Chronic stress and cancer progression through neuro-endocrine-immune networks (Review)

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Abstract. Chronic stress may influence cancer trajectories; however, the majority of current frameworks do not clearly define how organism-level regulation interacts with tumor behavior. The present review summarizes mechanistic and translational evidence to propose a testable model in which cancer progression can, in selected contexts, be understood as over-adaptation to sustained stress within a hierarchical neuro-endocrine-immune network. Within this framework, stress-related signals converge in brainstem-hypothalamic control circuits, and engage sympathetic, hypothalamic-pituitary-adrenal and vagal effector pathways, which may influence cellular programs, microenvironmental remodeling and systemic dissemination. The evidence is organized into three sections: Cellular adaptation, microenvironmental remodeling and systemic progression. This multiscale perspective provides a host-context framework for understanding how chronic stress-related physiology may interact with tumor-intrinsic processes. Therapeutic implications are also discussed, including psychosocial support, exercise, mindfulness-based interventions, vagal modulation and perioperative β-blocker/COX-2 strategies. At present, the strongest clinical evidence for these approaches supports improvements in symptoms, patient-reported outcomes and selected biomarkers, whereas durable effects on tumor control or survival remain uncertain. Overall, this framework is presented as a conceptual and testable model intended to guide future research on host-tumor interactions in cancer.

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Contents

1. Introduction

In the clinic, some patients can live for years despite carrying a measurable tumor burden, indicating that survival cannot be reliably inferred from lesion size alone (1). This clinicopathological heterogeneity is partly explained by host variables already considered in clinical practice, including functional status, comorbidities, nutritional state and indices of systemic inflammation; these factors add prognostic value beyond anatomic staging (2,3). Expanding on this, converging evidence has indicated that chronic stress engages neuro-endocrine-immune (NEI) circuits that influence vascular remodeling, immune set-points and metabolic allocation, thereby altering the conditions in which tumors persist or regress (4,5). These host-regulatory processes neither replace nor contradict tumor-intrinsic drivers; rather, they operate alongside them and can tip the same tumor burden toward divergent trajectories. Framing cancer within this combined tumor-host context thus provides a rationale for measuring, and, where feasible, modulating, stress-related NEI activity to reduce outcome variability.

Strengths and limitations of prevailing tumor-centered models. The Hallmarks of Cancer remains a powerful scaffold for characterizing tumor phenotypes (6), and cell-centric models explain much of cancer initiation and progression. These models detail cell-intrinsic programs (such as genome instability, proliferative signaling and resistance to cell death) and local ecological dynamics (for example, angiogenesis, immune evasion and stromal crosstalk). However, when considered alone, these tumor-centered models have three recurrent limitations relevant to prognosis and therapy: i) Cross-layer causality, they rarely formalize how organism-level states

(autonomic tone, endocrine rhythms, inflammatory set-points) propagate downward to enforce or relax cell-intrinsic hallmarks; ii) time and tempo, they seldom specify thresholds and feedback by which initially adaptive responses drift into self-reinforcing over-adaptation; and iii) host integration, although clinical prediction accounts for host variables, most frameworks do not explicitly represent the stress-regulatory circuits of the host that shape tumor-host trajectories (4,6).

NEI mechanisms as a plausible host-to-tumor relay. Biobehavioral and NEI research has shown that β-adrenergic and glucocorticoid receptor (GR) signaling interface with inflammation, angiogenesis and metabolism to influence the initiation, invasion and metastatic competence of cancer (4,5,7,8). Classical stress biology anticipated this, from Selye's 'diseases of adaptation' (9) to McEwen's allostasis/allostatic load concept (10), and modern multi-omics studies have provided supporting evidence (11-13). Across cohorts, chronic stress elicits a conserved transcriptional response to adversity (CTRA), characterized by upregulated NF-κB/activator protein 1 (AP-1) programs and downregulated type-I interferon (IFN) signaling, a leukocyte signature associated with poor cancer-related outcomes (11-13). In oncology-relevant high-load states, sympathetic tone remains persistently elevated, hypothalamic-pituitary-adrenal (HPA) axis negative feedback is blunted and vagal braking is reduced, yielding low-grade inflammation, metabolic bias and immunosuppression. These host shifts manifest as i) cellular stress memory (genomic instability, epigenetic reprogramming), ii) microenvironmental coupling of metabolism-inflammation-vasculature, and iii) systems-level immune evasion, dissemination and dormancy reactivation (11,12,14).

Several reviews have advanced the field from complementary but partially distinct perspectives. Dai *et al* (15) reviewed how chronic stress promotes cancer development through stress hormones, inflammation, immune suppression and tumor-microenvironmental remodeling. Huang *et al* (16) focused more specifically on psychological stress, emphasizing stress-related neuroendocrine signaling, immunosenescence, and the potential relevance of psychosocial or pharmacological stress management in patients with cancer. Liu *et al* (17) summarized the stress-immune-cancer axis, with particular emphasis on how chronic stress impairs antitumor immunity and reshapes the tumor immune microenvironment, while also discussing existing stress-management strategies and their limitations. Yan *et al* (18) extended this discussion in solid tumors by detailing how chronic stress affects not only tumor cells, but also immune cells, stromal components, tumor-associated nerves and treatment responsiveness, thereby linking mechanisms to possible interventions. Pu *et al* (19) reviewed neuro-immune crosstalk in cancer more broadly, highlighting bidirectional interactions between the nervous system and the tumor immune microenvironment beyond stress-specific pathways. Taken together, these reviews have established important foundations, but they have generally emphasized psychological stress, neuroendocrine mediators, immune dysregulation or local neuro-immune interactions as partially separate entry points.

