng, C. The emerging roles of ZDHHCs-mediated protein palmitoylation in the  
1059 antiviral innate immune responses. *Crit Rev Microbiol* **47**, 34-43,  
1060 doi:10.1080/1040841X.2020.1835821 (2021).

1061 132 Arbour, K. C. *et al.* Impact of Baseline Steroids on Efficacy of Programmed Cell Death-1 and  
1062 Programmed Death-Ligand 1 Blockade in Patients With Non-Small-Cell Lung Cancer. *J Clin*  
1063 *Oncol* **36**, 2872-2878, doi:10.1200/JCO.2018.79.0006 (2018).

1064 133 Maxwell, R. *et al.* Contrasting impact of corticosteroids on anti-PD-1 immunotherapy efficacy  
1065 for tumor histologies located within or outside the central nervous system. *Oncoimmunology* **7**,  
1066 e1500108, doi:10.1080/2162402X.2018.1500108 (2018).

1067 134 Aston, W. J. *et al.* Dexamethasone differentially depletes tumour and peripheral blood  
1068 lymphocytes and can impact the efficacy of chemotherapy/checkpoint blockade combination  
1069 treatment. *Oncoimmunology* **8**, e1641390, doi:10.1080/2162402X.2019.1641390 (2019).

1070 135 Papa, I. *et al.* T(FH)-derived dopamine accelerates productive synapses in germinal centres.  
1071 *Nature* **547**, 318-323, doi:10.1038/nature23013 (2017).

1072 136 van der Heijden, C. *et al.* Catecholamines Induce Trained Immunity in Monocytes In Vitro and  
1073 In Vivo. *Circ Res* **127**, 269-283, doi:10.1161/CIRCRESAHA.119.315800 (2020).

1074 137 Elenkov, I. J. in *NeuroImmune Biology* Vol. 7 189-206 (Elsevier, 2007).

1075 138 Arreola, R. *et al.* Immunomodulatory Effects Mediated by Dopamine. *J Immunol Res* **2016**,  
1076 3160486, doi:10.1155/2016/3160486 (2016).

1077 139 Baik, J. H. Stress and the dopaminergic reward system. *Exp Mol Med* **52**, 1879-1890,  
1078 doi:10.1038/s12276-020-00532-4 (2020).

1079 140 Bloomfield, M. A., McCutcheon, R. A., Kempton, M., Freeman, T. P. & Howes, O. The effects  
1080 of psychosocial stress on dopaminergic function and the acute stress response. *Elife* **8**,  
1081 doi:10.7554/eLife.46797 (2019).

1082 141 Saha, B., Mondal, A. C., Basu, S. & Dasgupta, P. S. Circulating dopamine level, in lung  
1083 carcinoma patients, inhibits proliferation and cytotoxicity of CD4<sup>+</sup> and CD8<sup>+</sup> T cells by D1  
1084 dopamine receptors: an in vitro analysis. *Int Immunopharmacol* **1**, 1363-1374,  
1085 doi:10.1016/s1567-5769(01)00068-6 (2001).

1086 142 Figueroa, C. *et al.* Inhibition of dopamine receptor D3 signaling in dendritic cells increases  
1087 antigen cross-presentation to CD8(+) T-cells favoring anti-tumor immunity. *J Neuroimmunol*  
1088 **303**, 99-107, doi:10.1016/j.jneuroim.2016.12.014 (2017).

1089 143 Hoepfner, L. H. *et al.* Dopamine D2 receptor agonists inhibit lung cancer progression by  
1090 reducing angiogenesis and tumor infiltrating myeloid derived suppressor cells. *Mol Oncol* **9**,  
1091 270-281, doi:10.1016/j.molonc.2014.08.008 (2015).

1092 144 Wu, J. *et al.* Dopamine inhibits the function of Gr-1+CD115<sup>+</sup> myeloid-derived suppressor cells  
1093 through D1-like receptors and enhances anti-tumor immunity. *J Leukoc Biol* **97**, 191-200,  
1094 doi:10.1189/jlb.5A1113-626RR (2015).

1095 145 Myers, S. A., Eriksson, N., Burow, R., Wang, S. C. & Muscat, G. E. Beta-adrenergic signaling

1096 regulates NR4A nuclear receptor and metabolic gene expression in multiple tissues. *Mol Cell*  
1097 *Endocrinol* **309**, 101-108, doi:10.1016/j.mce.2009.05.006 (2009).

1098 146 Liu, X. *et al.* Genome-wide analysis identifies NR4A1 as a key mediator of T cell dysfunction.  
1099 *Nature* **567**, 525-529, doi:10.1038/s41586-019-0979-8 (2019).

1100 147 Daher, C. *et al.* Blockade of beta-Adrenergic Receptors Improves CD8(+) T-cell Priming and  
1101 Cancer Vaccine Efficacy. *Cancer Immunol Res* **7**, 1849-1863, doi:10.1158/2326-6066.CIR-18-  
1102 0833 (2019).

1103 148 Nissen, M. D., Sloan, E. K. & Mattarollo, S. R. beta-Adrenergic Signaling Impairs Antitumor  
1104 CD8(+) T-cell Responses to B-cell Lymphoma Immunotherapy. *Cancer Immunol Res* **6**, 98-109,  
1105 doi:10.1158/2326-6066.CIR-17-0401 (2018).

1106 149 Qiao, G. *et al.* beta-Adrenergic signaling blocks murine CD8(+) T-cell metabolic  
1107 reprogramming during activation: a mechanism for immunosuppression by adrenergic stress.  
1108 *Cancer Immunol Immunother* **68**, 11-22, doi:10.1007/s00262-018-2243-8 (2019).

1109 150 Qin, J. F. *et al.* Adrenergic receptor beta2 activation by stress promotes breast cancer progression  
1110 through macrophages M2 polarization in tumor microenvironment. *BMB Rep* **48**, 295-300,  
1111 doi:10.5483/bmbrep.2015.48.5.008 (2015).

1112 151 Sloan, E. K. *et al.* The sympathetic nervous system induces a metastatic switch in primary breast  
1113 cancer. *Cancer Res* **70**, 7042-7052, doi:10.1158/0008-5472.CAN-10-0522 (2010).

1114 152 Mohammadpour, H. *et al.* beta2 adrenergic receptor-mediated signaling regulates the  
1115 immunosuppressive potential of myeloid-derived suppressor cells. *J Clin Invest* **129**, 5537-5552,  
1116 doi:10.1172/JCI129502 (2019).

1117 153 Cheng, Y. *et al.* Depression-Induced Neuropeptide Y Secretion Promotes Prostate Cancer  
1118 Growth by Recruiting Myeloid Cells. *Clin Cancer Res* **25**, 2621-2632, doi:10.1158/1078-  
1119 0432.CCR-18-2912 (2019).

1120 154 Kokolus, K. M. *et al.* Beta blocker use correlates with better overall survival in metastatic  
1121 melanoma patients and improves the efficacy of immunotherapies in mice. *Oncoimmunology* **7**,  
1122 e1405205, doi:10.1080/2162402X.2017.1405205 (2018).

1123 155 Bucsek, M. J. *et al.* beta-Adrenergic Signaling in Mice Housed at Standard Temperatures  
1124 Suppresses an Effector Phenotype in CD8(+) T Cells and Undermines Checkpoint Inhibitor  
1125 Therapy. *Cancer Res* **77**, 5639-5651, doi:10.1158/0008-5472.CAN-17-0546 (2017).

1126 156 Chen, M. *et al.* Adrenergic stress constrains the development of anti-tumor immunity and  
1127 abscopal responses following local radiation. *Nat Commun* **11**, 1821, doi:10.1038/s41467-020-  
1128 15676-0 (2020).

1129 157 Botta, F. & Maestroni, G. J. Adrenergic modulation of dendritic cell cancer vaccine in a mouse  
1130 model: role of dendritic cell maturation. *J Immunother* **31**, 263-270,  
1131 doi:10.1097/CJI.0b013e318160995e (2008).

1132 158 Hiller, J. G. *et al.* Pre-operative beta-blockade with propranolol reduces biomarkers of  
1133 metastasis in breast cancer: a Phase II randomized trial. *Clin Cancer Res*, doi:10.1158/1078-  
1134 0432.CCR-19-2641 (2019).

1135 159 Shaashua, L. *et al.* Perioperative COX-2 and beta-Adrenergic Blockade Improves Metastatic  
1136 Biomarkers in Breast Cancer Patients in a Phase-II Randomized Trial. *Clin Cancer Res* **23**,  
1137 4651-4661, doi:10.1158/1078-0432.CCR-17-0152 (2017).

1138 160 De Giorgi, V. *et al.* Propranolol for Off-label Treatment of Patients With Melanoma: Results  
1139 From a Cohort Study. *JAMA Oncol* **4**, e172908, doi:10.1001/jamaoncol.2017.2908 (2018).

1140 161 Phadke, S. & Clamon, G. Beta blockade as adjunctive breast cancer therapy: A review. *Crit Rev*  
1141 *Oncol Hematol* **138**, 173-177, doi:10.1016/j.critrevonc.2019.04.006 (2019).

1142 162 Zhang, S. *et al.* Neuroendocrine Regulation of Stress-Induced T Cell Dysfunction during Lung  
1143 Cancer Immunosurveillance via the Kisspeptin/GPR54 Signaling Pathway. *Adv Sci (Weinh)* **9**,  
1144 e2104132, doi:10.1002/advs.202104132 (2022).

1145 163 Hill, M. N. *et al.* Endogenous cannabinoid signaling is essential for stress adaptation. *Proc Natl*  
1146 *Acad Sci U S A* **107**, 9406-9411, doi:10.1073/pnas.0914661107 (2010).

1147 164 Xiong, X. *et al.* Cannabis suppresses antitumor immunity by inhibiting JAK/STAT signaling in  
1148 T cells through CNR2. *Signal Transduct Target Ther* **7**, 99, doi:10.1038/s41392-022-00918-y  
1149 (2022).

1150 165 Won, E. & Kim, Y. K. Stress, the Autonomic Nervous System, and the Immune-kynurenine  
1151 Pathway in the Etiology of Depression. *Curr Neuropharmacol* **14**, 665-673,  
1152 doi:10.2174/1570159x14666151208113006 (2016).

