Psychological stress and tumor progression: Molecular mechanisms and therapeutic implications (Review)

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Abstract. Psychological stress contributes to tumor progression through a number of biological pathways. Activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system induces the release of stress-related mediators, including catecholamines and glucocorticoids, which regulate tumor development and metastasis. The present review summarizes the molecular mechanisms underlying stress-mediated cancer progression at the cellular, immune and neural levels. At the cellular level, stress hormones modulate tumor cell proliferation, autophagy, metabolic reprogramming and stemness maintenance through signaling pathways such as dopamine receptor D2 (DRD2)/ERK/β-catenin and β2-adrenergic receptor/cyclic adenosine monophosphate (cAMP)/protein kinase A/cAMP-response element-binding protein. Within the tumor microenvironment, psychological stress promotes the accumulation of myeloid-derived suppressor cells, induces T-cell exhaustion, facilitates M2 macrophage polarization and enhances angiogenesis and lymphatic remodeling, collectively contributing to an immunosuppressive microenvironment. In addition, sympathetic, parasympathetic and sensory neurons directly regulate tumor cell behavior through pseudosynaptic interactions and neurotransmitter release, including glutamate, acetylcholine and norepinephrine, thereby establishing a neuro-immune-tumor regulatory network. Based on these mechanisms, emerging therapeutic strategies, including β-blockers, inhibitors targeting DRD2, lactate dehydrogenase A and G protein-coupled receptor kinase 3, neuromodulation approaches and psychosocial interventions, have demonstrated potential therapeutic value in preclinical and clinical studies. The present review systematically summarizes the complex molecular pathways associating psychological stress to tumor progression. Despite notable advances, challenges remain in understanding tumor-specific heterogeneity in stress signaling pathways and the spatiotemporal regulation of neuro-immune-tumor interactions. Future studies focusing on multimodal combination strategies may provide novel insights for integrating stress management into comprehensive cancer therapy.

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Contents

1. Introduction

Cancer is one of the leading causes of mortality worldwide, accounting for nearly 10 million deaths in 2020 (1), and its initiation and progression are associated with lifestyle, environmental exposure and genetic susceptibility. In recent years, increasing attention has been directed toward the role of psychosocial factors in tumor development with accumulating evidence demonstrating that chronic stress promotes tumor progression through neuroendocrine-mediated modulation of the tumor microenvironment, including effects on tumor cell stemness, metastasis and immune evasion (2-4). Following a cancer diagnosis, patients experiencing chronic psychological stress typically exhibit shortened survival, increased metastatic risk and accelerated disease progression (5,6). Epidemiological studies (7,8) have reported associations between persistent stress-related conditions, including anxiety, depression and social isolation and the risk of certain cancers; however, the strength and consistency of these associations vary across cancer types and study populations (9). For example, pretreatment emotional distress has been associated with worse clinical outcomes in patients with melanoma, including a lower

response to immune checkpoint blockade and an increased risk of disease progression (10). Although behavioral and treatment-associated factors may contribute to these associations, experimental studies (11,12) support the biological plausibility that stress-related neuroendocrine signaling may also influence tumor progression.

The physiological stress response primarily involves activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, leading to the release of glucocorticoids and catecholamines, including norepinephrine (NE) and epinephrine. These stress mediators subsequently activate intracellular signaling cascades by binding to specific receptors, such as β2-adrenergic and glucocorticoid receptors, across numerous cell types (13). Early studies (14,15) mainly focused on stress-induced immune suppression, suggesting that impaired immune surveillance represents a major mechanism underlying stress-mediated tumor progression. For example, chronic stress decreases natural killer (NK) cell cytotoxicity and impairs T-cell function, thereby weakening antitumor immunity (16). However, studies (9,14) using immunodeficient mouse models have demonstrated that chronic stress can still accelerate tumor growth, indicating that stress may also exert direct tumor-promoting effects independent of immune regulation.

Over the past decade, accumulating evidence has demonstrated that stress signaling directly regulates tumor cell behavior through a number of molecular pathways. For example, NE activates the adenosine monophosphate-activated protein kinase (AMPK)-UNC-51 like autophagy activating kinase 1 (ULK1) pathway through β2-adrenergic receptor (ADRB2) signaling, thereby inducing protective autophagy and promoting gastric cancer cell survival (17,18). In colorectal cancer, chronic stress enhances glycolytic enzyme expression through the β2-AR/protein kinase A (PKA)/cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) signaling cascade, leading to metabolic reprogramming and increased energy metabolism in tumor cells (19). Similarly, in breast cancer, epinephrine promotes cancer stem cell-like properties through activation of the lactate dehydrogenase A (LDHA)/ubiquitin-specific protease 28 (USP28)/MYC/snail family transcriptional repressor 2 (SLUG) pathway (20). An *et al* (21) showed chronic psychological stress notably influences the tumor microenvironment by promoting the expansion of myeloid-derived suppressor cells (MDSCs) through the β-AR/IL-6/STAT3 signaling pathway, thereby facilitating metastasis in breast cancer. Adrenergic signaling also impairs antitumor immunity by inducing metabolic dysfunction and exhaustion of $CD8^+$ T cells (22). Advances have also been achieved in the emerging field of neuro-tumor interactions. Magnon *et al* (23) demonstrated that sympathetic denervation markedly suppresses prostate cancer progression. Emerging evidence indicates that sensory neurons communicate directly with pancreatic cancer cells through glutamate-mediated pseudosynaptic interactions, thereby promoting tumor progression (24). Notwithstanding recent progress, key issues persist, such as the tumor-specific variability in stress signaling pathways, the temporal and spatial regulation of neuro-immune-tumor interactions and the combined influence of numerous stress-associated mechanisms. In addition, clinical translation remains challenging, particularly regarding patient stratification and the development of effective combination therapeutic strategies. Therefore, systematic investigation of stress-mediated tumor progression from the perspectives of tumor cell-intrinsic signaling, tumor microenvironment remodeling and neuro-tumor interactions is required. A deeper understanding of these mechanisms may provide a theoretical basis for integrating stress management into comprehensive cancer treatment and facilitating the clinical translation of novel therapeutic strategies.

The present review summarizes stress-mediated tumor progression from five interconnected biological perspectives, including tumor cell-intrinsic adaptation, metabolic reprogramming, immune suppression, neuro-tumor communication and angiogenic/metastatic remodeling, while discussing current evidence, limitations and future translational opportunities. A summary of representative cancer types, stress models, experimental systems and clinical relevance is provided in Table I.

2. Tumor cell-intrinsic adaptation under psychological stress

Adrenergic signaling promotes tumor survival

Cell survival and protective autophagy. The ADRB2/cAMP/PKA/CREB signaling pathway is widely recognized (18,25) as a central mechanism mediating the transmission of stress-related signals in tumor cells. In a number of malignancies, including gastric, colorectal and breast cancer, this pathway promotes tumor cell proliferation, inhibits apoptosis and enhances protective autophagy. Stress hormones directly bind to ADRB2, a G protein-coupled receptor, resulting in increased intracellular cAMP levels and subsequent activation of PKA. Activated PKA further phosphorylates downstream transcription factors, particularly cAMP response element-binding protein. Upon phosphorylation, CREB moves into the nucleus, where it modulates the transcription of genes involved in cell survival, such as Bcl-2, cyclin D1 and autophagy-related genes such as Bcl-2, cyclin D1, Beclin-1 and BNIP3, thereby promoting tumor cell viability (26).

Previous studies have demonstrated that induction of autophagy represents an important downstream consequence of β2-AR activation in gastric cancer cells. Specifically, NE activates the AMPK-ULK1 signaling pathway through the ADRB2/cAMP/PKA/CREB axis (27). Studies (28,29) have indicated that, during specific forms of regulated mitophagy, AMPK modulates autophagic activity through phosphorylation of ULK1 at serine residues 556 and 694). Collectively, the findings suggest that the ADRB2/cAMP/PKA/CREB signaling pathway promotes protective autophagy through activation of the AMPK-ULK1 axis, thereby supporting tumor cell survival under stress conditions. This adaptive mechanism enables malignant cells to tolerate nutrient deprivation and hypoxia, ultimately facilitating tumor progression (Fig. 1).

Another important downstream consequence of ADRB2 activation is the regulation of CREB-dependent transcription. In colorectal cancer, catecholamine stimulation activates the cAMP/PKA signaling pathway through β2-ARs, resulting in CREB1 phosphorylation and transcriptional activation of glycolytic enzymes (30).

Table I. Representative evidence supporting stress-associated mechanisms in cancer progression.

