https://doi.org/10.15407/exp-oncology.2025.02.127

V. Chekhun *, T. Burda, O. Mushii, A. Pavlova, T. Borikun, T. Zadvornyi, N. Lukianova

R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology, the NAS of Ukraine, Kyiv, Ukraine

* Correspondence: Email: chekhun@onconet.kiev.ua

STRESS-INDUCED MODULATION OF THE TUMOR MICROENVIRONMENT: MECHANISMS AND IMPLICATIONS FOR CANCER PROGRESSION

Chronic stress is one of the key exogenous factors that can significantly affect tumor cell biology by disrupting the regulation of the tumor microenvironment (TME), thereby promoting the manifestation of the malignant process. Activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system induced by stressors leads to the secretion of glucocorticoids and catecholamines, which contribute to the deregulation of microenvironmental components that determine the aggressiveness of malignant neoplasms. This review systematizes the current views on the impact of stress-induced signals on the immune, stromal, vascular, and metabolic components of the TME and analyzes their contribution to the formation of an aggressive tumor phenotype. Particular attention is given to the interplay between neurohumoral stress, the gut, and the intratumoral microbiome, forming a complex networked environment supporting tumor progression. Advancing the understanding of molecular interactions between stress mediators and cellular elements of the TME will provide a foundation for developing innovative therapeutic strategies targeting not only the tumor itself but also minimizing the adverse effects of stress on individual components of the TME.

Keywords: stress, tumor microenvironment, cancer progression.

According to the existing ideas, stress is a set of physiological and psychological reactions of the body to the factors that threaten its homeostasis. In other words, stress occurs when the action of external or internal factors exceeds the body's ability to maintain balance. Under such conditions, a complex "stress system" is activated to mobilize resources and restore the body's physiological balance. As a rule, short-term and moderate stress effects are adaptive, in particular, they train the response system and increase its resistance. In contrast, severe or prolonged stress can exceed the body's adaptation reserves and cause pathological changes in the functioning of organs and systems, worsening physical and mental health [1, 2].

In response to stressors, two major interconnected systems are activated in the body: the sympathoadrenal-medullary (SAM) axis and the hypothalamic-pituitary-adrenal (HPA) axis. Their actions are coordinated by the structures of the central nervous system that form a single integrative "stress network" [3]. Regardless of the type of signal, the

Citation: Chekhun V, Burda T, Mushii O, Pavlova A, Borikun T, Zadvornyi T, Lukianova N. Stress-induced modulation of the tumor microenvironment: mechanisms and implications for cancer progression. *Exp Oncol.* 2025; 47(2): 127-142. https://doi.org/10.15407/exp-oncology.2025.02.127

key point of integration is the paraventricular nucleus of the hypothalamus, which activates the HPA response through the secretion of corticotropin-releasing hormone (CRH) and vasopressin. These neuropeptides stimulate the anterior pituitary to produce adrenocorticotropic hormone (ACTH), which acts through the systemic bloodstream on the cells of the adrenal cortex and causes the secretion of glucocorticoids, mainly cortisol [4].

Glucocorticoids bind to mineralocorticoid (MR) and glucocorticoid receptors (GR), which are expressed in many tissues of the body, including the brain, liver, skeletal muscle, and cardiovascular system, as well as on immunocompetent cells. MRs have a high affinity for cortisol and are activated at basal concentrations, while GRs are less sensitive and are mainly activated at elevated hormone levels, particularly during stress. GR activation provides both genomic and non-genomic effects of stressors, including rapid changes in cellular excitability, metabolism, and immune response [4]. In parallel with the HPA axis, the sympathetic branch of the autonomic nervous system is activated by stressors. Sympathetic preganglionic neurons via the spinal ganglia activate postganglionic nerves, as well as the chromaffin cells of the adrenal medulla. Pheochromocytes release adrenaline and noradrenaline, which act on α- and β-adrenoreceptors located on the cells of the cardiovascular system, bronchi, liver, etc. Their action provides the classic "stress response": increased heart rate, vasoconstriction, blood pressure, hyperglycemia, bronchial dilation, and mobilization of energy resources [3, 4].

In the case of chronic stress, these regulatory mechanisms can be disrupted. Prolonged exposure to high concentrations of glucocorticoids reduces the sensitivity of GR, a phenomenon known as glucocorticoid resistance. This leads to excessive activation of the HPA axis, changes in gene expression, epigenetic modifications (e.g., hypermethylation of receptor or CRH gene promoters), and structural changes in the central nervous system, such as hippocampal atrophy, amygdala hyperactivation, and functional disorganization of the prefrontal cortex [4]. These changes underlie many systemic consequences of chronic stress [3]. In particular, from the cardiovascular system, it is associated with hypertension, atherosclerosis, and an increased risk of heart attacks [5]; from the metabolic side — with insulin resistance, abdominal obesity, and impaired lipid metabolism [6]; from the immune system — with immunosuppression or, conversely, with chronic inflammation [7]; from the nervous system — with anxiety and depressive disorders, memory and sleep disorders, and decreased adaptability and cognitive control [8]. In the context of cancer, the abovementioned neuroendocrine and immune changes caused by stress acquire special importance. It has been shown that the occurrence and progression of malignant neoplasms largely depend on the influence of external factors, in particular, chronic stress. However, acute stress reactions are characterized by short-term effects and, in some cases, can even temporarily strengthen individual links of immunity [9]. The action of chronic stress factors in cancer patients is involved in the modulation of the growth and progression of malignant neoplasms [10, 11]. It is the prolonged action of stress factors that is decisive in the biology of the tumor cell and tumor microenvironment (TME), regulating immune responses, angiogenesis, metabolism, extracellular matrix (ECM) remodeling, epithelial to mesenchymal transition (EMT), and sensitivity to therapy [10], and also correlates with a decrease in the overall and relapse-free survival of patients [11]. In this review, our attention is focused on highlighting the mechanisms through which stress hormones affect the functional activity of TME immune components, modify the cytokine profile at the tumor and organism levels, stimulate angiogenesis and ECM remodeling, modulate the processes of invasion and metastasis, and cause changes in the metabolic pathways.

The impact of distress on the TME immune component

The immune component of the TME traditionally includes several immune cells with different origins and functional activity, including dendritic cells, lymphocytes, macrophages, myeloid suppressor cells, etc. It has been established that the effect of stress on cancer patients is accompanied by a significant change in the TME immune cells' populational composition and modulation of their functional activity, which ultimately leads to the tumor escaping immune surveillance and causing long-term immunosuppression [12].

The action of acute stress is accompanied by the rapid release of catecholamines, which activate β-adrenoreceptors on immune cells, consequently

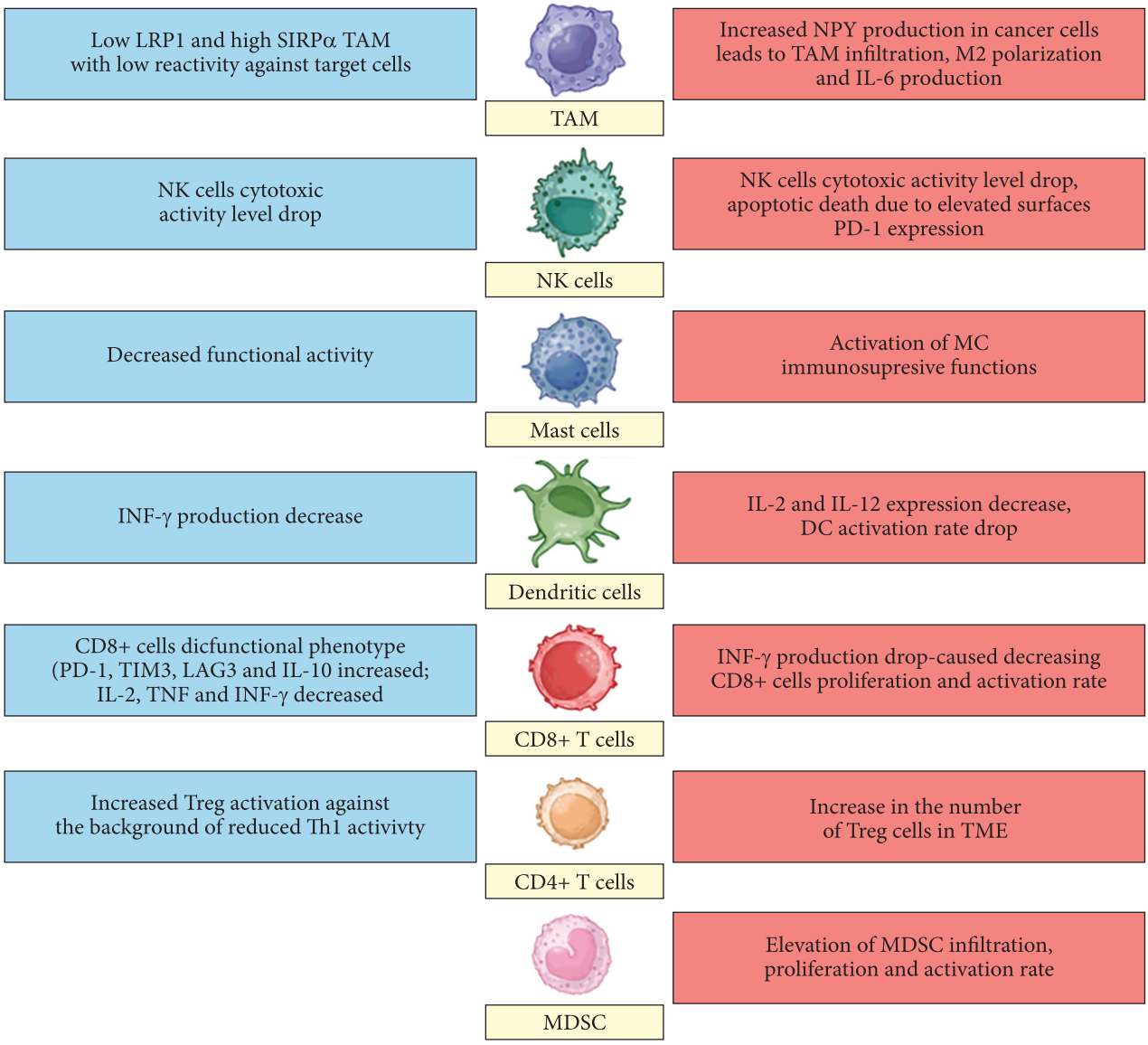

Fig. 1. The effect of acute and chronic stress factors on the immune cells in TME

