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

2
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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 20th century, only recently has it been considered that mental and physical health
41 may be inseparable¹ and that psychiatric diseases have a pathophysiological substratum
42 that reaches beyond the central nervous system².

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 angiogenesis³, 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 responses⁴. Moreover, emerging evidence
51 also supports the existence of bidirectional regulatory networks between the immune
52 and neuroendocrine systems⁵⁻⁷. 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^{8,9}. 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^{5,10}. 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^{7,14,15}. Conversely, manipulation of components
64 of the immune system has been shown to perturb neurobiological and behavioural
65 features in animal models^{16,17}.

66
67 Importantly, tumours are generally infiltrated by distinct leukocyte subpopulations¹⁸
68 and they are sometimes innervated or surrounded by nerve fibres¹⁹. In mouse prostate
69 tumour xenografts, sympathetic and parasympathetic nerve fibres were reported to
70 promote tumour development and dissemination, respectively²⁰. The pro-tumoral
71 effects of sympathetic adrenergic nerve fibres were partially attributed to metabolic
72 shifts in endothelial cells that drive local angiogenesis²¹. High densities of adrenergic
73 and cholinergic nerves also correlated with poor clinical outcomes in patients with
74 prostate cancer²⁰. 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 molecules²².
77 Although the communication between nerves and immune cells in tumours is starting
78 to be explored^{22,23}, 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 instability²⁴. In mice, there is also evidence that chronic stress can accelerate
84 tumorigenesis^{25,26}. 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 humans²⁷⁻²⁹. 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^{30,31}. 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 factors³², neuroanatomic features³³, and metabolic
96 patterns³⁴.

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 cancer³⁵. 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^{36,37}. 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 progression³⁸. 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)³⁹⁻⁴³. 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^{44,45}. 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 cancer⁴⁶.

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 mice⁴⁷⁻⁵².
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^{53,54}.

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^{25,55-62} (**Box 1**). Also, these factors can reshape the tumour stroma by
144 promoting angiogenesis, lymphogenesis, axonogenesis, and extracellular matrix
145 formation^{47,49,63-67} (**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^{68,69}. Surges of adrenaline and noradrenaline can activate α - or β -
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^{70,71}. 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 gland⁷². 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 reprogramming⁷³. Alternatively, they
171 can engage a high-affinity membrane receptor G-protein coupled receptor 97
172 (GPR97)⁷⁴ on leukocytes, which modulates the development and inflammatory
173 response of immune cells^{75,76}.

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 receptors⁷⁷. 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^{78,79}. 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^{80,81} 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^{82,83}. 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 μ , δ , or κ opioid receptors⁸⁴⁻⁸⁶.
189 The above-mentioned receptors have been identified not only on neurons, but also on a
190 diverse array of immune cells⁸⁷.

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 axis⁸⁸) and among different neuroendocrine elements (as exemplified by the interplay
195 between the SAM and HPA axes⁶⁸, as well as that between serotonergic neurons and
196 the HPA axis⁸⁹). 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^{7,9,14,15},
199 specialized endocrine cells^{90,91}, epithelial cells⁹², immune cells^{14,93}, and even gut
200 microbiota⁹⁴ (**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)⁶⁷. In
207 return, tumour innervation affects malignant growth and dissemination via locally
208 released neurotransmitters^{19,95}. 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 metastasis⁹⁶. 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^{97,98}. 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^{20,99}. 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^{20,67}. 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 contexture¹⁰⁰⁻¹⁰².

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 models¹⁰³. 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 response¹⁰⁴⁻¹⁰⁷. For example, in the context of viral infection, a glucocorticoid

235 surge induced by repeated restraint was shown to reduce the levels of CD8⁺ dendritic
236 cells (DCs) and downregulate their cross-presentation capabilities, thereby weakening
237 the priming of antigen-specific cytotoxic T lymphocytes (CTLs) in mice¹⁰⁸. In a mouse
238 model of moderate stress upon dietary restriction, glucocorticoid-induced upregulation
239 of chemokine receptor CXCR4 on memory CD8⁺ T cells facilitated their homing to the
240 bone marrow¹⁰⁹. This stress-induced preconditioning can enhance immune responses to
241 a secondary bacterial infection¹⁰⁹. Indeed, the immunoregulatory effect of
242 glucocorticoid is highly cell type-specific despite the ubiquitous expression of GR¹¹⁰.
243 This can be explained by the diversified transcriptional output and post-translational
244 modifications of GR in different cell types⁷³.

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)¹¹¹ and
248 trigger dopamine release^{112,113}. By engaging different subtypes of metabotropic G
249 protein-coupled dopamine receptors, it can stimulate the homing of naive CD8⁺ T
250 cells¹¹⁴, inhibit NK cell expansion and IFN γ production¹¹⁵, and alleviate the activation
251 of the NLRP3 inflammasome¹¹⁶. Surges of noradrenaline can rapidly boost antigen
252 capture by DCs via α 2-AR-mediated PI3K and ERK1/2 signalling upon acute
253 stress¹¹⁷. However, stimulating β 2-AR on LPS-treated DCs leads to preferential
254 secretion of IL-23 over IL-12p70, therefore augmenting T_H17 response and reducing
255 T_H1 response of CD4⁺ T cells¹¹⁸. β 2-adrenergic stimulation through catecholamines
256 can also enhance the suppressive function of regulatory T (T_{reg}) cells by upregulating
257 the expression of cytotoxic T-lymphocyte associated protein 4 (CTLA4)¹¹⁹.
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 responses¹²⁰. 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 α 9 nicotinic receptor and enhanced
265 their production of antibodies in response to immunization¹⁴. 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^{87,121}.