1153 166 Gao, F. G., Wan da, F. & Gu, J. R. Ex vivo nicotine stimulation augments the efficacy of  
1154 therapeutic bone marrow-derived dendritic cell vaccination. *Clin Cancer Res* **13**, 3706-3712,  
1155 doi:10.1158/1078-0432.CCR-07-0028 (2007).



- 1156 167 Dubeykovskaya, Z. *et al.* Neural innervation stimulates splenic TFF2 to arrest myeloid cell  
1157 expansion and cancer. *Nat Commun* **7**, 10517, doi:10.1038/ncomms10517 (2016).
- 1158 168 Liu, L. *et al.* Hippocampal metabolic differences implicate distinctions between physical and  
1159 psychological stress in four rat models of depression. *Transl Psychiatry* **8**, 4,  
1160 doi:10.1038/s41398-017-0018-1 (2018).
- 1161 169 Czeh, B. *et al.* Stress-induced changes in cerebral metabolites, hippocampal volume, and cell  
1162 proliferation are prevented by antidepressant treatment with tianeptine. *Proc Natl Acad Sci U S*  
1163 *A* **98**, 12796-12801, doi:10.1073/pnas.211427898 (2001).
- 1164 170 Peckett, A. J., Wright, D. C. & Riddell, M. C. The effects of glucocorticoids on adipose tissue  
1165 lipid metabolism. *Metabolism* **60**, 1500-1510, doi:10.1016/j.metabol.2011.06.012 (2011).
- 1166 171 Jia, H. M. *et al.* Chronic unpredictable mild stress leads to altered hepatic metabolic profile and  
1167 gene expression. *Sci Rep* **6**, 23441, doi:10.1038/srep23441 (2016).
- 1168 172 Rodrigues Mantuano, N. *et al.* Hyperglycemia Enhances Cancer Immune Evasion by Inducing  
1169 Alternative Macrophage Polarization through Increased O-GlcNAcylation. *Cancer Immunol*  
1170 *Res* **8**, 1262-1272, doi:10.1158/2326-6066.CIR-19-0904 (2020).
- 1171 This study explores how hyperglycemia drives tumour progression, by increasing O-GlcNAcylation in  
1172 tumour-associated macrophages to switch on the M2-like phenotype and favour cancer immune  
1173 evasion.
- 1174 173 Brzozowski, B. *et al.* Mechanisms by which Stress Affects the Experimental and Clinical  
1175 Inflammatory Bowel Disease (IBD): Role of Brain-Gut Axis. *Curr Neuropharmacol* **14**, 892-  
1176 900, doi:10.2174/1570159x14666160404124127 (2016).
- 1177 174 Patel, C. H., Leone, R. D., Horton, M. R. & Powell, J. D. Targeting metabolism to regulate  
1178 immune responses in autoimmunity and cancer. *Nat Rev Drug Discov* **18**, 669-688,  
1179 doi:10.1038/s41573-019-0032-5 (2019).
- 1180 175 Voss, K. *et al.* A guide to interrogating immunometabolism. *Nat Rev Immunol* **21**, 637-652,  
1181 doi:10.1038/s41577-021-00529-8 (2021).
- 1182 176 Nonogaki, K. & Iguchi, A. Stress, acute hyperglycemia, and hyperlipidemia role of the  
1183 autonomic nervous system and cytokines. *Trends Endocrinol Metab* **8**, 192-197,  
1184 doi:10.1016/s1043-2760(97)00038-6 (1997).
- 1185 177 Maduka, I. C., Neboh, E. E. & Ufelle, S. A. The relationship between serum cortisol, adrenaline,  
1186 blood glucose and lipid profile of undergraduate students under examination stress. *Afr Health*  
1187 *Sci* **15**, 131-136, doi:10.4314/ahs.v15i1.18 (2015).
- 1188 178 Mohammadpour, H., MacDonald, C. R., McCarthy, P. L., Abrams, S. I. & Repasky, E. A. beta2-  
1189 adrenergic receptor signaling regulates metabolic pathways critical to myeloid-derived  
1190 suppressor cell function within the TME. *Cell Rep* **37**, 109883,  
1191 doi:10.1016/j.celrep.2021.109883 (2021).
- 1192 179 Muthuswamy, R. *et al.* Epinephrine promotes COX-2-dependent immune suppression in  
1193 myeloid cells and cancer tissues. *Brain Behav Immun* **62**, 78-86, doi:10.1016/j.bbi.2017.02.008  
1194 (2017).
- 1195 180 Pearce, E. L., Poffenberger, M. C., Chang, C. H. & Jones, R. G. Fueling immunity: insights into  
1196 metabolism and lymphocyte function. *Science* **342**, 1242454, doi:10.1126/science.1242454  
1197 (2013).
- 1198 181 Picard, M. & McEwen, B. S. Psychological Stress and Mitochondria: A Systematic Review.  
1199 *Psychosom Med* **80**, 141-153, doi:10.1097/PSY.0000000000000545 (2018).
- 1200 182 Qiao, G. *et al.* Chronic Adrenergic Stress Contributes to Metabolic Dysfunction and an  
1201 Exhausted Phenotype in T Cells in the Tumor Microenvironment. *Cancer Immunol Res* **9**, 651-  
1202 664, doi:10.1158/2326-6066.CIR-20-0445 (2021).
- 1203 183 Tokunaga, A. *et al.* Selective inhibition of low-affinity memory CD8(+) T cells by  
1204 corticosteroids. *J Exp Med* **216**, 2701-2713, doi:10.1084/jem.20190738 (2019).
- 1205 184 Brand, A. *et al.* LDHA-Associated Lactic Acid Production Blunts Tumor Immunosurveillance  
1206 by T and NK Cells. *Cell Metab* **24**, 657-671, doi:10.1016/j.cmet.2016.08.011 (2016).
- 1207 185 Perego, M. *et al.* Reactivation of dormant tumor cells by modified lipids derived from stress-  
1208 activated neutrophils. *Sci Transl Med* **12**, doi:10.1126/scitranslmed.abb5817 (2020).
- 1209 186 Bresnick, A. R., Weber, D. J. & Zimmer, D. B. S100 proteins in cancer. *Nat Rev Cancer* **15**, 96-  
1210 109, doi:10.1038/nrc3893 (2015).
- 1211 187 Diskin, C., Ryan, T. A. J. & O'Neill, L. A. J. Modification of Proteins by Metabolites in  
1212 Immunity. *Immunity* **54**, 19-31, doi:10.1016/j.immuni.2020.09.014 (2021).
- 1213 188 Barth, E. *et al.* Glucose metabolism and catecholamines. *Crit Care Med* **35**, S508-518,  
1214 doi:10.1097/01.CCM.0000278047.06965.20 (2007).
- 1215 189 Zhang, D. *et al.* Metabolic regulation of gene expression by histone lactylation. *Nature* **574**,