reducing the effectiveness of the immune response by disrupting their functional activity [13]. At the same time, studies in in vivo and ex vivo systems have shown that chronic stress significantly changes the composition of the TME immune component. However, a common feature for the action of both acute and chronic stresses is, first of all, a decrease in the proportion of active cells involved in the effective elimination of malignantly transformed cells, against the background of an increase in the number of immunosuppressive cells in the tumor focus [14, 15]. In the following, we will consider the effect of stress factors on the main types of immune cells infiltrated into the TME in detail (Fig. 1).

Macrophages and monocytes. It has been established that distress modulates the functional activity of macrophages in the TME. Qin et al. [16] in the in vivo system of a 4T1 breast carcinoma model proved that chronic stress leads to M2 polarization of tumor-associated macrophages (TAMs) in the TME. It was shown that noradrenaline induces the secretion of neuropeptide Y (NPY) by malignantly transformed cells, which, in turn, acts as a chemoattractant for macrophages and stimulates their production of pro-inflammatory cytokine IL-6. In an in vitro prostate cancer (PCa) model with MycCaP cell transplants, as well as in transgenic Hi-myc mice with spontaneously induced tumors, it was demonstrated that the enhanced recruitment of M2-polarized TAMs from the bone marrow to the TME and the increase in the IL-6 levels in the tumor tissue were caused by the sympathetic in-

nervation signal NPY under the influence of chronic stress factors. The inhibition of the transmission of this signal reduced the migratory activity of macrophages, decreased the number of TAMs infiltrated into the TME, and suppressed tumor growth. Similar effects were observed in ex vivo experiments: in the prostate tissue of patients with severe depressive symptoms, an increase in the density of $CD68^+$ TAMs was recorded, as well as high levels of NPY and IL-6 expression compared to patients without signs of anxiety disorders [17].

Another mechanism by which stress disrupts the antitumor activity of TAMs is associated with the influence of glucocorticoids. In particular, these hormones cause an imbalance of the so-called "eat me" signaling receptors LRP1 and "don't eat me" SIRPα, which are expressed on the membranes of macrophages and prevent them from effectively recognizing and engulfing malignantly transformed cells. Modeling chronic unpredictable mild stress (CUMS) caused a decrease in the expression level of LRP1 on macrophage membranes due to GR-dependent inhibition of its transcription, and also led to the increased level of SIRPα, subsequently preventing the effective recognition and elimination of malignant cells. Restoring the balance between LRP1 and SIRPα in in vitro experiments by transfecting macrophages with artificially constructed LRP1 mini-receptors led to a decrease in SIRPα expression even under the influence of cortisol. In addition, the introduction of miRNA-4695-3p into the medium normalized the level of SIRPα. The effectiveness of SIRPα level correction was confirmed in in vivo experiments in mice with xenografts of colorectal cancer cells HCT116 and breast cancer (BCa) cells MDA-MB-231: the intraperitoneal administration of mini-receptors LRP1 or miRNA-4695-3p led to a decrease in TAMs levels, an increase in their phagocytic activity, and a slowdown in tumor growth [18].

Thus, stress signals both at the cellular and systemic levels contribute to the accumulation of macrophages and monocytes in the TME, which supports tumor growth, promotes chronic inflammation, and inhibits the activation of the immune response effector components.

Natural killer cells (NK-cells). NK-cells are the key effectors that play an important role in the detection and destruction of malignantly transformed and virus-infected cells. It has been proven that both acute and chronic stresses significantly affect their functional activity. On the one hand, in response to short-term stress, NK-cells are mobilized into the peripheral blood. At the same time, an excessive activation of the sympathetic nervous system and the release of adrenaline and prostaglandins can quickly suppress their cytotoxic effect. Rourke et al. [13] showed that the surgical removal of solid tumors, which was accompanied by the effect of stress on the body, led to a transient decrease in the level of NK-cells in the peripheral blood of patients and was associated with an increased metastasis risk. Under the conditions of chronic stress, an activation of β-adrenoreceptors inhibits NK-cell cytotoxicity by reducing the expression of the key activation molecules on their surface. Due to the depression in the TME of hepatocellular carcinoma, glucocorticoid-induced expression of PD-1 on NK-cells is determined. This leads to a decrease in their cytotoxicity, probably through activation of the PD-1/PD-L1 cascade, and is associated with a high risk of liver cancer progression [19]. In patients with BCa who had a high level of psychological stress, a decrease in the cytotoxic activity of peripheral blood NK-cells against the K562 cells was recorded when they were co-cultured in vitro. This weakening of functional activity correlated with changes in the expression of killer-cell immunoglobulin-like receptors, in particular, with an increase in the level of CD94 and a decrease in the level of CD158b expression on the surface of their plasma membranes [20]. In an in vivo system in mice, a surgical removal of B16F10.9 melanoma and Lewis lung carcinoma caused a stress response in mice, which was accompanied by an increase in corticosterone levels, a decrease in NK-cell cytotoxicity in the peripheral blood, a decrease in the expression of Fas ligand and CD11a on their surface, as well as a decrease in the number of circulating lymphocytes. The administration of the β-adrenergic blocker propranolol and the COX-2 inhibitor etodolac to mice before the surgical removal of experimental tumors reduced these immunosuppressive effects and contributed to the restoration of antitumor activity of NK-cells, which in turn was accompanied by a significant improvement in the relapse-free survival of experimental animals [21].

Thus, stress mediators both in acute and chronic stress conditions can suppress the functional

activity of NK-cells at the systemic level, which leads to a decrease in the efficiency of the innate immune response.

Mast cells (MCs). Several recent studies have shown that MCs are involved in the progression of solid tumors and act as modulators of the functional activity of certain types of immune cells and non-cellular fibrous structures in the tumor TME [22—24]. At the same time, the mechanisms of the influence of stress factors on MCs in the TME have not yet been fully elucidated. Sitte et al. [25] demonstrated that the social distress in patients with pancreatic ductal adenocarcinoma correlates with the decreased levels of MC infiltration in tumor tissue, which is supported by the results of studies in an in vivo system [26]. It has been proven that corticotropin-releasing hormone can activate brain MC, which is associated with an increased risk of brain metastasis [27]. The above data are supported by the ability of MC to affect the blood-brain barrier during acute stress [28]. However, an activation of the parasympathetic nervous system also indirectly causes MC degranulation through the HPA-axis with the participation of catecholamines [29]. Kurashima et al. [30] and Wang et al. [31] have shown that under stress, MCs release ATP-inducing ectonucleotidase, thus causing ATP hydrolysis and adenosine release, which contributes to immunosuppression.

Therefore, even though the role of MC in both the emergence and progression of solid tumors under conditions of distress has not been fully elucidated, the data available in the literature indicate the active involvement of these immune cells in the processes of TME modulation under the influence of stress factors.

Dendritic cells (DCs). DCs play a key role in the activation of adaptive immunity by presenting tumor antigens to T lymphocytes [32]. In an in vivo system on a mouse melanoma model, it was found that chronic stress inhibits DCs maturation, which is accompanied by a decrease in their ability to effectively present antigens, contributes to a weakening of the antitumor response, and also correlates with resistance to immunotherapy [33]. Activation of glucocorticoid receptors on DCs at the transcriptional level suppresses the expression of IL-2 and IL-12 involved in DCs activation [34]. Matyszak et al. [35] showed that the use of a synthetic analog of cortisol—dexamethasone in the early stages of DCs maturation weakens their ability to stimulate a Th1 response, reducing the production of interferon-γ (IFNγ) and increasing the level of the immunosuppressive T-regulatory cells (T-reg), the main mediator of which is IL-10.

As a result of these disorders, under the influence of stress factors, the presentation of tumor antigens by DCs is suppressed, which contributes to the weakening of immune control in the TME.