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 immunotherapy¹⁸. 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_{reg} cells, as well as defective IFN γ production by T
281 cells in the skin⁵⁰. Also, high levels of stress have been associated with impaired NK
282 cell function in patients with ovarian and breast cancer^{122,123}. 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 changes¹⁰⁵ (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 survival¹²⁴. 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 compromised⁵². 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 failure⁵². 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 immunosuppression⁵².
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^{128,129}.

315

316 Within the TME, cells of the monocyte-macrophage lineage can also produce
317 glucocorticoids, which cause CD8⁺ 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 melanoma¹³⁰. 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^{52,131}. High expression of *TSC22D3* has also been identified as
326 a negative prognostic marker in patients with colorectal, lung, or gastric cancer⁵².
327 Indeed, patients with non-small cell lung cancer who received corticosteroids had poor
328 responses to PD1/PD-L1 blockade¹³². 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 TME¹³³. 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 chemoimmunotherapy¹³⁴. Nevertheless, glucocorticoid treatment did not
338 cause noticeable inhibition in the therapeutic control of mesothelioma in mice treated
339 with highly efficacious cancer therapies¹³⁴. 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^{135,136},
347 they are generally viewed as immunosuppressive^{116,137,138}. Aversive stimuli can
348 promote mesolimbic dopamine release in mice and humans^{112,113,139}, whereas long-term
349 exposure to psychosocial adversity may dampen the dopaminergic activity¹⁴⁰. 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)¹⁴¹. 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 responses¹⁴². 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 infiltration¹⁴³. By acting on D1-like receptors, dopamine can
360 also attenuate nitric oxide (NO) production by GR1⁺CD115⁺ monocytic MDSCs and
361 reverse local immunosuppression in mouse models of lung cancer and melanoma¹⁴⁴.

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 NR4A¹⁴⁵, among which NR4A1 is a key mediator of T cell
366 dysfunction¹⁴⁶. High expression of NR4A1 represses the transcription of several
367 effector molecules, whereas genetic deletion of *Nr4a1* in mice boosts immune
368 responses against tumours¹⁴⁶. Catecholamines are very efficient at inhibiting the
369 priming of anti-tumour CD8⁺ T cell responses, which may be explained by the fact that
370 naïve T cells express comparatively high levels of β 2-ARs¹⁴⁷. In a mouse model of B-
371 cell lymphoma, chronic stimulation with the non-selective β -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⁺T cell responses¹⁴⁸. Further studies
375 showed that sustained β -AR signalling in CD8⁺ T cells dampened their metabolic
376 adaptation upon activation, leading to impaired glucose uptake, glycolysis, and
377 mitochondrial function¹⁴⁹. Stress-induced catecholamine surges also favour myeloid
378 cell-mediated immunosuppression. In mouse models of breast cancer, β 2-adrenergic
379 signalling was reported to promote the M2 polarization of macrophages¹⁵⁰ and their
380 infiltration in the primary tumour parenchyma to accelerate metastatic dissemination¹⁵¹.
381 It also supports the accumulation of MDSCs in the TME and upregulates the expression
382 of arginase-1 and PD-L1¹⁵². 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⁺
385 tumour-associated macrophages (TAMs) and local immunosuppression¹⁵³ (**Fig. 3**).

386

387 The genetic deletion or pharmaceutical inhibition of β 2-AR (with ICI118.551 or
388 propranolol), but not the blockade of β 1-ARs (with metoprolol)¹⁵⁴, enhanced the
389 efficacy of anti-PD1 therapy in mouse models of melanoma and breast cancer^{154,155}.
390 Similarly, blocking adrenergic stress or β 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 cancer¹⁵⁶. β 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 thymoma¹⁵⁷. Recent clinical studies prove the concept that
395 pharmacological blockade of β -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 β -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⁺ TAMs and CTLs¹⁵⁸. In another randomized
401 placebo-controlled phase II clinical trial for patients with breast cancer, perioperative
402 inhibition of β -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 factors¹⁵⁹. This combination therapy
405 also enhanced the production of IL-12, IFN γ and CD11a (a NK activation marker),
406 suppressed the secretion of IL-6 and C-reactive protein, and attenuated the mobilization
407 of CD16⁻ monocytes¹⁵⁹. 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 melanoma¹⁶⁰. In a
410 retrospective clinical study of patients with metastatic melanoma, pan β -AR
411 antagonists, rather than β 1-AR selective blockers, seemed to prolong overall survival
412 following immunotherapy with IL-2 plus CTLA4- and/or PD1-targeted checkpoint
413 therapy¹⁶¹. Future studies may explore predictive biomarkers, optimize therapeutic
414 regimens, and develop combinatory approaches to utilize β -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 exhaustion¹⁶². Endogenous cannabinoids (such as anandamide
425 and 2-arachidonoylglycerol) are actively involved in stress adaptation and regulation of
426 the HPA axis¹⁶³. 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 cancer¹⁶⁴.