- 1216 575-580, doi:10.1038/s41586-019-1678-1 (2019).
- 1217 190 Chang, Y. H., Weng, C. L. & Lin, K. I. O-GlcNAcylation and its role in the immune system. *J*
- 1218 *Biomed Sci* **27**, 57, doi:10.1186/s12929-020-00648-9 (2020).
- 1219 191 Xiu, F., Stanojic, M., Diao, L. & Jeschke, M. G. Stress hyperglycemia, insulin treatment, and
- 1220 innate immune cells. *Int J Endocrinol* **2014**, 486403, doi:10.1155/2014/486403 (2014).
- 1221 192 Picard, M., Juster, R. P. & McEwen, B. S. Mitochondrial allostatic load puts the 'gluc' back in
- 1222 glucocorticoids. *Nat Rev Endocrinol* **10**, 303-310, doi:10.1038/nrendo.2014.22 (2014).
- 1223 193 Jiang, H. *et al.* Protein Lipidation: Occurrence, Mechanisms, Biological Functions, and
- 1224 Enabling Technologies. *Chem Rev* **118**, 919-988, doi:10.1021/acs.chemrev.6b00750 (2018).
- 1225 194 Wild, A. R. *et al.* Exploring the expression patterns of palmitoylating and de-palmitoylating
- 1226 enzymes in the mouse brain using the curated RNA-seq database BrainPalmSeq. *Elife* **11**,
- 1227 doi:10.7554/eLife.75804 (2022).
- 1228 195 Zareba-Kozioł, M. *et al.* Stress-induced Changes in the S-palmitoylation and S-nitrosylation of
- 1229 Synaptic Proteins. *Mol Cell Proteomics* **18**, 1916-1938, doi:10.1074/mcp.RA119.001581
- 1230 (2019).
- 1231 196 Yao, H. *et al.* Inhibiting PD-L1 palmitoylation enhances T-cell immune responses against
- 1232 tumours. *Nat Biomed Eng* **3**, 306-317, doi:10.1038/s41551-019-0375-6 (2019).
- 1233 197 Cryan, J. F. *et al.* The Microbiota-Gut-Brain Axis. *Physiol Rev* **99**, 1877-2013,
- 1234 doi:10.1152/physrev.00018.2018 (2019).
- 1235 198 Morais, L. H., Schreiber, H. L. t. & Mazmanian, S. K. The gut microbiota-brain axis in
- 1236 behaviour and brain disorders. *Nat Rev Microbiol* **19**, 241-255, doi:10.1038/s41579-020-00460-
- 1237 0 (2021).
- 1238 199 Mittal, R. *et al.* Neurotransmitters: The Critical Modulators Regulating Gut-Brain Axis. *J Cell*
- 1239 *Physiol* **232**, 2359-2372, doi:10.1002/jcp.25518 (2017).
- 1240 200 Wu, M. *et al.* Associations between disordered gut microbiota and changes of neurotransmitters
- 1241 and short-chain fatty acids in depressed mice. *Transl Psychiatry* **10**, 350, doi:10.1038/s41398-
- 1242 020-01038-3 (2020).
- 1243 201 Jiang, H. *et al.* Altered fecal microbiota composition in patients with major depressive disorder.
- 1244 *Brain Behav Immun* **48**, 186-194, doi:10.1016/j.bbi.2015.03.016 (2015).
- 1245 202 Jiang, H. Y. *et al.* Altered gut microbiota profile in patients with generalized anxiety disorder. *J*
- 1246 *Psychiatr Res* **104**, 130-136, doi:10.1016/j.jpsychires.2018.07.007 (2018).
- 1247 203 Hollins, S. L. & Hodgson, D. M. Stress, microbiota, and immunity. *Current Opinion in*
- 1248 *Behavioral Sciences* **28**, 66-71, doi:<https://doi.org/10.1016/j.cobeha.2019.01.015> (2019).
- 1249 204 Gao, X. *et al.* Chronic stress promotes colitis by disturbing the gut microbiota and triggering
- 1250 immune system response. *Proc Natl Acad Sci U S A* **115**, E2960-E2969,
- 1251 doi:10.1073/pnas.1720696115 (2018).
- 1252 205 Viaud, S. *et al.* The intestinal microbiota modulates the anticancer immune effects of
- 1253 cyclophosphamide. *Science* **342**, 971-976, doi:10.1126/science.1240537 (2013).
- 1254 206 Yu, L. X. & Schwabe, R. F. The gut microbiome and liver cancer: mechanisms and clinical
- 1255 translation. *Nat Rev Gastroenterol Hepatol* **14**, 527-539, doi:10.1038/nrgastro.2017.72 (2017).
- 1256 207 Lebeer, S., Vanderleyden, J. & De Keersmaecker, S. C. Host interactions of probiotic bacterial
- 1257 surface molecules: comparison with commensals and pathogens. *Nat Rev Microbiol* **8**, 171-184,
- 1258 doi:10.1038/nrmicro2297 (2010).
- 1259 208 Ochoa-Reparaz, J. *et al.* Central nervous system demyelinating disease protection by the human
- 1260 commensal *Bacteroides fragilis* depends on polysaccharide A expression. *J Immunol* **185**, 4101-
- 1261 4108, doi:10.4049/jimmunol.1001443 (2010).
- 1262 209 Zitvogel, L., Ayyoub, M., Routy, B. & Kroemer, G. Microbiome and Anticancer
- 1263 Immunosurveillance. *Cell* **165**, 276-287, doi:10.1016/j.cell.2016.03.001 (2016).
- 1264 210 Fluckiger, A. *et al.* Cross-reactivity between tumor MHC class I-restricted antigens and an
- 1265 enterococcal bacteriophage. *Science* **369**, 936-942, doi:10.1126/science.aax0701 (2020).
- 1266 This study reports that naturally processed cancer antigens and microbial peptides may share cross-
- 1267 reactive T cell epitopes, which can be targeted for cancer immunotherapy.
- 1268 211 Ruff, W. E. & Kriegel, M. A. Autoimmune host-microbiota interactions at barrier sites and
- 1269 beyond. *Trends Mol Med* **21**, 233-244, doi:10.1016/j.molmed.2015.02.006 (2015).
- 1270 212 Ait-Belgnaoui, A. *et al.* Prevention of gut leakiness by a probiotic treatment leads to attenuated
- 1271 HPA response to an acute psychological stress in rats. *Psychoneuroendocrinology* **37**, 1885-
- 1272 1895, doi:10.1016/j.psyneuen.2012.03.024 (2012).
- 1273 213 Ait-Belgnaoui, A. *et al.* *Bifidobacterium longum* and *Lactobacillus helveticus* Synergistically
- 1274 Suppress Stress-related Visceral Hypersensitivity Through Hypothalamic-Pituitary-Adrenal
- 1275 Axis Modulation. *J Neurogastroenterol Motil* **24**, 138-146, doi:10.5056/jnm16167 (2018).

1276 214 Routy, B. *et al.* Gut microbiome influences efficacy of PD-1-based immunotherapy against  
1277 epithelial tumors. *Science* **359**, 91-97, doi:10.1126/science.aan3706 (2018).

1278 215 Gopalakrishnan, V. *et al.* Gut microbiome modulates response to anti-PD-1 immunotherapy in  
1279 melanoma patients. *Science* **359**, 97-103, doi:10.1126/science.aan4236 (2018).

1280 216 Matson, V. *et al.* The commensal microbiome is associated with anti-PD-1 efficacy in metastatic  
1281 melanoma patients. *Science* **359**, 104-108, doi:10.1126/science.aao3290 (2018).

1282 217 Routy, B. *et al.* The gut microbiota influences anticancer immunosurveillance and general health.  
1283 *Nat Rev Clin Oncol* **15**, 382-396, doi:10.1038/s41571-018-0006-2 (2018).

1284 218 Merchak, A. & Gaultier, A. Microbial metabolites and immune regulation: New targets for  
1285 major depressive disorder. *Brain Behav Immun Health* **9**, 100169,  
1286 doi:10.1016/j.bbih.2020.100169 (2020).

1287 219 Sittipo, P., Choi, J., Lee, S. & Lee, Y. K. The function of gut microbiota in immune-related  
1288 neurological disorders: a review. *J Neuroinflammation* **19**, 154, doi:10.1186/s12974-022-  
1289 02510-1 (2022).

1290 220 Kim, C. H. Immune regulation by microbiome metabolites. *Immunology* **154**, 220-229,  
1291 doi:10.1111/imm.12930 (2018).

1292 221 Zhao, L. *et al.* TGR5 deficiency activates antitumor immunity in non-small cell lung cancer via  
1293 restraining M2 macrophage polarization. *Acta Pharm Sin B* **12**, 787-800,  
1294 doi:10.1016/j.apsb.2021.07.011 (2022).

1295 222 You, W. *et al.* Farnesoid X Receptor Constructs an Immunosuppressive Microenvironment and  
1296 Sensitizes FXR(high)PD-L1(low) NSCLC to Anti-PD-1 Immunotherapy. *Cancer Immunol Res*  
1297 **7**, 990-1000, doi:10.1158/2326-6066.CIR-17-0672 (2019).

1298 223 Kenison, J. E. *et al.* The aryl hydrocarbon receptor suppresses immunity to oral squamous cell  
1299 carcinoma through immune checkpoint regulation. *Proc Natl Acad Sci U S A* **118**,  
1300 doi:10.1073/pnas.2012692118 (2021).

1301 224 Bachem, A. *et al.* Microbiota-Derived Short-Chain Fatty Acids Promote the Memory Potential  
1302 of Antigen-Activated CD8(+) T Cells. *Immunity* **51**, 285-297 e285,  
1303 doi:10.1016/j.immuni.2019.06.002 (2019).

1304 This study shows that microbiota-derived metabolites, short-chain fatty acids, can guide the metabolic  
1305 rewiring that increases the memory potential of antigen-specific CD8<sup>+</sup> T cells.

1306 225 Botticelli, A. *et al.* Gut metabolomics profiling of non-small cell lung cancer (NSCLC) patients  
1307 under immunotherapy treatment. *J Transl Med* **18**, 49, doi:10.1186/s12967-020-02231-0 (2020).

1308 226 Nomura, M. *et al.* Association of Short-Chain Fatty Acids in the Gut Microbiome With Clinical  
1309 Response to Treatment With Nivolumab or Pembrolizumab in Patients With Solid Cancer  
1310 Tumors. *JAMA Netw Open* **3**, e202895, doi:10.1001/jamanetworkopen.2020.2895 (2020).

1311 227 Schneider, M. A. *et al.* Attenuation of peripheral serotonin inhibits tumor growth and enhances  
1312 immune checkpoint blockade therapy in murine tumor models. *Sci Transl Med* **13**, eabc8188,  
1313 doi:10.1126/scitranslmed.abc8188 (2021).

1314 228 Bravo, J. A. *et al.* Ingestion of Lactobacillus strain regulates emotional behavior and central  
1315 GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci U S A* **108**,  
1316 16050-16055, doi:10.1073/pnas.1102999108 (2011).

1317 229 Kienzl, M., Kargl, J. & Schicho, R. The Immune Endocannabinoid System of the Tumor  
1318 Microenvironment. *Int J Mol Sci* **21**, doi:10.3390/ijms21238929 (2020).

1319 230 Huang, D. *et al.* Cancer-cell-derived GABA promotes beta-catenin-mediated tumour growth  
1320 and immunosuppression. *Nat Cell Biol* **24**, 230-241, doi:10.1038/s41556-021-00820-9 (2022).

1321 231 Zhang, B. *et al.* B cell-derived GABA elicits IL-10(+) macrophages to limit anti-tumour  
1322 immunity. *Nature* **599**, 471-476, doi:10.1038/s41586-021-04082-1 (2021).

1323 232 Luqman, A., Nega, M., Nguyen, M. T., Ebner, P. & Gotz, F. SadA-Expressing Staphylococci in  
1324 the Human Gut Show Increased Cell Adherence and Internalization. *Cell Rep* **22**, 535-545,  
1325 doi:10.1016/j.celrep.2017.12.058 (2018).

1326 233 Williams, B. B. *et al.* Discovery and characterization of gut microbiota decarboxylases that can  
1327 produce the neurotransmitter tryptamine. *Cell Host Microbe* **16**, 495-503,  
1328 doi:10.1016/j.chom.2014.09.001 (2014).

1329 234 Bauknecht, P. & Jekely, G. Ancient coexistence of norepinephrine, tyramine, and octopamine  
1330 signaling in bilaterians. *BMC Biol* **15**, 6, doi:10.1186/s12915-016-0341-7 (2017).

1331 235 Connil, N. *et al.* Identification of the Enterococcus faecalis tyrosine decarboxylase operon  
1332 involved in tyramine production. *Appl Environ Microbiol* **68**, 3537-3544,  
1333 doi:10.1128/aem.68.7.3537-3544.2002 (2002).

1334 236 Lameris, T. W. *et al.* Catecholamine handling in the porcine heart: a microdialysis approach. *Am*  
1335 *J Physiol* **277**, H1562-1569, doi:10.1152/ajpheart.1999.277.4.H1562 (1999).

