Role of stress in the pathogenesis of cancer (Review)

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Abstract. Stress is a state of disrupted homeostasis, triggered by intrinsic or extrinsic factors, the stressors, which are counteracted by various physiological and behavioural adaptive responses. Stress has been linked to cancer development and incidence for decades; however, epidemiological studies and clinical trials have yielded contradictory results. The present review discusses the effects of stress on cancer development and the various underlying mechanisms. Animal studies have revealed a clear link between stress and cancer progression, revealing molecular, cellular and endocrine processes that are implicated in these effects. Thus, stress hormones, their receptor systems and their intracellular molecular pathways mediate the effects of stress on cancer initiation, progression and the development of metastases. The mechanisms linking stress and cancer progression can either be indirect, mediated by changes in the cancer microenvironment or immune system dysregulation, or direct, through the binding of neuroendocrine stress-related signalling molecules to cancer cell receptors. Stress affects numerous anti- and pro-cancer immune system components, including host resistance to metastasis, tumour retention and/or immune suppression. Chronic psychological stress through the elevation of catecholamine levels may increase cancer cell death resistance. On the whole, stress is linked to cancer development and incidence, with psychological stressors playing a crucial role. Animal studies have revealed a better link than human ones, with stress-related hormones influencing tumour development, migration, invasion and cell proliferation. Randomized controlled trials are required to further evaluate the long-term cancer outcomes of stress and its management.

Contents

1. Introduction

Stress can be defined as a state of disrupted homeostasis triggered by intrinsic or extrinsic stressors, which is counteracted by a plethora of physiological and behavioural adaptive responses aiming to re-establish the altered equilibrium of the organism (1-3). The concept of a corporal 'steady state' that was defined with the Greek-derived term '*homeostasis*' in the beginning of the 20th century, was initially described by ancient Greek natural philosophers, with the words 'harmonious balance', and 'isonomia', later termed 'eucrasia' by Hippocrates and 'eustatheia', by Epicurus, revealing an intellectual understanding of this fundamental concept (1). Lifestyle in contemporary civilizations has evolved and changed considerably from that of our forefathers, and in combination with the lengthening of human life expectancy, has allowed the currently high incidence of 'affluence-related' disorders (1,4). External stressors of modern life, mainly chronic psycho-socio-economic stress and protracted crises, such as

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the circumstances encountered with the COVID-19 pandemic, economic conditions and climate change, underscore the need to further comprehend stress and its effects on humanity (5-10). This is of particular importance, as uncontrolled chronic stress can have unfavourable, potentially hazardous outcomes, as evidenced by an ever-growing list of stress-related disorders, including several forms of cancer (2,5,11).

Stress has been linked to cancer development and incidence for a number of decades, if not millennia; however, epidemiological studies and clinical trials have produced contradictory results (3,11,12). Thus, psychological stressors have been linked to the development of cancer since the 2nd century CE, with the ancient Greek physician, Galen, noticing that tumours of the reproductive organs were more frequent in women with 'melancholic natures' (12). Other researchers have noted the importance of psychological variables in the occurrence of cancer in women, such as those with 'greater sensitivity and frustration'; however, these studies were based on limited observations and/or personal concerns (12,13).

It has been consistently demonstrated that the immune system plays a critical role in inhibiting cancer progression (12,14). Numerous preclinical and clinical psychoneuroimmunological and neurobiological investigations have been published over the past three decades, delving into the processes behind the linkages between stress and cancer, and have revealed molecular, cellular and endocrine processes that may be implicated in these effects (12,15-18). Animal studies have revealed a clearer link than clinical human studies, indicating that stress can exacerbate the hallmarks of cancer, promoting tumour growth and metastasis by directly altering the molecular properties of malignant tissue, its microenvironment, its anti-host immune reaction activity, and other indirect cancer progression modifiers, as will be further analysed in the present review (12). Of note, discrepancies in preclinical and clinical or epidemiological research observations may be explained as follows: Firstly, preclinical studies link stressful conditions or stress-relieving activities with phases of cancer development on natural or transplanted tumours that are particularly susceptible to the effects of stress; secondly, theoretical and methodological challenges in carrying out human studies that obscure the influence of stress on cancer development (12).

The aim of the present review was to discuss stress and its relation to cancer, examining various pathways that drive carcinogenesis. The review initially summarizes epidemiological data from human studies examining the risk of cancer development and progression related to stress. Focus is then paid to the mechanistic aspects of stress physiology and the discussion of the mechanisms through which stress affects the molecular features of malignant tissue, its microenvironment and its anti-host immune reaction. Furthermore, other, indirect cancer progression modifiers, that promote the growth and spread of numerous cancer forms are also reviewed. The synthesis of the present review may have practical clinical implications.

2. Epidemiological observations

There is accumulating evidence to indicate that stress increases the risk of developing cancer; nevertheless, not all human studies on this topic are consistent (19). A meta-analysis of 12 European cohort studies found no association between work-related stress and overall cancer risk or, more specifically, colorectal, lung, breast, or prostate cancer risk (20). However, another meta-analysis that investigated the association between work-related stress and cancer risk, and focused on colorectal, lung and oesophageal cancers, found a significant association between stress and the risk of cancer development in populations primarily from North America and Europe (21). In addition, another meta-analysis of 53 studies indicated that stress-related psychosocial variables were linked to an increased cancer incidence in healthy populations, a decreased survival time and an increased mortality rate in patients with cancer (22). Stress-prone personalities, unfavourable coping mechanisms, negative emotional responses and a poor quality of life have also been linked to an increased cancer incidence and mortality rate, as well as to a decreased survival time (22). Of note, the same meta-analysis found that there were publication biases and methodological heterogeneity and potential errors in the studies examined; the authors of that study suggested caution in interpreting the findings and emphasized the need for further investigations (11,23). Previous studies have linked specific stressors, such as cold climates, bereavement, war and depression, to a higher incidence of cancers (24-27). However, others studies have shown no association between stress and ovarian or breast cancer (28,29).

