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Yuting Ma, Guido Kroemer

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

2  
3                   **Yuting Ma<sup>1\*</sup>, Guido Kroemer<sup>1-5\*</sup>**

4  
5                   <sup>1</sup> National Key Laboratory of Immunity and Inflammation, Suzhou Institute of Systems Medicine,  
6 Chinese Academy of Medical Sciences & Peking Union Medical College, Suzhou, Jiangsu, China

7                   <sup>2</sup> Equipe labellisée par la Ligue contre le cancer, Université de Paris, Sorbonne Université, INSERM  
8 U1138, Centre de Recherche des Cordeliers, Institut Universitaire de France, Paris, France

9                   <sup>3</sup> Metabolomics and Cell Biology Platforms, Gustave Roussy Cancer Campus, Villejuif, France

10                  <sup>4</sup> Pôle de Biologie, Hôpital Européen Georges Pompidou, AP-HP, Paris, France

11                  <sup>5</sup> Karolinska Institute, Department of Women's and Children's Health, Karolinska University Hospital,  
12 Stockholm, Sweden

13  
14 All correspondence should be addressed to: Yuting Ma (yuting\_ma1984@163.com)

15 \*These authors share senior authorship

16

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>.

## 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

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712

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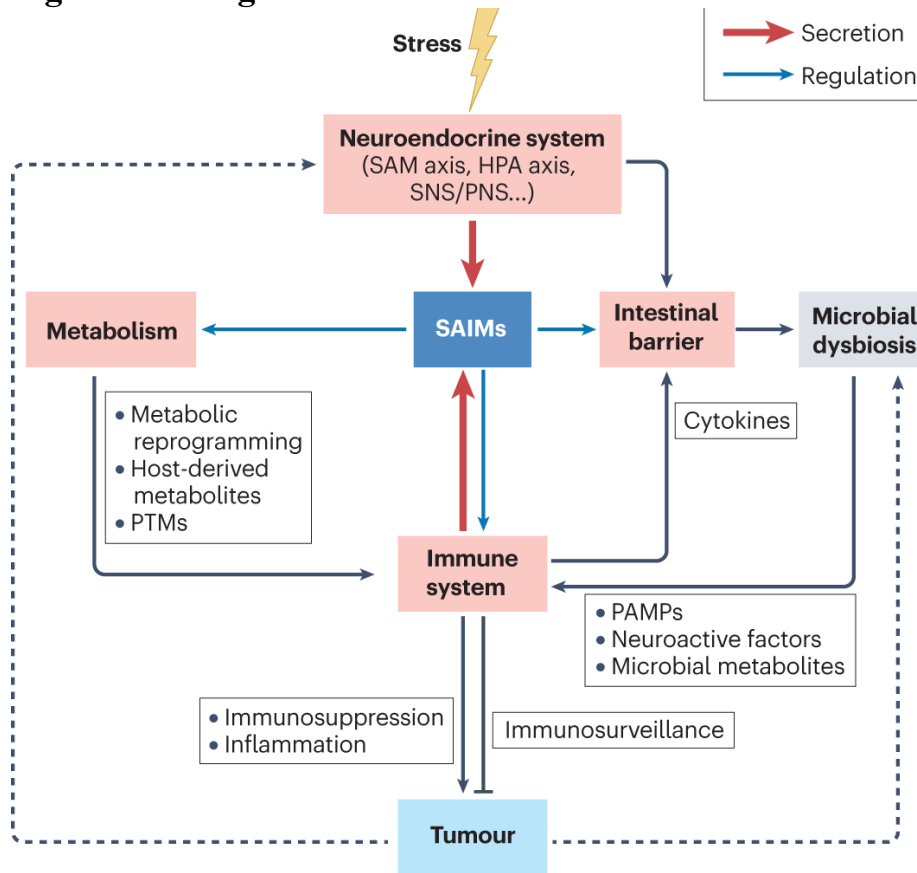
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## Figures and legends