- 1336 237 Weis, W. I. & Kobilka, B. K. The Molecular Basis of G Protein-Coupled Receptor Activation. *Annu Rev Biochem* **87**, 897-919, doi:10.1146/annurev-biochem-060614-033910 (2018).
- 1337
- 1338 238 Kepp, O., Marabelle, A., Zitvogel, L. & Kroemer, G. Oncolysis without viruses - inducing systemic anticancer immune responses with local therapies. *Nat Rev Clin Oncol* **17**, 49-64, doi:10.1038/s41571-019-0272-7 (2020).
- 1339
- 1340
- 1341 239 Foster, J. A., Rinaman, L. & Cryan, J. F. Stress & the gut-brain axis: Regulation by the microbiome. *Neurobiol Stress* **7**, 124-136, doi:10.1016/j.ynstr.2017.03.001 (2017).
- 1342
- 1343 240 Vuong, H. E., Yano, J. M., Fung, T. C. & Hsiao, E. Y. The Microbiome and Host Behavior. *Annu Rev Neurosci* **40**, 21-49, doi:10.1146/annurev-neuro-072116-031347 (2017).
- 1344
- 1345 241 Sidler, D. *et al.* Colon cancer cells produce immunoregulatory glucocorticoids. *Oncoimmunology* **1**, 529-530, doi:10.4161/onci.19459 (2012).
- 1346
- 1347 242 Verhoeven, G. T. *et al.* Glucocorticoids hamper the ex vivo maturation of lung dendritic cells from their low autofluorescent precursors in the human bronchoalveolar lavage: decreases in allostimulatory capacity and expression of CD80 and CD86. *Clin Exp Immunol* **122**, 232-240, doi:10.1046/j.1365-2249.2000.01354.x (2000).
- 1348
- 1349
- 1350
- 1351 243 Rea, D. *et al.* Glucocorticoids transform CD40-triggering of dendritic cells into an alternative activation pathway resulting in antigen-presenting cells that secrete IL-10. *Blood* **95**, 3162-3167 (2000).
- 1352
- 1353
- 1354 244 Kim, K. D., Choe, Y. K., Choe, I. S. & Lim, J. S. Inhibition of glucocorticoid-mediated, caspase-independent dendritic cell death by CD40 activation. *J Leukoc Biol* **69**, 426-434 (2001).
- 1355
- 1356 245 Herold, M. J., McPherson, K. G. & Reichardt, H. M. Glucocorticoids in T cell apoptosis and function. *Cell Mol Life Sci* **63**, 60-72, doi:10.1007/s00018-005-5390-y (2006).
- 1357
- 1358 246 Talaber, G. *et al.* Mitochondrial translocation of the glucocorticoid receptor in double-positive thymocytes correlates with their sensitivity to glucocorticoid-induced apoptosis. *Int Immunol* **21**, 1269-1276, doi:10.1093/intimm/dxp093 (2009).
- 1359
- 1360
- 1361 247 Lowenberg, M. *et al.* Rapid immunosuppressive effects of glucocorticoids mediated through Lck and Fyn. *Blood* **106**, 1703-1710, doi:10.1182/blood-2004-12-4790 (2005).
- 1362
- 1363 248 Wu, Y. *et al.* The disbalance of LRP1 and SIRPalpha by psychological stress dampens the clearance of tumor cells by macrophages. *Acta Pharm Sin B* **12**, 197-209, doi:10.1016/j.apsb.2021.06.002 (2022).
- 1364
- 1365
- 1366 249 Xie, Y. *et al.* Glucocorticoids inhibit macrophage differentiation towards a pro-inflammatory phenotype upon wounding without affecting their migration. *Dis Model Mech* **12**, doi:10.1242/dmm.037887 (2019).
- 1367
- 1368
- 1369 250 Lu, Y. *et al.* Glucocorticoid receptor promotes the function of myeloid-derived suppressor cells by suppressing HIF1alpha-dependent glycolysis. *Cell Mol Immunol* **15**, 618-629, doi:10.1038/cmi.2017.5 (2018).
- 1370
- 1371
- 1372 251 Xiang, Z. *et al.* Dexamethasone suppresses immune evasion by inducing GR/STAT3 mediated downregulation of PD-L1 and IDO1 pathways. *Oncogene* **40**, 5002-5012, doi:10.1038/s41388-021-01897-0 (2021).
- 1373
- 1374
- 1375 252 Eddy, J. L., Krukowski, K., Janusek, L. & Mathews, H. L. Glucocorticoids regulate natural killer cell function epigenetically. *Cell Immunol* **290**, 120-130, doi:10.1016/j.cellimm.2014.05.013 (2014).
- 1376
- 1377
- 1378 253 Quatrini, L. *et al.* Endogenous glucocorticoids control host resistance to viral infection through the tissue-specific regulation of PD-1 expression on NK cells. *Nature Immunology* **19**, 954-962, doi:10.1038/s41590-018-0185-0 (2018).
- 1379
- 1380
- 1381 254 Cavalcanti, D. M. *et al.* Endogenous glucocorticoids control neutrophil mobilization from bone marrow to blood and tissues in non-inflammatory conditions. *Br J Pharmacol* **152**, 1291-1300, doi:10.1038/sj.bjp.0707512 (2007).
- 1382
- 1383
- 1384 255 Nadkarni, S. *et al.* Investigational analysis reveals a potential role for neutrophils in giant-cell arteritis disease progression. *Circ Res* **114**, 242-248, doi:10.1161/CIRCRESAHA.114.301374 (2014).
- 1385
- 1386
- 1387 256 Walther, A., Riehemann, K. & Gerke, V. A novel ligand of the formyl peptide receptor: annexin I regulates neutrophil extravasation by interacting with the FPR. *Mol Cell* **5**, 831-840, doi:10.1016/s1097-2765(00)80323-8 (2000).
- 1388
- 1389
- 1390 257 Saffar, A. S., Ashdown, H. & Gounni, A. S. The molecular mechanisms of glucocorticoids-mediated neutrophil survival. *Current drug targets* **12**, 556-562, doi:10.2174/138945011794751555 (2011).
- 1391
- 1392
- 1393 258 Staedtke, V. *et al.* Disruption of a self-amplifying catecholamine loop reduces cytokine release syndrome. *Nature* **564**, 273-277, doi:10.1038/s41586-018-0774-y (2018).
- 1394
- 1395 259 Cao, M. *et al.* Chronic restraint stress promotes the mobilization and recruitment of myeloid-

1396 derived suppressor cells through beta-adrenergic-activated CXCL5-CXCR2-Erk signaling  
1397 cascades. *Int J Cancer* **149**, 460-472, doi:10.1002/ijc.33552 (2021).

1398 260 Karvonen, H. *et al.* Glucocorticoids induce differentiation and chemoresistance in ovarian  
1399 cancer by promoting ROR1-mediated stemness. *Cell Death Dis* **11**, 790, doi:10.1038/s41419-  
1400 020-03009-4 (2020).

1401 261 Hara, M. R. *et al.* A stress response pathway regulates DNA damage through beta2-  
1402 adrenoreceptors and beta-arrestin-1. *Nature* **477**, 349-353, doi:10.1038/nature10368 (2011).

1403 262 Sood, A. K. *et al.* Adrenergic modulation of focal adhesion kinase protects human ovarian  
1404 cancer cells from anoikis. *J Clin Invest* **120**, 1515-1523, doi:10.1172/JCI40802 (2010).

1405 263 Dwyer, A. R. *et al.* Glucocorticoid Receptors Drive Breast Cancer Cell Migration and Metabolic  
1406 Reprogramming via PDK4. *Endocrinology* **164**, doi:10.1210/endocr/bqad083 (2023).

1407 264 Karra, A. G. *et al.* Increased Expression of the Mitochondrial Glucocorticoid Receptor Enhances  
1408 Tumor Aggressiveness in a Mouse Xenograft Model. *Int J Mol Sci* **24**,  
1409 doi:10.3390/ijms24043740 (2023).

1410 265 Tiwari, R. K. *et al.* Epinephrine facilitates the growth of T cell lymphoma by altering cell  
1411 proliferation, apoptosis, and glucose metabolism. *Chem Biol Interact* **369**, 110278,  
1412 doi:10.1016/j.cbi.2022.110278 (2023).

1413 266 Talaber, G., Jondal, M. & Okret, S. Local glucocorticoid production in the thymus. *Steroids* **103**,  
1414 58-63, doi:10.1016/j.steroids.2015.06.010 (2015).

1415 267 Croft, A. P. *et al.* Effects of minor laboratory procedures, adrenalectomy, social defeat or acute  
1416 alcohol on regional brain concentrations of corticosterone. *Brain Res* **1238**, 12-22,  
1417 doi:10.1016/j.brainres.2008.08.009 (2008).

1418 268 Cima, I. *et al.* Intestinal epithelial cells synthesize glucocorticoids and regulate T cell activation.  
1419 *J Exp Med* **200**, 1635-1646, doi:10.1084/jem.20031958 (2004).

1420 269 Nagashima, H. *et al.* Neuropeptide CGRP Limits Group 2 Innate Lymphoid Cell Responses and  
1421 Constrains Type 2 Inflammation. *Immunity* **51**, 682-695 e686,  
1422 doi:10.1016/j.immuni.2019.06.009 (2019).

1423 270 Reigstad, C. S. *et al.* Gut microbes promote colonic serotonin production through an effect of  
1424 short-chain fatty acids on enterochromaffin cells. *FASEB J* **29**, 1395-1403, doi:10.1096/fj.14-  
1425 259598 (2015).

1426 271 Yano, J. M. *et al.* Indigenous bacteria from the gut microbiota regulate host serotonin  
1427 biosynthesis. *Cell* **161**, 264-276, doi:10.1016/j.cell.2015.02.047 (2015).

1428 This study highlights that certain bacterial species can act as important modulators of host 5-HT  
1429 biosynthesis and its downstream bioactivities.

1430 272 Finocchiaro, L. M. *et al.* Serotonin and melatonin synthesis in peripheral blood mononuclear  
1431 cells: stimulation by interferon-gamma as part of an immunomodulatory pathway. *J Interferon*  
1432 *Res* **8**, 705-716, doi:10.1089/jir.1988.8.705 (1988).