By contrast, the present review is organized around a unified organism-level NEI framework that treats psychosocial adversity, infection/inflammation, metabolic strain and tissue injury as distinct but convergent forms of biologically relevant stress information. The current review further emphasizes how these inputs may be integrated through shared brainstem-hypothalamic and peripheral regulatory circuits, and propagated through sympathetic, HPA and vagal pathways across three interconnected levels of cancer progression: Cellular adaptation, microenvironmental remodeling and systemic dissemination. Thus, the present review complements prior work not by restating that stress influences cancer, but by integrating psychological and physiological stress within a common host-regulatory architecture and by framing tumor progression as a multiscale host-tumor process.

A working premise and architecture. As a working premise, the present review considers cancer progression to be shaped, in part, by over-adaptation, responses that preserve short-term survival under sustained threat at the expense of long-term homeostasis. To make this premise testable rather than purely rhetorical, evidence has been organized into a hierarchical architecture: Cellular > microenvironmental > systemic, where each level exhibits emergent properties not observable from lower levels alone. This multiscale integration may help explain why single-target interventions underperform in some settings and suggests that coordinated modulation across layers could be required in stress-dominant phenotypes. Clinically, modifiable upstream inputs (such as psychosocial support, structured exercise, mindfulness-based practices, vagal modulation and short-window perioperative β-blocker/COX-2 inhibition) can shift stress-related biomarkers, and are being tested as adjuncts to optimize timing and responsiveness to standard therapies (20). The mixed results possibly reflect heterogeneous stress phenotypes and mistimed interventions, underscoring the need for adequately powered prospective trials.

Guiding questions. The present review selected the following guiding questions: i) Can 'stress-vulnerable' cancer subtypes be identified using integrated NEI-genomic profiling? ii) What is the optimal timing and combination of NEI interventions relative to standard oncological treatments? iii) How can preclinical NEI mechanisms be translated into scalable clinical protocols? iv) Under what conditions do tumor-intrinsic programs dominate irrespective of NEI state, and how should this guide patient selection and trial design?

2. NEI network mechanisms

Biological stressors are first sensed by the peripheral immune system, which serves as an input layer translating danger signals into inflammatory mediators within the NEI network. At the cellular level, pattern-recognition receptors (PRRs), including Toll-like receptors (TLRs), RIG-I-like receptors and NOD-like receptors, recognize pathogen-associated molecular patterns and damage-associated molecular patterns (DAMPs), and activate NF-κB/MAPK and related inflammatory programs, thereby generating mediators such as IL-1β, TNF-α and IL-6 (21,22). In the context of the present review, the importance of PRR/TLR signaling is considered less in receptor subclass detail than in its capacity to convert peripheral danger sensing into signals that can