Examining stress and cancer progression (often by evaluating the survival rates of patients with cancer) can be relatively challenging. Stress, including life events, is often assessed without regarding the time of cancer detection, while its impact on cancer progression is not assessed (11). In addition, the majority of patients with cancer experience some levels of distress, which may influence cancer progression regardless of baseline stress levels; this may mask the association between stress levels and cancer progression, but could allow for the observation of the beneficial effects of stress-reducing interventions (11,30). Emotional distress in patients with cancer increases mental health issues, which, in turn, may affect cancer prognosis and increase mortality rates (31,32). Psychological stress and discomfort have also been linked to increased mortality rates (33). A recent meta-analysis demonstrated that stressor-specific and cancer-specific effects on survival were evident (11). Depression in patients with breast cancer increases the risk of cancer-specific mortality, while low social support in combination with depression may increase the risk of cancer-related mortality (11,34-36).

The inconsistent effects of stress on cancer development and incidence and heterogeneous approaches, preclude a solid aetiological relation. The subjective stress perception of patients with cancer is influenced by disease burden, resulting in biased retrospective assessments (11). Malignant transformation in humans is a prolonged process characterized by long-term 'dormancy' and a high prevalence of subclinical cancer (37). Cancer incidence may be increased by disease initiation, escape from dormancy, or a more rapid progression to clinical manifestation (11). Despite the controversies associated with human studies, data from animal models are more consistent, as is presented below, in the pathophysiological sections of the present review, following a brief description of stress physiology.

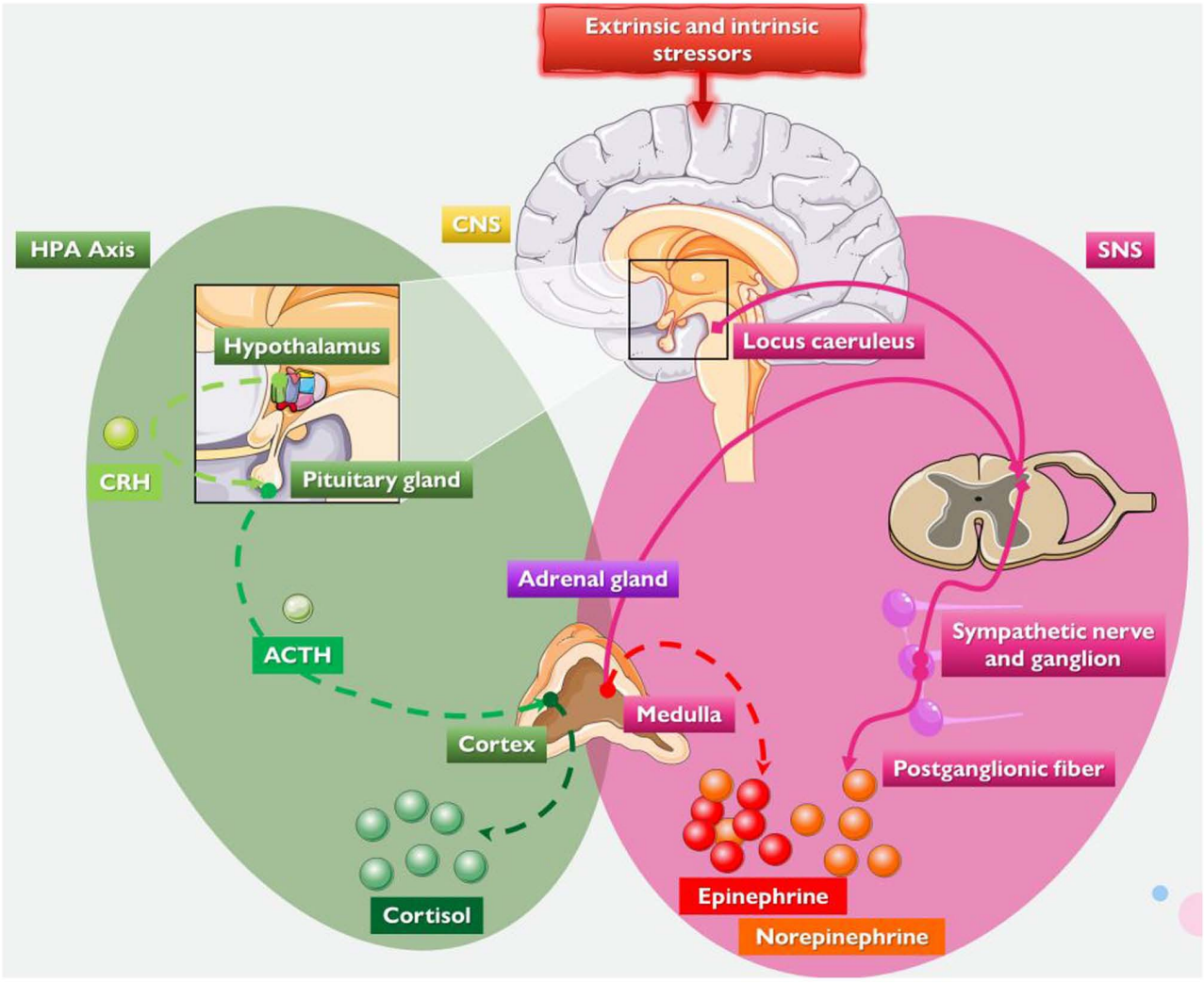

Figure 1. The neuroendocrine systems involved in the physiological stress response. Stress may be induced by a variety of psychological, physiological, or environmental factors which are processed by the CNS. The two principal neuroendocrine response systems involved are the SNS and the HPA axis. The HPA axis components are illustrated in the green scheme. The hypothalamus secretes CRH, which stimulates the pituitary gland to synthesise and secrete ACTH, which triggers adrenal cortex glucocorticoid, (cortisol or corticosterone), secretion and release. The components of the SNS are shown in the purple scheme. The locus caeruleus and other brainstem nuclei release NE and activate the SNS in response to stress. Sympathetic postganglionic nerve terminals generate vesicles containing NE when triggered. The SNS innervates the adrenal medulla, causing it to generate and release NE and epinephrine. CNS, central nervous system; SNS, sympathetic nervous system; HPA axis, hypothalamus-pituitary-adrenal axis; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; NE, norepinephrine. Parts of this image were derived from the free medical site http://smart.servier.com/ (accessed on July 15, 2023) by Servier, licenced under a Creative Commons Attribution 3.0 Unported Licence.