429

430 In response to persistent stress, the stress-relieving activities of the parasympathetic
431 system, vagal responses, and ACh production are often suppressed¹⁶⁵. 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 γ production and inhibiting the progression of breast
436 cancer in mice²². 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 treatment²². Reportedly, synthetic agonists of α 7-AChR display
439 anti-inflammatory, antiproliferative and tumour suppressive properties in both mice and
440 humans¹⁰⁰. 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 vaccines¹⁶⁶. 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 cancer¹⁶⁷ (**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^{17,168-172}. 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 metabolites¹⁷³. 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^{168,169}, in peripheral organs (such as
468 the liver and the adipose tissue)^{170,171}, as well as in circulating and tissue-resident
469 immune cells¹⁷. 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 cells¹⁷⁴, which can be mechanistically explained by
472 energy supply, macromolecule synthesis, signal transduction, and post-translational
473 modifications¹⁷⁵.

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^{176,177}. 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 β 2-AR stress pathway was found to
480 dictate the immunosuppressive function of MDSCs and TAMs by causing a series of
481 metabolic changes^{178,179}. 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 MDSCs¹⁷⁸. The
484 immunosuppressive effect of β 2-AR signalling in TAMs can be strengthened by
485 inflammatory mediators, mainly through elevating the COX-2/PGE2 system¹⁷⁹. 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^{180,181}. In mouse models of melanoma and
489 colon cancer, chronic stress was found to dampen T-cell glycolysis and oxidative
490 phosphorylation via β 2-AR signalling, thus causing T cell exhaustion in the TME¹⁸². 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 blockade¹⁸³. Chronic stress-induced adrenaline was reported to upregulate
495 lactate dehydrogenase A (LDHA) and enhance glycolysis in mouse and human
496 mammary tumours⁶¹. 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 melanoma¹⁸⁴. 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 γ in T cells and NK cells¹⁸⁴. In response to
501 SAIMs such as glucocorticoids, catecholamines, and 5-HT, neutrophils can rapidly
502 release the inflammatory cytokines S100A8 and S100A9¹⁸⁵, which are known to
503 mediate immune evasion in cancer¹⁸⁶. 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 pathway¹⁸⁵. 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 proteins¹⁸⁷.
513 Several studies showed that stress-induced catecholamines can enhance glycolysis and
514 lactate production^{61,188}. In mouse models of lung cancer and melanoma, the
515 accumulation of exogenous or endogenous lactate in TAMs has been validated¹⁸⁹. 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 state¹⁸⁹.

518

519 The immunoregulatory potential of other metabolite-dependent post-translational
520 modifications have been documented¹⁸⁷, but discoveries regarding their association
521 with stress and SAIMs have just begun to emerge. The addition of O-linked β -N-
522 acetylglucosamine (O-GlcNAc) to serine or threonine residues of target proteins is
523 mediated by O-GlcNAc transferase¹⁹⁰. 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 cells¹⁹⁰. It is noteworthy that stress-induced release of cortisol and catecholamines
527 often cause hyperglycemia and immune dysregulation^{191,192}. 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 humans¹⁷². 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 acyltransferases¹⁹³. These enzymes are expressed in a region- and cell-type

533 specific pattern in the mouse brain¹⁹⁴, and chronic exposure to restraint stress can
534 significantly alter the synaptic palmitoyl-proteome¹⁹⁵. Interestingly, ZDHHC3-
535 mediated palmitoylation can stabilize PD-L1 by blocking its ubiquitination and
536 degradation¹⁹⁶. Pharmacological inhibition or genetic silencing of ZDHHC3 can
537 decrease PD-L1 expression on tumour cells and enhance anti-tumour T-cell
538 immunity¹⁹⁶. 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 system¹⁹⁷. 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 brain¹⁹⁸. 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^{173,199,200}. Indeed, faecal samples harvested from
551 patients with major depressive disorder contain more *Enterobacteriaceae* and *Allistipes*,
552 but less *Faecalibacterium*^{201,202}, 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 reduced²⁰².

556

557 A balanced microbiota is vital for immune homeostasis, whereas stress-induced
558 dysbiosis often leads to immune dysregulation^{2,203}. 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 colitis²⁰⁴. GI
561 dysbiosis allows bacteria to invade the mucosal barriers and migrate into lymphoid
562 nodes²⁰⁵ and other tissues²⁰⁶, leading to the exposure of pathogen-associated molecular
563 patterns (PAMPs)²⁰³ 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^{207,208}. Moreover,
567 microbial and tumour-associated antigens may share cross-reactive T cell epitopes^{209,210},
568 and microbial peptides were reported to boost anti-tumour immunity via antigenic
569 mimicry²¹¹. 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^{212,213}.
573 Dysbiosis of the microflora has been shown to compromise anticancer immunity and
574 the therapeutic benefits of cancer immunotherapy²¹⁴⁻²¹⁶. Conversely, a high abundance
575 of commensal bacteria and probiotics is associated with efficient immunotherapeutic
576 responses in patients with melanoma²¹⁶, supporting the idea that bacteria that promote
577 general health also promote anticancer immunity²¹⁷.