Cancer type	Stress model/ stress measurement	Major pathway	Experimental system	Biological outcome	Clinical relevance
Gastric	Chronic stress/ norepinephrine stimulation	ADRB2-AMPK-ULK1	Cell line + mouse model	Protective autophagy and survival	Potential stress-targeted therapy
Breast cancer	Chronic unpredictable stress	β-AR/IL-6/STAT3	Mouse model	MDSC expansion and metastasis	Immune suppression
Melanoma	Adrenergic stress	β-AR signaling	Mouse model + clinical samples	$CD8^+$ T cell exhaustion	Immunotherapy response
Glioblastoma	Chronic stress	DRD2/ERK/β-catenin	Cell + animal model	Tumor progression	Potential DRD2 targeting
Pancreatic ductal adenocarcinoma	Neuron-derived glutamate	NMDAR2D/GRIN2D	Mouse model + molecular analysis	Neural invasion	Neuro-tumor therapeutic target
Prostate cancer	Sympathetic innervation	ADRB2/ADRB3	Mouse model	Tumor progression	Clinical translation challenges

ADRB2, β2-adrenergic receptor; AMPK, adenosine monophosphate-activated protein kinase; ULK1, UNC-51 like autophagy activating kinase 1; β-AR, β-adrenergic receptor; MDSC, myeloid-derived suppressor cells; DRD2, dopamine receptor D2; NMDAR2D/GRIN2D, N-methyl-D-aspartate receptor subunit 2D.

ADRB2-mediated calcium signaling and insulin-like growth factor 2 (IGF2) secretion. The ADRB2/PKA/voltage-dependent calcium channel (VDCC)/Ca^{2+}/IGF2 signaling pathway functions as an important signal amplification mechanism in stress-mediated tumor progression. Through calcium-dependent exocytosis, the pathway rapidly promotes the release ofIGF2, which subsequently activate downstream signaling pathways associated with tumor cell survival. In lung cancer, activation of this signaling cascade enhances the survival of lung epithelial cells and contributes to tumorigenesis (31).

NE activates the ADRB2/cAMP/PKA signaling pathway, which subsequently stimulates L-type VDCCs and induces Ca^{2+} influx. The resulting calcium-dependent exocytosis promotes the secretion of IGF2, leading to sustained activation of IGF-1 receptor (IGF-1R) signaling. Consequently, this signaling cascade facilitates the acquisition of tumor-associated phenotypes by lung epithelial cells and supports the survival of precancerous cells despite carcinogen-induced genetic damage, thereby promoting lung tumorigenesis (Fig. 2) (31).

Collectively, these observations suggest that VDCCs represent a promising therapeutic target for interrupting stress-induced calcium signaling (32).

Mechanistically, the ADRB2/PKA/VDCC/Ca^{2+}/IGF2 axis illustrates that adrenergic signaling amplifies tumor progression not only through intracellular signaling but also by promoting calcium-dependent growth factor secretion.

Angiogenic signaling. The Notch signaling pathway serves as an important mediator associating stress-related signaling to tumor angiogenesis and primarily contributes to the pro-angiogenic effects induced by catecholamines. Catecholamines upregulate the expression of Jagged1, a signaling molecule targeting the Notch receptor through activation of the β2-AR/PKA/mTOR signaling pathway. Increased Jagged1 expression subsequently activates Notch signaling in endothelial cells of blood vessels, thereby promoting the proliferation of tumor-associated vascular endothelium.

In breast cancer, NE stimulation increases the expression of the Notch ligand Jagged1 in tumor cells, which subsequently activates Notch signaling in adjacent endothelial cells. Pharmacological inhibition of β2-AR, PKA or mTOR signaling markedly attenuates Jagged1 induction, highlighting the key role of the β2-AR/PKA/mTOR axis in stress-induced angiogenic signaling (33). Activation of endothelial Notch signaling further enhances vascular endothelial activity and promotes tumor angiogenesis, as demonstrated in both *in vitro* co-culture systems and mouse xenograft models (34,35).

Beyond Jagged1-mediated signaling, other Notch ligands also contribute to tumor vascular remodeling. Delta-like ligand 4, a key regulator of vascular development, has been shown to modulate tumor angiogenesis and represents a potential therapeutic target for anti-angiogenic strategies (35). Collectively, these findings suggest that stress-associated adrenergic signaling promotes tumor angiogenesis not only through direct regulation of pro-angiogenic factors but also through tumor-endothelial communication mediated by Notch signaling.

Dopamine (DA) signaling promotes tumor plasticity

DA receptor D2 (DRD2)/ERK/β-catenin signaling. The DRD2/ERK/β-catenin signaling pathway represents an important mechanism through which DA-mediated signaling promotes tumor progression, particularly in glioblastoma (GBM).

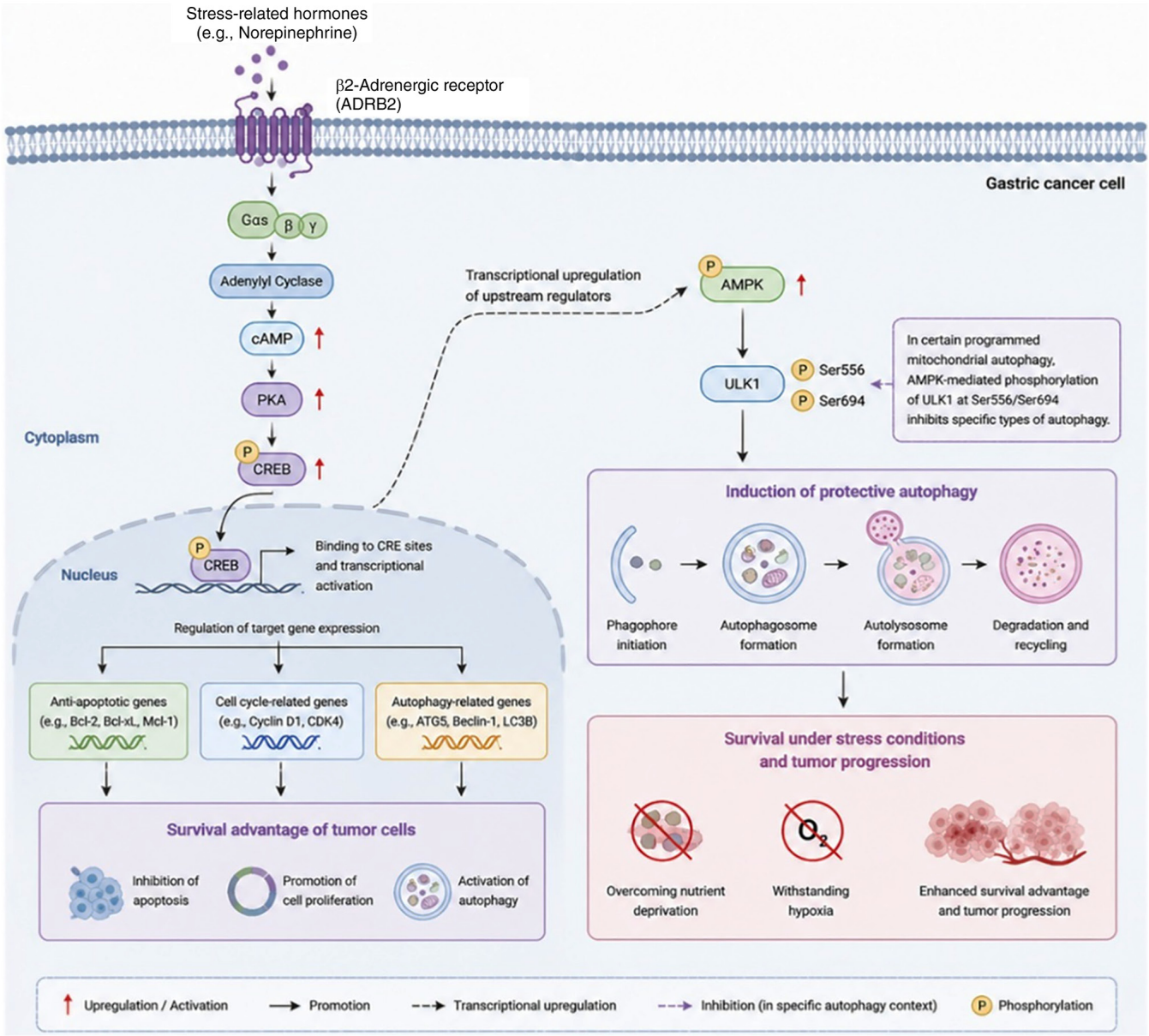

Figure 1. Schematic representation of the ADRB2/cAMP/PKA/CREB signaling cascade. Norepinephrine, a stress-associated hormone, triggers the activation of the ADRB2, which then initiates the adenylate cyclase-mediated cAMP/PKA signaling pathway. Downstream, CREB is phosphorylated and translocates into the nucleus. This drives higher expression of genes associated to anti-apoptotic effects (Bcl-2), cell cycle advancement (Cyclin D1) and autophagy regulation (ATG5, Beclin-1 and LC3B). In parallel, this signaling pathway enhances protective autophagy through stimulation of the AMPK-ULK1 axis, allowing tumor cells to survive under nutrient deprivation and hypoxic conditions, thereby providing a net survival benefit. ADRB2, β2-adrenergic receptor; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; CREB, cAMP response element-binding protein; AMPK, AMP-activated protein kinase; ULK1, UNC-51-like kinase 1; CRE, cAMP response element; ATG5, autophagy protein 5; LC3B, microtubule-associated protein 1 light chain 3β.