3. Physiological stress responses

Stress was initially described Walter Cannon, followed by Hans Selye (1,38-40). The latter scientist, defined stress as the body's response to stimuli to preserve homeostasis, obviously meaning the adaptive response of the organism to stress (11,40,41). As aforementioned, living organisms maintain homeostasis, a term introduced by Cannon, i.e., a complex dynamic equilibrium, which is constantly challenged by stressors inherent to life's demands, such as routine activities and life-changing or threatening events (1,3,42-44). Thus, stress, is a state where homeostasis is threatened or perceived to be threatened, and is re-established through the complex repertoire of behavioural and physiological adaptive responses, which, among others, includes the mobilisation of metabolic energy to sustain crucial physiological adaptive responses (1,3,42-45). Stressor magnitude and chronicity are crucial; the adaptive homeostatic systems of organisms activate compensatory responses when stressors exceed thresholds, ensuring adaptive responses to the stressor (1). A summary of the neuroendocrine systems involved in the physiological stress response is presented in Fig. 1.

The 'stress syndrome' corresponds to the physiological adaptive response that coordinates homeostasis and protects organisms during acute stress (1,46). It involves the central nervous system (CNS) and peripheral organs and tissues, and it facilitates adaptive functions, such as arousal and cardiopulmonary function, and inhibits non-adaptive ones, such as eating, growth and reproduction (47). Stress-related changes increase oxygenation and nutrient supply to the brain, heart and skeletal muscles, crucial for central coordination and the 'fight or flight' reaction (1,48). The CNS retains basal homeostasis and processes and integrate responses to various stimuli, including physiological reactions to external or internal

stressors (1,3,42-44). The CNS orchestrates the complex adaptation to stress by stimulating the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis, inducing the secretion respectively of cortisol and adrenergic hormones, primarily noradrenaline (norepinephrine) and adrenaline (epinephrine), while it withdraws the activity of the parasympathetic nervous system (3,42-46).

The HPA axis is activated or dysregulated by mental health issues and/or behavioural changes, including depression and social isolation, influencing pro-inflammatory and anti-inflammatory stress-related immunomodulatory molecules and pathways [including the cellular glucocorticoid signalling system, interleukin (IL)-2 and interferon-γ] (1,11,43,49-52). The hypothalamus, part of the HPA axis, secretes corticotropin-releasing hormone, stimulating adrenocorticotropic hormone secretion by the anterior pituitary gland, which stimulates the production of glucocorticoids by the adrenal cortex, i.e., cortisol in primates and corticosterone in rodents (1,11,43,53).

During stress, the SNS increases the release of the catecholamines norepinephrine and epinephrine by the systemic sympathetic system and the adrenal medulla (1,11,43). The neurohormones norepinephrine and epinephrine cause arousal, increase the metabolic rate, stimulate the cardiopulmonary system, enhance gluconeogenesis, glycogenolysis, proteolysis and lipolysis, and increase catabolism (1,3,11,42-44). Stress-induced hormones also affect other key physiological and biochemical procedures, including various brain networks (e.g., reward), and the water and electrolyte equilibrium (1,3,11,42-44).

The dose-response curve for homeostatic processes, including the stress system, has an inverted U shape (1,46,48,54). Basal, healthy homeostasis occurs in the centre of the curve, the ideal region (1,46,48). Inadequate adaptation, known as low allostasis or '*cacostasis*', or an excessive response, known as high allostasis, or '*cacostasis*', may yield suboptimal consequences (1). In high allostasis, both the intensity and duration of stressors are key predictors of their effects. Thus, both hypofunction and hyperfunction of the homeostatic systems may have negative consequences, including a decreased survival and higher morbidity (1,46,48). When the stress exceeds the ability of the individual to manage it, it becomes deleterious, and the risk for illness increases by ~20% (11,55-57).

The interaction of homeostasis-disrupting stressors and stressor-activated adaptive responses can result in one of three outcomes: normal match, which yields the organism to its basal homeostasis or '*eustasis*'; defective match, which results in '*cacostasis*'; or improved match, which results in a new, more resilient equilibrium, '*hyperstasis*' (1,46,48). Patients are at a greater risk when allostasis becomes demanding and the allostatic load exceeds overload thresholds (11,55-57). The duration and intensity of the response to stress vary significantly among individuals, and are influenced by physiological factors, psychosocial characteristics and previous stressful life events, such as childhood trauma (11,55-57). As a result, patients may respond differently to stressors such as cancer diagnosis, treatment and survival.

Overall, the predominant effects of deleterious stress can lead to the development of various chronic diseases and comorbidities, including dysmetabolic conditions and cardiometabolic diseases, which predispose to cancer development via various mechanisms, indirect or direct (*vide infra*) (2,58-65). The following sections focus on cancer pathophysiology and its hallmarks, and thereafter, on the direct impact of stress on these.