T-lymphocytes. One of the key roles in the formation of an effective antitumor immune response is played by T-cells. Cytotoxic $CD8^+$ T-lymphocytes directly destroy malignantly transformed cells, while $CD4^+$ T-helpers coordinate the activity of the immune system. At the same time, T-reg cells limit excessive activation of immunity, but in the conditions of the TME, their immunosuppressive effect contributes to the avoidance of immune surveillance [36, 37]. It has been shown that chronic stress leads to a shift in the balance of T-cell subpopulations toward the immunosuppressive link. In particular, after activation of β2-adrenoreceptors (β2-AR) on immune cells, a decrease in the number of effector $CD8^+$ T-lymphocytes is observed in the tumor focus against the background of a simultaneous increase in the population of T-regs [38]. At the same time, many works have shown that under the influence of acute stress, the number of T-regs decreases. In particular, in the spleen of mice with 4T1 mammary adenocarcinoma under conditions of acute repetitive restraint stress (aRRS), a decrease in the proportion of $FoxP3^+$ Treg was recorded, and as a result, an increase in the relative number of $CD8^+$ T-cells [39]. It has been proven that adrenergic signaling from β2-AR directly inhibits the activation and proliferation of cytotoxic T-lymphocytes. In the Eμ-myc B-cell lymphoma model, it was shown that prolonged activation of β2-AR using isoprenaline led to a decrease in the IFNγ production and cytolytic activity of $CD8^+$ T cells in the blood of experimental animals [40]. It was found that prolonged exposure to dexamethasone on circulating $CD8^+$ T-lymphocytes of humans and mice in an in vitro system led to the formation of a dysfunctional phenotype characterized by high expression of immune checkpoint molecules PD-1, TIM-3, and LAG-3, decreased production of pro-inflammatory cytokines IL-2, TNF-α, and IFN-γ, and increased secretion of immunosuppressive IL-10. These phenotypic

changes in lymphocytes were observed in an in vivo experiment in mice with B16F10 melanoma and in patients with colorectal cancer, where glucocorticoid signaling activity correlated with reduced effector potential of $CD8^+$ T-cells [41]. Geng et al. [42] in an in vivo system on a lung adenocarcinoma model found that noradrenaline, acting on tumor cells, increases their secretion of immunosuppressive factors (CXCL9 and adenosine), which complicates the chemotaxis of $CD8^+$ T-cells to the TME and contributes to the resistance to anti-PD-1 therapy. In the 4T1 mammary adenocarcinoma model, it was found that chronic social isolation of mice is accompanied by a significant decrease in the number of $CD8^+$ T cells in the spleen and activated $CD3^+CD69^+$ T-lymphocytes, which was associated with a decrease in animal survival rates [39]. It has been shown that activation of β2-AR on the surface of T-regs causes an increase in their immunosuppressive function, which is implemented through the cAMP/PKA cascade, an increase in the CTLA-4 expression, and a decrease in the IL-2 mRNA levels of $CD4^+$ T-cells. At the same time, an increase in the conversion of CD4+Foxp3– cells into Foxp3+ induced T-regs was observed [43]. Also, blocking β-adrenergic receptors with propranolol in the conditions of modeling chronic adrenergic stress on transplanted melanoma (B16-OVA) and colorectal cancer (CT26.CL25) in the in vivo system can partially restore normal activation and metabolism of T-lymphocytes and increase the effectiveness of antitumor immunotherapy [44].

Thus, chronic stress causes depletion of the pool of cytotoxic T-lymphocytes, increases the immunosuppressive effect of T-regs, and reduces the effectiveness of the antitumor immune response.

Myeloid-derived suppressor cells (MDSCs). Acute and chronic stress can modify the functional activity of MDSCs, which play an important role in the formation of an immunosuppressive TME. Thus, Kume et al. [45] found that stress in mice caused by the removal of experimental tumors is accompanied by a significant increase in the number of MDSCs in the TME of renal cell carcinoma. Studies on in vitro and in vivo models have shown that in the context of chronic stress, adrenergic signaling plays a key role, causing the activation and accumulation of MDSCs in the TME with high proliferative activity [46]. In vivo experiments on a 4T1 BCa model have shown that increased serum norepinephrine levels and increased tyrosine hydroxylase expression in the bone marrow of mice, as a result of chronic stress, activate the IL-6/JAK/STAT3 signaling pathway. This promotes the accumulation of MDSCs in the spleen, bone marrow, peripheral blood, and lungs of experimental animals, and also increases the incidence of metastasis of this tumor to the lungs. At the same time, pharmacological blockade of β2-AR with propranolol suppressed these effects, reducing the number of MDSCs in the blood and lungs and reducing the incidence of pulmonary metastases in mice that were injected with tumor cells after stress exposure [47]. In a study by Cao et al. [48] using the H22 hepatocellular carcinoma model, it was shown that chronic stress induced by immobilization of animals stimulates the release of MDSCs from the bone marrow and their migration to the spleen and TME. It should be noted that these processes are accompanied by an increase in the expression of the chemokine receptor CXCR2 and the activation of the MAPK/Erk signaling cascade in MDSCs, as well as the induction of the ligand CXCL5 expression in tumor tissue.

Thus, stress hormones not only promote the migration of MDSCs to the site of tumor growth but also enhance their immunosuppressive function, creating favorable conditions for tumor progression.

The effect of stress on the cytokine profile. Stress factors significantly affect the cytokine profile of both innate and adaptive immune cells, contributing to immunosuppression and chronic inflammation. Norepinephrine induces the secretion of proinflammatory IL-6 in macrophages [17] and significantly increases the levels of IL-6 and IL-8 in human melanoma cells [49], due to the activation of the IL-6/JAK/STAT3 signaling pathway in the TME during chronic stress [47]. In the serum of BCa patients with signs of depression, prolonged elevations of the proinflammatory cytokines TNF-α and IL-1β have been recorded [50]. Activation of β2-AR with isoprenaline or other agonists leads to inhibition of IFN-γ production [40], reduces the level of IL-2 in $CD4^+$ T cells [43], and enhances the immunosuppressive function of T-regulatory cells. Similarly, dexamethasone reduces IFN-γ production and promotes an increase in IL-10 levels, while the activation of glucocorticoid receptors leads to inhibition of IL-2 and IL-12 gene transcription in DCs at early stages of their matura-

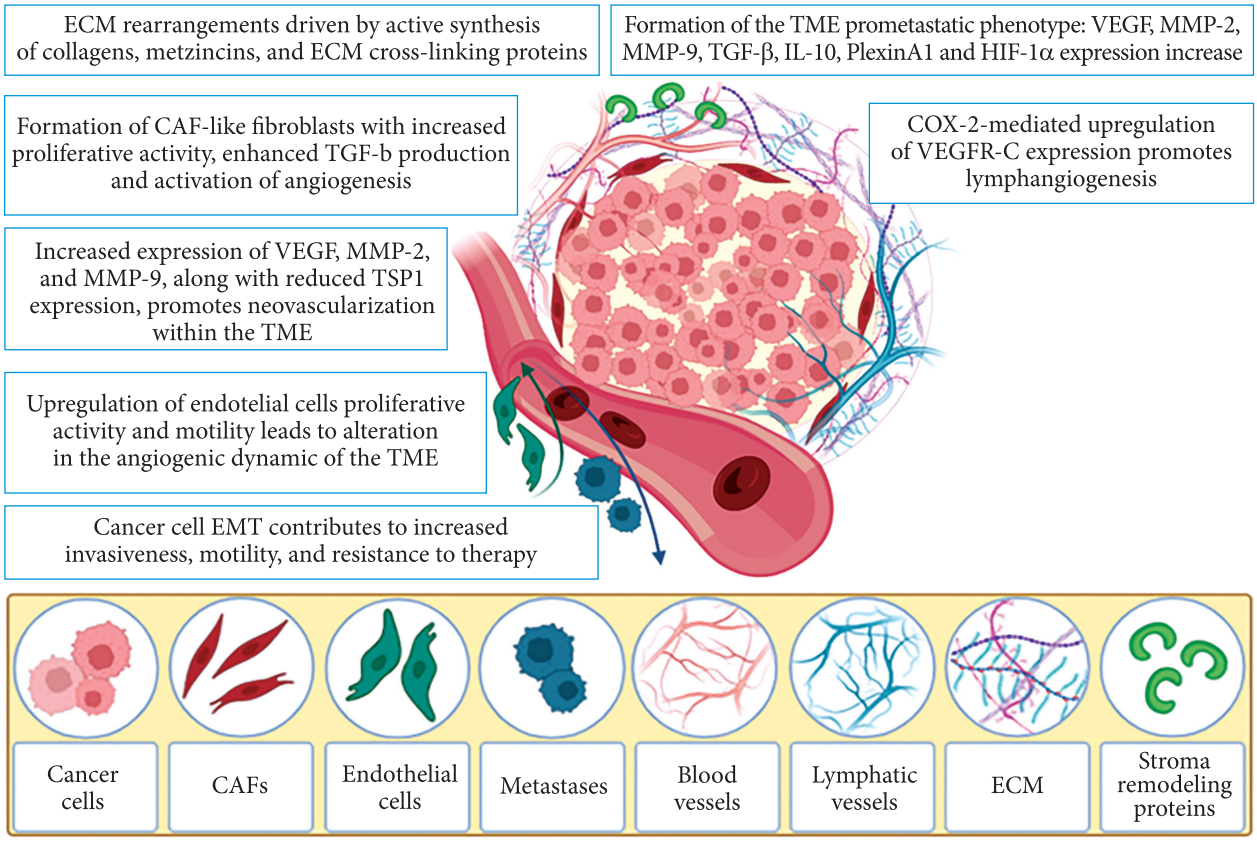

Fig. 2. Effects of distress on the formation of metastatic potential of neoplasms

tion [34, 35]. Long-term exposure to dexamethasone induces a dysfunctional phenotype of $CD8^+$ T lymphocytes, which is accompanied by a decrease in the production of IL-2, TNF-α, and IFN-γ and an increase in the secretion of IL-10 [41].