Chronic psychological stress increases DA production in GBM, leading to activation of DRD2 signaling. Sustained DRD2 activation stimulates the ERK signaling pathway, which suppresses glycogen synthase kinase-3β (GSK3β) activity and promotes β-catenin stabilization and nuclear translocation. Activated β-catenin subsequently drives transcriptional programs associated with tumor proliferation, stemness and malignant progression. In parallel, ERK1/2 signaling upregulates tyrosine hydroxylase (TH), the rate-limiting enzyme in DA biosynthesis, thereby increasing DA production and establishing an autocrine positive-feedback loop that further amplifies DRD2 signaling. Collectively, the DRD2/ERK/β-catenin signaling axis and the DA/ERK/TH regulatory circuit reinforce stress-induced glioblastoma progression through sustained activation of oncogenic signaling (36).

DRD2-mediated stabilization of hypoxia-inducible factor-1α (HIF-1α) promotes epithelial-mesenchymal transition (EMT). Beyond activation of the ERK/β-catenin pathway, DRD2 also promotes tumor progression by stabilizing HIF-1α. Within the nucleus, DRD2 interacts with the tumor suppressor von Hippel-Lindau (VHL) protein and competes with HIF-1α for VHL binding. This interaction reduces the ubiquitin-mediated degradation of HIF-1α, leading to its stabilization and subsequent induction of EMT. During EMT, epithelial cells lose polarity and intercellular

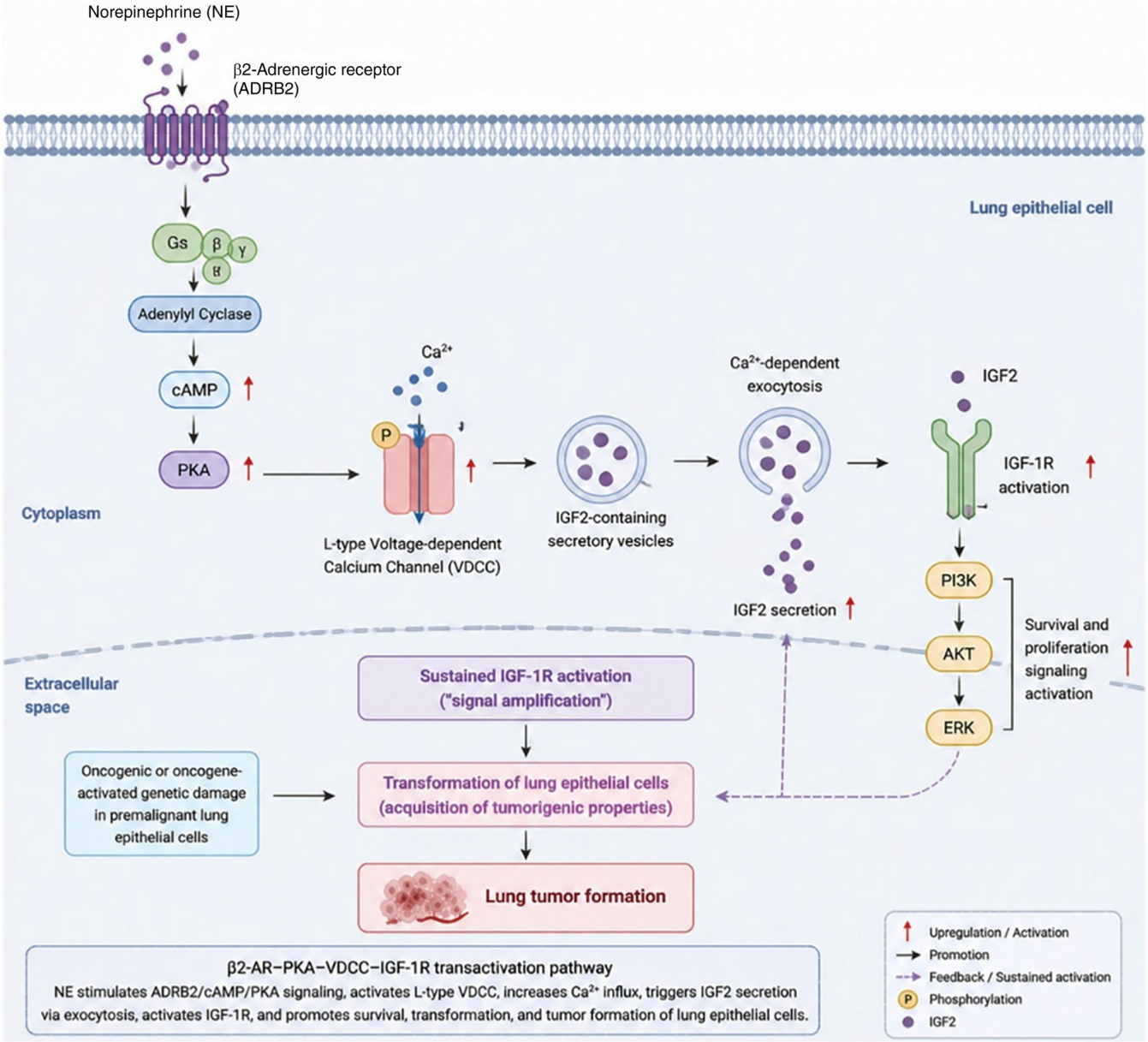

Figure 2. Schematic representation of the ADRB2/PKA/VDCC/Ca^{2+}/IGF2 signaling pathway. Norepinephrine triggers the ADRB2/cAMP/PKA signaling cascade, which then activates L-type VDCCs and allows Ca^{2+} ions to enter the cell. This Ca^{2+}-dependent exocytosis boosts IGF2 secretionand the released IGF2 continuously activates the IGF-1R, ultimately driving the malignant transformation of pulmonary epithelial cells. ADRB2, β2-adrenergic receptor; PKA, protein kinase A; VDCC, voltage-dependent calcium channel; IGF2, insulin-like growth factor 2; IGF-1R, IGF-1 receptor; cAMP, cyclic adenosine monophosphate.

adhesion while acquiring mesenchymal characteristics, ultimately enhancing migratory and invasive capacities and facilitating tumor metastasis (37).

Collectively, these findings indicate that DRD2 contributes to tumor progression through a number of mechanisms. In addition to promoting proliferative signaling, DRD2 enhances tumor cell plasticity by stabilizing HIF-1α and inducing EMT, thereby expanding the spectrum of stress-induced malignant phenotypes.

Stress-induced metabolic reprogramming. Unlike genetic alterations that constitutively rewire cancer metabolism, psychological stress induces a dynamic metabolic adaptation through neuroendocrine signaling. Recent studies (38,39) indicate that stress hormones and neuron-derived neurotransmitters converge on glycolytic pathways to support tumor cell survival, stemness and metastatic dissemination.

In breast cancer, chronic stress-induced adrenergic signaling promotes metabolic reprogramming through activation of the LDHA/USP28/MYC/SLUG axis. Stress-released adrenaline enhances LDHA activity, resulting in increased lactate production and intracellular acidification. The altered intracellular pH environment facilitates USP28-mediated deubiquitination and stabilization of the oncogenic transcription factor MYC. Stabilized MYC subsequently activates SLUG transcription, promoting the acquisition of breast cancer stem cell-like properties and enhancing tumor cell plasticity (40).

In pancreatic ductal adenocarcinoma (PDAC), stress-associated metabolic reprogramming can also be mediated through direct neuron-tumor communication. Neuron-derived glutamate promotes glycolytic adaptation in pancreatic ductal adenocarcinoma cells by inducing Ca^{2+} influx and activating the calcium/calmodulin-dependent protein kinase (CaMK)II/ERK-MAPK signaling cascade. This pathway enhances hexokinase 2 expression through m6A RNA modification, resulting in increased glycolytic activity that supports tumor growth and metastatic dissemination. In addition, glutamate release from sensory neurons is regulated by the IGF-1/IGF-1R/transient receptor potential vanilloid 1/PI3K/Akt signaling axis, establishing a reciprocal regulatory interaction between pancreatic cancer cells and surrounding neural components (41).

Collectively, these findings suggest that metabolic reprogramming is a common downstream consequence of stress signaling in cancer. Although different tumor types utilize distinct upstream mediators, both adrenergic hormones and neuron-derived neurotransmitters ultimately enhance glycolytic activity to support tumor cell survival, stemness and metastatic progression. However, current evidence is largely based on experimental models, and further studies are required to determine whether these mechanisms are broadly applicable across different human cancers (Table II).

3. Pressure-induced reshaping of the tumor microenvironment

In addition to directly reshaping tumor cell metabolism, chronic stress profoundly alters the composition and function of immune cells within the tumor microenvironment.

Stress-induced expansion of MDSCs. Chronic psychological stress promotes the expansion of MDSCs, a heterogeneous population of immature myeloid cells that serve a central role in tumor immune evasion. In a chronic unpredictable stress model, activation of β1- and β2-ARs stimulated the IL-6/STAT3 signaling pathway, leading to MDSC expansion and enhanced pulmonary metastasis. Pharmacological inhibition of IL-6/STAT3 attenuated MDSC accumulation and reduced metastatic dissemination, highlighting the importance of β-adrenergic signaling in stress-induced immunosuppression (42).