1433 273 Kushnir-Sukhov, N. M., Brown, J. M., Wu, Y., Kirshenbaum, A. & Metcalfe, D. D. Human mast  
1434 cells are capable of serotonin synthesis and release. *J Allergy Clin Immunol* **119**, 498-499,  
1435 doi:10.1016/j.jaci.2006.09.003 (2007).

1436 274 Leon-Ponte, M., Ahern, G. P. & O'Connell, P. J. Serotonin provides an accessory signal to  
1437 enhance T-cell activation by signaling through the 5-HT7 receptor. *Blood* **109**, 3139-3146,  
1438 doi:10.1182/blood-2006-10-052787 (2007).

1439 275 Brenner, B. *et al.* Plasma serotonin levels and the platelet serotonin transporter. *J Neurochem*  
1440 **102**, 206-215, doi:10.1111/j.1471-4159.2007.04542.x (2007).

1441 276 Cox, M. A. *et al.* Beyond neurotransmission: acetylcholine in immunity and inflammation. *J*  
1442 *Intern Med*, doi:10.1111/joim.13006 (2019).

1443 277 Pirzgalska, R. M. *et al.* Sympathetic neuron-associated macrophages contribute to obesity by  
1444 importing and metabolizing norepinephrine. *Nat Med* **23**, 1309-1318, doi:10.1038/nm.4422  
1445 (2017).

1446 278 Kiecolt-Glaser, J. K. *et al.* Yoga's impact on inflammation, mood, and fatigue in breast cancer  
1447 survivors: a randomized controlled trial. *J Clin Oncol* **32**, 1040-1049,  
1448 doi:10.1200/JCO.2013.51.8860 (2014).

1449 279 Stagl, J. M. *et al.* A randomized controlled trial of cognitive-behavioral stress management in  
1450 breast cancer: survival and recurrence at 11-year follow-up. *Breast Cancer Res Treat* **154**, 319-  
1451 328, doi:10.1007/s10549-015-3626-6 (2015).

1452 280 Teo, I., Krishnan, A. & Lee, G. L. Psychosocial interventions for advanced cancer patients: A  
1453 systematic review. *Psychooncology* **28**, 1394-1407, doi:10.1002/pon.5103 (2019).

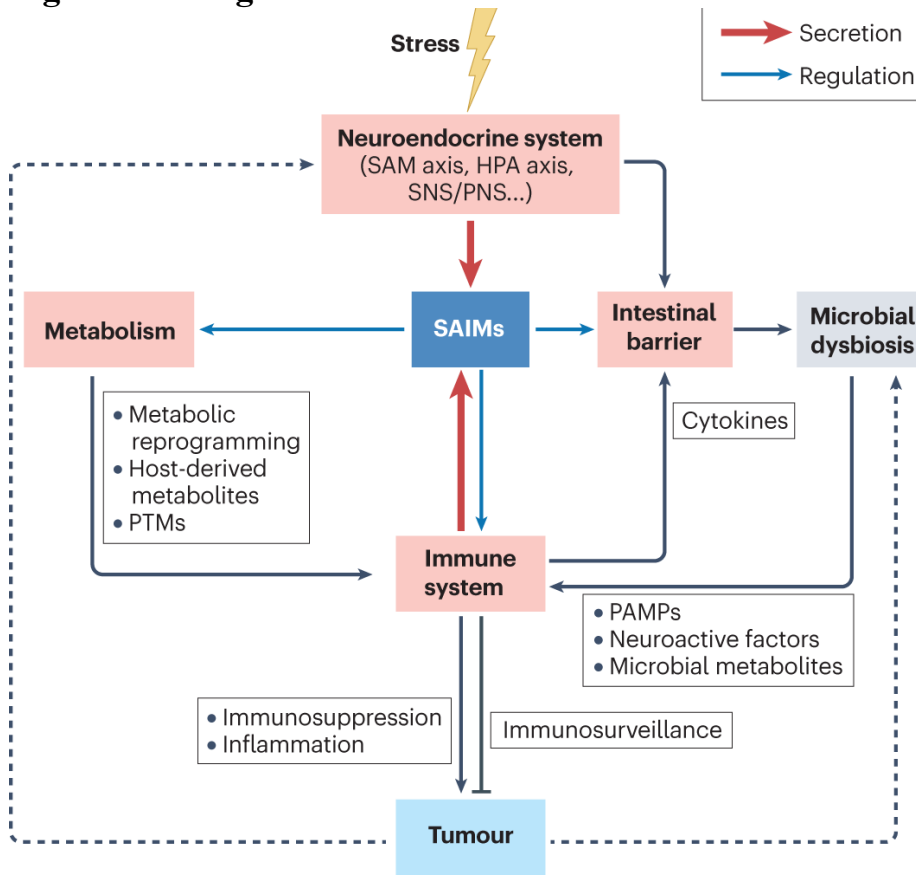
1454 281 Dethlefsen, C. *et al.* Exercise-Induced Catecholamines Activate the Hippo Tumor Suppressor  
1455 Pathway to Reduce Risks of Breast Cancer Development. *Cancer Res* **77**, 4894-4904,

1456 doi:10.1158/0008-5472.CAN-16-3125 (2017).  
1457 282 Huang, C. W. *et al.* Irisin, an exercise myokine, potently suppresses tumor proliferation,  
1458 invasion, and growth in glioma. *FASEB J* **34**, 9678-9693, doi:10.1096/fj.202000573RR (2020).  
1459 283 Sarkar, D. K., Murugan, S., Zhang, C. & Boyadjieva, N. Regulation of cancer progression by  
1460 beta-endorphin neuron. *Cancer Res* **72**, 836-840, doi:10.1158/0008-5472.CAN-11-3292 (2012).  
1461 284 Harber, V. J. & Sutton, J. R. Endorphins and exercise. *Sports Med* **1**, 154-171,  
1462 doi:10.2165/00007256-198401020-00004 (1984).  
1463 285 Hojman, P. *et al.* Exercise-induced muscle-derived cytokines inhibit mammary cancer cell  
1464 growth. *Am J Physiol Endocrinol Metab* **301**, E504-510, doi:10.1152/ajpendo.00520.2010  
1465 (2011).  
1466 286 Hamy, A. S. *et al.* Comedications influence immune infiltration and pathological response to  
1467 neoadjuvant chemotherapy in breast cancer. *Oncoimmunology* **9**, 1677427,  
1468 doi:10.1080/2162402X.2019.1677427 (2020).  
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**Figures and legends**



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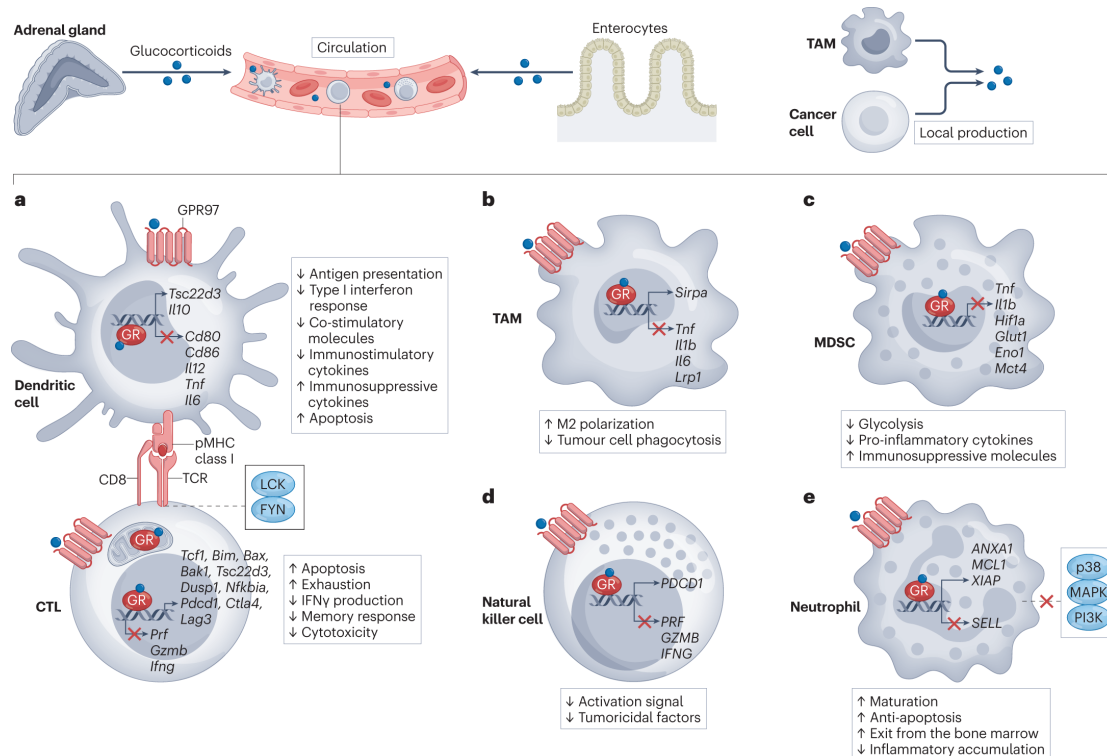
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**Fig. 1. The effects of stress on cancer.** Overview of the intricate relationships between the neuroendocrine system, immune system, metabolic process, gut microbiota, and cancer under conditions of stress. Stress can provoke the SAM and HPA axes for systemic adaptations and stimulate the peripheral nervous system (including sympathetic and parasympathetic nervous system (SNS and PNS)) for localized adjustments. This leads to altered secretion of SAIMs, which engage their corresponding receptors on immune cells and directly reshape the immune landscape of tumours. It is noteworthy that immune cells can also generate SAIMs. Stress-triggered systemic changes, including metabolic reprogramming and dysbiosis of microbiota, can sculpture the tumour macroenvironment. SAIMs are closely involved in the metabolic fluctuations and functional alterations of circulating and tissue-resident immune cells, which can be attributed to changes in their energy supply, macromolecule synthesis, signal transduction, and transcriptional networks. Moreover, some bioactive metabolites generated upon stress can induce PTMs (such as lactylation, O-GlcNAcylation and palmitoylation) of target proteins to enable immunoregulation. Importantly, stress-induced proinflammatory cytokines and neuroendocrine factors often compromise the intestinal integrity and cause microbial imbalance. Structural components from the gastrointestinal microflora (such as PAMPs), immunoregulatory metabolites, and neuroactive factors can stimulate corresponding receptors or sensors on immune cells and modulate their response to cancer. Besides, cancer diagnosis, tumour progression and treatment may lead to long-term alterations in neuroendocrine circuitries, which may associate with dysbiosis and immune dysregulation.