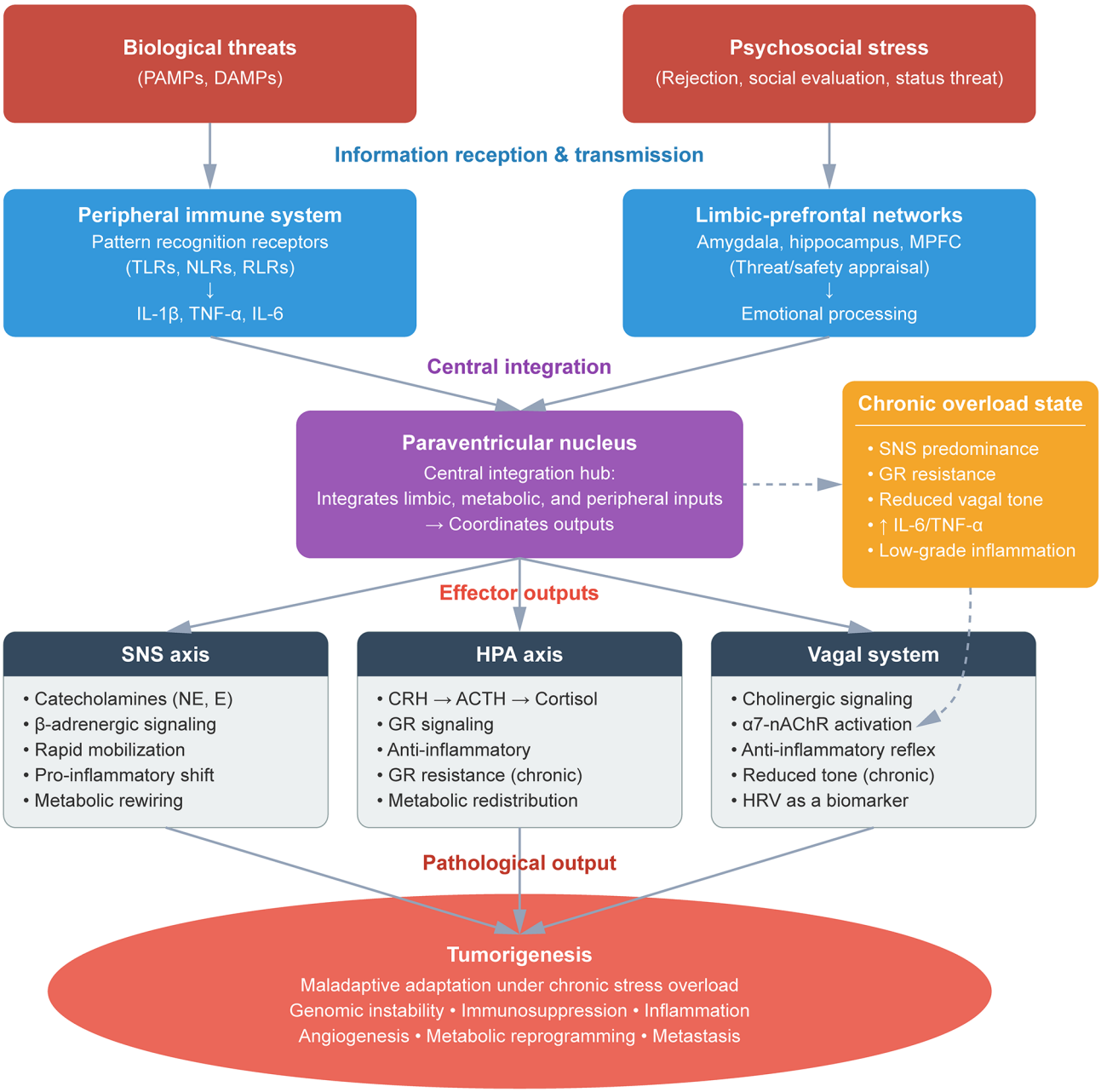

Figure 1. Stress-information network linking chronic stress overload to tumorigenesis. Schematic representation of the neuro-endocrine-immune network integrating peripheral and psychosocial stress signals. Biological stressors, including PAMPs and DAMPs, activate peripheral immune pattern-recognition receptors, whereas psychosocial stressors are processed through limbic-prefrontal appraisal. These signals converge within brainstem-hypothalamic integration networks, including hypothalamic nodes such as the paraventricular nucleus, which coordinate three principal effector outputs: SNS activation, with NE/E release; HPA axis activation, with glucocorticoid output; and vagal modulation of the anti-inflammatory reflex. Under chronic stress conditions, persistent SNS predominance, GR resistance, reduced vagal tone and sustained low-grade inflammation may create a feed-forward cycle (indicated by dashed arrows) that promotes angiogenesis, metabolic rewiring and immune evasion, thereby creating conditions that favor tumor initiation and progression as maladaptive responses to chronic stress overload. α7-nAChR; α7 nicotinic acetylcholine receptor; ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; DAMP, damage-associated molecular pattern; E, epinephrine; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal; HRV, heart-rate variability; MPFC, medial prefrontal cortex; NE, norepinephrine; NLR, NOD-like receptor; PAMP, pathogen-associated molecular pattern; SNS, sympathetic nervous system; TLR, Toll-like receptor; RLR, RIG-I-like receptor.

be relayed to central stress-regulatory circuits (23). Tissue injury and necrosis release DAMPs that engage PRRs and induce sterile inflammation. Within the NEI framework, unresolved signaling of this type provides a continuing peripheral input that may reinforce chronic stress-related inflammation (24,25) (Fig. 1).

These immune-derived peripheral signals then reach the brain through complementary neural and humoral routes, enabling their integration within brainstem-hypothalamic stress-control networks. Specifically, immune-to-nerve signaling activates vagal afferents, which relay to the nucleus tractus solitarius and onward to hypothalamic control nodes, providing near-real-time context for central integration (26,27). In parallel, circulating cytokines and hormones access the brain via circumventricular organs, specialized transport across the blood-brain barrier or secondary messengers, which

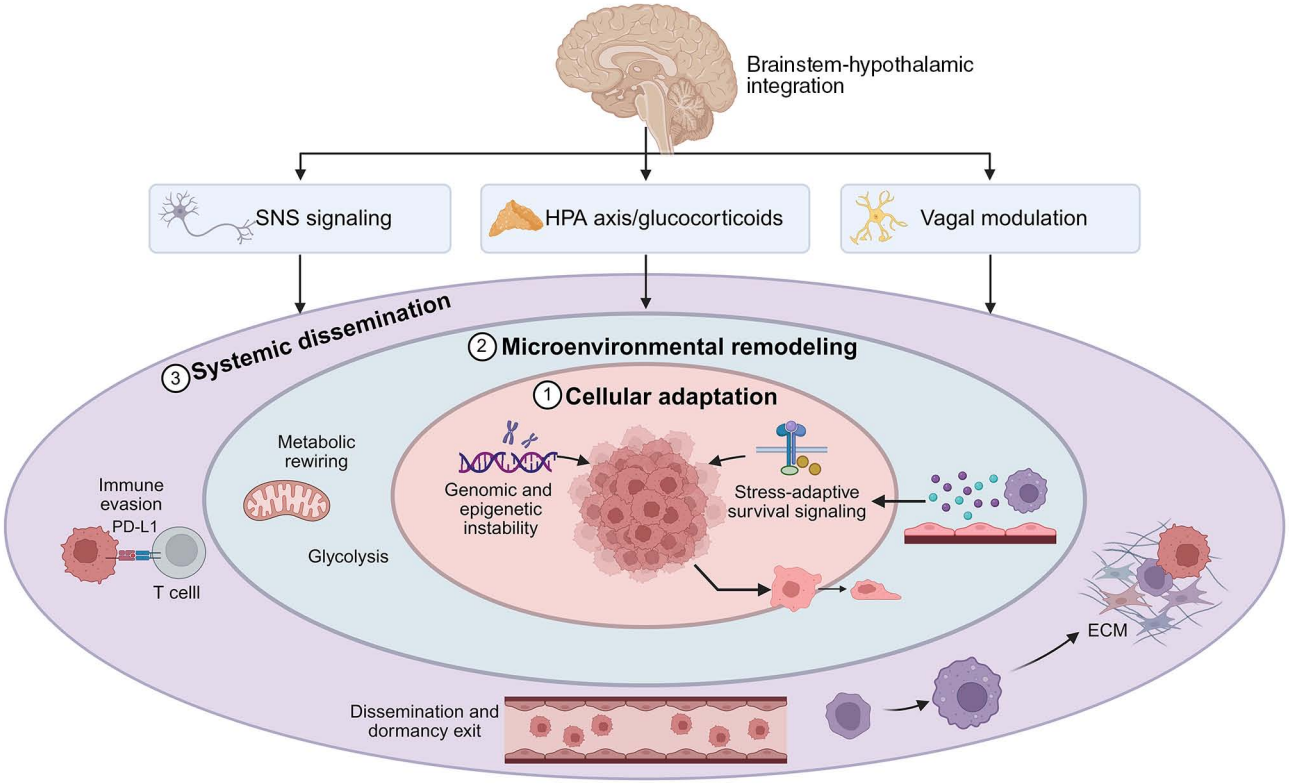

Figure 2. Three-level model of stress-driven cancer progression. Schematic overview of a three-level model in which chronic stress-related neuro-endocrine signaling shapes cancer progression across interconnected levels: Cellular adaptation, microenvironmental remodeling and systemic dissemination. ECM, extracellular matrix; HPA, hypothalamic-pituitary-adrenal; PD-L1, programmed death-ligand 1; SNS, sympathetic nervous system.

supply broader but slower inputs than the rapid neural vagal afferent route (28-30).