These findings indicate that chronic stress promotes tumor immune evasion by expanding immunosuppressive myeloid populations, thereby creating a microenvironment permissive for metastatic progression.

$CD8^+$ T-cell dysfunction and exhaustion. Chronic stress-induced adrenergic signaling impairs the antitumor activity of $CD8^+$ T cells by promoting an exhausted phenotype. In melanoma, activation of AR signaling upregulates inhibitory receptors, including programmed cell death protein 1 (PD-1) and T-cell immunoglobulin and mucin-domain containing-3 (Tim-3), thereby driving $CD8^+$ T-cell exhaustion. This exhausted state is further characterized by metabolic dysfunction and impaired effector function, ultimately contributing to immunosuppression within the tumor microenvironment (43).

Accumulating evidence suggests that metabolic fitness is a key determinant of $CD8^+$ T-cell antitumor activity. Within the tumor microenvironment, metabolic competition between tumor cells and immune cells may further aggravate stress-induced T-cell dysfunction by limiting nutrient availability and impairing cellular bioenergetics. Consequently, stress-associated immune suppression may involve not only immune checkpoint activation but also immune metabolic reprogramming, providing a potential mechanistic association between chronic stress and resistance to cancer immunotherapy. Together, these findings indicate that immune checkpoint signaling, and immune metabolic dysfunction may cooperatively contribute to stress-associated immunosuppression and reduced responsiveness to immunotherapy (44,45).

Stress-induced macrophage polarization. Chronic stress promotes macrophage polarization toward an immunosuppressive M2-like phenotype within the lung tumor microenvironment. Elevated expression of the long non-coding RNA, HIF1A-antisense RNA 3 (AS3), activates HIF-1α signaling through interaction with Y-box binding protein 1, establishing a positive feedback loop that sustains HIF1A-AS3/HIF-1α activation. This signaling axis induces M2-like macrophage polarization, enhances macrophage motility and impairs macrophage phagocytic activity, thereby promoting immune evasion and lung cancer progression (Fig. 3) (46).

Chronic stress reshapes the immune microenvironment not only by altering immune cell composition but also by reprogramming macrophage phenotype toward an immunosuppressive state.

Stress-induced NK-cell dysfunction. Chronic stress suppresses NK cell-mediated antitumor immunity through neuroimmune interactions within the pancreatic tumor microenvironment.

In pancreatic cancer, elevated integrin α-5 (ITGA5) expression enhances interactions between tumor cells and Schwann cells (SCs), thereby promoting perineural invasion (PNI). SCs subsequently undergo a transition toward a repair-like phenotype and secrete nerve growth factor (NGF), which stimulates neurogenesis while simultaneously suppressing IFN-γ-mediated NK-cell cytotoxicity. The resulting impairment of NK-cell function contributes to immune evasion and pancreatic cancer progression (47). These findings suggest that stress-associated neuroimmune interactions impair NK-cell-mediated tumor surveillance, thereby associating PNI with immune suppression in pancreatic cancer.

Stress-induced neutrophil activation and neutrophil extracellular traps (NET) formation. Neutrophils represent another important immune component affected by chronic stress within the tumor microenvironment. Stress-induced glucocorticoid release promotes neutrophil activation and the formation of NETs, thereby creating an immunologically permissive environment that favors tumor progression. NET formation contributes to metastatic dissemination by altering the surrounding stromal environment and promoting interactions between immune cells, fibroblasts and tumor cells (48). Following NET induction, activated fibroblasts increase fibronectin production and release MMPs, resulting in extracellular

Table II. Major stress-induced signaling pathways underlying tumor cell-intrinsic adaptation.

Biological theme	Stress mediator	Major signaling pathway	Representative tumor	Major biological effect
Cell survival and protective autophagy	NE	ADRB2/cAMP/PKA/CREB → AMPK/ULK1	Gastric cancer	Cell survival and protective autophagy
Calcium-dependent growth factor secretion	NE	ADRB2/PKA/VDCC/Ca^{2+}/IGF2	Lung cancer	Growth factor secretion and tumor initiation
Angiogenic signaling	Catecholamines	ADRB2/PKA/mTOR/Jagged1/Notch	Breast cancer	Angiogenesis
Tumor plasticity	DA	DRD2/ERK/β-catenin	Glioblastoma	Proliferation and stemness
EMT	DA	DRD2/VHL/HIF-1α	Numerous tumors	EMT and invasion
Metabolic reprogramming	Adrenaline	LDHA/USP28/MYC/SLUG	Breast cancer	Glycolysis and stemness
Metabolic reprogramming	Glutamate	CaMKII/ERK/HK2	Pancreatic ductal adenocarcinoma	Glycolysis and metastasis

NE, norepinephrine; DA, dopamine; ADRB2, β2-adrenergic receptor; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; CREB, cAMP response element-binding protein; AMPK, AMP-activated protein kinase; ULK1, UNC-51-like kinase 1; IGF2, insulin-like growth factor 2; DRD2, dopamine receptor D2; VHL, von Hippel-Lindau; HIF-1α, hypoxia-inducible factor 1-α; LDHA, lactate dehydrogenase A; USP28, ubiquitin-specific protease 28; SLUG, snail family transcriptional repressor 2; CaMKII, calcium/calmodulin-dependent protein kinase II; HK2, hexokinase 2; EMT, epithelial-mesenchymal transition.

matrix (ECM) remodeling. These changes enhance tumor cell migration and invasion, associating stress-induced immune alterations with metastatic progression (Fig. 4; Table III) (48).

4. Neuro-tumor communication and neuroimmune regulation

Sympathetic nerve-tumor communication. Sympathetic nerve fibers are actively present within the tumor microenvironment and represent a notable source of catecholamine signals. NE released from sympathetic terminals directly regulates tumor cell behavior through AR, particularly ADRB2. In gastric cancer, sympathetic-derived NE activates ADRB2-mediated AMPK-ULK1 signaling, promoting protective autophagy and enabling tumor cells to survive under stress conditions (27). In prostate cancer, sympathetic denervation or genetic disruption of ADRB2/ADRB3 signaling markedly suppresses tumor progression, highlighting the functional importance of sympathetic innervation in tumor development (49). In genitourinary malignancy, the effects of stress-related signaling may also be shaped by sex hormone receptor activity and the tissue-specific immune microenvironment. In prostate cancer, androgen receptor signaling may interact with adrenergic and glucocorticoid pathways to regulate tumor cell plasticity, inflammatory signaling and immune-cell recruitment. In bladder cancer, sex hormone receptor expression and sex-associated differences in immune composition may likewise influence the biological consequences of chronic stress. These observations suggest that adrenergic and glucocorticoid signaling should not be considered in isolation, but rather within the broader context of hormone-dependent and immune-regulatory networks in genitourinary tumors (50).

Beyond direct regulation of tumor cells, sympathetic signaling also reshapes the surrounding tumor ecosystem. NE released from sympathetic nerves activates cAMP/PKA-dependent transcriptional programs, including CREB, NF-κB and STAT3, which promote angiogenic and metastatic responses through regulation of VEGF and MMP (51). In addition, chronic psychological stress enhances sympathetic activation, increasing NE levels in circulation and tumor tissues. This sustained adrenergic stimulation promotes tumor growth and immune remodeling, including β-adrenergic-mediated recruitment of myeloid cells through the C-X-C motif chemokine receptor type 2/C-X-C motif chemokine ligand 2/C-X-C motif chemokine ligand 2 pathway in hepatocellular carcinoma (52,53).

Collectively, these findings establish sympathetic innervation as an important regulator of tumor biology by integrating neural signals with tumor cell adaptation, immune remodeling, angiogenesis and metastatic progression. However, the biological consequences of sympathetic signaling are likely to vary according to tumor lineage, hormone receptor status and the composition of the local immune microenvironment. Further studies are therefore needed to elucidate the spatial organization, temporal dynamics and clinical importance of sympathetic innervation across different tumor types.