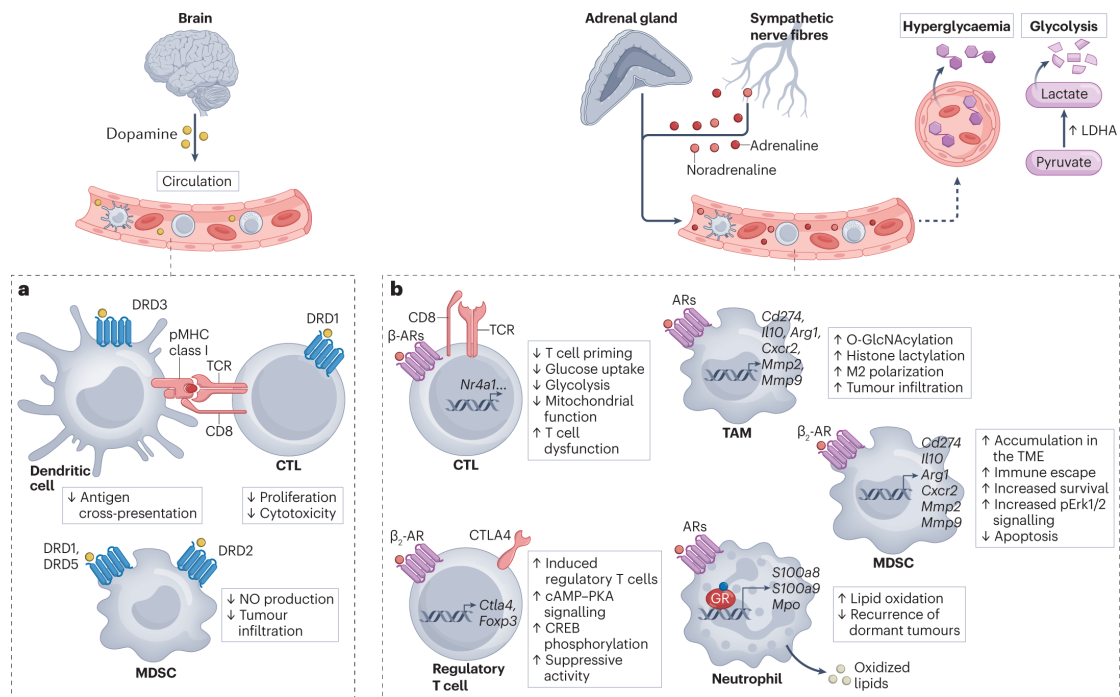


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**Fig. 2. The effect of glucocorticoids on the immune system and anti-cancer immune responses.** Stress-induced elevation of circulating glucocorticoids can be largely attributed to the activation of the HPA axis and increased secretion from the adrenal glands. Moreover, glucocorticoids can be produced by enterocytes in the gut and diffuse into the circulation. During malignant progression, local synthesis of glucocorticoids by tumour cells and tumour-infiltrating myeloid cells is often enhanced<sup>130,241</sup>. Elevated glucocorticoids in the circulation and in the TME can engage their nuclear receptor (GR) or membrane receptor (GPR97) on immune cells<sup>73,74</sup>. This leads to transcriptional reprogramming and altered signal transduction<sup>105</sup>, thus influencing the viability, differentiation, migration, metabolic patterns, and function of different immune cell populations. a) Glucocorticoids confer immunosuppressive properties on DCs by down-regulating co-stimulatory molecules (such as CD80 and CD86)<sup>242</sup>, immunostimulatory cytokines (such as IL-12, IL-6 and TNF) and type I IFN response, whilst augmenting the secretion of immunosuppressive cytokines (such as IL-10)<sup>243</sup>. Stress-induced GR signalling in DCs can elevate the transcription of *Tsc22d3*, which impairs type I IFN response and MHC class I/II antigen presentation pathways, thus compromising anti-tumour immune responses<sup>52</sup>. Glucocorticoid-induced downregulation of anti-apoptotic molecules leads to apoptosis of DCs and this process is independent of caspase activation<sup>244</sup>. By stimulating the expression of BCL-2 interacting mediator of cell death (*Bim*), which in turn activates BCL2 antagonist/killer 1 (*Bak1*) and BCL2-associated X protein (*Bax*) in T cells, glucocorticoids can elicit the mitochondrial pathway of apoptosis<sup>245</sup>. Moreover, translocation of ligand-bound GR to the mitochondria can disrupt their membrane integrity and activate the intrinsic apoptotic pathway in T cells<sup>246</sup>. Glucocorticoids can rapidly attenuate TCR signalling by abrogating the recruitment and activation of LCK/FYN and blocking the phosphorylation of their downstream signalling intermediates<sup>105,247</sup>. They also dampen the effector programmes of T cells by upregulating immunosuppressive genes (*Tsc22d3*, *Dusp1*, and *Nfkb1a*) and co-inhibitory molecules (*Pcdcl1*, *Ctla4*, *Lag3*), while downregulating multiple co-stimulatory molecules, cytokines, and



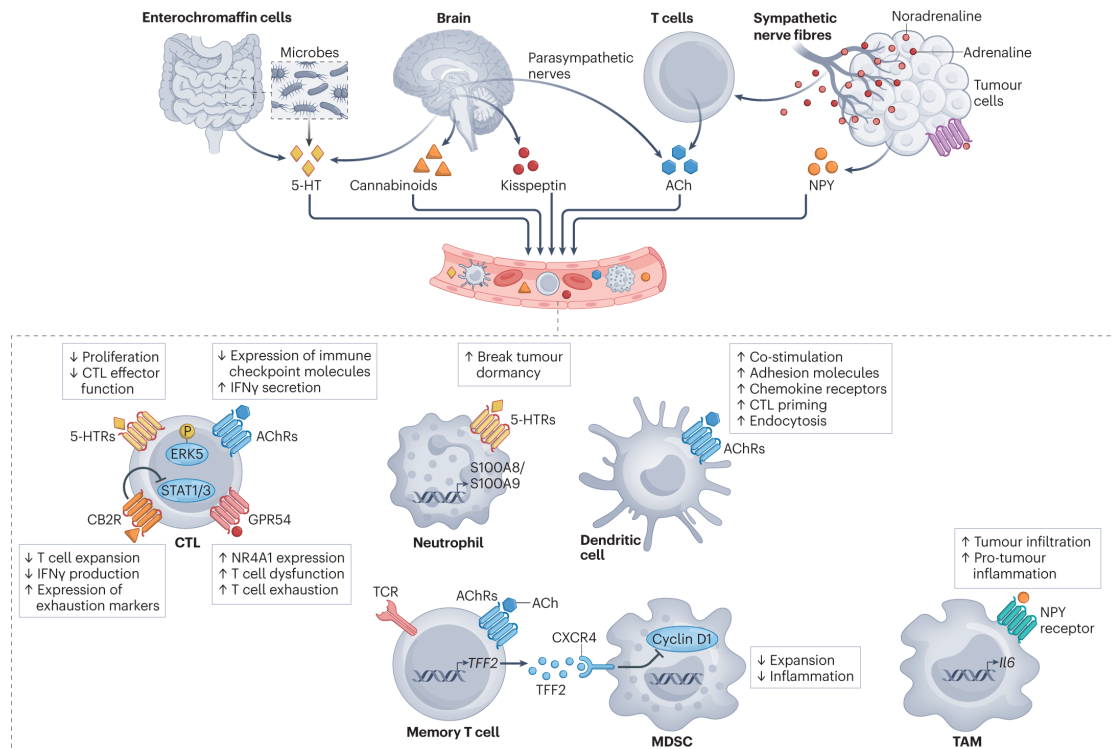
1529 chemokines<sup>104</sup>. Ligand-engaged GR can drive various transcriptomic and epigenetic  
1530 changes that favour the differentiation of memory precursor T cells and T<sub>reg</sub> cells,  
1531 whereas strongly restraining T<sub>H1</sub> differentiation and the effector phenotype of CTLs  
1532 (via upregulating TCF1)<sup>104,130</sup>. b) Liganded GR can disturb TAM-mediated clearance  
1533 of tumour cells by the trans-repression of “eat me” signal receptor (low-density  
1534 lipoprotein receptor-related protein-1, *Lrp1*) and the elevation of “don't eat me” signal  
1535 receptor (signal regulatory protein  $\alpha$ , *Sirpa*)<sup>248</sup>. Glucocorticoids can also drive TAMs  
1536 towards M2-like phenotype and inhibit the expression of inflammatory cytokines  
1537 (such as TNF, IL-1 $\beta$  and IL-6)<sup>249</sup>. c) GR signalling can promote the  
1538 immunosuppressive activity of MDSCs by inhibiting the expression of hypoxia-  
1539 inducible factor 1- $\alpha$  (*Hif1a*), glycolysis-related genes (such as *Glut1*, *Eno1* and  
1540 *Mct4*)<sup>250</sup> and pro-inflammatory cytokines (such as *Tnf* and *Il1b*)<sup>251</sup>. d) Glucocorticoids  
1541 dampen the cytolytic activity of NK cells by reducing histone acetylation at the  
1542 promoter or enhancer regions of tumoricidal factors such as perforin (*PRF*), granzyme  
1543 B (*GZMB*), and IFN $\gamma$  (*IFNG*)<sup>252</sup>. They also limit the production of IFN $\gamma$  by  
1544 upregulating checkpoint receptor PD1<sup>253</sup>. e) Glucocorticoids can accelerate neutrophil  
1545 exit from the bone marrow by reducing the expression of adhesion molecules (such as  
1546 PECAM-1, ICAM-1 and VCAM-1) on endothelial cells<sup>254</sup> (not shown). They also  
1547 block the accumulation of neutrophils in inflamed tissues by downregulating L-  
1548 selectin (*SELL*) and upregulating Annexin A1 (*ANXA1*, which mediates the shedding  
1549 of *SELL*)<sup>255,256</sup>. Moreover, glucocorticoids exhibit an anti-apoptotic effect on  
1550 neutrophils by directly activating p38 MAPK and PI3K and upregulating myeloid cell  
1551 leukemia-1 (*MCL1*) and X-linked inhibitor of apoptosis proteins (*XIAP*)<sup>257</sup>.  
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**Fig. 3. The effect of catecholamines on the immune system and anti-cancer immune responses.** Stress-induced hyperactivation of the SAM axis can generate high levels of catecholamines, such as dopamine produced in the brain and adrenaline and noradrenaline released from the adrenal glands and sympathetic nerve fibres<sup>68,69</sup>. Moreover, cancer immunotherapy with oncolytic bacteria or CAR-T cells can trigger a self-amplifying catecholamine loop in myeloid cells, which leads to cytokine release syndrome<sup>258</sup> (not shown). Catecholamines can either promote (sometimes) or suppress (generally) tumor immunosurveillance by engaging diversified catecholamine receptors on immune cells. For example, elevation of plasma dopamine can engage DRD1 and increase intracellular cAMP in T cells, hence blocking their proliferation and cytotoxicity<sup>141</sup>. It can attenuate CTL response against tumours by eliciting DRD3 signalling in DCs and inhibiting their antigen cross-presentation<sup>142</sup>. However, dopamine can also stimulate DRD1, DRD5 and DRD2 on MDSCs and unleash anti-tumour immunity by reducing their accumulation in the TME and production of NO<sup>143,144</sup>. Surges of adrenaline and noradrenaline can stimulate  $\alpha$ - or  $\beta$ -adrenaline receptors (ARs) on immune cells. Activation of these G-protein-coupled receptors often leads to impaired priming and metabolic defects of T cells (such as impaired glucose uptake, glycolysis, and mitochondrial function), resulting in T cell dysfunction<sup>145-149</sup>.  $\beta$ 2-AR activation can facilitate the conversion of naïve T cells to FOXP3<sup>+</sup> T<sub>reg</sub> cells and enhance their suppressive activities by increasing intracellular cAMP, PKA-dependent CREB phosphorylation, and CTLA4 expression<sup>119</sup>. Adrenaline and noradrenaline also promote tumour infiltration and M2-polarization of TAMs, thus accelerating the progression and metastatic spreading of tumours<sup>150,151</sup>. Stress-induced catecholamines can boost hyperglycemia and glycolysis, which augment O-GlcNAcylation of target proteins and lactylation of histones in TAMs. This favours their M2-like polarization and supports the immune evasion of colorectal cancer in mice and humans<sup>172,189</sup>.  $\beta$ 2-AR signalling in MDSCs leads to downregulation of apoptosis-related genes and upregulation of arginase-1 and PD-L1, thus favouring their survival and immunosuppressive properties<sup>152</sup>. The  $\beta$ 2-AR axis also promotes tumour progression via the CXCL5-CXCR2 axis and ERK pathway, which enhance the mobilization of MDSCs and local immunosuppression<sup>259</sup>. Upon