Beyond physical injury, social-environmental adversity (for example, rejection, social evaluation, status threat or loss) can be appraised by the brain as threat-relevant information. These cues are processed within limbic-prefrontal circuits (amygdala, hippocampus, medial prefrontal cortex). Their outputs converge with somatic inputs within brainstem-hypothalamic control networks, prominently at hypothalamic nodes such as the paraventricular nucleus (PVN). At the PVN, these hypothalamic threat signals bias autonomic and HPA outputs, and can upshift inflammatory activity even without tissue damage. This conceptual pathway is captured by the social signal transduction and social safety frameworks (14,31-34).

From brainstem-hypothalamic control networks, including hypothalamic nodes such as the PVN, three principal effector outputs coordinate organism-wide responses. i) Sympathetic nervous system (SNS) axis: Rapid β-adrenergic mobilization reallocates blood flow, energy and leukocyte trafficking. ii) HPA axis: Corticotropin-releasing hormone > adrenocorticotropic hormone > adrenal glucocorticoids cascade; this axis produces pulse-like outputs constrained by negative feedback. iii) Vagal axis: Parasympathetic efferent fibers implement the cholinergic anti-inflammatory reflex and restrain macrophage cytokine release via α7 nicotinic acetylcholine (ACh) receptors (α7-nAChRs) (14,35). Under an acute challenge, these brainstem-hypothalamic programs are typically phasic, rapidly engaged and actively terminated as negative feedback restores baseline. However, with repeated or prolonged exposure, experience-dependent plasticity may emerge at the input level, where limbic-prefrontal appraisal converges on brainstem-hypothalamic command networks, and consolidate at the output level as a gradual tilt toward sustained SNS and HPA activation with reduced vagal restraint. This re-weighting resets physiological set-points, sustaining low-grade inflammation, endothelial activation and tissue-remodeling signals even between stressors (36). The resulting state may shift physiological priorities from recognition or elimination toward repair or tolerance. These shifts may foster angiogenesis, stromal activation and immune evasion, and thereby create conditions that favor the selection and maintenance of stress-adapted malignant phenotypes (6,33).

3. Three stages of stress-driven cancer progression

Under sustained overload, organisms develop a persistent 'mobilize-over-brake' bias, where sympathetic drive dominates and vagal/HPA feedback weakens. Repair is reinterpreted as growth, scarcity drives metabolic capture, danger signaling recruits vascular and stromal scaffolds, and immune surveillance is reprogrammed. Thus, within this framework, several cancer hallmarks may also be interpreted as multiscale consequences of persistent stress-system imbalance rather than as purely cell-autonomous abnormalities. As summarized in Fig. 2, these processes can be organized into three interconnected levels: Cellular adaptation, microenvironmental remodeling and systemic dissemination.

Level 1: Cellular adaptation. Under chronic stress, cells prioritize short-term survival over tissue homeostasis through coordinated shifts in genome maintenance, chromatin state and metabolic control.

DNA damage mechanisms. Chronic stress destabilizes the genome via convergent endocrine-inflammatory routes. On the endocrine arm, β-adrenergic catecholamines accelerate p53 turnover through a β2-adrenergic receptor (β2-AR)-β-arrestin-1-AKT-MDM2 cascade. This lowers checkpoint competence and increases DNA-damage burden, whereas pharmacological β-blockade prevents this accumulation (37,38). Beyond proteolysis, β-adrenergic tone promotes oxidative DNA damage. For example, norepinephrine increases γH2AX foci and neutral comet-assay readouts in epithelial ovarian cancer cells, consistent with double-strand DNA breaks; these effects are abrogated by propranolol (39). Glucocorticoids promote genomic instability through several converging mechanisms, including induced inducible nitric oxide synthase-dependent reactive oxygen species/reactive nitrogen species and DNA damage in models of breast cancer (40). In addition, GR cross-talk with p53/Hdm2 dampens p53 function (41,42). *In vivo*, chronic restraint stress elevates glucocorticoids, activates the SGK1-MDM2 axis, and attenuates p53, thereby promoting tumorigenesis (43).

Epigenetic reprogramming. On the GR arm, AP-1-primed enhancers and preestablished chromatin contacts enable rapid GR loading. Subsequently, enhanced H3K27ac via CBP/p300 reinforces transcriptional 'memory' linked to dormancy and anti-androgen resistance (44-46). On the catecholamine arm, β-adrenergic cAMP/PKA > CREB recruits CBP/p300 to CRE enhancers, thereby converting acute spikes into permissive enhancer landscapes (47,48). Metabolic coupling then locks these programs in place. IDH-driven 2-hydroxyglutarate inhibits TET/KDM demethylases, and histone lactylation ties glycolytic flux to gene activation (49-51). Collectively, GR/β-AR signaling plus metabolite-chromatin crosstalk establishes hard-to-reverse epigenetic programs that underpin adaptive tumor phenotypes, including dormancy-associated persistence and anti-androgen resistance (44-46,52,53).