4. Cancer hallmarks and the determination of the phases of oncogenesis

Multiple pathways are involved in the development of cancer, including the upregulation of pro-oncogenes and the suppression of onco-suppressor genes, as reviewed extensively elsewhere (66-73). In oncogenesis, the shift from a cell's original state to a malignant state is a process that requires the cell to surmount its anti-oncogenic milestones (74,75). Cancer is caused by various genetic and epigenetic alterations in (stem) cells, primarily involving mutations, deletions, inversions, amplifications and chromosome translocations resulting, among others, in an altered oncogene activity (66,76-78). Based on these characteristics, the hallmarks of cancer have been compiled, as described Hanahan and Weinberg (79,80). These features, which are distinguishing characteristics with evolutionary benefits (80,81), include the capability of infinite cell proliferation, persistent angiogenesis, resilience to cell death, the potential of invasion and metastasis, the ability to evade growth inhibitors, and self-sufficiency in growth factors (74,79,82,83).

The dysregulation of metabolism, a mechanism that plays a critical role in cellular stress signalling pathways and procedures (including mitochondrial functions), and the avoidance of the immune system are two additional characteristics of cancer that have recently emerged (74,80,84). One of the most essential qualities of tumour cells is their capacity to withstand environmental stresses, such as hypoxia, nutritional deprivation and DNA-damaging agents (74,83). Cellular stress is an extrinsic element that influences cancer formation and development. It consists of oxidative stress generated by reactive oxygen species, metabolic stress owing to increased metabolic demands and genotoxic stress, which involves DNA damage (74,85). Cellular stress generally initiates the process of cell death (74,85). Nevertheless, cancer cells can tolerate cellular stress by modifying gene expression, metabolism and escaping growth inhibitory signals (74,80,81,83,86). Notably, pre-malignant or malignant foci can be eliminated, become dormant or grow slowly, or progress to clinical manifestation (37).

Some phases of this heterogeneous non-linear process may theoretically be more important than others (11). Examples include activating the angiogenic switch, allowing growth or escape from dormancy, interacting with immune cells, circulating tumour cells passing through capillaries, and the survival of tumour-associated lymphocytes (87-92). During such potentially critical times, the impact of stress may be amplified (11,74,85). Furthermore, whether stress exacerbates or alleviates malignant processes may be affected by the stage of malignant growth, unique tumour features and the range of stress responses (11). Additionally, immune-tumour interactions may either attenuate or accelerate tumour development, and stress hormones can influence both processes (15,51,93-96). Consequently, it is anticipated that interactions between stress