Parasympathetic nerve-tumor communication. The parasympathetic nervous system exerts context-dependent effects on tumor progression, with both tumor-promoting and tumor-suppressive functions observed across different cancer types. Unlike sympathetic signaling, which is generally associated with stress-induced tumor progression, parasympathetic signaling appears to regulate tumor behavior through

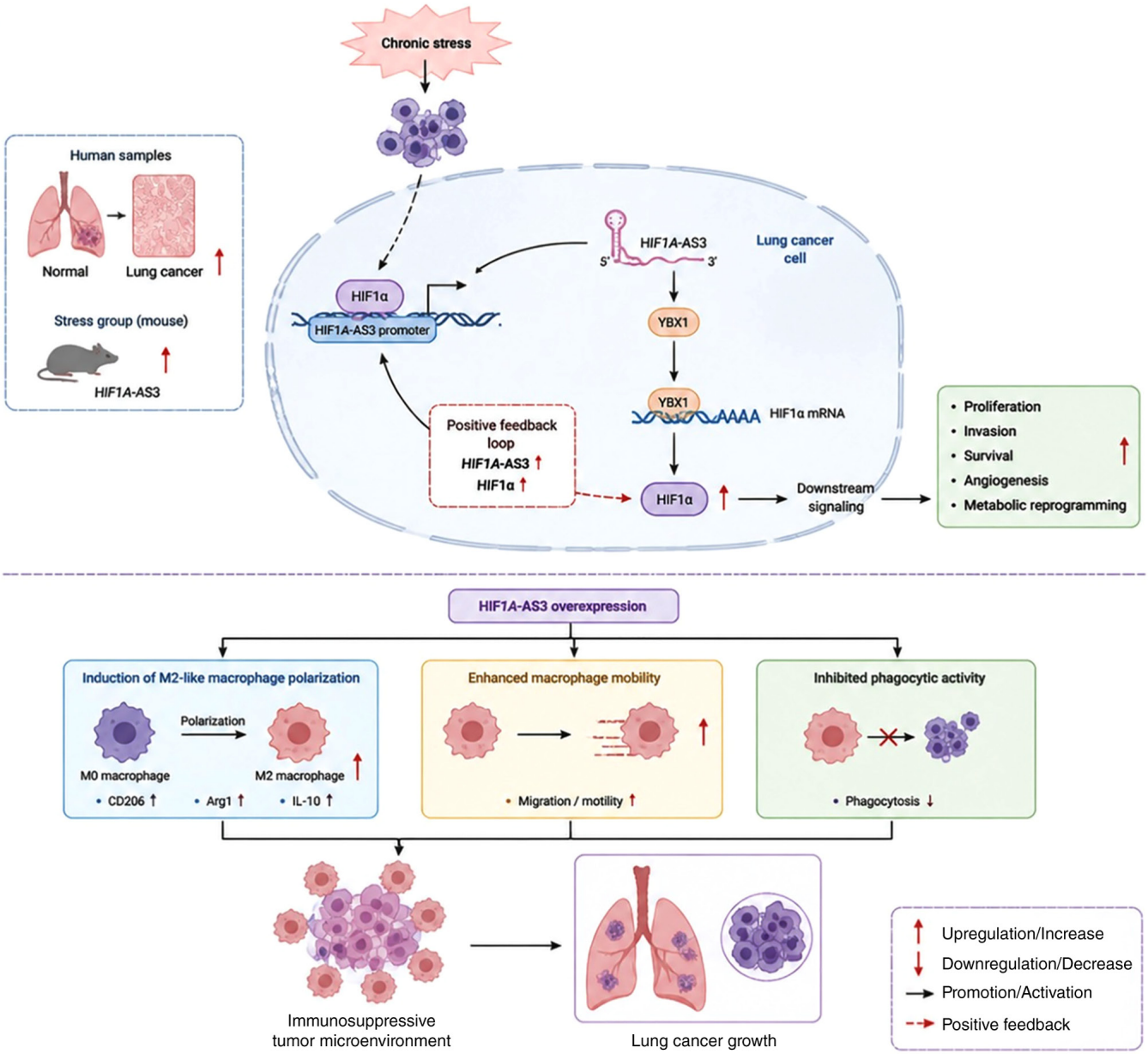

Figure 3. Schematic representation of the HIF1A-AS3/HIF-1α positive feedback loop in lung cancer under chronic stress. Chronic stress increases HIF1A-AS3 expression, which directly interacts with YBX1 to activate HIF-1α signaling, thereby initiating downstream oncogenic pathways. HIF-1α, in turn, transcriptionally upregulates HIF1A-AS3 via its promoter, establishing a reciprocal positive feedback loop. This loop promotes tumor cell proliferation, invasion and metabolic reprogramming, while simultaneously inducing M2-like macrophage polarization and suppressing phagocytosis, ultimately creating an immunosuppressive microenvironment that accelerates lung cancer progression. HIF1A-AS3, hypoxia-inducible factor 1α antisense RNA 3; YBX1, Y-box-binding protein 1; GCs, glucocorticoids; NETs, neutrophil extracellular traps; ECM, extracellular matrix.

tissue-specific neurotransmitter pathways and immune modulation (54).

In gastric cancer, parasympathetic signaling promotes tumor progression primarily through acetylcholine (ACh)-mediated activation of muscarinic acetylcholine receptor M3 (CHRM3). Activation of CHRM3 stimulates downstream Wnt/yes-associated protein, ERK1/2 and PI3K/AKT signaling pathways, thereby enhancing tumor cell proliferation, survival and migration. In addition, ACh signaling promotes EGFR activation and induces MMP-7 expression, further facilitating malignant progression (54). These findings indicate that cholinergic signaling can directly regulate tumor cell behavior through receptor-dependent mechanisms.

Conversely, parasympathetic activity may exert antitumor effects in certain contexts. In breast cancer models, modulation of parasympathetic nerve activity reduced tumor growth and metastatic dissemination, which was associated with decreased PD-1/programmed death-ligand 1 expression and enhanced antitumor immune responses. Notably, parasympathetic activation did not markedly alter tumor-infiltrating lymphocyte numbers but instead influenced immune function by regulating immune checkpoint expression and promoting IFN-γ production (50).

Beyond direct neural regulation, ACh-mediated signaling also contributes to tumor-associated neurogenesis. ACh released from tuft cells promotes neural development within and

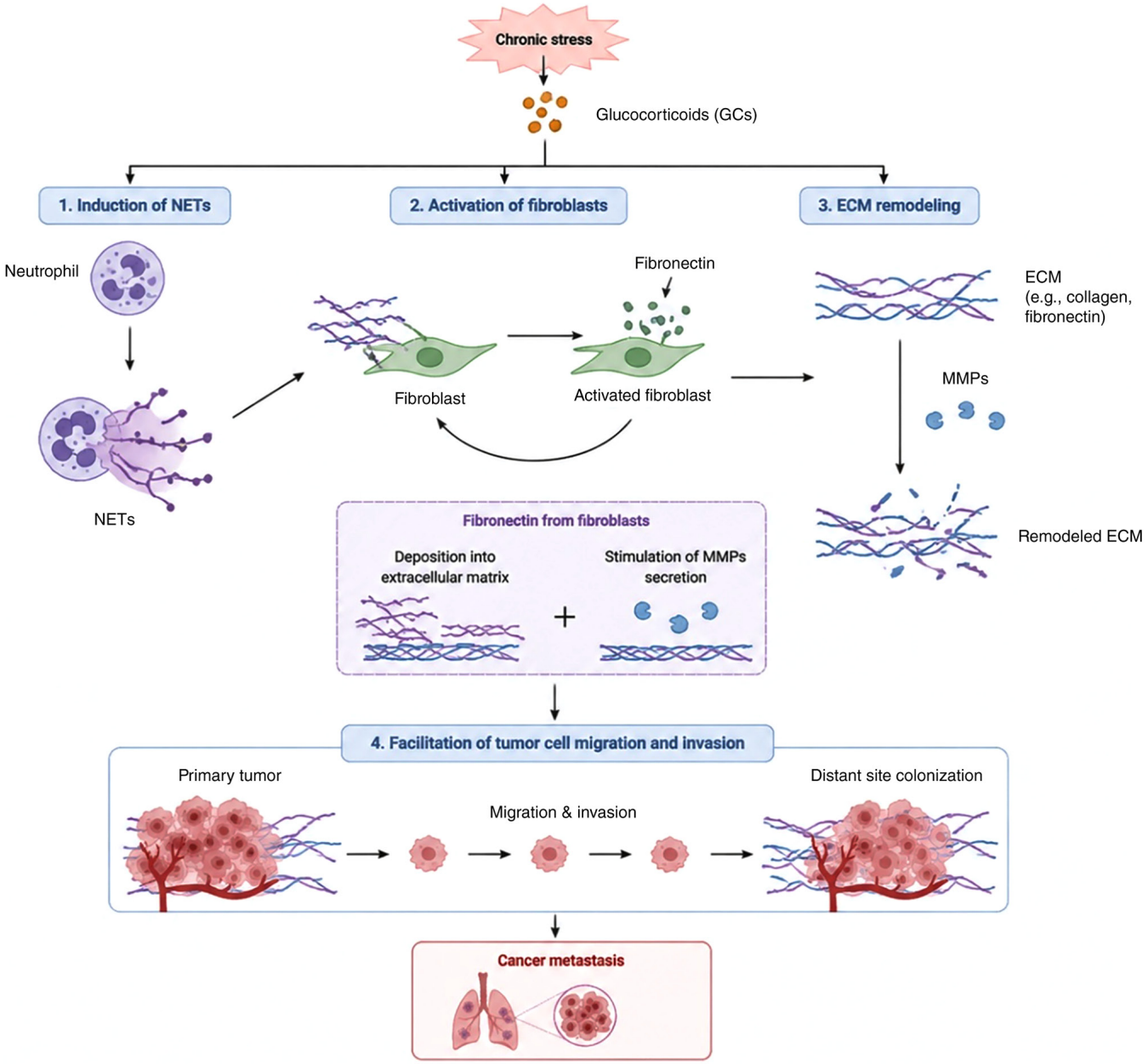

Figure 4. Schematic overview of how chronic stress promotes metastasis by triggering NET-dependent ECM remodeling. Under chronic stress, the body releases glucocorticoids, which then stimulate neutrophils to form neutrophil NETs. After NETs are generated, they activate fibroblasts and thereby increase the production and deposition of fibronectin in the ECM. In parallel, NETs also promote the secretion of MMPs, leading to further changes in the ECM. Collectively, these events support tumor cell migration, invasion and eventual distant metastatic spread. GCs, glucocorticoids; NETs, neutrophil extracellular traps; ECM, extracellular matrix; MMPs, matrix metalloproteinases.

around tumor tissues through interactions with neurotrophic growth factors, establishing a feedback loop that facilitates neural remodeling in the tumor microenvironment (55).