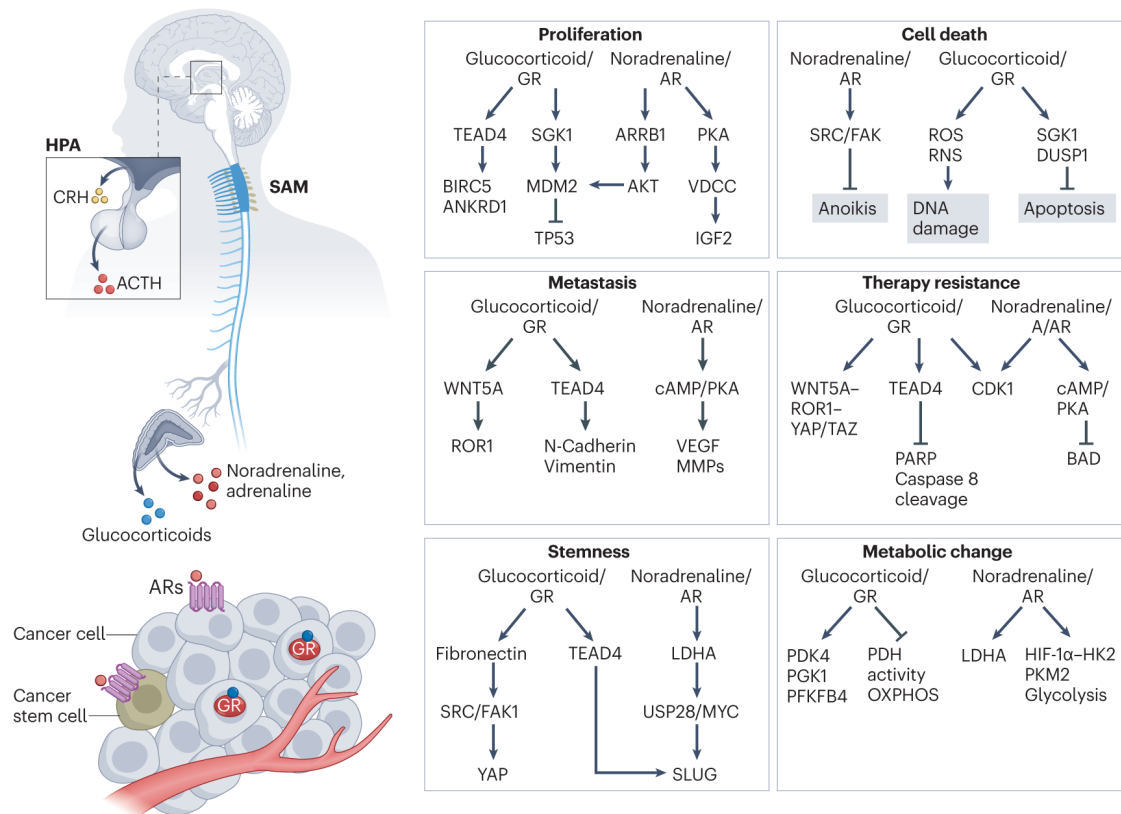
1585 stimulation with norepinephrine, neutrophils rapidly release S100A8/A9 and activate  
1586 myeloperoxidase (MPO) to generate oxidized lipids, which further reactivate dormant  
1587 tumour cells<sup>185</sup>.  
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**Fig. 4. The effect of other SAIMs on the immune system and anti-cancer immune responses.** Acute stress and chronic stress adaptation responses result in the release of SAIMs other than glucocorticoids and catecholamines. For example, 5-HT generated from the brain, enterochromaffin cells, or gut microbes can block the accumulation of CTLs in the TME and reduce their production of IFN $\gamma$  and GZMB<sup>227</sup>. Once engaged by endogenous cannabinoids, cannabinoid receptor 2 (CBR2) can bind to JAK1 and inhibit the phosphorylation of STAT1 and STAT3. This causes impeded expansion and antitumor function of CTLs<sup>164</sup>. Stress can augment the level of plasma kisspeptin and the expression of its receptor GPR54 on tumor-infiltrating T cells. This leads to T cell dysfunction and exhaustion, due to ERK5-mediated NR4A1 activation<sup>162</sup>. Persistent stress can block the parasympathetic system, vagal responses, and ACh production<sup>165</sup>. However, parasympathetic neurostimulation of tumours can significantly reduce the expression of immune checkpoint molecules (such as PD1 and FOXP3) on tumour-infiltrating CTLs and augment their capability to produce IFN $\gamma$ <sup>22</sup>. 5-HT-triggered rapid release of S100A8/A9 from neutrophils can break tumour dormancy<sup>185</sup> and facilitate tumour immune evasion<sup>186</sup>. Agonistic stimulation of nicotinic AChRs on DCs can upregulate the expression of costimulatory molecules, adhesion molecule CD11b, and chemokine receptor CCR7, which boost their capacity of endocytosis, CTL priming and IL-12 secretion<sup>166</sup>. Moreover, vagal nerve stimulation can potentiate the secretion of TFF2 from ACh-producing splenic memory T cells, which inhibits the development of colorectal cancer in mice by engaging CXCR4 on MDSCs and inhibits their expansion<sup>167</sup>. Besides, noradrenaline-induced production of NPY from tumour cells can recruit macrophages to the TME and boost their secretion of pro-tumoural cytokine IL-6<sup>153</sup>.