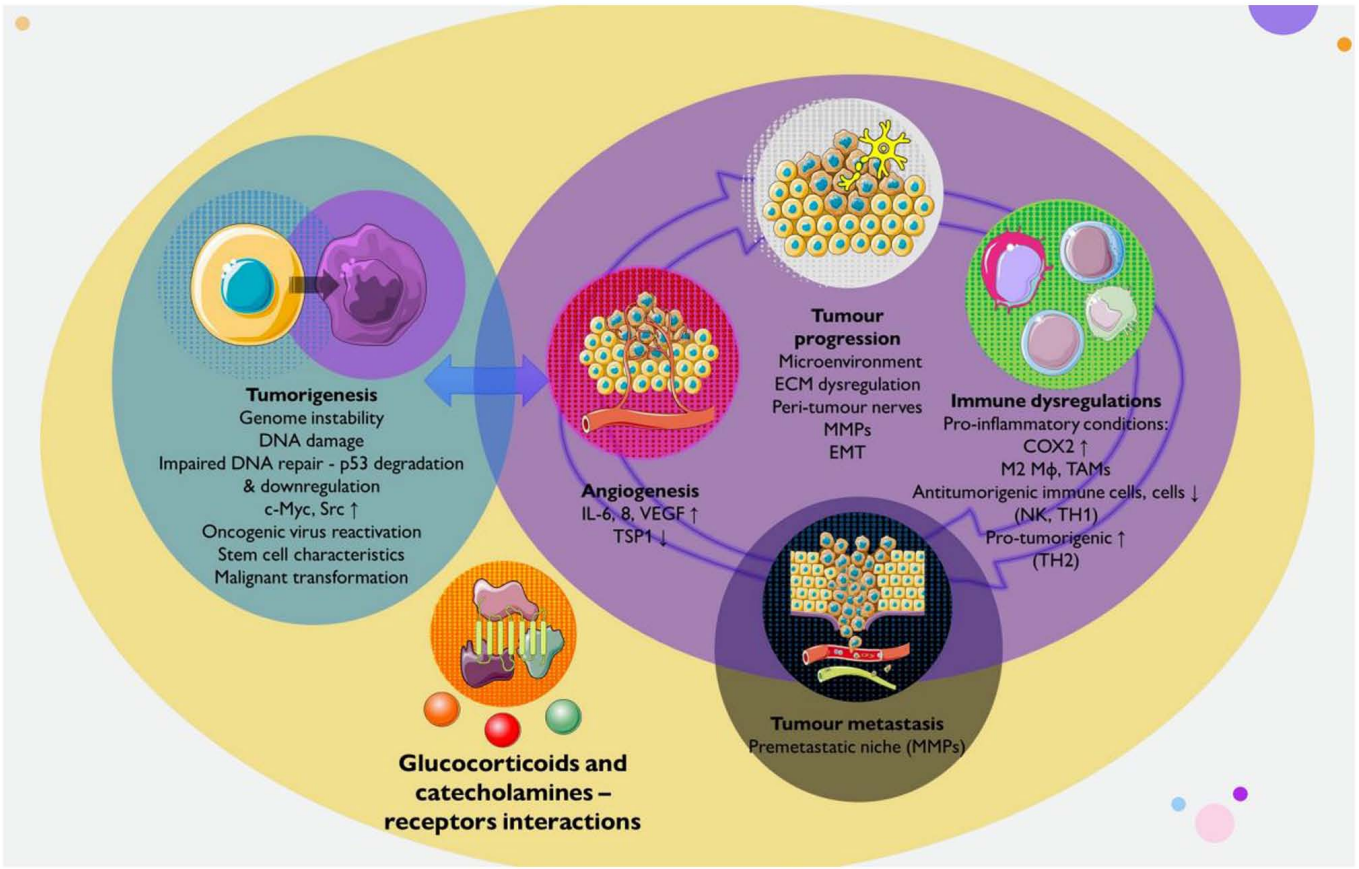

Figure 2. Effects of stress on cancer initiation, progression, metastasis and underlying mechanisms. The schematic diagram presents the effects of stress on the biological behaviours of tumours. Glucocorticoids and catecholamines produced by the activated neuroendocrine stress system are involved in tumour regulation by binding to their respective receptors. Stress may promote tumorigenesis through genomic instability, DNA damage, the reactivation of latent oncogenic infections, the upregulation of oncogenes, the acquisition of stem cell-like characteristics and eventually, malignant transformation. Stress can facilitate tumour progression through various mechanisms, including alterations in the tumour microenvironment through the stimulation of MMPs, ECM remodelling, neo-angiogenesis and neurogenesis. Stress can promote tumour metastasis by establishing a premetastatic microenvironment and premetastatic niches, and by remodelling the lymphatic vasculature. Distress can induce pro-inflammatory conditions, as well as immune suppression, by reducing the infiltration and function of effector immune cells, such as TH and NK cells, and by promoting the infiltration and function of suppressive cells, including TH2 cells, M2 Mϕ (macrophages), and TAMs. C-Myc, cellular myelocytomatosis oncogene; COX2, cyclooxygenase 2; Src, proto-oncogene tyrosine-protein kinase Src; IL, interleukin; VEGF, vascular endothelial growth factor; TSP1, thrombospondin 1 (anti-angiogenic factor); MMPs, matrix metalloproteinases; ECM, extracellular matrix; TH1, T-helper 1 cells; TH2, TH1, T-helper 2 cells; NK, natural killer; TAMs, tumour-associated macrophages. Parts of this image were derived from the free medical site http://smart.servier.com/(accessed on July 15, 2023) by Servier, licenced under a Creative Commons Attribution 3.0 Unported Licence.

and cancer would be non-linear, with the impact of stress potentially altering the anticipated responses, depending on the stage of cancer progression (11).

Synchronized acute or chronic stress events with a critical cancer phase may, in theory, exert a more prominent effect on cancer growth than non-synchronized events (11). Animal models can focus on critical times by using specific cancer types and stress paradigms, optimizing the understanding of the effects of stress on cancer cells (11). For instance, stressing animals before and after tumour cell injection has been shown to exacerbate the unfavourable effects on the ability of marginating pulmonary natural killer (NK) cells to prevent experimental lung metastasis (89,97,98). On the contrary, chronic stressors do not affect initial breast cancer tumour formation in animal models, but accelerate dissemination and metastasis. Social isolation prior to inoculation does not affect primary tumour development but, after already-palpable tumours were present, it accelerates their growth (99-101). Of note, some of the aforementioned key oncogenic pathophysiological phases may not be identified in a clinical setting, whereas others, particularly those associated with cancer therapeutic interventions, are known to influence cancer progression and may be exploited to reduce the effects of stress on cancer growth (11).

The sections that follow concentrate on various hallmarks and stages of oncogenesis and cancer development, which may be affected by stress. A summary of the effects of stress on cancer initiation, progression, metastasis and selected underlying mechanisms is illustrated in Fig. 2.

5. Pathophysiological mechanisms of the effects of stress on cancer

Cancer pathogenesis/tumorigenesis. Stress-cancer interactions have been studied via various strategies, including exposure to stressors in laboratory animals and retrospective clinical studies in humans (12). A considerable body of evidence suggests that stress can aggravate the majority of hallmarks of cancer, including genome instability, tumour-promoting inflammation, immune resistance, proliferative signalling,

resistance to cell death, angiogenesis, and invasion and metastasis (11,12,80). Stress hormones, their receptor systems and intracellular molecular pathways of adrenergic receptors (ARs) and glucocorticoid receptors (GCRs) have been shown to mediate these effects (102-105). Stress may contribute to cancer initiation, progression and the development of metastasis (12). Herein, tumour initiation is defined and referred to as the transition of non-malignant to malignant tissue, as opposed to tumour progression, which arises after this transformation, despite the fact that the majority of cancer hallmarks may affect both the onset and progress of the disease (11). Recently, it was also shown that tumour-derived cytokines, immune mediators and neurotransmitters can potentially control neuroendocrine centres and modulating body homeostasis (106). These findings suggest a bidirectional communication between local autonomic and sensory nerves, and the tumour may affect the brain and HPA and other axes (106).

i) Stress ignites cancer initiation. The ancient Greek physician, Galen, observed a higher incidence of cancer in women who were melancholy, and early experiments revealed increased cancer incidence in stressed animals (12,107,108). However, the direct effect of stress on cancer initiation remains a matter of debate. It is also unclear whether stress is responsible for new cancer induction or only leads to the clinical manifestation of previously present dormant cancer through other processes, for instance, neo-angiogenesis (12). Retrospective and/or prospective clinical studies have demonstrated higher stress levels in relation to breast cancer, while others have shown no association (12,28,34,109,110). However, these studies use a flawed case-control design due to the presence or suspicion of cancer at the time of stress assessment (12,109). Prospective studies have found that women with high stress levels had a 2-fold higher risk of developing breast cancer than those with no stress, while, by contrast, women with low stress levels had a reduced risk of developing breast cancer (12,109,110). Of general note, the outcomes of clinical studies have been inconclusive, as they result from highly individual differences in perception of stressor intensity in humans, leading to significant differences in neuroendocrine stress responses between individuals (12).