Accumulated experimental and clinical data indicate that the action of stress mediators, such as catecholamines and glucocorticoids, significantly changes the cytokine profile of the TME, contributing to a shift toward immunosuppression. These changes are realized through the inhibition of the synthesis of key pro-inflammatory cytokines (IL-2, F-α, and IFN-γ), responsible for the activation of the antitumor immune response, and an increase in the production of immunosuppressive molecules, in particular IL-10. Stress hormones can also induce increased expression of immunosuppressive factors, such as CXCL9, adenosine, and CTLA-4, and activate signaling pathways such as IL-6/JAK/STAT3, which contribute to the formation of a tolerant, chronic inflammatory environment favorable for tumor progression.

Thus, chronic stress acts as a potent immunomodulatory factor that can reduce the effectiveness of natural and therapeutically induced antitumor immune responses.

Stress-induced rearrangements in the stroma of neoplasms

The stromal component of the TME is a functionally active network that includes fibroblasts, endothelial and mesenchymal cells, as well as a dense meshwork of ECM. In the interaction with transformed cells, these elements create a complex signaling ecosystem that supports tumor growth, promotes its invasion, remodels tissue architecture, and ensures the development of vascularization [51, 52]. In response to systemic factors, including stress hormones, the stroma undergoes phenotypic changes that are accompanied by the activation of angio- and lymphangiogenesis, changes in the structure of the ECM, and increased cellular plasticity. Such a restructuring of the TME not only contributes to the progression of the tumor process but also creates the prerequisites for metastasis, in particular through forming new vascular networks and facilitating the migration of tumor cells (Fig. 2) [37, 53, 54].

Cancer-associated fibroblasts (CAFs). CAFs are the key cellular elements of the stromal component of the TME, playing a leading role in the secretion of growth factors, remodeling of the ECM, and maintaining the vital activity of malignantly transformed cells [55, 56]. It has been shown that the chronic activation of the adrenergic signaling system promotes the transformation of normal fibroblasts into CAF with pronounced protumoral properties. In particular, it has been demonstrated that the activation of α2-AR located on fibroblast membranes using the agonist clonidine in vitro promotes the proliferation of these cells and stimulates the secretion of transforming growth factor β (TGF-β), which, in turn, induces polarization of myofibroblasts into CAF and causes intensification of angiogenesis processes in the TME [10].

In addition, the activation of β-adrenoceptors on the surface of CAF stimulates the synthesis of collagen and other ECM components, as a result of which the tumor stroma acquires greater density and signs of fibrosis. In a study by Nagaraja et al. [57], when simulating chronic stress by daily physical immobilization of experimental animals with ovarian cancer Skov3-ip1, HeyA8, or ID8-ip, a significant increase in the number of CAF in the tumor tissue was recorded, characterized by the expression of α-SMA, as well as an increase in the level of collagen expression. The increase in collagen formation was dependent on the β2-AR — CREB — INHBA (inhibin βA) signaling cascade: INHBA expression in tumor cells increased under the influence of norepinephrine, which caused the activation of CAF through the ACVR2b receptor and a Smad2/3-dependent mechanism. A blockade of β2-AR with propranolol, inhibition of INHBA or ACVR2b resulted in a significant reduction in both the number of CAF and the level of collagen deposition in the tumor focus.

The data presented indicate that stress mediators significantly change the functional activity of fibroblasts, providing support for the growth of tumors and their progression. Activated CAFs serve as a source of proangiogenic and immunosuppressive factors, and the changes in the ECM structure that they initiate create a favorable environment for tumor invasion and metastasis.

Changes in ECM composition under stress conditions. The TME includes not only cellular elements but also the ECM, which plays a key role in ensuring the structural integrity of the tissue and signaling between cells [58]. In addition to the ECM, proteins involved in tumor stroma remodeling processes should also be considered separately in the context of the stromal component of the TME in solid tumors [59]. It has been proven to date that stress hormones can modify the ECM in two ways: through direct activation of CAFs and by modulating signaling pathways in transformed cells.

Chronic adrenergic stimulation activates the β2-AR–cAMP–PKA signaling pathway in PCa cells, leading to the focal adhesion kinase (FAK) phosphorylation and activation of metalloproteinases MMP-2 and MMP-9. In the Hi-myc transgenic mouse model, as well as in orthotopic models in BALB/c nude mice inoculated with PC-3 or 22Rv1 PCa cells under chronic unpredictable stress (CUMS), significant ECM remodeling was observed: collagen and laminin degradation, fiber compaction, and alignment were observed. As a result, directional "pathways" were formed that facilitate tumor cell migration and promote their invasion into surrounding tissues [60].

Studies show that under stress, tumors often have a loose, degraded matrix with radially oriented collagen fibers, a structure that facilitates invasion and cell migration beyond the primary tumor. The elevated levels of catecholamines activate the production of lysyl oxidase (LOX) and other enzymes that contribute to collagen crosslinking and the formation of a stiffer ECM CAF. When modeling chronic stress using estrogen-sensitive BCa (MCF-7) implanted in immunodeficient BALB/c nu/nu mice, an increase in LOX2 and SDF-1 expression in CAF was recorded, which contributed to tumor growth and enhanced invasive activity of neoplastic cells [56].

The effect of stress on angiogenesis and the metastatic potential of tumors

One of the most significant consequences of stress for the TME is the increased neovascularization. An increase in the density of the vascular network in combination with changes in adhesive properties and invasive activity leads to cell motility alteration, which directly affects the processes of metastasis. Under the influence of catecholamines, which interact with β-AR on endothelial and malignantly

transformed cells, the release of proangiogenic factors is activated. In particular, noradrenaline triggers signaling pathways that stimulate the proliferation and migration of endothelial cells and their secretion of VEGF [53]. In vivo experiments using ovarian and lung carcinoma models, an increase in the expression of proangiogenic molecules such as VEGF, MMP-2, and MMP-9 was noted in the tumor tissue of animals in a state of distress and correlated with the volume and weight of tumors, as well as the number of distant metastases [61], which was accompanied by an increase in the density of the vascular network in tumors [62]. Similar results were observed in nasopharyngeal carcinoma cells of the HONE-1, HNE-1, and CNE-1 lines, where norepinephrine dose-dependently increased the production of VEGF, MMP-2, and MMP-9, as well as the invasiveness and angiogenic activity of tumor cells. These effects were neutralized by propranolol and MMP inhibitors, confirming the involvement of β-adrenergic signaling in neovascularization, invasion, and metastasis [63]. Budiu et al. [39] showed in an in vivo experimental model of 4T1 BCa that both chronic stress (social isolation) and acute stress (short-term physical restraint) promote angiogenesis: an increased expression of the endothelial marker CD31 was recorded in tumor tissue and lung metastases. This was accompanied by an increase in the microvessel density, remodeling of the tumor vascular network, and a decrease in animal survival rates. In a study on MC3T3-E1 osteoblasts and primary isolated human osteoblasts, it was shown that the stimulation of β2-AR with isoprenaline, which mimics sympathetic activation during chronic stress, induces HIF-1α expression and secretion of the chemokine CXCL12. When co-cultivating osteoblasts with human PC-3 and DU-145 PCa cells, the authors of [64] noted a significant increase in the migratory potential of malignantly transformed cells, their invasive activity, and the expression of EMT markers. The use of inhibitors of β2-AR (ICI118,551), HIF-1α (YC-1), or CXCR4 (LY2510924) abolished these effects, suggesting a critical role for the β2-AR–HIF-1α–CXCL12/CXCR4 signaling cascade in stimulating the metastatic potential of PCa under the influence of sympathetic activation caused by chronic stress. Hulsurkar et al. [65] showed that chronic behavioral stress activates CREB through β-adrenergic signaling, which, in turn, induces the expression of histone deacetylase 2 (HDAC2) in PCa xenograft tissue in vivo. This enzyme epigenetically represses the transcription of thrombospondin-1 (TSP1), a potent inhibitor of angiogenesis. At the same time, Lu et al. [66] demonstrated that the activation of the PlexinA1/VEGFR2-JAK2-STAT3 signaling cascade promotes angiogenesis under conditions of β2-AR stimulation. In mice with gastric cancer tumors (MGC803), isoprenaline injections increased the expression of VEGF, PlexinA1, and VEGFR2 and caused JAK2/STAT3 activation, which was accompanied by enhanced angiogenic activity. Blocking PlexinA1 suppressed these effects, indicating a key role of this pathway in mediating stress-induced angiogenesis. Zhou et al. [67] reported that β2-AR stimulation causes inhibition of PPARγ expression in BCa cells, which promotes VEGF/FGF2-mediated angiogenesis. An in vivo study using 4T1 BCa tumors in socially isolated animals demonstrated an increase in the vascular density and levels of angiogenic factors, while β2-AR blockade or PPARγ activation abolished these effects.