## Boxes

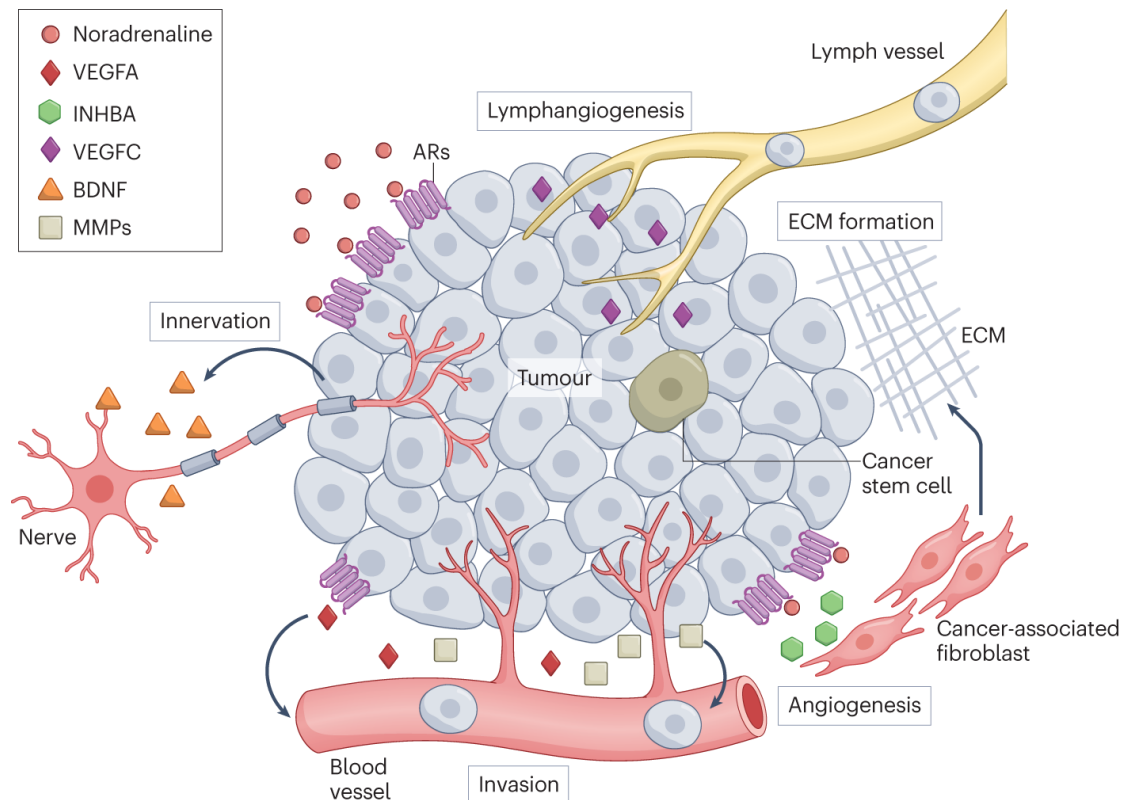


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**Box 1. Direct effects of stress on cancer cells.** Biological features of tumour cells, such as proliferation, cell death, metastasis, therapy resistance, stemness and metabolic changes can be affected by stress-induced neuroendocrine factors. For example, a glucocorticoid surge during chronic restraint can accelerate radiation-induced tumorigenesis by activating the kinase SGK1 and the E3 protein ubiquitin ligase MDM2, which subsequently attenuate the expression and tumour-suppressive function of TP53<sup>25</sup>. Glucocorticoids can activate the transcription factor TEAD4 in breast cancer cells, which facilitates tumour growth and metastasis by upregulating genes related to proliferation (such *BIRC5* and *ANKRD1*), epithelial-mesenchymal transition, and cancer stem cell traits<sup>55</sup>. Cancer progression-induced increase of glucocorticoids can activate GR and escalate metastatic colonization of breast cancer cells in distant organs by upregulating the expression of receptor tyrosine kinase like orphan receptor 1 (ROR1) and its ligand WTN5A<sup>56</sup>. Glucocorticoid administration also favours the evasion of cell death by elevating the expression of pro-survival and anti-apoptotic proteins (such as SGK1 and DUSP1) on cancer cells<sup>57</sup>. In contrast, stress-induced glucocorticoids and their synthetic mimetics can promote cell death by augmenting the production of reactive oxygen and nitrogen species, which cause DNA damage and impaired DNA repair in human and mouse breast cancer cells<sup>60</sup>. Additionally, glucocorticoids can promote cancer stemness and chemoresistance by activating TEAD4<sup>55</sup> and YAP<sup>59,260</sup>. Likewise, catecholamines are closely involved in the initiation, progression, dissemination, and therapeutic resistance of tumours. For example, chronic catecholamine stimulation leads to excessive DNA damage and genomic instability in the thymus and testes by triggering TP53 degradation via  $\beta$ -arrestin-1 (ARRB1)/AKT-mediated MDM2 activation<sup>261</sup>. Noradrenaline can induce PKA-dependent phosphorylation of voltage-dependent calcium channels (VDCC), which facilitates the secretion of insulin-like growth factor 2 (IGF2) and lung epithelial cell transformation in mice<sup>26</sup>. Stress-

1646 induced adrenaline elevates LDHA and enhances stem-like traits of human breast  
1647 cancer cells through metabolic rewiring and USP28/MYC/SLUG signalling<sup>61</sup>. Also,  
1648 noradrenaline exhibits antiapoptotic effects on human prostate and breast cancer  
1649 cells, by inactivating the apoptosis promoter BAD<sup>62</sup>. It can also activate SRC-  
1650 dependent phosphorylation of the kinase FAK and render human ovarian cancer  
1651 cells resistant to anoikis<sup>262</sup>. Glucocorticoid- and catecholamine-induced metabolic  
1652 reprogramming also favour tumour growth and metastasis, owing to the  
1653 transcriptional regulation genes related to glycolysis and oxidative phosphorylation  
1654 (OXPHOS), such as pyruvate dehydrogenase kinase 4 (PDK4), phosphoglycerate  
1655 kinase 1 (PGK1), (6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4)  
1656 PFKFB4<sup>263</sup>, pyruvate dehydrogenase (PDH)<sup>264</sup>, hexokinase 2 (HK2), pyruvate  
1657 kinase M2 (PKM2)<sup>265</sup>, and LDHA<sup>61</sup>.  
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**Box 2. Direct effects of stress on the tumour stroma.** Stress can modulate various stromal components of tumours. In preclinical models of ovarian, breast, and colon cancers, noradrenaline-stimulated secretion of inhibin  $\beta$  A (INHBA) from cancer cells can activate cancer-associated fibroblasts (CAFs), leading to increased collagen deposition and extracellular matrix formation<sup>63</sup>. In mouse models of ovarian and nasopharyngeal cancer, stress-induced activation of  $\beta$ 2-AR signalling can increase the expression of vascular endothelial growth factor-A (VEGF-A) and matrix metalloproteinases (MMPs) on tumour cells, which promote angiogenesis and malignant outgrowth<sup>47,64</sup>. The catecholamine receptor  $\beta$ 2-AR on vascular endothelial cells can also promote angiogenesis by directly forming a complex with VEGFR2<sup>66</sup>. Moreover, noradrenaline can stimulate local lymphogenesis and enhance metastatic progression by inducing the secretion of PGE2 and VEGF-C from TAMs and malignant cells<sup>49</sup>. It is noteworthy that sustained adrenergic signalling can stimulate the production of brain-derived neurotrophic factor (BDNF) from mouse ovarian and colon cancer cells, which promotes axonogenesis in the TME and favours tumour growth and metastasis<sup>67</sup>.

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### Box 3. Peripheral sources of neuroendocrine factors

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Steroidogenesis and glucocorticoid production has been observed in the thymus<sup>266</sup>, brain<sup>267</sup>, and in colon epithelial cells<sup>92,268</sup>. Glucocorticoid production by tumour-infiltrating myeloid cells has been reported to facilitate the emergence of dysfunctional CD8<sup>+</sup> T cells<sup>130</sup>. Myeloid cells expressing tyrosine hydroxylase largely contribute to the catecholamine surge in response to T-cell-activating therapies, which augments pro-inflammatory circuitries and can cause cytokine release syndrome<sup>258</sup>. In the lung, pulmonary neuroendocrine cells are rich sources of GABA

1688 and calcitonin gene-related peptide (CGRP), which can stimulate neighbouring group  
1689 2 innate lymphoid cells (ILC2s) and modulate allergic responses<sup>90,269</sup>. In the GI tract,  
1690 catecholamines from sympathetic nerves can engage basolateral  $\alpha$ 2-adrenoreceptors  
1691 and trigger 5-HT release from adjacent chromogranin A<sup>+</sup> enterochromaffin cells<sup>91</sup>.  
1692 Enterochromaffin cell-mediated production of 5-HT can be enhanced by short-chain  
1693 fatty acids (SCFAs) from the gut microbiota<sup>270</sup>, as well as specific metabolites  
1694 generated by indigenous spore-forming bacteria in the gut (such as  $\alpha$ -tocopherol, p-  
1695 aminobenzoate, and tyramine)<sup>271</sup>. Moreover, 5-HT biosynthesis has been  
1696 documented in various immune cell subsets, including mast cells, monocytes, and T  
1697 cells<sup>272-274</sup>. Platelets can store large quantities of 5-HT in their dense granules and  
1698 secrete these upon activation<sup>275</sup>. Moreover, T cells can generate ACh, which induces  
1699 local vasodilation and allows for T cell extravasation<sup>276</sup>. Histamine released by mast  
1700 cells can modulate allergic and inflammatory responses<sup>82</sup>. Intriguingly, immune cells  
1701 may also enable the local clearance of neuroendocrine factors, as exemplified by  
1702 adipose-tissue associated macrophages and sympathetic neurons that express the  
1703 noradrenaline transporter as well as enzymes that degrade noradrenaline<sup>277</sup>.

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#### 1705 **Box 4. Stress management affects cancer immunosurveillance**

1706 Stress management with physical, mindfulness-based, or cognitive-behavioural  
1707 approaches (such as yoga, Tai-Chi, other stress-reducing exercises, meditation, and  
1708 relaxation) has been associated with immunological changes, such as reduced  
1709 inflammation, increased T<sub>H</sub>1 responses, and enhanced NK cell activity<sup>278</sup>.  
1710 Psychological interventions were shown to significantly reduce the risk of mortality  
1711 and cancer recurrence in patients with early-stage breast cancer, when provided post-  
1712 surgery and prior to adjuvant therapies<sup>279</sup>. These regimens also improve the quality  
1713 of life and subjective well-being of patients with cancer<sup>280</sup>. Of note, running-induced  
1714 catecholamines (which cannot be categorized as a ‘psychological stress’) can activate  
1715 YAP/TAZ phosphorylation in breast cancer cells and inhibit tumour outgrowth in  
1716 immunodeficient mice<sup>281</sup>. This indicates that the short-term peaks of catecholamines,  
1717 endogenous opioids, and myokines following exercise may prevent the development  
1718 and progression of cancer<sup>282-285</sup>. Intriguingly, some psychiatric drugs can exhibit  
1719 immunostimulatory properties (such as influencing the density of tumour-infiltrating  
1720 lymphocytes). For example, in patients with triple negative breast cancer, the usage  
1721 of psycholeptics or psychoanaleptics was associated with higher rate of pathological  
1722 complete responses<sup>286</sup>. At present, it remains unclear which cell subsets and receptors  
1723 respond to these drugs and whether their impact on the TME and cancer outcome is  
1724 on-target or off-target.