Oncogenic signaling. Chronic stress hormones can engage oncogenic signaling programs associated with aberrant proliferation and related malignant phenotypes in several tumor contexts. At the cellular level, β-adrenergic inputs engage Src/FAK to confer anoikis resistance and a survival advantage; this mechanism has been validated in human ovarian cancer cells and linked to metastatic spread (54,55). In early serous carcinogenesis, norepinephrine (NE) directly induces anoikis resistance in fallopian tube precursor cells via β-ARs, suggesting adrenergic blockade as an interception strategy (56). In colorectal cancer (CRC), NE activates a CREB1 > microRNA (miR)-373 program that accelerates proliferation and metastasis (57). Chronic stress also drives β2-AR-PKA-CREB1-dependent glycolytic reprogramming by upregulating glucose transporter 1 (GLUT1), hexokinase 2 (HK2) and PFKP to fuel tumor cell proliferation (58). In glioma, stress hormones accelerate proliferation through PI3K-AKT downstream of GR and β-ARs (59). Complementing catecholamines, glucocorticoids potentiate tumorigenicity by activating TEAD4 to sustain stemness, survival, metastasis and chemoresistance, and by transcriptionally upregulating GRP78 to expand breast cancer stem-like populations under chronic psychological stress (60,61).

Thus, cellular adaptation reveals how chronic stress can dismantle cellular quality control through β-AR and GR pathways, and compromise genomic integrity (for example, p53-linked checkpoint control), epigenetic stability (CBP/p300-linked enhancer remodeling) and growth control (β-adrenergic/CREB and GR/TEAD4 signaling).

Level 2: Microenvironmental remodeling. Building on cellular stress adaptation, microenvironmental remodeling represents the tissue-level response. Here, individual cellular changes coalesce into microenvironmental alterations and broader tissue remodeling. Through coordinated neuro-endocrine signaling, chronic stress reprograms energy metabolism and modifies the tumor microenvironment to create a self-sustaining, pro-tumor system. This can be understood as a 'reset' of homeostasis under persistent stress load.

Metabolic rewiring. Chronic activation of the catecholaminergic and HPA axes remodels tumor metabolism as a systems-level over-adaptation to stress. Catecholamines acting through the β-adrenergic-cAMP/PKA pathway potentiate hypoxia-inducible factor 1 (HIF-1) transcriptional activity under normoxia. This upregulates canonical glycolytic modules [GLUT1, HK2, pyruvate dehydrogenase kinases (PDKs)/lactate dehydrogenase A] and reallocates carbon flux toward rapid ATP generation and biosynthetic support (62,63). In parallel, GR signaling induces PDK4, inhibits pyruvate dehydrogenase and redirects pyruvate fate. This program is directly linked to migratory capacity and metabolic rerouting in breast cancer models (64). Within metabolic inhibitory and homeostatic maintenance pathways, wild-type p53 restrains glycolysis via TIGAR and sustains mitochondrial oxidative phosphorylation (OXPHOS) via SCO2 (65,66); however, chronic restraint stress reduces p53 abundance/function and accelerates tumorigenesis (43). In parallel, common mutant p53 variants acquire glycolysis-promoting activities, including GLUT1 membrane translocation, which reinforce a Warburg-biased state (67). Additionally, stress signaling confers phenotype-dependent metabolic plasticity. In defined contexts, β2-adrenergic input can shift metabolism away from glycolysis and toward oxidative pathways, including OXPHOS and fatty-acid oxidation (68). Beyond cancer cells, adrenergic innervation activates an endothelial angio-metabolic switch that fosters a pro-tumor vascular niche (69). Collectively, these observations illustrate a stress-responsive network, spanning receptor signaling to metabolic gatekeepers, which stabilizes switchable glycolytic and oxidative states. This is consistent with tumor evolution as a chronic-stress over-adaptation rather than a fixed metabolic fate.

Angiogenesis and inflammation. Classic stromal biology views tumors as 'wounds that do not heal', in which proangiogenic and inflammatory programs fail to switch off (70). This framework helps explain the sustained activation of stress axes (such as SNS/HPA). Catecholamines and glucocorticoids can convert adaptive injury responses into a stabilized tissue state that hard-wires neovascularization and immune skewing, an archetype of over-adaptation. Mechanistically, chronic stress

elevates intratumoral catecholamines, tumor burden, and microvessel density *in vivo* (5). In parallel, NE upregulates VEGF, IL-6, IL-8 and matrix metalloproteinases (MMP-2/-9) in cancer cells, thereby promoting endothelial activation and invasive remodeling; these effects are attenuated by β-blockade (71,72). Beyond tumor-intrinsic transcriptional programs, adrenergic innervation acts directly on endothelial β-ARs to rewire endothelial metabolism, suppress OXPHOS and trigger an angiogenic switch that accelerates tumor growth (69). In parallel, sustained β-adrenergic input raises tumor-cell CCL2/MCP-1, thereby promoting tumor-associated macrophage recruitment and ovarian carcinoma growth (73); it also drives M2 polarization that supports invasion and dissemination (74). Previous reports have shown that NE induces β2-AR > IL-6 > STAT3 signaling in breast cancer cells to polarize M2 macrophages and enhance migration in a paracrine manner (74,75). Systemically, sympathetic activation can engage a macrophage-dependent metastatic switch (76). Notably, VEGF not only promotes vessel sprouting, but also suppresses dendritic cell (DC) maturation and shapes an immune-repressed niche (77-79). In parallel, VEGF-C-driven lymphangiogenesis expands lymphatic endothelial programs that secrete prostanoids and TGF-β, thereby inhibiting DC maturation and dampening local immunity (80). The perioperative stress surge is a window to co-tune this network. Randomized phase-II biomarker trials have shown that a combination of propranolol (β-blocker) and etodolac (COX-2 inhibitor) favorably modulates metastasis-related inflammatory/angiogenic biomarkers (20,81). In a separate pilot randomized controlled trial (RCT) involving patients with CRC, an improved 5-year disease-free survival was reported with this combination (82). Modern syntheses support combining anti-VEGF with immune checkpoint blockade to reverse VEGF-driven immunosuppression and enhance antitumor immunity (83,84). Collectively, these findings suggest that angiogenesis may be closely linked to inflammation through stress-related circuitry. In this sense, cancer progression may be viewed as a chronic-stress over-adaptation rather than a transient repair response.