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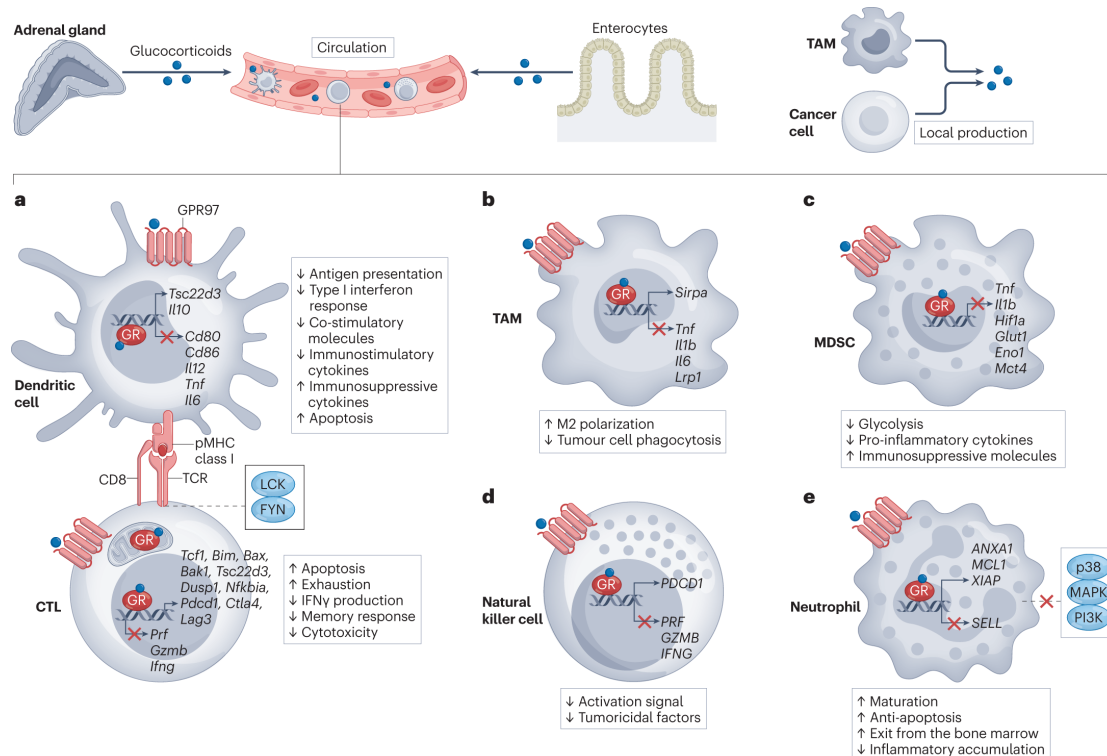
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**Fig. 1. The effects of stress on cancer.** Overview of the intricate relationships between the neuroendocrine system, immune system, metabolic process, gut microbiota, and cancer under conditions of stress. Stress can provoke the SAM and HPA axes 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.