Chronic stress can also promote lymphangiogenesis in the TME by increasing COX-2 expression in the TAM, which stimulates VEGF-C-dependent de novo lymphatic vessel formation. In an orthotopic human BCa model generated by transplantation of human BCa cell line MDA-MB-231 into BALB/c nu/nu mice, daily immobilization for three weeks resulted in increased lymphatic vessel density in intratumoral and peritumoral zones and enhanced lymphogenic metastasis. These effects were reversed by the pharmacological blockade of COX-2 or β2-AR [68].

Stress factors can also enhance the invasive and metastatic properties of tumor cells by inducing EMT. Kume et al. [45] demonstrated that postoperative stress is associated with an increase in the number of circulating MDSCs and their increased secretion of TGF-β1, VEGF, and IL-10, which promotes EMT and lung metastasis. Furthermore, it was shown that norepinephrine directly activates EMT in gastric adenocarcinoma cell lines BGC-823 and SGC-7901 by reducing E-cadherin expression and increasing vimentin, HIF-1α, and Snail levels. These effects were realized through the activation of β2-AR and the TGF-β/Smad3/Snail and HIF-1α/Snail signaling cascades, which indicates the potential role of adrenergic stimulation in triggering

EMT [69, 70]. As a result, the cells lose adhesive properties, acquire high motility and resistance to anoikis, facilitating their dissemination in the primary tumor and exit into the bloodstream.

Chronic stress is associated with a more aggressive clinical course of malignant neoplasms. Tian et al. showed that patients with depression are more likely to have metastases and recurrences of some tumors, including BCa, PCa, and lung carcinoma, which confirms the role of stress in the regulation of EMT [11]. It is important to note that acute stress in real-life conditions often overlaps with chronic stress and immune depletion, so its contribution is difficult to assess separately. However, current data demonstrate that even short-term stress responses can "wake up" tumor cells, accelerating the transition from a dormant state to active growth and spread throughout the body [71].

Metabolic and physicochemical adaptation of the TME to stress

Chronic stress significantly affects the organization of metabolic cascades in the TME, which contributes to the disruption of energy metabolism in both tumor and immune cells. In particular, it has been shown that activation of β2-AR on the surface of BCa cells causes a switch in their energy metabolism from oxidative phosphorylation to aerobic glycolysis (the Warburg effect), which was accompanied by an increase in the expression of glycolytic enzymes (in particular, lactate dehydrogenase A) and the accumulation of lactate in the TME. The acidic environment formed due to an excess of lactate enhances the invasive potential of tumor cells and the immunosuppressive activity of MDSCs and T-regs. In addition, under such conditions, the stability of the *MYC* oncogene in malignant cells is maintained, leading to the activation of the transcription factor Slug, promoting EMT and enhancing the expression of genes associated with the stemness properties of transformed cells [72].

In cells of the immune system, stress signals interfere with normal metabolism. In particular, studies in recent years have shown that in T lymphocytes, chronic stress reduces mitochondrial activity, causing "metabolic exhaustion" [44]. At the same time, in MDSCs, stress activates NRF2-dependent antioxidant pathways, which makes these cells metabolically resilient (in particular, resistant to oxidative stress) and allows them to maintain functional activity even under aggressive TME conditions [73]. At the same time, β-adrenergic signals have been shown to inhibit oxidative phosphorylation in endothelial cells, promoting angiogenesis in a mouse model of PCa [74].

Chronic stress increases the levels of reactive oxygen species (ROS) in the TME, including superoxide anion ($O_2\bullet^-$), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH•), which damage DNA, proteins, and lipids of tumor cells and play a signaling role in key biological processes, including tumor progression, proliferation, angiogenesis, metastasis, and chemoresistance. Oxidative stress is closely associated with inflammatory processes. Aboelella et al. [73] reported that macrophages and leukocytes in the TME produce ROS via NADPH oxidase (NOX), which enhances non-selective cell damage in the inflammatory focus.

The accumulation of ROS in the TME also serves as a signal that activates the pro-oncogenic factors NF-κB and HIF-1α (Fig. 3). This leads to increased expression of genes encoding immune checkpoints (CTLA-4, PD-L1), growth factors (TGF-α, VEGF), and metabolic enzymes (IDO), which contributes to increased immunosuppression and angiogenesis [75]. ROS are involved in the initiation of EMT and metastasis through the activation of MMPs, which degrade ECM components.

High levels of ROS in the TME induce T-cell apoptosis through increased Fas expression and decreased Bcl-2, which reduces the effectiveness of the antitumor immune response. They also suppress the functional activity of T- and NK-cells by blocking NF-κB and reducing the production of IFN-γ, TNF-α, and IL-2. Against this background, MDSCs remain resistant to oxidative stress due to the activation of NRF2-mediated antioxidant mechanisms. They not only remain viable under oxidative stress conditions but also use ROS as a "weapon", releasing H_2O_2 and other free radicals to suppress the functional activity of cytotoxic effector cells of the innate and adaptive immune systems. However, a decrease in NOX2 activity or neutralization of H_2O_2 by catalase promotes the transformation of MDSCs into macrophages, which leads to the loss of their immunosuppressive activity [73].

Thus, stress triggers a vicious cycle where oxidative stress and inflammation mutually reinforce

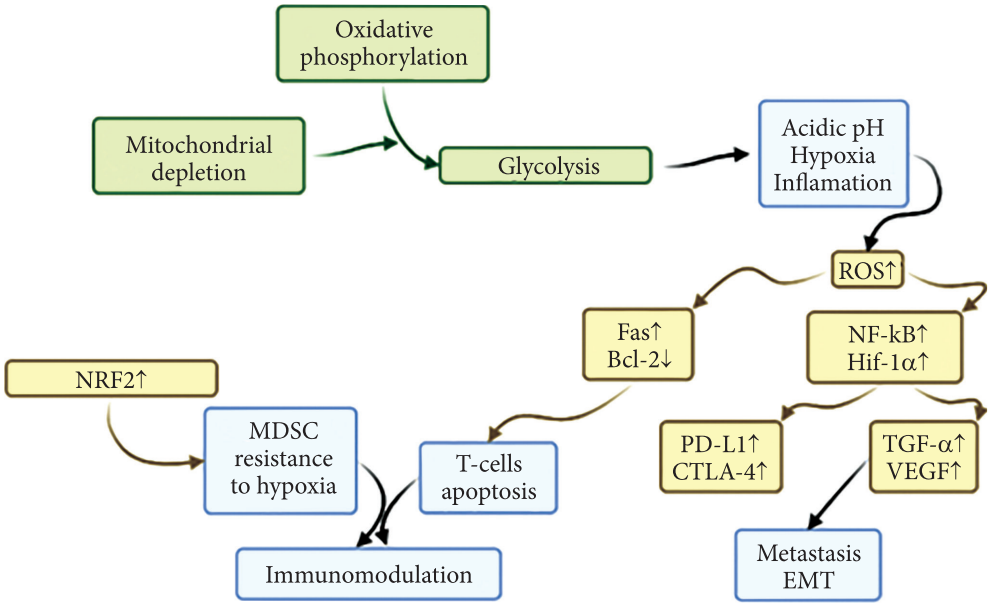

Fig. 3. Effects of stress on the metabolism and physicochemical conditions in the TME

each other, leading to the formation of a metabolic environment favorable for tumor progression, with suppression of the immune response, tissue damage, and subsequent recruitment of inflammatory cells to the TME.

The modulatory role of stress in the formation of the intestinal and tumor microbiome

The effect of stress factors is also directly associated with changes in the composition of the body's microbiome, including intestinal and tumor microflora [76]. The intratumoral microbiome — a collection of microorganisms in tumor tissue — has been identified in several solid tumors. The studies of the last decade prove that the tumor microbiome plays a significant role in the modulation of the TME, immune response, and the effectiveness of therapy [77, 78]. It has been shown that acute stress can indirectly affect the intratumoral microbiome through increased intestinal permeability and the systemic effects of stress mediators. This creates conditions for bacterial translocation into the bloodstream and potentially to the TME, especially under weakened barrier conditions (e.g., postoperative or pain stress) [79]. Niu et al. [80] demonstrated in an in vitro system that norepinephrine and epinephrine, which are released during acute stress, stimulate the growth of enterotoxigenic *Escherichia coli* and increase biofilm formation and expression of virulence genes (*estA, estB, elt*). Such microorganisms can colonize tumor tissue under stress conditions. Although direct data on changes in the intratumoral microbiota during acute stress are lacking, the described mechanisms suggest its potential role in shaping the pathological profile of the TME.

However, chronic stress causes dysbiosis of the intestinal microflora and TME, affecting the microorganisms' survival, growth, and metabolism [81]. It has been proven that both glucocorticoids and catecholamines enhance the rate of reproduction and virulence of pathogenic bacteria [80] and at the same time suppress the normobiota, in particular *Lactobacillus* and *Bifidobacterium* [81, 82]. It has been shown that the microbiota of tumor tissue of human colorectal cancer transplants of the HCT116 line in experimental animals under conditions of chronic immobilization stress was characterized by an increase in the proportion of representatives of the *Ruminococcaceae_UCG-014* strain, which was accompanied by an increase in the levels of IL-6, adrenaline, noradrenalineand, and TNF-α in the TME [83]. At the same time, modulation of chronic psychological stress caused an intensification of purine metabolism in the intestinal epithelium in experimental animals, which led to a decrease in the availability of guanine, a substrate for *Bifidobacterium animalis*. As a result, researchers recorded a decrease in the number of *Bifidobacteria* in the colon, while oleic acid accumulated in the feces and serum of animals,

which in the tumor focus enhanced the metastatic activity of malignant cells [82].