Collectively, parasympathetic signaling represents a context-dependent regulator of tumor progression. The divergent effects between tumor types may depend on receptor expression patterns, cellular targets and the surrounding immune microenvironment.

Sensory neuron-tumor communication through glutamatergic pseudosynapse. Sensory neurons can directly communicate with tumor cells through glutamatergic pseudosynapses. In PDAC, sensory nerve terminals form synapse-like contacts with tumor cells that express high levels of the N-methyl-D-aspartate receptor subunit, NMDAR2D, also known as GRIN2D. Neuron-derived glutamate activates these receptors and promotes Ca^{2+}-dependent signaling in PDAC cells. Glutamate stimulation also enhances GRIN2D expression through the CaMKIV/CREB signaling pathway, thereby reinforcing tumor responsiveness to neural inputs. Functional studies (56,57) in mouse models further indicate that GRIN2D is required for tumor growth and neural innervation. Collectively, these findings identify glutamatergic pseudosynaptic communication as a direct mechanism through which sensory neurons promote pancreatic cancer progression (Fig. 5) (58).

Table III. Stress-induced alterations in the tumor immune microenvironment.

Immune cell	Stress mediator	Major pathway	Functional consequence	Tumor type
MDSCs	Catecholamines	β-AR/IL-6/STAT3	Expansion of MDSCs	Breast cancer
$CD8^+$ T cells	Adrenergic signaling	PD-1/Tim-3	T-cell exhaustion	Melanoma
Macrophages	HIF1A-AS3	HIF-1α/YBX1	M2 polarization	Lung cancer
Natural killer cells	ITGA5/nerve growth factor	IFN-γ inhibition	Reduced cytotoxicity	Pancreatic cancer
Neutrophils	Glucocorticoids	Neutrophil extracellular traps	Extracellular matrix remodeling	Numerous tumors

MDSCs, myeloid-derived suppressor cells; β-AR, β-adrenergic receptor; PD-1, programmed cell death protein 1; Tim-3, T-cell immunoglobulin and mucin-domain containing-3; HIF-1α, hypoxia-inducible factor 1α; HIF1A-AS3, HIF1A antisense RNA 3; YBX1, Y-box-binding protein 1; ITGA5, Integrin subunit α5.

Context-dependent effects of neurotransmitters. Neurotransmitter-mediated tumor regulation is not restricted to nerve-derived signals. In glioblastoma, tumor-derived DA can establish an autocrine DRD2/ERK/TH feedback loop that sustains oncogenic signaling. This finding illustrates that neurotransmitter signaling within tumors may involve both neural and tumor-cell-derived sources.

Overall, neuro-tumor communication is mediated by diverse neurotransmitters whose biological effects depend on their cellular source, receptor distribution and tumor context. NE and glutamate generally promote tumor progression through sympathetic and sensory neural inputs, whereas ACh may exert either tumor-promoting or tumor-suppressive effects. DA further illustrates that neurotransmitter signaling may also arise from tumor-cell-autonomous production rather than exclusively from neural innervation (Table IV).

5. Stress-induced vascular remodeling and metastatic dissemination

Stress-induced angiogenesis. Angiogenesis is an key component of tumor progression, providing oxygen and nutrients while facilitating local invasion and metastatic dissemination. Chronic stress promotes angiogenic remodeling by shifting the balance between pro-angiogenic and anti-angiogenic signals within the tumor microenvironment. Although adrenergic signaling can increase the expression of VEGF, its angiogenic effects also involve suppression of endogenous anti-angiogenic regulators.

In prostate cancer, stress-associated cAMP/PKA/CREB signaling promotes angiogenesis through two downstream regulatory branches involving histone deacetylase 2 (HDAC2) and G protein-coupled receptor kinase 3 (GRK3). HDAC2 contributes to the epigenetic repression of thrombospondin-1 (TSP1), whereas GRK3 suppresses the expression of both TSP1 and plasminogen activator inhibitor-2 (PAI2). As TSP1 and PAI2 normally restrain vascular growth, their downregulation creates a microenvironment favorable for endothelial activation and neovascularization. Together with increased VEGF signaling, these alterations enhance tumor vascularization and support prostate cancer progression (Fig. 6) (59).

Collectively, stress-induced angiogenesis is driven not only by increased production of pro-angiogenic mediators but also by the loss of endogenous angiogenic restraints. This coordinated remodeling of vascular signaling may facilitate tumor growth and metastatic dissemination; however, the clinical relevance of these mechanisms remains to be established.

Stress-induced lymphangiogenesis and lymphatic dissemination. Chronic psychological stress promotes lymphatic remodeling within and surrounding the tumor microenvironment, thereby facilitating lymphatic metastasis. Activation of β-adrenergic signaling enhances the remodeling of tumor-associated lymphatic vessels, while sympathetic nervous system activity regulates lymphatic flow dynamics. These alterations are characterized by increased lymphatic vessel density, lymphatic vessel dilation and enhanced lymphatic drainage, creating favorable conditions for the dissemination of tumor cells through the lymphatic circulation (60). Collectively, these findings suggest that stress-induced lymphangiogenesis not only provides structural routes for metastatic spread but also promotes the efficient transport of tumor cells to regional lymph nodes and distant metastatic sites.

Together, stress-induced remodeling of both blood and lymphatic vasculature provides complementary routes that support tumor growth and metastatic dissemination.

6. Treatment and prevention

β-blockers. β-AR antagonists, particularly the non-selective β-blocker propranolol, have demonstrated potential in alleviating immunosuppression and enhancing the efficacy of immune checkpoint inhibitors in both preclinical and retrospective clinical studies. In a melanoma mouse model, combined treatment with propranolol and anti-PD-1 therapy markedly enhanced antitumor activity, resulting in delayed tumor progression, increased infiltration of $CD8^+$ T lymphocytes into the tumor microenvironment, and restoration of T-cell effector function (61). This synergistic effect is considered to result from the ability of propranolol to attenuate chronic stress-induced T-cell exhaustion.

In mouse models subjected to chronic adrenergic stress, treatment with propranolol markedly decreased the proportion of tumor-infiltrating lymphocytes expressing exhaustion markers, including PD-1, Tim-3 and lymphocyte activation gene 3. Concurrently, propranolol expands the population