Preclinical data published over the years have highlighted the potential role of mediators of the neuroendocrine stress response (particularly norepinephrine, epinephrine and cortisol) in processes related to carcinogenesis which act directly on cancer cells and promote tumour growth (5,12,102,111-113). Inflammation, angiogenesis, genomic instability, metastasis and the expression of stem cell-like genes are all facilitated by the binding of stress hormones to their receptors (5,102,111). This occurs through the epigenetic alteration or the activation of a variety of mechanisms. Moreover, chronic stress-induced tumour cells become resistant to apoptosis and cancer therapy (5,103).

ii) Stress, genomic instability, DNA damage and the onset of cancer. Cancer is primarily caused by random mutations in non-cancerous stem cells during DNA replication, with environmental factors and inherited predispositions accounting for only a third of variation among tissues (74,76,85,114-116). Notably, carcinogenic infections account for 13-15% of human cancers, and stress may increase the risk of developing cancer by promoting the spread or reactivation of latent oncogenic viruses (68,115,117-122). Stress hormones can reactivate oncogenic viruses, such as human papilloma virus, Epstein-Barr virus, Kaposi sarcoma-associated herpesvirus, and hepatitis B and C viruses, stimulate oncogenes in infected cells, reduce interferon production and impair antiviral immunity (123-126). Psychosocial stress is an environmental factor that contributes to cancer induction by increasing somatic DNA mutation frequency and sensitizing cells to environmental carcinogens (127). Research has demonstrated that exposure to swim stress, noise, or foot shock increases chromosomal aberrations and sister chromatid exchanges in bone marrow cells (128). In healthy female workers, poor stress-coping behaviours have been shown to result in increased levels of cancer-related oxidative DNA damage in leukocytes, and these biomarkers of DNA damage are associated with average working hours, self-blame coping strategies and recent family loss (128). Highly distressed individuals have a reduced DNA repair in lymphocytes exposed to γ-irradiation, while chronically stressed individuals are more sensitive to DNA damage induction by external factors, such as H_2O_2 and γ-radiation (129,130). These findings suggest that psychological stress may increase susceptibility to environmental mutagenic agents (130).

Studies using mechanistic approaches have been carried out in order to obtain an understanding of the processes and pathways linking stress and mutation, including AR and GCR signalling pathways and the ATR-p21 pathway (11,12). It has been demonstrated that some stressors cause DNA damage and hinder DNA repair, which may favour malignant transformation (11). Specifically, it has been shown that serum from stressed animals or adrenaline, noradrenaline and cortisol (each component alone and synergistically when combined) enhances DNA damage and/or inhibits DNA repair following UV irradiation (131). In non-cancerous murine and human cell lines, adrenaline receptor AR-mediated reactive oxygen species production and arrestin-MDM2-dependent p53 degradation aggravated DNA damage and hindered DNA repair (132).

Chronic stress induces these two AR-mediated processes, and glucocorticoid-mediated responses can also boost MDM2-dependent p53 downregulation and increase apoptosis resistance in response to ionising radiation (133,134). In mice expressing c-Myc, a proto-oncogene, the HPA axis was investigated in cancer induction (135,136). Mice developed intraepithelial prostate neoplasia (PIN) and this progressed to invasive adenocarcinoma (135). Chemical sympathectomy, administered at a young age, reduced the incidence of PIN by 83%. However, the effect of sympathectomy was not observed in adult individuals, as the PIN had already developed in adult mice (135). β2- and β3-ARs play a primary role in prostate adenocarcinoma development, and the deletion of genes for these receptors leads to a significant reduction in the incidence of adenocarcinoma in genetically modified mice (135).

Norepinephrine, epinephrine and cortisol increase the formation of oxygen radicals, causing DNA damage and reducing cell repair processes (12). It has been shown that the short-term exposure to physiological concentrations of these substances induces at least a 5-fold increase in DNA damage in treated murine 3T3 cells (113,131,132). Pre-treatment with an antagonist of ARs or GCRs protected these cells from DNA damage (131). Norepinephrine and cortisol reduced DNA

repair in 3T3 cells exposed to UV radiation (131). The infusion of isoproterenol, an β-AR agonist, induces the degradation of the tumour suppressor protein, p53, in mouse thymus cells, while propranolol increases the gene expression of p53 in primary melanoma-derived and metastasis-derived tumours in mice (132,137). Chronic restraint stress attenuates p53 functions and promotes ionizing radiation-induced tumorigenesis in $p53^{+/-}$ mice, with glucocorticoids playing a central role in these processes (134). β-adrenergic signalling also participates in the activation of oncogenes, with the stimulation of ovarian cancer cells with norepinephrine significantly activates oncogene Src (138). A similar effect of adrenergic signalling on the gene expression of Her2 has also been described (139).

Rather than focusing on intermediate signs, such as DNA damage or the reactivation of carcinogenic viruses, several *in vivo* animal investigations on the influence of stress on carcinogenesis have been conducted (11). Restraint stress, social isolation and a cold ambient temperature, all lead to carcinogen-induced cancer development (134,140-142). Repetitive restraint stress enhances pancreatic carcinogenesis in transgenic models of spontaneous cancer via AR signalling (143), although sympathetic denervation results in a reduction in carcinogenesis in models of prostate cancer (135). Models based on accelerated cancer induction struggle to differentiate the effects of stress on tumour initiation and development due to the overlap between the time course of stress and the initiation and progression periods (134,143-145).