Psychological distress and comorbid depression in patients with BCa are associated with a worse prognosis. In particular, Ye et al. [84] showed that chronic cold stress in BALB/c mice with transplanted 4T1 tumors led to a significant decrease in the number of representatives of the *Blautia* genus in the intestine, accompanied by a decrease in the level of acetate in the tumor, which is necessary to maintain the activity of CD8+ T cells. In in vivo experiments, the authors observed a reduced level of TME infiltration by cytotoxic T lymphocytes, a decrease in IFN-γ production, and accelerated tumor growth with active metastasis. Similar effects were also observed in an ex vivo study, where women with comorbid depression had lower serum acetate levels, a reduced number of CD8+ T lymphocytes in tumor tissue, and a higher incidence of metastasis.

Thus, stress factors affect the intratumoral microbiome, causing changes in its composition and metabolic activity. Under stress conditions, a decrease in the number of symbiotic bacteria and an increase in pathobionts in tumor tissue are observed, which is accompanied by the formation of an immunosuppressive TME and cancer progression.

Conclusions

The accumulated experimental and clinical data convincingly indicate that both acute and especially chronic stress radically modify the TME, contributing to the progression of malignant neoplasms. Through the activation of the HPA axis and the sympathetic nervous system, stress mediators change the cellular composition of the TME, induce immunosuppression, angiogenesis, EMT, ECM remodeling, and metabolic and oxidative disorders. These changes create a favorable environment for the survival and spread of tumor cells.

It is especially important that these effects are not limited to one component of the TME, but are systemic: they disrupt both the functional activity of immune cells, signaling, and metabolic pathways and the molecular biological characteristics of the TME itself. This allows us to consider stress as one of the key factors determining the course of cancer, regardless of the stage or histological type of the tumor.

In the context of clinical oncology, these findings are of practical importance. On the one hand, they emphasize the need for in-depth study of neurohumoral mechanisms of TME regulation, and on the other hand, they justify the feasibility of integrating psychological support, pharmacological blockade of stress-induced signaling pathways, or other stress control strategies into the overall management plan for cancer patients.

Thus, future research should focus on:

- the molecular interaction between stress mediators and TME cells;
- search for stress-induced molecular biological markers;
- development of combined therapeutic approaches that include not only tumor targeting but also neutralization of the adverse effects of stress.

This opens the way to personalized, comprehensive, and holistic care for patients, taking into account not only biological but also psycho-emotional factors of the disease.

Funding

This study was supported by the Research Program «Development of Technology for Identification of Stress-Induced Factors of Initiation of Bone Tissue Metastatic Lesion» (No. 0125U000655) funded by the National Academy of Sciences of Ukraine

REFERENCES

1. Gold PW, Wong ML. The neuroendocrinology of stress and the importance of a proper balance between the mineralocorticoid and glucocorticoid receptors. *Mol Psychiatry.* 2025;30(1):1-3. https://doi.org/10.1038/s41380-024-02686-3
2. Agorastos A, Chrousos GP. The neuroendocrinology of stress: the stress-related continuum of chronic disease development. *Mol Psychiatry.* 2022;27(1):502-513. https://doi.org/10.1038/s41380-021-01224-9
3. Godoy LD, Rossignoli MT, Delfino-Pereira P, et al. A comprehensive overview on stress neurobiology: basic concepts and clinical implications. *Front Behav Neurosci.* 2018;12:127. https://doi.org/10.3389/fnbeh.2018.00127
4. Herman JP, McKlveen JM, Ghosal S, et al. Regulation of the hypothalamic-pituitary-adrenocortical stress response. *Compr Physiol.* 2016;6(2):603-621. https://doi.org/10.1002/cphy.c150015
5. Meng LB, Zhang YM, Luo Y, et al. Chronic stress a potential suspect zero of atherosclerosis: a systematic review. *Front Cardiovasc Med.* 2021;8:738654. https://doi.org/10.3389/fcvm.2021.738654

6. Aschbacher K, Kornfeld S, Picard M, et al. Chronic stress increases vulnerability to diet-related abdominal fat, oxidative stress, and metabolic risk. *Psychoneuroendocrinology.* 2014;46:14-22. https://doi.org/10.1016/j.psyneuen.2014.04.003
7. Morey JN, Boggero IA, Scott AB, Segerstrom SC. Current directions in stress and human immune function. *Curr Opin Psychol.* 2015;5:13-17. https://doi.org/10.1016/j.copsyc.2015.03.007
8. Hassamal S. Chronic stress, neuroinflammation, and depression: an overview of pathophysiological mechanisms and emerging anti-inflammatories. *Front Psychiatry.* 2023;14:1130989. https://doi.org/10.3389/fpsyt.2023.1130989
9. Dhabhar FS, McEwen BS. Acute stress enhances while chronic stress suppresses cell-mediated immunity in vivo: a potential role for leukocyte trafficking. *Brain Behav Immun.* 1997;11(4):286-306. https://doi.org/10.1006/brbi.1997.0508
10. Lei Y, Liao F, Tian Y, et al. Investigating the crosstalk between chronic stress and immune cells: implications for enhanced cancer therapy. *Front Neurosci.* 2023;17:1321176. https://doi.org/10.3389/fnins.2023.1321176
11. Tian W, Liu Y, Cao C, et al. Chronic stress: impacts on tumor microenvironment and implications for anti-cancer treatments. *Front Cell Dev Biol.* 2021;9:777018. https://doi.org/10.3389/fcell.2021.777018
12. Du X, Jiang F, Fan R, Kong J. Impact of stress on tumor progression and the molecular mechanisms of exercise intervention: from psychological stress to tumor immune escape. *Psycho-Oncologie.* 2025;19(1):3596-3596. https://doi.org/10.18282/po3596
13. O'Rourke K, Huddart S. Surgical stress response and cancer outcomes: a narrative review. *Dig Med Res.* 2020;3:dmr-20-94. https://doi.org/10.21037/dmr-20-94
14. Thapa S, Cao X. Nervous regulation: beta-2-adrenergic signaling in immune homeostasis, cancer immunotherapy, and autoimmune diseases. *Cancer Immunol Immunother.* 2023;72(8):2549-2556. https://doi.org/10.1007/s00262-023-03445-z
15. Antoni MH, Dhabhar FS. The impact of psychosocial stress and stress management on immune responses in patients with cancer. *Cancer.* 2019;125(9):1417-1431. https://doi.org/10.1002/cncr.31943
16. Qin JF, Jin FJ, Li N, et al. Adrenergic receptor β2 activation by stress promotes breast cancer progression through macrophages M2 polarization in tumor microenvironment. *BMB Rep.* 2015;48(5):295-300. https://doi.org/10.5483/bmbrep.2015.48.5.008
17. Cheng Y, Tang XY, Li YX, et al. Depression-induced neuropeptide Y secretion promotes prostate cancer growth by recruiting myeloid cells. *Clin Cancer Res.* 2019;25(8):2621-2632. https://doi.org/10.1158/1078-0432.CCR-18-2912
18. Wu Y, Luo X, Zhou Q, et al. The disbalance of LRP1 and SIRPα by psychological stress dampens the clearance of tumor cells by macrophages. *Acta Pharm Sin B.* 2022;12(1):197-209. https://doi.org/10.1016/j.apsb.2021.06.002
19. Zhao Y, Jia Y, Shi T, et al. Depression promotes hepatocellular carcinoma progression through a glucocorticoid-mediated upregulation of PD-1 expression in tumor-infiltrating NK cells. *Carcinogenesis.* 2019;40(9):1132-1141. https://doi.org/10.1093/carcin/bgz017
20. Varker KA, Terrell CE, Welt M, et al. Impaired natural killer cell lysis in breast cancer patients with high levels of psychological stress is associated with altered expression of killer immunoglobin-like receptors. *J Surg Res.* 2007;139(1):36-44. https://doi.org/10.1016/j.jss.2006.08.037
21. Glasner A, Avraham R, Rosenne E, et al. Improving survival rates in two models of spontaneous postoperative metastasis in mice by combined administration of a beta-adrenergic antagonist and a cyclooxygenase-2 inhibitor. *J Immunol.* 2010;184(5):2449-2457. https://doi.org/10.4049/jimmunol.0903301
22. Zadvornyi T, Lukianova N, Borikun T, et al. Mast cells as a tumor microenvironment factor associated with the aggressiveness of prostate cancer. *Neoplasma.* 2022;69(6):1490-1498. https://doi.org/10.4149/neo_2022_221014N1020
23. Mushii O, Pavlova A, Bazas V, et al. Osteopontin-regulated changes in the mast cell population associated with breast cancer. *Exp Oncol.* 2024;46(3):209-220. https://doi.org/10.15407/exp-oncology.2024.03.209
24. Mushii O, Pavlova A, Bazas V, et al. Mast cells as a factor in regulation of breast cancer stromal component associated with breast cancer aggressiveness. *Exp Oncol.* 2025;46(4):311-323. https://doi.org/10.15407/exp-oncology.2024.04.311
25. Sitte A, Goess R, Tüfekçi T, et al. Correlation of intratumoral mast cell quantity with psychosocial distress in patients with pancreatic cancer: the PancStress study. *Sci Rep.* 2024;14(1):26285. https://doi.org/10.1038/s41598-024-77010-8
26. Liu Y, Fang X, Yuan J, et al. The role of corticotropin-releasing hormone receptor 1 in the development of colitis-associated cancer in mouse model. *Endocr Relat Cancer.* 2014;21(4):639-651. https://doi.org/10.1530/ERC-14-0239
27. Theoharides TC, Rozniecki JJ, Sahagian G, et al. Impact of stress and mast cells on brain metastases. *J Neuroimmunol.* 2008;205(1-2):1-7. https://doi.org/10.1016/j.jneuroim.2008.09.014
28. Esposito P, Chandler N, Kandere K, et al. Corticotropin-releasing hormone and brain mast cells regulate blood-brain-barrier permeability induced by acute stress. *J Pharmacol Exp Ther.* 2002;303(3):1061-1066. https://doi.org/10.1124/jpet.102.038497
29. Baldwin AL. Mast cell activation by stress. *Methods Mol Biol.* 2006;315:349-360. https://doi.org/10.1385/1-59259-967-2:349
30. Kurashima Y, Kiyono H, Kunisawa J. Pathophysiological role of extracellular purinergic mediators in the control of intestinal inflammation. *Med Inflamm.* 2015;2015:427125. https://doi.org/10.1155/2015/427125