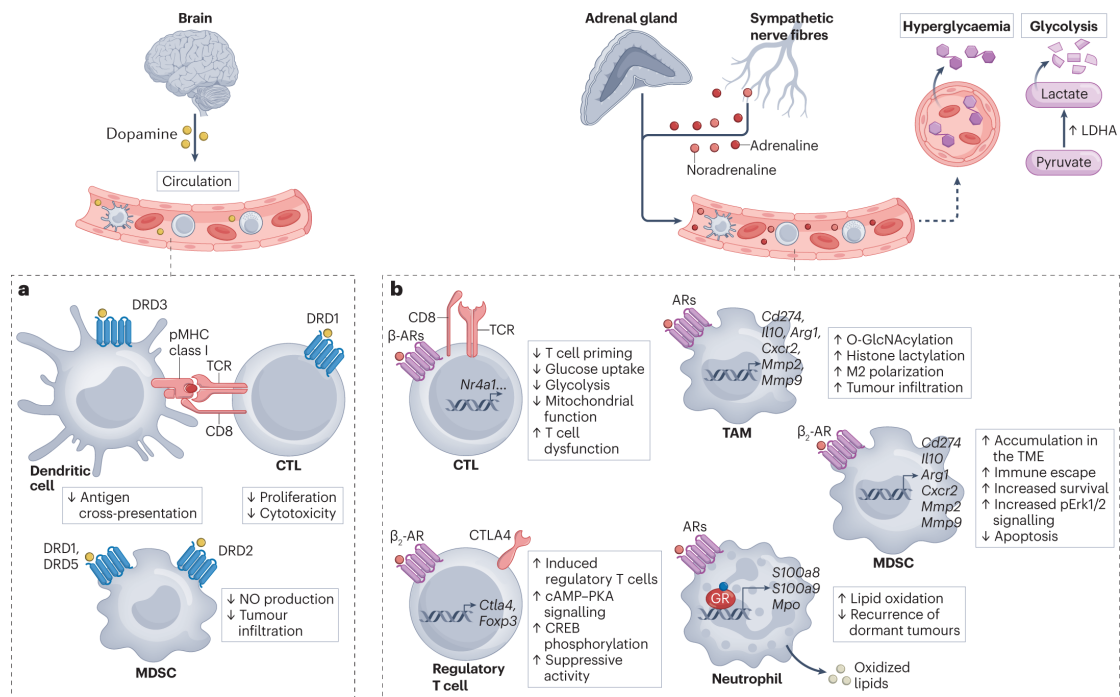


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**Fig. 2. The effect of glucocorticoids on the immune system and anti-cancer immune responses.** Stress-induced elevation of circulating glucocorticoids can be largely attributed to the activation of the HPA axis and increased secretion from the adrenal 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 (*Pdcd1*, *Ctla4*, *Lag3*), while downregulating multiple co-stimulatory molecules, cytokines, and



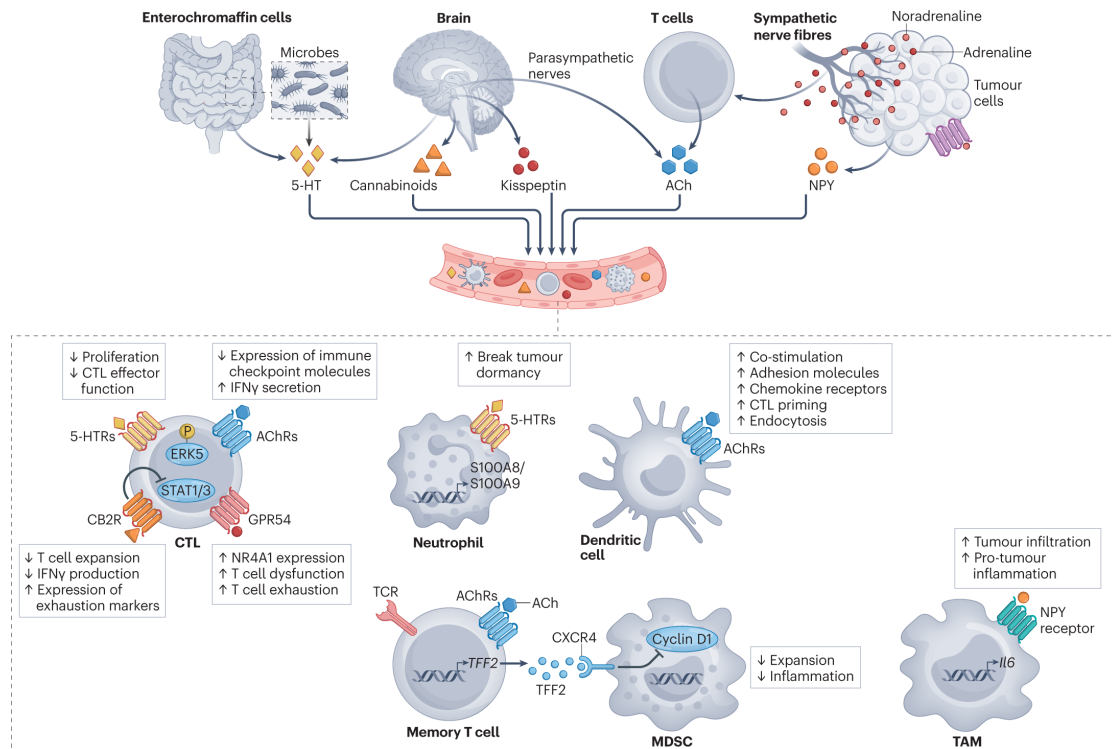
1529 chemokines<sup>104</sup>. Ligand-engaged GR can drive various transcriptomic and epigenetic  
1530 changes that favour the differentiation of memory precursor T cells and T<sub>reg</sub> cells,  
1531 whereas strongly restraining T<sub>H1</sub> differentiation and the effector phenotype of CTLs  
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