578

579 GI microflora-derived metabolites also exhibit immunoregulatory properties^{218,219}.
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), respectively²²⁰. 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 cancer²²¹.
588 High expression of FXR in mouse lung cancer cells also creates an immunosuppressive
589 microenvironment and causes CTL inactivation and exhaustion²²². 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 regression²²³. Stress-associated enteric dysbiosis can
593 reduce the abundance of SCFA-producing bacteria in patients with generalized anxiety
594 disorder²⁰². In mice, it was shown that SCFAs contribute to the development of CD8⁺
595 memory T cells²²⁴. Of note, in patients with solid tumours, the outcome of PD1-targeted
596 immune checkpoint inhibitors correlated with the abundance of SCFAs^{225,226}.
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 epithelium²¹³, and indigenous spore-forming bacteria have been identified as important
605 modulators of this process²¹². Indeed, gut 5-HT accounts for a substantial proportion of
606 the total pool of 5-HT in the body²¹². Depletion of 5-HT cargo or inhibition of 5-HT
607 release can enhance the accumulation and effector function of the CD8⁺ T cells,
608 decrease PD-L1 expression, and delay the outgrowth of pancreatic and colorectal
609 tumours in mice²²⁷. 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* DG⁹⁴) or influence the expression
612 of their receptors (such as *Lactobacillus rhamnosus*-dependent regulation of GABA
613 receptors in the brain via the vagus nerve²²⁸). 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 growth²²⁹. In mouse models of lung and colon cancer,
616 GABA signalling can promote local immunosuppression by excluding T cells from the
617 TME²³⁰ and eliciting IL-10-producing anti-inflammatory TAMs²³¹. It was reported that
618 *Staphylococcus pseudintermedius* can generate dopamine and 5-HT²³², while
619 *Firmicutes* (such as *Clostridium sporogenes* and *Ruminococcus gnavus*) can
620 decarboxylate tryptophan to produce β -arylamine neurotransmitter tryptamine²³³. The
621 opportunistic pathogen *Enterococcus faecalis* can generate tyramine (the invertebrate
622 equivalent of noradrenaline²³⁴) via tyrosine decarboxylases²³⁵. Accumulated tyramine
623 can engage trace amine-associated receptors (TAARs) and induce the release of
624 catecholamine stores from nerve terminals in porcines²³⁶. 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 abnormalities¹⁰. 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 tolerated²³⁷. 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^{125,126}. 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 metastases²³⁸. 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^{239,240}. 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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695

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712

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714

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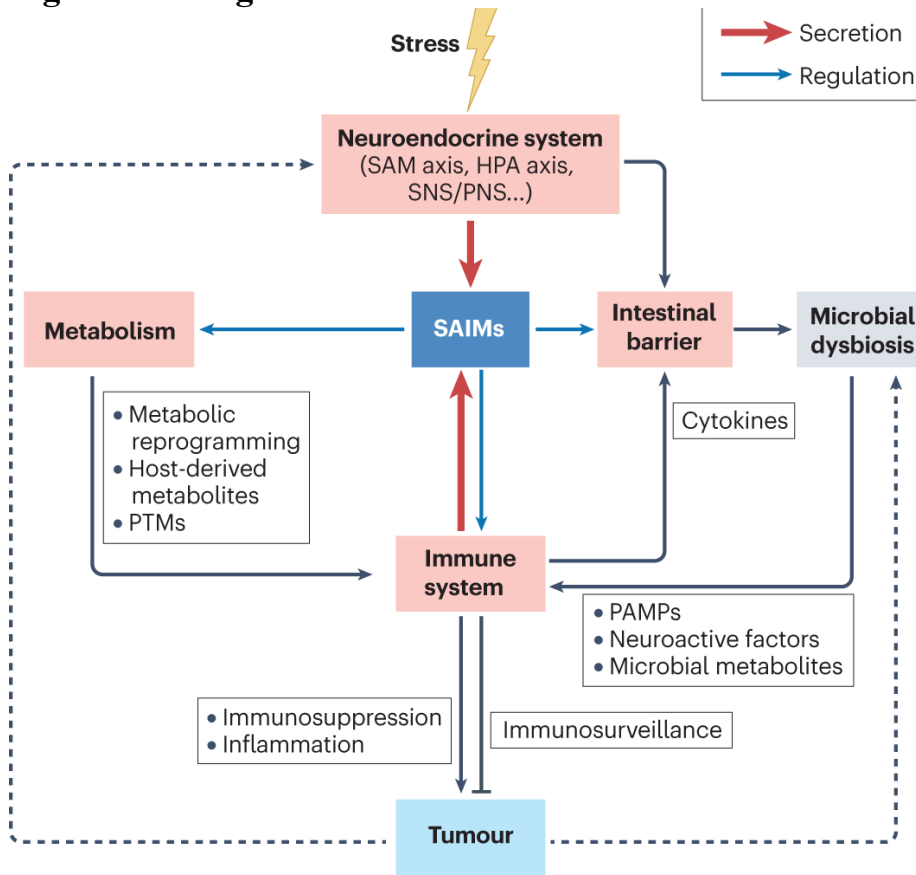
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Figures and legends