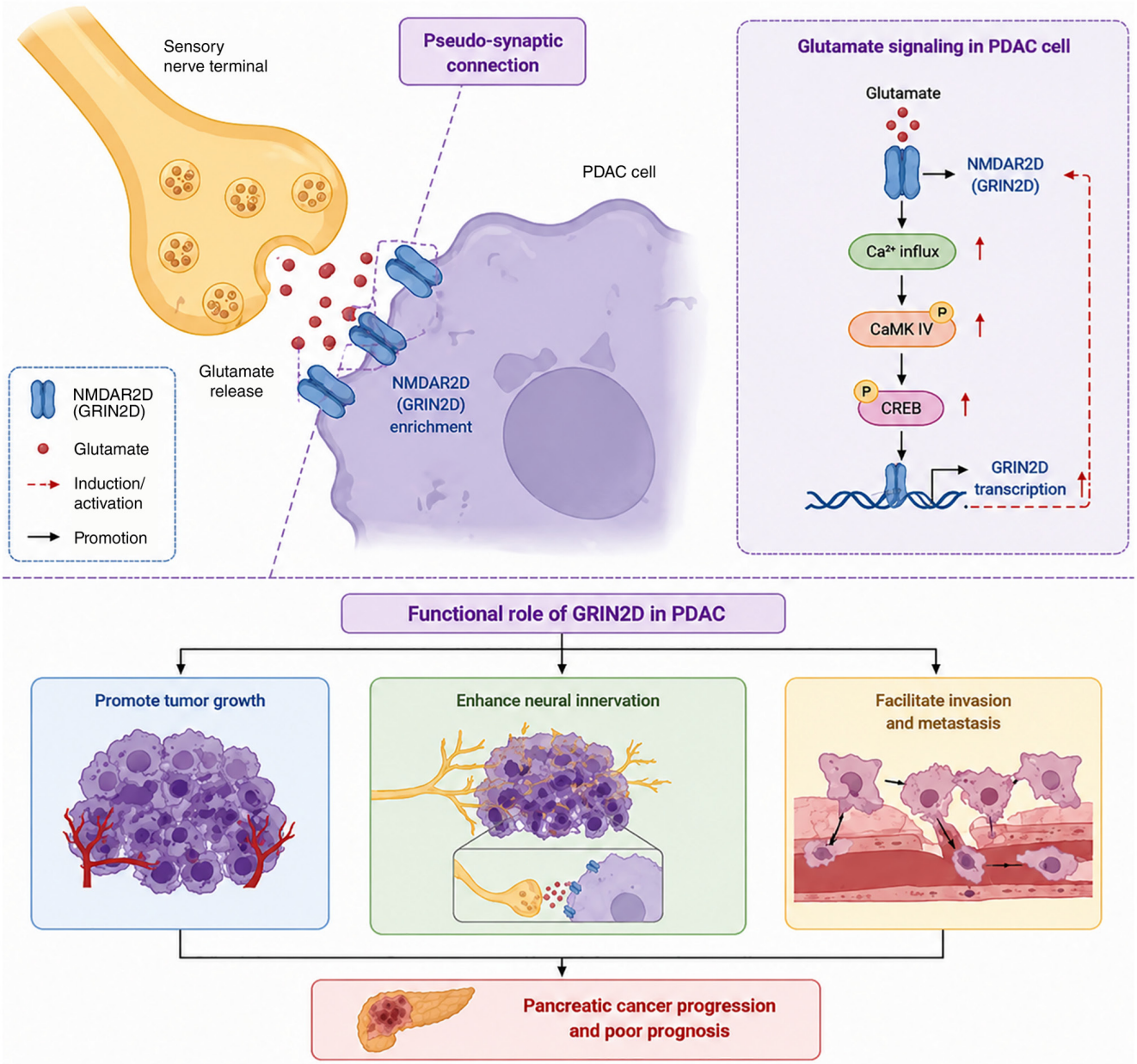

Figure 5. Schematic representation of sensory neuron-driven pancreatic cancer progression through glutamatergic pseudosynapses. Sensory nerve terminals form pseudosynaptic contacts with PDAC cells and release glutamate. The released glutamate binds to NMDAR2D (GRIN2D) receptors, which are expressed on the surface of the cancer cells. This binding leads to Ca^{2+} influx and, in turn, activates the CaMK IV-CREB signaling pathway. As a result, tumor proliferation, neural innervation, cellular invasion and metastatic spread are promoted. PDAC, pancreatic ductal adenocarcinoma; NMDAR2D/GRIN2D, N-methyl-D-aspartate receptor subunit 2D; CaMK IV, calcium/calmodulin-dependent protein kinase IV; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element-binding protein.

of pre-exhausted T cells, which exhibit greater self-renewal potential and enhanced antitumor effector activity (62). In breast cancer models, β-AR antagonists were also found to improve the efficacy of anti-PD-1 therapy by reducing MDSC accumulation and suppressing their immunosuppressive functions (63). Furthermore, β-blockers have been reported to enhance the effectiveness of both chemotherapy and radiotherapy, underscoring their broad immunomodulatory properties (64).

Retrospective clinical studies further support these preclinical findings. In patients with melanoma, treatment with β-blockers, particularly β2-selective antagonists administered for non-oncological indications, was associated with notably improved responses to immunotherapy compared with patients who were not receiving these agents (65). In a separate phase II biomarker-driven clinical study, patients with breast cancer who received propranolol for one week before surgical intervention displayed elevated infiltration of $CD68^+$ macrophages and $CD8^+$ T cells within the tumor microenvironment. This increase in immune cell presence was associated with downregulation of genes associated to metastatic progression and inflammatory signaling pathways (63). Additionally, a phase I clinical trial evaluating the combination of propranolol with the anti-PD-1 antibody pembrolizumab in patients with advanced melanoma reported encouraging therapeutic results (66).

Table IV. Neuro-tumor interactions and potential therapeutic strategies.

Neural component	Neurotransmitter	Major receptor/pathway	Biological effect	Potential therapeutic target
Sympathetic nerve	Norepinephrine	ADRB2	Growth and invasion	β-blockers
Parasympathetic nerve	Acetylcholine	CHRM3	Context-dependent	CHRM3 inhibitors
Sensory neuron	Glutamate	NMDAR2D	Pseudosynapse	NMDAR inhibitors
Dopamine	Dopamine	DRD2	Plasticity	DRD2 antagonists
Tumor-Schwann cell	Nerve growth factor	ITGA5	Perineural invasion.	ITGA5 inhibitors

ADRB2, β2 adrenergic receptor; CHRM3, muscarinic acetylcholine receptor M3; NMDAR, N-methyl-D-aspartate receptor; DRD2, dopamine receptor D2; ITGA5, integrin subunit α5.

Collectively, the favorable results observed in epidemiological studies, clinical investigations and mechanistic research provide a strong theoretical rationale for combining β-blockers with immunotherapy. At present, numerous clinical trials are ongoing to further evaluate the efficacy and safety of this combined therapeutic strategy.

Targeting key nodes. Because stress-induced carcinogenesis involves numerous complex signaling pathways, therapeutic strategies targeting key molecular mediators may provide substantial clinical benefits. Among these approaches, autophagy inhibition has been extensively investigated. Since tumor cells typically depend on protective autophagy to adapt to stress and resist chemotherapy or radiotherapy, inhibition of autophagy may enhance the therapeutic efficacy of conventional anticancer treatments (67). In gastric cancer, chronic stress activates the AMPK-ULK1 signaling pathway through ADRB2, thereby inducing protective autophagy and promoting tumor cell proliferation and survival. These findings suggest that pharmacological inhibition of autophagy may attenuate the tumor-promoting effects of chronic stress (27).

In addition, HDAC inhibitors exert antitumor activity by inducing endoplasmic reticulum stress. Previous studies (67,68) have indicated that HDAC inhibition activates the protein kinase R-like endoplasmic reticulum kinase-eukaryotic translation initiation factor 2α pathway, thereby initiating the unfolded protein response and ultimately promoting apoptosis of tumor cells . In prostate cancer, HDAC2 is a key mediator of stress-induced angiogenesis. During tumor progression, CREB facilitates tumor growth by epigenetically repressing the anti-angiogenic factor TSP1 via upregulation of HDAC2. Collectively, these observations suggest that HDAC2-targeted inhibitors could serve as a potential therapeutic strategy for aggressive prostate cancer. Additional mechanistic insights are provided in the section on prostate cancer.

GRK3, an important downstream component of the ADRB signaling pathway, has also emerged as a potential therapeutic target in prostate cancer. Previous studies have demonstrated that GRK3 is important for metastatic tumor cell survival and proliferation. Furthermore, elevated GRK3 expression promotes angiogenesis through downregulation of TSP1 and PAI-2, thereby facilitating prostate cancer progression and metastasis (69). Importantly, GRK3 is transcriptionally regulated by CREB and functions as a key mediator within the chronic stress-activated cAMP/PKA/CREB signaling pathway. Suppression of GRK3 expression inhibits neuroendocrine differentiation while simultaneously increasing the proliferation of neuroendocrine prostate cancer cells. Therefore, the development of selective GRK3 kinase inhibitors may provide a promising therapeutic strategy for aggressive prostate cancer subtypes.

DRD2 antagonists have also demonstrated antitumor potential in a number of cancer models. In particular, the classical DRD2 antagonist trifluoperazine (TFP) has shown inhibitory effects on glioblastoma growth through suppression of tumor cell proliferation and survival. The therapeutic efficacy of TFP may depend on the specific DA receptor expression profile within tumors (70). In stress-induced tumor models, tissue factor pathway inhibitor (TFPI) promotes degradation of HIF-1α through disruption of the interaction between DRD2 and VHL, thereby inhibiting stress-induced tumor growth. TFP has been shown to suppress tumor cell proliferation and migration in breast cancer models, primarily through antagonism of DRD2 (71).

LDHA represent another important strategy for reversing tumor-associated metabolic reprogramming. In breast cancer, chronic stress-induced epinephrine exposure promotes aerobic glycolysis through activation of LDHA. Elevated lactate production subsequently induces USP28-mediated deubiquitination and stabilization of MYC, ultimately activating the SLUG promoter and promoting cancer stem cell-like phenotypes (72). Drug screening studies (72,73) further demonstrated that vitamin C suppresses LDHA activity and attenuates chronic stress-induced cancer stem cell-like characteristics, suggesting its potential therapeutic value in stress-associated breast cancer

Neuromodulation strategies. Chemical sympathectomy represents an important experimental strategy for validating the role of the sympathetic-tumor axis in tumor progression. In a murine prostate cancer model, selective ablation of peripheral sympathetic nerves using 6-hydroxydopamine notably suppressed tumor growth (74). Similarly, in gastric cancer models, administration of 6-hydroxydopamine attenuated the tumor-promoting effects of chronic stress and restored serum catecholamine levels to baseline values. Relevant signaling mechanisms are discussed in the ADRB2-related section of gastric cancer. As an important approach for regulating parasympathetic nervous system activity, vagus nerve stimulation has also attracted attention because of its potential antitumor