31. Wang L, Sikora J, Hu L, et al. ATP release from mast cells by physical stimulation: a putative early step in activation of acupuncture points. *Evid Based Complement Alternat Med.* 2013;2013:350949. https://doi.org/10.1155/2013/350949
32. Gardner A, Ruffell B. Dendritic cells and cancer immunity. *Trends Immunol.* 2016;37(12):855-865. https://doi.org/10.1016/j.it.2016.09.006
33. Sommershof A, Scheuermann L, Koerner J, Groettrup M. Chronic stress suppresses anti-tumor TCD8+ responses and tumor regression following cancer immunotherapy in a mouse model of melanoma. *Brain Behav Immun.* 2017;65:140-149. https://doi.org/10.1016/j.bbi.2017.04.021
34. Maestroni GJ, Mazzola P. Langerhans cells beta 2-adrenoceptors: role in migration, cytokine production, Th priming and contact hypersensitivity. *J Neuroimmunol.* 2003;144(1-2):91-99. https://doi.org/10.1016/j.jneuroim.2003.08.039
35. Matyszak MK, Citterio S, Rescigno M, Ricciardi-Castagnoli P. Differential effects of corticosteroids during different stages of dendritic cell maturation. *Eur J Immunol.* 2000;30(4):1233-1242. https://doi.org/10.1002/(SICI)1521-4141(200004)30:4<1233::AID-IMMU1233>3.0.CO;2-F
36. Ahmed H, Mahmud AR, Siddiquee MF, et al. Role of T cells in cancer immunotherapy: opportunities and challenges. *Cancer Pathog Ther.* 2022;1(2):116-126. https://doi.org/10.1016/j.cpt.2022.12.002
37. de Visser KE, Joyce JA. The evolving tumor microenvironment: from cancer initiation to metastatic outgrowth. *Cancer Cell.* 2023;41(3):374-403. https://doi.org/10.1016/j.ccell.2023.02.016
38. Colon-Echevarria CB, Lamboy-Caraballo R, Aquino-Acevedo AN, Armaiz-Pena GN. Neuroendocrine regulation of tumor-associated immune cells. *Front Oncol.* 2019;9:1077. https://doi.org/10.3389/fonc.2019.01077
39. Budiu RA, Vlad AM, Nazario L, et al. Restraint and social isolation stressors differentially regulate adaptive immunity and tumor angiogenesis in a breast cancer mouse model. *Cancer Clin Oncol.* 2017;6(1):12-24. https://doi.org/10.5539/cco.v6n1p12
40. Nissen MD, Sloan EK, Mattarollo SR. β-adrenergic signaling impairs antitumor CD8+ T-cell responses to B-cell lymphoma immunotherapy. *Cancer Immunol Res.* 2018;6(1):98-109. https://doi.org/10.1158/2326-6066.CIR-17-0401
41. Acharya N, Madi A, Zhang H, et al. Endogenous glucocorticoid signaling regulates CD8+ T cell differentiation and development of dysfunction in the tumor microenvironment. *Immunity.* 2020;53(3):658-671.e6. https://doi.org/10.1016/j.immuni.2020.08.005
42. Geng Q, Li L, Shen Z, et al. Norepinephrine inhibits CD8+ T-cell infiltration and function, inducing anti-PD-1 mAb resistance in lung adenocarcinoma. *Br J Cancer.* 2023;128(7):1223-1235. https://doi.org/10.1038/s41416-022-02132-7
43. Guereschi MG, Araujo LP, Maricato JT, et al. Beta2-adrenergic receptor signaling in CD4+ Foxp3+ regulatory T cells enhances their suppressive function in a PKA-dependent manner. *Eur J Immunol.* 2013;43(4):1001-1012. https://doi.org/10.1002/eji.201243005
44. Qiao G, Chen M, Mohammadpour H, et al. Chronic adrenergic stress contributes to metabolic dysfunction and an exhausted phenotype in T cells in the tumor microenvironment. *Cancer Immunol Res.* 2021;9(6):651-664. https://doi.org/10.1158/2326-6066.CIR-20-0445
45. Kume H, Homma Y, Shinohara N, et al. Perinephric invasion as a prognostic factor in non-metastatic renal cell carcinoma: analysis of a nation-wide registry program. *Jpn J Clin Oncol.* 2019;49(8):772-779. https://doi.org/10.1093/jjco/hyz054
46. Iñigo-Marco I, Alonso MM. Destress and do not suppress: targeting adrenergic signaling in tumor immunosuppression. *J Clin Invest.* 2019;129(12):5086-5088. https://doi.org/10.1172/JCI133115
47. An J, Feng L, Ren J, et al. Chronic stress promotes breast carcinoma metastasis by accumulating myeloid-derived suppressor cells through activating β-adrenergic signaling. *Oncoimmunology.* 2021;10(1):2004659. https://doi.org/10.1080/2162402X.2021.2004659
48. Cao M, Huang W, Chen Y, et al. Chronic restraint stress promotes the mobilization and recruitment of myeloid-derived suppressor cells through β-adrenergic-activated CXCL5-CXCR2-Erk signaling cascades. *Int J Cancer.* 2021;149(2):460-472. https://doi.org/10.1002/ijc.33552
49. Yang EV, Kim SJ, Donovan EL, et al. Norepinephrine upregulates VEGF, IL-8, and IL-6 expression in human melanoma tumor cell lines: implications for stress-related enhancement of tumor progression. *Brain Behav Immun.* 2009;23(2):267-275. https://doi.org/10.1016/j.bbi.2008.10.005
50. Bouchard LC, Antoni MH, Blomberg BB, et al. Postsurgical depressive symptoms and proinflammatory cytokine elevations in women undergoing primary treatment for breast cancer. *Psychosom Med.* 2016;78(1):26-37. https://doi.org/10.1097/PSY.0000000000000261
51. Lukianova N, Mushii O, Zadvornyi T, Chekhun V. Development of an algorithm for biomedical image analysis of the spatial organization of collagen in breast cancer tissue of patients with different clinical status. *FEBS Open Bio.* 2024;14(4):675-686. https://doi.org/10.1002/2211-5463.13773
52. Lukianova N, Zadvornyi T, Mushii O, et al. Evaluation of diagnostic algorithm based on collagen organization parameters for breast tumors. *Exp Oncol.* 2022;44(4):281-286. https://doi.org/10.32471/exp-oncology.2312-8852.vol-44-no-4.19137
53. Hondermarck H, Jobling P. The sympathetic nervous system drives tumor angiogenesis. *Trends Cancer.* 2018;4(2):93-94. https://doi.org/10.1016/j.trecan.2017.11.008