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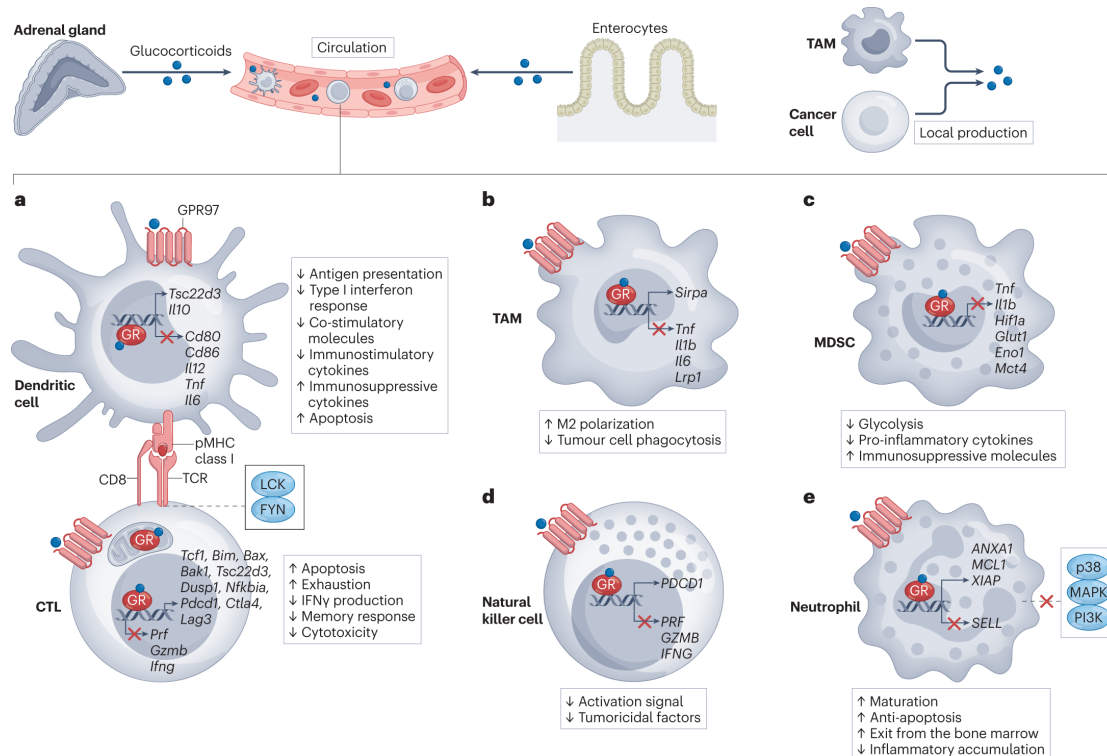
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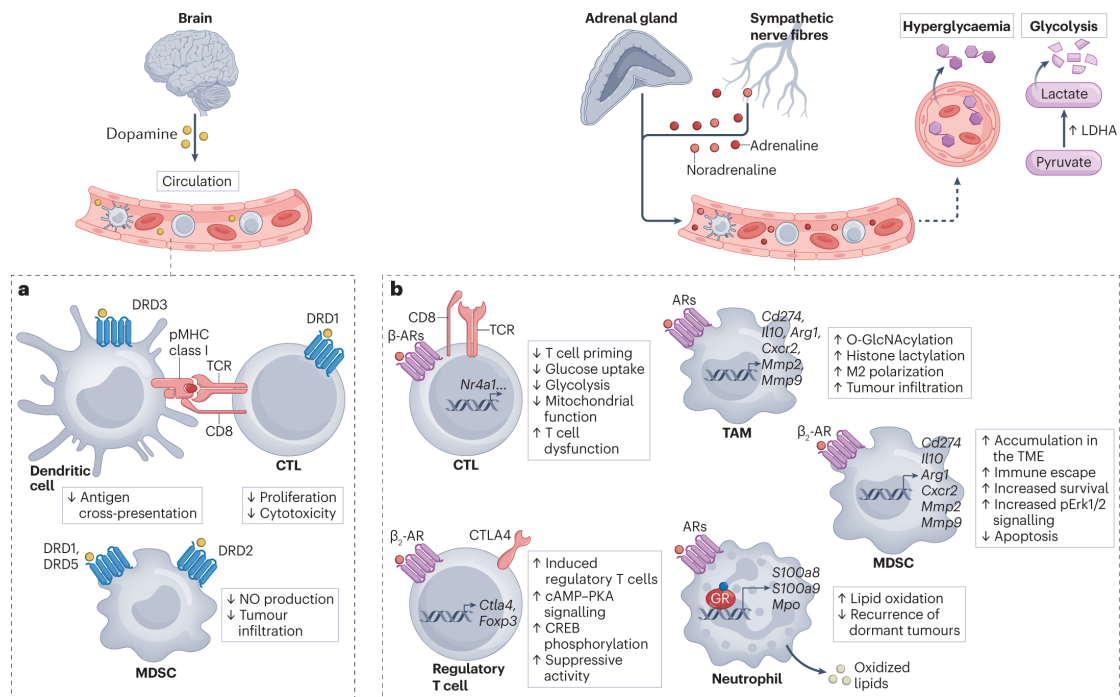
Fig. 1. The effects of stress on cancer. Overview of the intricate relationships between the neuroendocrine system, immune system, metabolic process, gut microbiota, and cancer under conditions of stress. Stress can provoke the SAM and HPA axes for systemic adaptations and stimulate the peripheral nervous 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^{130,241}. Elevated glucocorticoids in the circulation and in the TME can engage their nuclear receptor (GR) or membrane receptor (GPR97) on immune cells^{73,74}. This leads to transcriptional reprogramming and altered signal transduction¹⁰⁵, 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)²⁴², 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)²⁴³. 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 responses⁵². Glucocorticoid-induced downregulation of anti-apoptotic molecules leads to apoptosis of DCs and this process is independent of caspase activation²⁴⁴. 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 apoptosis²⁴⁵. Moreover, translocation of ligand-bound GR to the mitochondria can disrupt their membrane integrity and activate the intrinsic apoptotic pathway in T cells²⁴⁶. Glucocorticoids can rapidly attenuate TCR signalling by abrogating the recruitment and activation of LCK/FYN and blocking the phosphorylation of their downstream signalling intermediates^{105,247}. 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