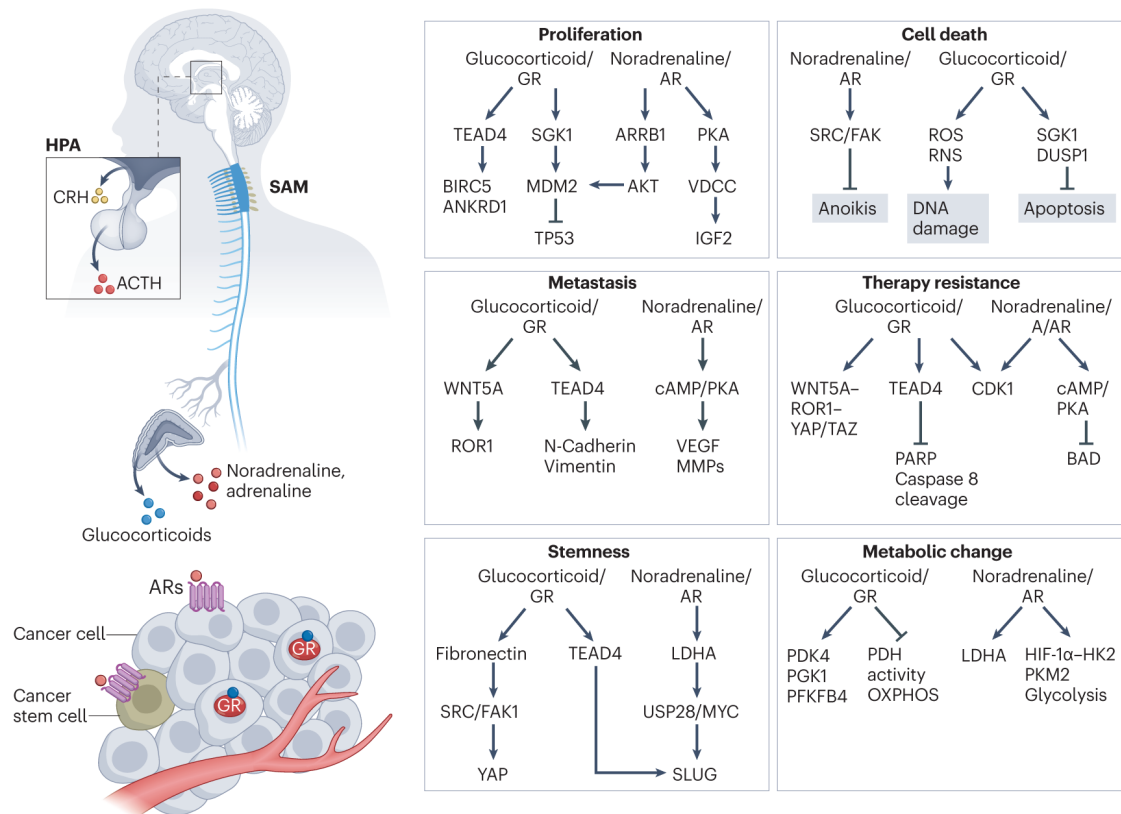
1585 stimulation with norepinephrine, neutrophils rapidly release S100A8/A9 and activate  
1586 myeloperoxidase (MPO) to generate oxidized lipids, which further reactivate dormant  
1587 tumour cells<sup>185</sup>.  
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**Fig. 4. The effect of other SAIMs 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