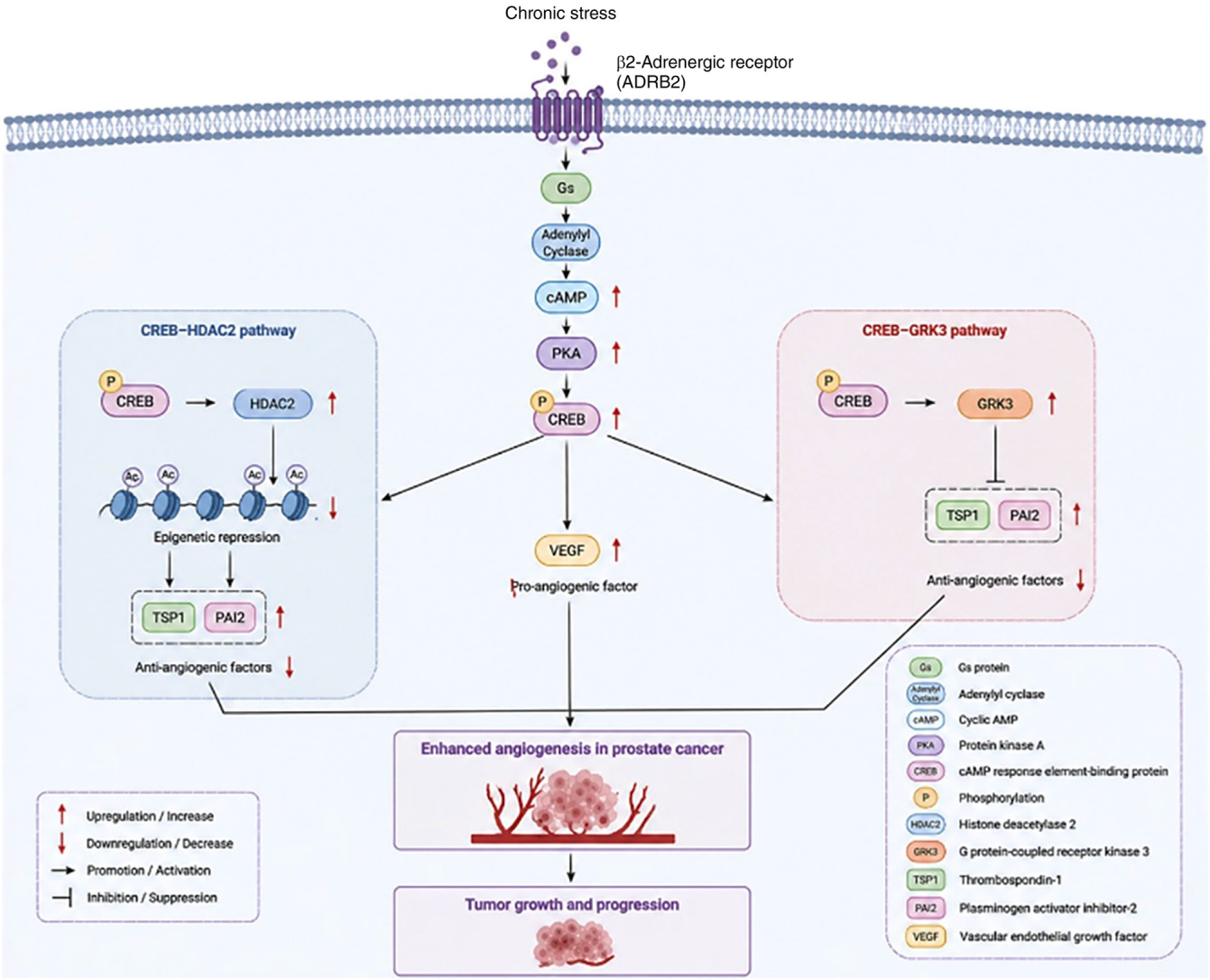

Figure 6. Schematic representation of stress-induced angiogenic signaling in prostate cancer. Chronic stress activates ADRB2 on tumor cells, triggering the Gs/cAMP/PKA/CREB signaling axis. CREB regulates angiogenesis via two downstream pathways: the CREB-HDAC2 pathway, in which HDAC2-mediated epigenetic repression decreases anti-angiogenic factors TSP1 and PAI2; and the CREB-GRK3 pathway, in which GRK3 suppresses TSP1 and PAI2. Both pathways converge to upregulate VEGF, a major pro-angiogenic factor, resulting in enhanced angiogenesis and subsequent tumor growth and progression. Red arrows indicate upregulation, down arrows indicate downregulation and black arrows represent promotion or inhibition as indicated in the diagram. ADRB2, β2-adrenergic receptor; Gs, G protein; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; CREB, cAMP response element-binding protein; HDAC2, histone deacetylase 2; GRK3, G protein-coupled receptor kinase 3; TSP1, thrombospondin-1; PAI2, plasminogen activator inhibitor-2; VEGF, vascular endothelial growth factor.

effects. Experimental evidence (75) demonstrated that vagus nerve stimulation suppresses tumor growth and metastasis through reduction of PD-1 and forkhead box (FOX) P3 expression in tumor-infiltrating lymphocytes.

Targeting NMDARs represents another important strategy for modulating glutamatergic signaling during neuro-tumor interactions. In pancreatic cancer, sensory neurons establish functional pseudosynaptic connections with NMDAR2D receptors expressed on tumor cells through glutamate release, thereby promoting tumor progression and neural invasion (53). In addition, targeting ITGA5 disrupts interactions between tumor cells and SCs. Tumor cells expressing ITGA5 adhere to fibronectin within the SC-associated ECM, reprogramming SCs and promoting NGF production. Preclinical studies (42,47) further suggest that combination treatment with the ITGA5 inhibitor cilengitide and anti-PD-1 immunotherapy enhances therapeutic efficacy, highlighting the potential of targeting neuroimmune interactions in pancreatic cancer.

Suppression of NETs is an important strategy for inhibiting stress-induced metastasis through modulation of neutrophil activity. Chronic stress increases glucocorticoid production, thereby promoting NET formation and establishing a microenvironment favorable for metastatic progression (76).

Psychological interventions and exosomes. Imipramine, a tricyclic antidepressant, has potential therapeutic benefits in cancer treatment through suppression of metastasis-associated exosome production. Imipramine not only alleviates depressive symptoms in patients with cancer but also inhibits communication between tumor cells and stromal cells through blockade of exosome release. Collectively, these effects contribute to marked tumor regression in breast cancer models (77).

In addition, imipramine derivatives have been reported to suppress breast cancer progression and metastasis through inhibition of the FOXM1-mediated DNA repair pathway. This therapeutic effect selectively targets tumor cells while exerting minimal effects on normal cells (77).

In breast cancer, patients participating in stress management interventions maintained or enhanced T cell proliferative activity, whereas patients in control groups exhibited progressive declines in immune function (78). Similarly, among patients with melanoma receiving immunotherapy, individuals experiencing high levels of emotional distress demonstrated notably lower objective response rates compared with emotionally stable patients (37 vs. 69%) (79). Stress-induced glucocorticoid release has been shown to impair treatment-associated antitumor immune surveillance, at least partially through upregulation of TSC22 domain family protein 3 expression (80).

Collectively, these findings suggest that incorporation of psychological stress management into immunotherapeutic regimens may represent a promising adjunctive strategy for improving the efficacy of cancer immunotherapy.

7. Conclusions and future perspectives

Recent evidence suggests that psychological stress promotes tumor progression through a number of interconnected mechanisms. Within tumor cells, stress hormones activate signaling pathways such as ADRB2/cAMP/PKA/CREB and DRD2/ERK/β-catenin, thereby regulating tumor cell proliferation, protective autophagy and metabolic reprogramming. Within the tumor microenvironment, chronic stress promotes the accumulation of MDSCs, induces T-cell exhaustion, facilitates M2 macrophage polarization and enhances angiogenesis, collectively contributing to an immunosuppressive microenvironment. In addition, at the neuro-tumor interface, sympathetic, parasympathetic and sensory nerves directly regulate tumor behavior through neurotransmitter release and pseudosynaptic communication. Based on these mechanisms, therapeutic strategies including β-blockers, inhibitors targeting DRD2, LDHA and GRK3, as well as psychological interventions, have demonstrated promising therapeutic potential.

Despite substantial progress, several important limitations remain in current research. First, the tumor-specific heterogeneity of stress-related signaling pathways remains incompletely understood. In addition, systematic investigation of the spatiotemporal dynamics underlying neuro-immune-tumor interactions is still lacking. Studies examining synergistic interactions among numerous stress-associated mechanisms also remain limited. Furthermore, clinical translation remains challenging due to the lack of validated stress-related biomarkers, uncertainty regarding patient selection, limited prospective clinical trials and difficulties in translating findings from experimental stress models to heterogeneous human cancer populations.

Single-cell and spatial multi-omics technologies may provide deeper insight into the cellular heterogeneity of stress-associated tumor microenvironments. Combination strategies integrating β-adrenergic blockade with immune checkpoint inhibitors represent another promising direction for future research and warrant further evaluation in prospective clinical trials. In addition, stress-associated biomarkers for patient stratification are required to identify patient populations most likely to benefit from stress-targeted interventions. Through multidisciplinary collaboration and continued mechanistic investigation, stress management strategies may ultimately be integrated more effectively into comprehensive cancer treatment paradigms.

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Authors' contributions

YZ wrote the manuscript. YK contributed to the literature search. SZ generated the figures, ensured visual data accuracy and contributed to drafting the manuscript. YZ and YK reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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