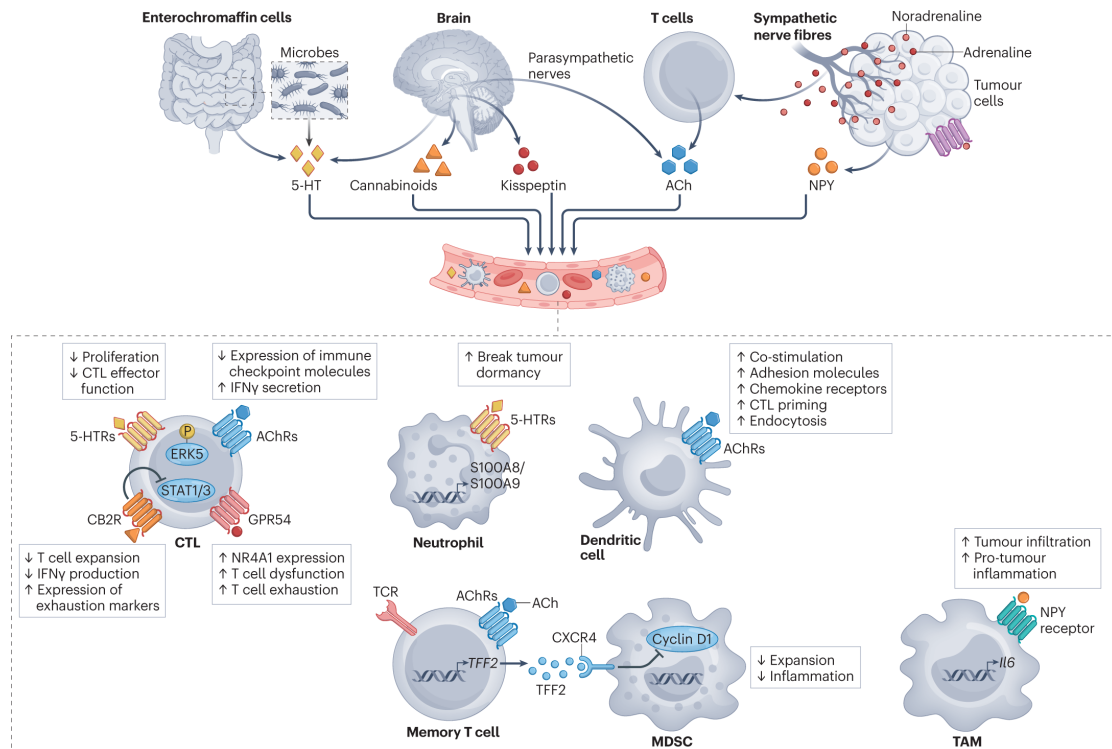
1529 chemokines¹⁰⁴. Ligand-engaged GR can drive various transcriptomic and epigenetic
1530 changes that favour the differentiation of memory precursor T cells and T_{reg} cells,
1531 whereas strongly restraining T_{H1} differentiation and the effector phenotype of CTLs
1532 (via upregulating TCF1)^{104,130}. 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 α , *Sirpa*)²⁴⁸. Glucocorticoids can also drive TAMs
1536 towards M2-like phenotype and inhibit the expression of inflammatory cytokines
1537 (such as TNF, IL-1 β and IL-6)²⁴⁹. c) GR signalling can promote the
1538 immunosuppressive activity of MDSCs by inhibiting the expression of hypoxia-
1539 inducible factor 1- α (*Hif1a*), glycolysis-related genes (such as *Glut1*, *Eno1* and
1540 *Mct4*)²⁵⁰ and pro-inflammatory cytokines (such as *Tnf* and *Il1b*)²⁵¹. 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 γ (*IFNG*)²⁵². They also limit the production of IFN γ by
1544 upregulating checkpoint receptor PD1²⁵³. 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 cells²⁵⁴ (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*)^{255,256}. 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*)²⁵⁷.
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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^{68,69}. 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 syndrome²⁵⁸ (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 cytotoxicity¹⁴¹. It can attenuate CTL response against tumours by eliciting DRD3 signalling in DCs and inhibiting their antigen cross-presentation¹⁴². 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^{143,144}. Surges of adrenaline and noradrenaline can stimulate α - or β -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 dysfunction¹⁴⁵⁻¹⁴⁹. β 2-AR activation can facilitate the conversion of naïve T cells to FOXP3⁺ T_{reg} cells and enhance their suppressive activities by increasing intracellular cAMP, PKA-dependent CREB phosphorylation, and CTLA4 expression¹¹⁹. Adrenaline and noradrenaline also promote tumour infiltration and M2-polarization of TAMs, thus accelerating the progression and metastatic spreading of tumours^{150,151}. 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^{172,189}. β 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 properties¹⁵². The β 2-AR axis also promotes tumour progression via the CXCL5-CXCR2 axis and ERK pathway, which enhance the mobilization of MDSCs and local immunosuppression²⁵⁹. Upon