Gut-brain-tumor axis. The gut microbiome functions as a biochemical translator of stress. Psychosocial stressors can reshape microbial communities, whereas microbial metabolites and vagus-mediated signals reciprocally modify central stress circuits and immune tone (85,86). Chronic stress is associated with the depletion of butyrate-producing taxa and reduced levels of short-chain fatty acids. Butyrate functions both as an epithelial energy source and as an epigenetic regulator, and its depletion may increase immune activation thresholds while biasing the system toward proinflammatory and proangiogenic states (87). Stress- and inflammation-related signaling can activate the TDO/IDO > kynurenine > aryl hydrocarbon receptor pathway, thereby transducing psychological-inflammatory signals into immune suppression and adaptive phenotypes (88). In a testable CRC model, chronic stress was shown to deplete *Lactobacillus johnsonii* and its metabolite protocatechuic acid (PCA), thus relieving restrained Wnt/β-catenin signaling, enhancing stemness and accelerating tumor progression. Microbial or PCA supplementation, however, may reverse these phenotypes (89).

Microenvironmental remodeling proposes that stress transforms the tissue ecosystem through interconnected axes: Metabolic reprogramming (HIF-1α-driven Warburg shift), vascular-inflammatory coupling (VEGF-IL-6 feed-forward loops) and microbial dysbiosis (butyrate depletion and kynurenine accumulation). These changes are not independent; instead, they form an integrated information network in which metabolites serve as signals, inflammation drives angiogenesis, and microbial products modulate both immunity and epigenetics. This microenvironmental perturbation creates the milieu for systemic dissemination, where local adaptation breaches tissue boundaries to become organism-wide dysregulation.

Level 3: Systemic dissemination. Systemic dissemination marks the transition from localized adaptation to whole-organism dysregulation. Under persistent stress load, catecholamine-glucocorticoid signaling and low-grade inflammation first reset immune surveillance to suppressive set points, then weaken vascular or barrier controls, and prime motility and survival, so that metastasis emerges as a system-level consequence of persistent mobilization with impaired resolution.

Immune evasion. Chronic β-adrenergic signaling blunts cytotoxic T-cell function and undermines checkpoint blockade efficacy (90). At the tumor-immune interface, β3-adrenergic signaling on tumor-infiltrating lymphocytes sustains IFN-γ-dependent programmed death-ligand 1 (PD-L1) expression, thereby reinforcing local immunosuppression (91). In cancer cells, GR activation upregulates PD-L1 and downregulates major histocompatibility complex (MHC)-I, thereby reducing antigen visibility (8), whereas in T cells endogenous glucocorticoids drive a dysfunctional trajectory characterized by increased expression of inhibitory receptors (7). Exogenous or elevated endogenous glucocorticoids can further suppress type-I IFN signaling and antigen presentation, thereby compromising immunotherapy efficacy (7,8). Some tumors locally regenerate active steroids, for example through 11β-HSD-mediated recycling, thereby creating GR 'hot spots' that favor regulatory T-cell activity (92). In addition, β2-adrenergic signaling promotes expansion of myeloid-derived suppressor cells and enhances their suppressive function (93). Chronic stress also activates hematopoietic stem cells and biases hematopoietic output toward inflammatory myeloid lineages (94). Mechanistically, tumoral CD73 restricts anti-programmed cell death protein 1 efficacy, whereas co-blockade of CD73 or A2A can restore activity and improve tumor control in multiple mouse models (95,96). Beyond hardwired mutations, reversible epigenetic silencing of MHC-I processing machinery is frequent and druggable (97,98).

Invasion and metastasis. Metastasis is not a random process. Under chronic neuro-endocrine drive, metastasis may follow a structured sequence. β2-AR-cAMP/PKA signaling stabilizes and activates HIF-1α even under normoxic conditions, thereby providing a permissive signal for epithelial-mesenchymal transition (EMT)-associated transcriptional reprogramming (62). In pancreatic cancer, NE engages the β2-AR-HIF-1α-SNAIL axis to promote tumor growth, angiogenesis and EMT under stress (99). Chronic stress also

downregulates miR-337-3p, thereby releasing STAT3 activity, and accelerating EMT and metastasis in breast cancer (100). Together, these observations support the presence of a structured neuro-tumor interface in selected contexts (76,101). As another example, catecholamines elevate MMP-2 and MMP-9 levels, and remodel the pericellular matrix, thereby reducing mechanical barriers (102). Adrenergic activation of FAK confers anoikis resistance (55), and sustained β-adrenergic/PKA signaling promotes YAP1-associated adaptive phenotypes in subsets of tumors (103). During dissemination and reseeding, a PGC-1α-driven OXPHOS and fatty-acid metabolic program supplies bioenergetic support and enhances metastatic fitness (104). Chronic stress also reshapes the pulmonary niche in ways that favor metastasis, with neutrophils and neutrophil extracellular traps (NETs) acting as critical mediators in this process (105). For example, a previous study reported that NET-induced laminin remodeling activates integrin signaling that can awaken dormant cancer cells, thereby converting latent reservoirs into active disease (106). This process may be interpreted as a paradigmatic misdeployment of a pathogen-capture program within the host stress-regulatory network. Even before tumor cells arrive, stress-related β-adrenergic and glucocorticoid outputs can condition distant organs for metastatic colonization. Moreover, chronic psychological stress can program a lung premetastatic niche through β-adrenergic signaling (107). For example, it has been demonstrated that systemically mobilized VEGF receptor 1^+ bone marrow-derived cells home early to future metastatic sites (108), whereas tumor-derived exosomes bearing specific integrin 'barcodes' program stromal and immune cells to confer organotropism (109).