54. Zhao Y, Shen M, Wu L, et al. Stromal cells in the tumor microenvironment: accomplices of tumor progression? *Cell Death Dis.* 2023;14(9):587. https://doi.org/10.1038/s41419-023-06110-6
55. Chen X, Song E. Turning foes to friends: targeting cancer-associated fibroblasts. *Nat Rev Drug Discov.* 2019;18(2):99-115. https://doi.org/10.1038/s41573-018-0004-1
56. Shiga K, Hara M, Nagasaki T, et al. Cancer-associated fibroblasts: their characteristics and their roles in tumor growth. *Cancers (Basel).* 2015;7(4):2443-2458. https://doi.org/10.3390/cancers7040902
57. Nagaraja AS, Dood RL, Armaiz-Pena G, et al. Adrenergic-mediated increases in INHBA drive CAF phenotype and collagens. *JCI Insight.* 2017;2(16):e93076. https://doi.org/10.1172/jci.insight.93076
58. Chekhun V, Mushii O, Zadvornyi T, et al. Features of COL1A1 expression in breast cancer tissue of young patients. *Exp Oncol.* 2023;45(3):351-363. https://doi.org/10.15407/exp-oncology.2023.03.351
59. Lukianova N, Mushii O, Borikun T, et al. Pattern of MMP2 and MMP9 expression depends on breast cancer patients' age. *Exp Oncol.* 2023;45(1):17-27. https://doi.org/10.15407/exp-oncology.2023.01.017
60. Cheng Y, Gao XH, Li XJ, et al. Depression promotes prostate cancer invasion and metastasis via a sympatheticcAMP-FAK signaling pathway. *Oncogene.* 2018;37(22):2953-2966. https://doi.org/10.1038/s41388-018-0177-4
61. Wu X, Liu BJ, Ji S, et al. Social defeat stress promotes tumor growth and angiogenesis by upregulating vascular endothelial growth factor/extracellular signal-regulated kinase/matrix metalloproteinase signaling in a mouse model of lung carcinoma. *Mol Med Rep.* 2015;12(1):1405-1412. https://doi.org/10.3892/mmr.2015.3559
62. Thaker PH, Han LY, Kamat AA, et al. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. *Nat Med.* 2006;12(8):939-944. https://doi.org/10.1038/nm1447
63. Yang EV, Sood AK, Chen M, et al. Norepinephrine up-regulates the expression of vascular endothelial growth factor, matrix metalloproteinase (MMP)-2, and MMP-9 in nasopharyngeal carcinoma tumor cells. *Cancer Res.* 2006;66(21):10357-10364. https://doi.org/10.1158/0008-5472.CAN-06-2496
64. Huang Z, Li G, Zhang Z, et al. β2AR-HIF-1α-CXCL12 signaling of osteoblasts activated by isoproterenol promotes migration and invasion of prostate cancer cells. *BMC Cancer.* 2019;19(1):1142. https://doi.org/10.1186/s12885-019-6301-1
65. Hulsurkar M, Li Z, Zhang Y, et al. Beta-adrenergic signaling promotes tumor angiogenesis and prostate cancer progression through HDAC2-mediated suppression of thrombospondin-1. *Oncogene.* 2017;36(11):1525–1536. https://doi.org/10.1038/onc.2016.319
66. Lu Y, Zhao H, Liu Y, et al. Chronic stress activates PlexinA1/VEGFR2-JAK2-STAT3 in vascular endothelial cells to promote angiogenesis. *Front Oncol.* 2021;11:709057. https://doi.org/10.3389/fonc.2021.709057
67. Zhou J, Liu Z, Zhang L, et al. Activation of β2-adrenergic receptor promotes growth and angiogenesis in breast cancer by down-regulating PPARγ. *Cancer Res Treat.* 2020;52(3):830-847. https://doi.org/10.4143/crt.2019.510
68. Le CP, Nowell CJ, Kim-Fuchs C, et al. Chronic stress in mice remodels lymph vasculature to promote tumour cell dissemination. *Nat Commun.* 2016;7:10634. https://doi.org/10.1038/ncomms10634
69. Shan T, Cui X, Li W, et al. Novel regulatory program for norepinephrine-induced epithelial-mesenchymal transition in gastric adenocarcinoma cell lines. *Cancer Sci.* 2014;105(7):847-856. https://doi.org/10.1111/cas.12438
70. Zhang P, Liu Y, Feng Y, Gao S. SNAIL gene inhibited by hypoxia-inducible factor 1α (HIF-1α) in epithelial ovarian cancer. *Int J Immunopathol Pharmacol.* 2016;29(3):364-375. https://doi.org/10.1177/0394632016641423
71. Perego M, Tyurin VA, Tyurina YY, et al. Reactivation of dormant tumor cells by modified lipids derived from stress-activated neutrophils. *Sci Transl Med.* 2020;12(572):eabb5817. https://doi.org/10.1126/scitranslmed.abb5817
72. Cui B, Luo Y, Tian P, et al. Stress-induced epinephrine enhances lactate dehydrogenase A and promotes breast cancer stem-like cells. *J Clin Invest.* 2019;129(3):1030-1046. https://doi.org/10.1172/JCI121685
73. Aboelella NS, Brandle C, Kim T, Ding ZC, Zhou G. Oxidative stress in the tumor microenvironment and its relevance to cancer immunotherapy. *Cancers (Basel).* 2021;13(5):986. https://doi.org/10.3390/cancers13050986
74. Zahalka AH, Arnal-Estapé A, Maryanovich M, et al. Adrenergic nerves activate an angio-metabolic switch in prostate cancer. *Science*. 2017;358(6361):321-326. https://doi.org/10.1126/science.aah5072
75. Seebacher NA, Krchniakova M, Stacy AE, et al. Tumour microenvironment stress promotes the development of drug resistance. *Antioxidants (Basel)*. 2021;10(11):1801. https://doi.org/10.3390/antiox10111801
76. Zemanová N, Anzenbacher P, Zapletalová I, et al. The role of the microbiome and psychosocial stress in the expression and activity of drug metabolizing enzymes in mice. *Sci Rep*. 2020;10(1):8529. https://doi.org/10.1038/s41598-020-65595-9
77. Yang L, Li A, Wang Y, Zhang Y. Intratumoral microbiota: roles in cancer initiation, development and therapeutic efficacy. *Signal Transduct Target Ther.* 2023;8(1):35. https://doi.org/10.1038/s41392-022-01304-4
78. Zhang T, Gao G, Sakandar HA, et al. Gut dysbiosis in pancreatic diseases: a causative factor and a novel therapeutic target. *Front Nutr.* 2022;9:814269. https://doi.org/10.3389/fnut.2022.814269
79. Leigh SJ, Uhlig F, Wilmes L, et al. The impact of acute and chronic stress on gastrointestinal physiology and function: a microbiota-gut-brain axis perspective. *J Physiol.* 2023;601(20):4491-4538. https://doi.org/10.1113/JP281951
80. Niu L, Gao M, Wen S, et al. Effects of catecholamine stress hormones norepinephrine and epinephrine on growth, antimicrobial susceptibility, biofilm formation, and gene expressions of enterotoxigenic *Escherichia coli*. *Int J Mol Sci.* 2023;24(21):15646. https://doi.org/10.3390/ijms242115646

81. Cao Q, Zhao M, Su Y, et al. Chronic stress dampens *Lactobacillus johnsonii*-mediated tumor suppression to enhance colorectal cancer progression. *Cancer Res.* 2024;84(5):771-784. https://doi.org/10.1158/0008-5472.CAN-22-3705
82. He Z, Liu C, Lan P. Association of gut microbe and stress-related cancer metastasis and oleic acid degradation. *J Clin Oncol.* 2024;42:e15517. https://doi.org/10.1200/JCO.2024.42.16_suppl.e15517
83. Zhao L, Hou X, Feng Y, et al. A chronic stress-induced microbiome perturbation, highly enriched in Ruminococcaceae_UCG-014, promotes colorectal cancer growth and metastasis. *Int J Med Sci.* 2024;21(5):882–895. https://doi.org/10.7150/ijms.90612
84. Ye L, Hou Y, Hu W, et al. Repressed Blautia-acetate immunological axis underlies breast cancer progression promoted by chronic stress. *Nat Commun.* 2023;14(1):6160. https://doi.org/10.1038/s41467-023-41817-2

Submitted: May 05, 2025

В. Чехун, Т. Бурда, О. Мушій, А. Павлова,
Т. Борікун, Т. Задворний, Н. Лук'янова

Інститут експериментальної патології, онкології та радіобіології
ім. Р.Є. Кавецького НАН України, Київ, Україна

СТРЕС-ІНДУКОВАНА МОДУЛЯЦІЯ ПУХЛИННОГО МІКРООТОЧЕННЯ: МЕХАНІЗМИ ТА НАСЛІДКИ ДЛЯ ПРОГРЕСУВАННЯ РАКУ

Хронічний стрес є одним із ключових екзогенних факторів, що можуть суттєво впливати на біологію пухлинних клітин шляхом порушення регуляції пухлинного мікрооточення (ПМО), сприяючи таким чином маніфестації пухлинного процесу. Активація гіпоталамо-гіпофізарно-наднирникової осі та симпатичної нервової системи, індукована стресовими чинниками, призводить до секреції глюкокортикоїдів і катехоламінів, які сприяють дерегуляції компонентів мікрооточення, що визначають агресивність злоякісних новоутворень. У цьому огляді систематизовано сучасні уявлення щодо впливу сигналів, індукованих стресом, на імунні, стромальні, судинні та метаболічні компоненти ПМО та проаналізовано їхній внесок у формування агресивного фенотипу пухлини. Особлива увага приділяється взаємозв'язку нейрогуморального стресу, кишкового та внутрішньопухлинного мікробіому, які формують складне мережеве середовище, що підтримує прогресію пухлини. Поглиблення розуміння молекулярних взаємодій між медіаторами стресу та клітинними елементами ПМО створить підґрунтя для розробки інноваційних терапевтичних стратегій, спрямованих не лише на саму пухлину, а й на мінімізацію несприятливого впливу стресу на окремі компоненти пухлинного мікрооточення.

Ключові слова: стрес, пухлинне мікрооточення, пухлинна прогресія.