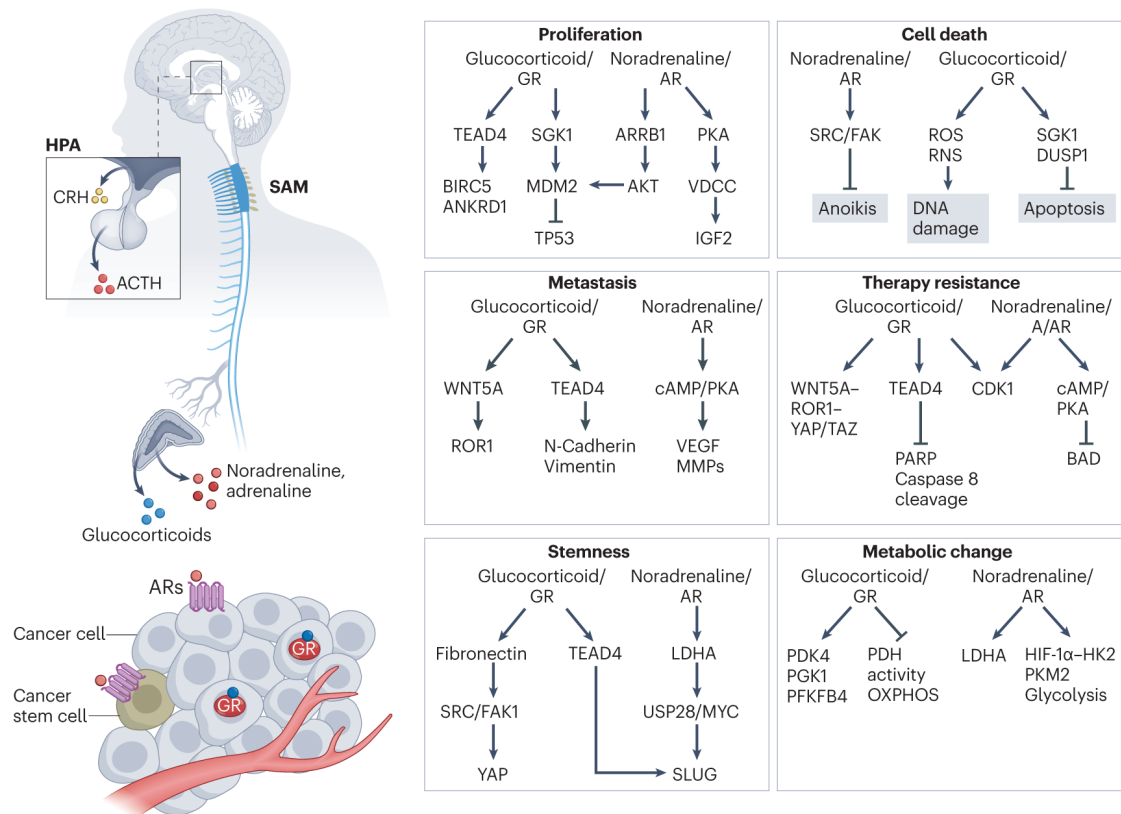
1585 stimulation with norepinephrine, neutrophils rapidly release S100A8/A9 and activate
1586 myeloperoxidase (MPO) to generate oxidized lipids, which further reactivate dormant
1587 tumour cells¹⁸⁵.
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Fig. 4. The effect of other SAIMs on the immune 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 γ and GZMB²²⁷. 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 CTLs¹⁶⁴. 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 activation¹⁶². Persistent stress can block the parasympathetic system, vagal responses, and ACh production¹⁶⁵. 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 γ ²². 5-HT-triggered rapid release of S100A8/A9 from neutrophils can break tumour dormancy¹⁸⁵ and facilitate tumour immune evasion¹⁸⁶. 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 secretion¹⁶⁶. 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 expansion¹⁶⁷. Besides, noradrenaline-induced production of NPY from tumour cells can recruit macrophages to the TME and boost their secretion of pro-tumoural cytokine IL-6¹⁵³.