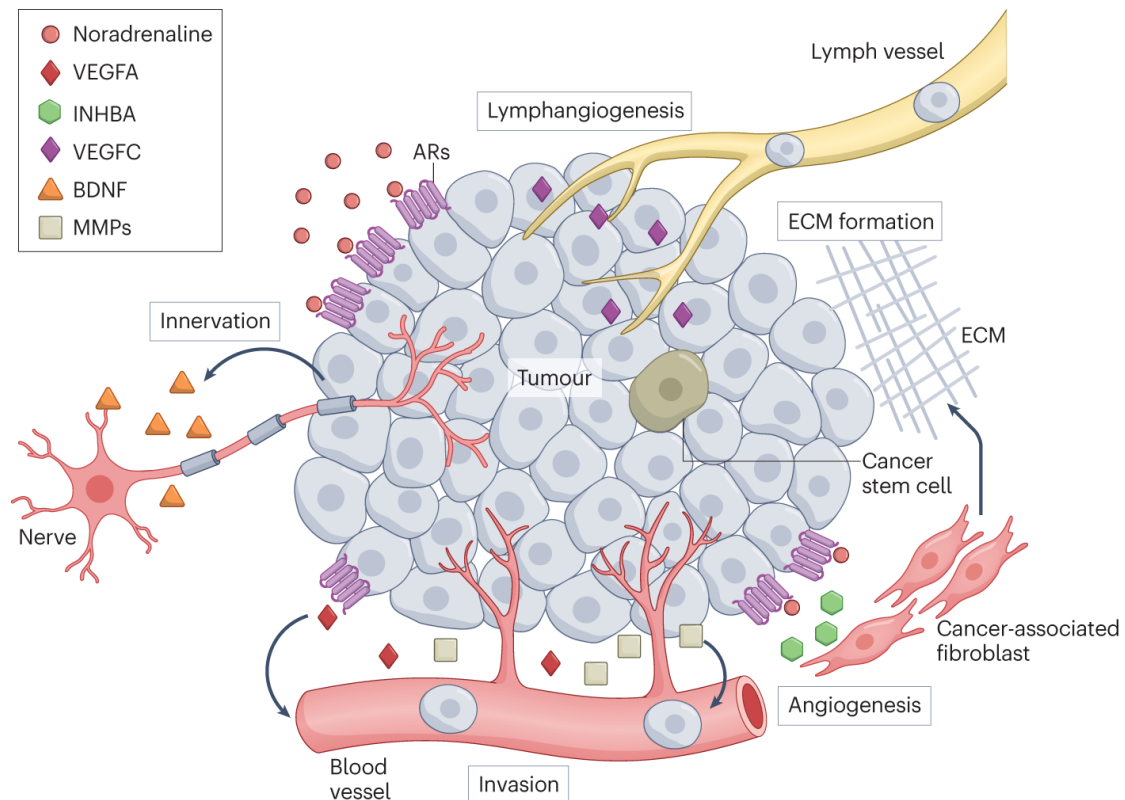


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**Box 1. Direct effects of stress on cancer cells.** Biological features of tumour cells, such as proliferation, cell death, metastasis, therapy resistance, stemness and metabolic changes can be affected by stress-induced neuroendocrine factors. For 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.