Vagal signaling and tumor behavior. Generally, the vagus nerve acts as a systems-level brake, the net effect of which tends to be tumor-suppressive, but context-dependent. Through the cholinergic anti-inflammatory pathway (ACh > α7-nAChR), vagal efferents dampen IL-1β/IL-6/TNF-α release and stabilize the internal milieu, thereby supporting immune surveillance and reducing stress-amplified pro-metastatic programs (35,110). In patients with cancer, lower cardiac vagal tone, typically indexed by heart-rate variability (HRV), is consistently associated with poorer cancer outcomes, positioning vagal activity as a measurable systems biomarker (111). Preclinical studies have further demonstrated that preserving vagal signaling can limit peritoneal metastasis in murine gastric cancer and that modulating the brain-liver vagal axis can deter cancer-associated cachexia, reinforcing a causal link at the organismal level (112,113). However, cell-intrinsic cholinergic signaling can also activate α7-nAChR or related receptors on tumor or endothelial cells, which may engage PI3K-AKT/ERK pathways and favor proliferation or angiogenesis under specific inflammatory or metabolic contexts (114,115).

Three-stage integration and boundary conditions. The integrative framework suggested in the present study supports the view that cancer progression can be understood as a multiscale adaptive process under chronic stress, spanning cellular, microenvironmental and host stress-system levels. In level 1 (cellular adaptation), stress exposure can select for stress-adapted clones through genomic and epigenetic reprogramming. Level 2 (microenvironmental remodeling) consolidates a supportive ecosystem via metabolic-vascular-inflammatory coupling. Level 3 (systemic dissemination) enables breach of local containment through immune escape, systemic inflammation and metastatic dissemination. These levels are hierarchically organized yet tightly interconnected: Cellular metabolites can remodel the microenvironment, tissue inflammation can feed back to cellular programs and systemic cues may prime distant niches. This multilevel coupling offers one explanation for why single-node targeting often yields limited durability, suggesting that effective control may require strategies that address multiple levels of the stress-adaptation cascade rather than isolated pathways.

To avoid overstatement, the present discussion refers to known cancers and defined experimental tumor contexts, rather than to occult tumor initiation in otherwise healthy tissues. Notably, tumor progression is not uniformly NEI-dependent, and this review does not propose that systemic NEI signaling universally dominates tumor-intrinsic oncogenic programs. In specific contexts, tumor-intrinsic pathways may dominate independently of, or more proximally than, systemic NEI inputs. For example, in established CRC, APC loss and constitutive Wnt/β-catenin signaling can sustain proliferation and immune exclusion in a largely tumor-intrinsic manner (116). In clinically recognized pancreatic ductal adenocarcinoma, KRAS-centered signaling can maintain tumor survival and metabolic rewiring, supporting continued growth even when host NEI inputs are weak or heterogeneous (117,118). In recurrent glioblastoma, RTK-associated growth programs together with PI3K/AKT/mTOR activity and AP-1-mediated mesenchymal transition may function as dominant mechanisms of persistence and therapeutic resistance (119,120). Accordingly, the present model does not argue that NEI signaling uniformly overrides tumor genetics; rather, it proposes that, in known cancers, NEI networks interact with tumor-intrinsic programs, and that their relative dominance is context-, genotype-, stage- and treatment-state dependent.

To facilitate cross-cancer comparison, the representative *in vitro* and *in vivo* evidence for NEI signaling in the major cancer models discussed in the present review is summarized in Table I (5,8,39,55,57-61,63,71,73-76,89,99,100,107).

4. Clinical interventions

This section discusses restructuring upstream stress-information flow within the NEI network. By leveraging psychosocial support [safety-congruent inputs (121,122)], exercise [a physiological outlet that completes the mobilization/action loop (123,124)], mindfulness/meditation [top-down inhibition and cognitive reappraisal of stress (125,126)], vagal modulation [the cholinergic anti-inflammatory reflex (110,127)] and select pharmacological/perioperative strategies [for example short-window β-blocker/COX-2 inhibitor use (81,82)], sustained overload from threat and uncertainty across the stress axes (inputs > SNS mobilization > HPA/vagal braking) may be reduced. The goal is to decouple and recalibrate chronic low-grade inflammation, metabolic reprogramming and tumor-ecosystem drivers of progression, thereby providing more favorable windows for radio-, chemo- and immunotherapy.

Table I. NEI signaling in cancer models.

Cancer type	*In vitro* evidence	*In vivo* evidence	NEI-related mechanisms	(Refs.)
Ovarian cancer	Norepinephrine promoted DNA damage, invasion and anoikis resistance	Chronic stress increased catecholamines, angiogenesis, macrophage recruitment and tumor burden in orthotopic models	β-adrenergic signaling; β2-AR/β-arrestin-1/ AKT/MDM2; Src/FAK; MCP-1-related macrophage recruitment	(5,39,55, 71,73)
Breast cancer	Stress mediators promoted migration, EMT, stem-like traits and M2-like macrophage polarization	Chronic stress enhanced metastasis and pre-metastatic niche formation	β2-adrenergic signaling; GR signaling; IL-6/STAT3; TEAD4-related programs	(60,61,74-76, 100,107)
Colorectal cancer	Norepinephrine promoted proliferation, migration/ invasion and glycolytic adaptation	Chronic stress accelerated tumor progression and microbiota-related remodeling	β2-adrenergic signaling; CREB1/miR-373; glycolytic rewiring; gut-brain-tumor axis	(57,58,89)
Pancreatic cancer	β-adrenergic and glucocorticoid signaling promoted survival, invasion and immune evasion	Stress-related signaling promoted tumor growth and angiogenesis	β2-adrenergic signaling; HIF-1α; GR-dependent immune evasion	(8,63,99)
Glioma	Stress hormones promoted glioma cell proliferation through PI3K/AKT activation	Chronic stress increased glioma growth	β-adrenergic signaling; GR signaling; PI3K/AKT	(59)

β2-AR, β2-adrenergic receptor; EMT, epithelial-mesenchymal transition; GR, glucocorticoid receptor; HIF-1α, hypoxia-inducible factor-1α; miR-373, microRNA-373; NEI, neuro-endocrine-immune.