Boxes

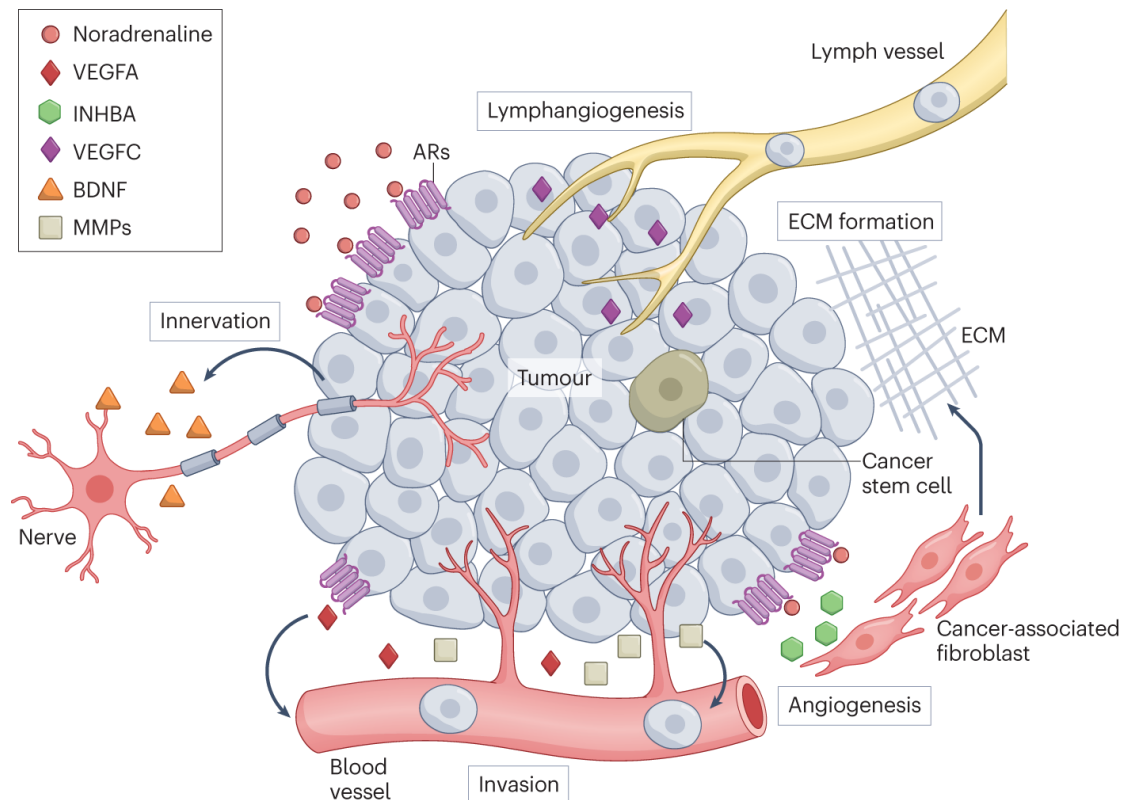


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Box 1. Direct effects of stress on cancer cells. Biological features of tumour cells, such as proliferation, cell death, metastasis, therapy resistance, stemness and metabolic changes can be affected by stress-induced neuroendocrine factors. For example, 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 TP53²⁵. 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 traits⁵⁵. 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 WTN5A⁵⁶. 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 cells⁵⁷. 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 cells⁶⁰. Additionally, glucocorticoids can promote cancer stemness and chemoresistance by activating TEAD4⁵⁵ and YAP^{59,260}. 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 β -arrestin-1 (ARRB1)/AKT-mediated MDM2 activation²⁶¹. 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 mice²⁶. Stress-

1646 induced adrenaline elevates LDHA and enhances stem-like traits of human breast
1647 cancer cells through metabolic rewiring and USP28/MYC/SLUG signalling⁶¹. Also,
1648 noradrenaline exhibits antiapoptotic effects on human prostate and breast cancer
1649 cells, by inactivating the apoptosis promoter BAD⁶². It can also activate SRC-
1650 dependent phosphorylation of the kinase FAK and render human ovarian cancer
1651 cells resistant to anoikis²⁶². 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 PFKFB4²⁶³, pyruvate dehydrogenase (PDH)²⁶⁴, hexokinase 2 (HK2), pyruvate
1657 kinase M2 (PKM2)²⁶⁵, and LDHA⁶¹.
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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 β A (INHBA) from cancer cells can activate cancer-associated fibroblasts (CAFs), leading to increased collagen deposition and extracellular matrix formation⁶³. In mouse models of ovarian and nasopharyngeal cancer, stress-induced activation of β 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^{47,64}. The catecholamine receptor β 2-AR on vascular endothelial cells can also promote angiogenesis by directly forming a complex with VEGFR2⁶⁶. Moreover, noradrenaline can stimulate local lymphogenesis and enhance metastatic progression by inducing the secretion of PGE2 and VEGF-C from TAMs and malignant cells⁴⁹. 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 metastasis⁶⁷.

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Box 3. Peripheral sources of neuroendocrine factors

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Steroidogenesis and glucocorticoid production has been observed in the thymus²⁶⁶, brain²⁶⁷, and in colon epithelial cells^{92,268}. Glucocorticoid production by tumour-infiltrating myeloid cells has been reported to facilitate the emergence of dysfunctional CD8⁺ T cells¹³⁰. 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 syndrome²⁵⁸. 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^{90,269}. In the GI tract,
1690 catecholamines from sympathetic nerves can engage basolateral α 2-adrenoreceptors
1691 and trigger 5-HT release from adjacent chromogranin A⁺ enterochromaffin cells⁹¹.
1692 Enterochromaffin cell-mediated production of 5-HT can be enhanced by short-chain
1693 fatty acids (SCFAs) from the gut microbiota²⁷⁰, as well as specific metabolites
1694 generated by indigenous spore-forming bacteria in the gut (such as α -tocopherol, p-
1695 aminobenzoate, and tyramine)²⁷¹. Moreover, 5-HT biosynthesis has been
1696 documented in various immune cell subsets, including mast cells, monocytes, and T
1697 cells²⁷²⁻²⁷⁴. Platelets can store large quantities of 5-HT in their dense granules and
1698 secrete these upon activation²⁷⁵. Moreover, T cells can generate ACh, which induces
1699 local vasodilation and allows for T cell extravasation²⁷⁶. Histamine released by mast
1700 cells can modulate allergic and inflammatory responses⁸². 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 noradrenaline²⁷⁷.

1704

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_H1 responses, and enhanced NK cell activity²⁷⁸.
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 therapies²⁷⁹. These regimens also improve the quality
1713 of life and subjective well-being of patients with cancer²⁸⁰. 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 mice²⁸¹. This indicates that the short-term peaks of catecholamines,
1717 endogenous opioids, and myokines following exercise may prevent the development
1718 and progression of cancer²⁸²⁻²⁸⁵. 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 responses²⁸⁶. 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.