Stress promotes cancer progression. Hans Selye (40) also suggested that stress may increase cancer growth. Animals studies have shown that stress can lead to cancer progression (146). The mechanisms linking stress and cancer progression are either indirect, mediated by changes in the cancer microenvironment, immune system dysregulation/inhibition, or direct, through the binding of neuroendocrine stress-related signalling molecules to cancer cell receptors (12):

i) Tumour microenvironment (TME). The neuroendocrine system modifies the TME in a manner that favours cancer progression (5,111). The TME is composed of immune cells and other stromal cells, such as fibroblasts, adipocytes and endothelial cells, in addition to extracellular components (extracellular matrix) (5,147). These components pertain to the circulatory system, lymphatic system and peripheral nerves, and they support cancer cells (148). Chronic stress-related hormones influence tumour development, including interactions between cancer cells, and invading immune and stromal cell populations in the TME; recent research indicates that tumours can attract nerves into the TME and form peri-tumour nerves, which influence carcinogenesis, angiogenesis, invasion and metastasis (5,149,150).

ii) Stress and the induction of (lymph)angiogenesis. The *in vitro* activation of AR on cancer cells increases the synthesis and release of angiogenic factors (12,151). Adrenaline and noradrenaline promote angiogenesis by increasing the production and synthesis of angiogenic factors, such as vascular endothelial growth factor (VEGF), IL-8, IL-6 and enzymes, such as matrix metalloproteinases (MMPs) (151-155). The potentiating effect of VEGF production by cancer cells is induced by neuropeptide Y, a co-transmitter of norepinephrine (156). It has been shown that ovarian orthotopic tumours exhibit an increased vascularization and VEGF expression in stressed mice and the effect is mediated through β2-AR (18). In the same study, 2-AR-cyclic AMP-protein kinase A signalling was shown to boost tumour VEGF production, vascularization and proliferation (18). It has been found that stress-induced AR signalling significantly decreases the expression of the anti-angiogenic factor, thrombospondin 1, in prostate cancer xenografts through epigenetic regulation, resulting in similar outcomes in pancreatic, colorectal and breast cancer models (99,157-160). Finally, chronic restraint stress in mice has been shown to remodel the lymphatic vessels around tumour tissue, mediated by the activation of β-AR on tumour-associated macrophages (161). This effect stimulates the production of VEGFC by tumour cells (161).

iii) Inflammation and immunomodulation are hampered by stress. Stress causes inflammation, anti-inflammation, as well as immune evasion (15). In animal models and patients with cancer, the effects of stress on the activity and distribution of ARs, prostaglandin receptors and GCRs have been extensively investigated (15,94,105,162,163). The pro-inflammatory effects of stress, as well as its implications on immune system dysregulation that allows cancer to avoid destruction are addressed in the following sections.

a) Stress and cancer-promoting inflammation. Pro-inflammatory molecules released by immune cells can lead to mutagenic processes, transforming normal cells into cancer cells (164). Stress can affect inflammation-related mutagenic processes by activating the sympathetic nervous system (165). A previous study on diethyl nitrosamine-induced hepatocarcinogenesis in rats demonstrated that sympathectomy with 6-hydroxydopamine reduced the development of hepatocellular carcinoma (165). However, prazosin, an α-AR antagonist, led to carcinoma development in up to 64% of rats. Sympathetic innervation is crucial for maintaining the liver inflammatory microenvironment, which initiates hepatocellular carcinoma development (165). Stress-induced-adrenergic signalling increases inflammation in malignant cells and tumour-associated macrophages (TAMs), leading to an increased expression of cyclooxygenase 2, prostaglandin secretion and increase levels of pro-inflammatory cytokines such as IL-6, which in turn increases macrophage recruitment and M2-pro-inflammatory-polarization (99,151,153,161,166-169). Social isolation and depression are linked to an increased M2 polarization in breast tumours, while higher levels of depression and an increased expression of genes encoding AR and prostaglandins predict a decreased survival rate of cancer patients (166,170).

b) Stress and avoidance of immune destruction. According to animal and human research, stress affects numerous anti- and pro-cancer immune system components (12). Chronic stress in humans has been shown to suppress host resistance to metastasis, causing lung tumour retention and metastasis (98). An acute stressor, such as swimming stress, suppresses NK cell activity and increases lung tumour retention (98). This effect can be attenuated or prevented by reducing the release of norepinephrine and epinephrine or using β1- and β2-blockers (98). However, the administration of epinephrine or other agonists of β-AR can also suppress NK cell activity and increase lung tumour retention (17). This suggests that

acute stress suppresses NK cell activity and compromises resistance to NK-sensitive metastasis (17,98).

Stress-induced-adrenergic signalling or agonists can inhibit NK cell activity against tumour cells, leading to increased lung metastases (17,89,97,98,171,172). A lower NK cytotoxicity in patients with ovarian cancer is linked to less social support and depression (173). Stress induces a shift from T-helper 1 cell (TH1) to T-helper 2 cell (TH2) cytokine production, increasing tumour growth in colorectal and squamous cell carcinoma mouse models (140,174,175). A depressive and worried mood are related to a decreased TH1 cell/TH2 cell-type cytokine ratio in patients with ovarian cancer (176). The stress-induced-adrenergic response promotes tumour growth by upregulating suppressive immune cells, such as myeloid-derived suppressor cells (MDSCs) and regulatory T-cells (140,158,163,175,177). Higher levels of stress are associated with a decrease in the number of circulating MDSCs (178). Additionally, chronic sound stress has been shown to increase colon cancer progression, plasma norepinephrine and corticosterone levels, and to induce a shift in the TH1 to TH2 response (158,174). Similar effects of stress on immunological functions have been observed in clinical investigations, including a reduction in protective immunity, the exacerbation of chronic inflammation, and the enhancement of immunosuppressive processes (15).

iv) Direct effects of stress on cancer cells. Stress hormones, which can be generated systemically or even secreted locally in the TME by infiltrating sympathetic nerve endings, immune cells, or tumour cells per se can have direct effects on cancer cells and boosting their malignant properties (139,179-182). Both noradrenaline and adrenaline enhance cancer cell proliferation, as well as survival (through anti-apoptosis), cell migration and invasion, epithelial-mesenchymal transition (EMT), the production of prostaglandins and the activation of MMPs (100,152,166,183-190). In animal models, psychological or physiological stressors (such as social confrontation, restraint and surgery) have been shown to enhance tumour development and metastasis by activating tumour the AR, as demonstrated by pharmacological or molecular blockage, or genetic knockout (18,99,175,183,188,191-193).

A recent study demonstrated that tumour innervation led to the advancement of cancer (194). Tumours can generate neural growth agents that promote sympathetic tumour innervation. During stress-induced sympathetic activation, higher tumour noradrenaline levels establish a feedforward loop that promotes cancer progression (143). Multiple cancer forms express AR, and higher levels of tumour noradrenaline and/or plasma adrenaline are associated with larger tumour size, advanced stage, lymph node metastases and/or a shorter survival (143,152,166,167,183,184,187,189,190,195).

In vitro and *in vivo*, stress-related hormones may promote the growth of cancer cells (12). AR activation has been shown to stimulate the proliferation of lung adenocarcinoma, pancreatic cancer and fibrosarcoma cells (196-198). Glucocorticoids have also been found to exert a stimulatory effect on cancer cell proliferation. Studies have demonstrated that physiological concentrations of hydrocortisone promote the proliferation of cell lines from metastatic breast carcinomas (199,200). Cortisol and its metabolite cortisone have been shown to stimulate prostate cancer cell growth in the absence of androgens (18).

Chronic behavioural stress can increase tissue catecholamine levels and promote the growth and invasiveness of ovarian carcinoma cells, primarily through the activation of β2-AR (18). The effect of stress on cancer cell resistance to death supports previous findings, such as the inhibition of the apoptosis of prostate and breast cancer cells by epinephrine, chemical sympathectomy increasing the gene expression of apoptotic factors in mouse melanoma tumours, and selective antagonists of β1- and β2-AR on colorectal cancer cell growth (16,201,202). Psychologic stress can inhibit apoptosis, but this effect is prevented by administration of a selective β2-AR antagonist (16).

Stress and metastasis. Numerous of the aforementioned and other stress-induced processes contribute to metastasis, in addition to promoting initiation and progression. Stress significantly increases the development of metastases, as demonstrated by studies on colon carcinoma, nasopharyngeal carcinoma, and ovarian cancer cells (203-205). As previously demonstrated, norepinephrine treatment increases the locomotor activity of colon carcinoma cells; however, this effect is blocked by propranolol (203). MMP-2 and MMP-9 levels have also been shown to be increased in the cell culture supernatant, whereas this effect is blocked by propranolol (206). Other examples include studies in mice, demonstrating that stress-induced AR activation promotes circulating tumour cell migration to the bones via the increased expression of RANKL by bone marrow-derived stem cells or to the lungs via the CC-chemokine ligand 2-CC-chemokine receptor 2-mediated attraction of macrophages, thereby forming pre-metastatic niches and increasing organ-specific metastasis (191,207). Additionally, stress increases tumour and stromal cell MMP production, tumour cell anoikis resistance, and cancer cell EMT, thus boosting malignant cell detachment, invasiveness and circulation survival (99,100,157,183, 186,188-190,208).

Perceived stress, depressive symptoms, or social isolation have been shown to be associated with the increased expression of EMT-related genes in tumours in patients with breast and ovarian cancer, as well as higher levels of MMP-9 in tumour cells and/or TAMs (99,206). In numerous mouse models, AR inhibition significantly reduces experimental and spontaneous metastases (89,99,161,183,191,207,209). Similar to how tumour AR expression levels have been associated with lymph node metastasis in patients with gastric and lung cancer, incidental AR-blocker use has been linked to a lower risk of developing metastasis or recurrence in patients with breast and ovarian cancer, as well as to the improved survival of patients with melanoma and breast cancer, but not lung and ovarian cancer (161,183,210-216).

It has been demonstrated that chronic stress in cancer patients with elevated depressive symptoms and low social support leads to a 30-fold increase in metastasis to distant tissues (99). Stress-induced lymphatic vessel rearrangement may also contribute to cancer cell dissemination (161). β2-AR activation reduces deformability in metastatic human breast cancer cells, rendering them more invasive (217). Randomized controlled trials are required to evaluate the effects of

AR-blockers on long-term cancer outcomes due to the discrepancies in the analysed indices (such as metastasis vs. survival), the diversity of cancer types and the uncontrolled settings of correlational research (10).

6. Conclusions and future perspectives

The present review indicates that stress has been linked to cancer development and incidence for a number of decades. Psychological stressors have been linked to cancer development, with the immune system playing a critical role in inhibiting cancer progression. Recent research has advanced the current understanding of the role of stress in cancer induction, growth and metastasis development, with the SNS and HPA axis playing crucial roles. Animal studies have revealed a clearer link than clinical human studies, suggesting that stress factors can exacerbate cancer hallmarks and promote growth and metastasis by directly affecting malignant tissue, its microenvironment, antitumor immune activity and other indirect cancer progression modifiers. Stress-related hormones can influence tumour development, migration, invasion, and cancer cell proliferation. The therapeutic potential of these pathophysiological mechanisms is shown by the discovery of numerous procedures that are triggered by stress in patients with cancer; however, these are beyond the scope of this review and can be further investigated in the future. Randomized controlled trials are required to evaluate the effects of stress on long-term cancer outcomes. Psychological therapies can potentially target stress and benefit individuals. To minimize cancer recurrence and associated mortality, chronic stress-management interventions need to be tested during critical periods, accompanied by pharmacological approaches, and include individualized modules.

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DAS and VEG conceptualized the study. IGL, VEG, PP, GPC and DAS made a substantial contribution to the interpretation and analysis of data to be included in the review, and wrote and prepared the draft of the manuscript. DAS and GPC analysed the data from studies for inclusion in the review and provided critical revisions. All authors contributed to manuscript revision, and have read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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