Social support. Psychosocial support operates as a structured safety signal that down-shifts the stress network at its origin (threat/safety appraisal). Neurocircuit rebalancing (reduced limbic drive, strengthened medial prefrontal control) yields less SNS discharge, lower HPA burden and higher vagal tone, which in turn modulates tumor-relevant biology across angiogenesis, immunity, metabolism and dissemination (128). A meta-analysis encompassing 148 studies across patient and general populations has revealed that stronger social relationships are associated with lower mortality, an effect size consistent with a ~50% relative survival advantage (129). This supports the pathway 'safety signals > systemic homeostatic advantage'. Among cancer survivors, greater satisfaction with social support has been linked to lower CRP/IL-6/TNF-α levels and better survival (130). In RCTs in patients with breast cancer, structured cognitive-behavioral stress management has been shown to improve psychological outcomes long-term, and is associated with better disease-free and overall survival or favorable shifts in biological pathways (11,122). Although survival endpoints in oncological RCTs frequently show favorable but heterogeneous effects, evidence from a randomized trial in regional breast cancer indicates that psychosocial intervention can reduce recurrence and mortality, supporting the integration of psychosocial care into standard oncology practice (121). Notably, most trials primarily demonstrate improvements in quality of life and intermediate biomarkers, whereas disease-modifying effects (tumor control or survival) remain unsupported or inconsistent outside selected clinical contexts.

Exercise. Exercise channels stress-evoked mobilization into controlled skeletal-muscle work, and induces endocrine-like myokine signaling that resets autonomic and immune-metabolic tone (131,132). Tumor-relevant effects emerge across three linked domains as follows. Immune domain: A single bout of exercise acutely mobilizes cytotoxic lymphocytes in patients (133); in mice, voluntary running suppresses tumor growth via an adrenaline-IL-6-dependent NK-cell pathway, and training increases CXCR3-mediated intratumoral $CD8^+$ infiltration and sensitizes tumors to immune checkpoint blockade (134,135). Vascular-perfusion domain: Endurance training promotes vascular normalization, improves perfusion and reduces hypoxia, thereby enhancing drug and immune-cell delivery (136). Clinical translation domain: Guidelines recommend regular aerobic and resistance exercise during active cancer treatment and throughout post-treatment cancer survivorship, and perioperative prehabilitation has been shown to improve functional capacity (123,137-139). A phase III trial demonstrated that a 3-year structured program initiated after adjuvant chemotherapy prolongs disease-free survival in colon cancer, with signals suggesting a potential overall survival benefit (124). This trial provides rare randomized evidence that suggests a supervised, protocolized exercise intervention may improve hard oncological endpoints in a defined clinical setting. Nevertheless, several limitations should temper generalization. First, the evidence is currently anchored to a specific tumor type, stage and treatment window (post-adjuvant colon cancer), and it remains unknown whether similar

effects extend to other malignancies, biological subtypes or more aggressive disease contexts. Second, the intervention is intensive and behaviorally complex, being structured and sustained over multiple years, which raises concerns regarding adherence, scalability and potential co-interventions, such as concurrent lifestyle modifications, which may contribute to the observed benefit. Third, although the outcomes suggest a clinically meaningful effect, the trial alone does not establish which NEI-linked mechanisms, including immune trafficking, inflammatory tone, metabolic rewiring or vascular remodeling, are necessary or sufficient in humans. Collectively, these limitations underscore the need to conduct mechanistic studies and stratified replication across clinical settings (124).

Mindfulness-based stress reduction (MBSR). Chronic stress and depression accelerate cancer progression through persistent activation of NEI pathways and systemic inflammation. Mindfulness-based interventions (MBIs), including MBSR, have emerged as evidence-based strategies to buffer this burden. RCT and meta-analyses have consistently demonstrated reductions in anxiety, depression and cancer-related distress, alongside improvements in sleep and quality of life (125,126). These effects are mediated through stabilization of diurnal cortisol slopes, downregulation of proinflammatory cytokines, such as IL-6 and TNF-α, and preservation of telomere length in breast cancer survivors (140,141). Marinovic and Hunter (142) have emphasized that mindfulness may target the depression-inflammation axis, a shared pathway linking chronic stress to tumor incidence and adverse outcomes. While evidence for survival or recurrence reduction remains limited, international guidelines endorse MBIs as safe, scalable supportive care interventions that recalibrate stress appraisal and restore neuro-endocrine balance in oncology populations (143,144).

Vagal stimulation. Across various types of cancer, higher cardiac vagal activity, indexed by HRV, is associated with more favorable survival. A meta-analysis and oncological methods guidance support HRV as a prognostic signal while advocating standardized capture and prospective designs (127,145). Complementing observation with causality, preclinical work has shown that maintaining vagal signaling can limit peritoneal metastasis in murine gastric cancer models, and that manipulating brain-liver vagal communication can deter cancer-associated cachexia, strengthening the rationale for upstream modulation in oncology pathways (112,113). Translationally, noninvasive vagus nerve stimulation and HRV-oriented strategies are feasible adjuncts under exploration. Reviews of non-invasive vagus nerve stimulation, particularly transcutaneous auricular and cervical approaches, summarize candidate indications, safety considerations and practical stimulation parameters, but cancer-specific RCTs are still needed to determine its clinical value in oncology (146,147). Finally, evidence on anti-inflammatory end-points remains mixed, underscoring the importance of precision phenotyping and adequate power in future trials (148).

β-blockers and antidepressants. Beyond relieving depression/anxiety, selective serotonin reuptake inhibitors (SSRIs) modulate stress physiology. Namely, even short courses of SSRIs can steepen the diurnal cortisol slope, reflecting a healthier HPA axis rhythm (149), and RCTs/meta-analyses have shown downregulation of IL-6/TNF-α (150,151). In oncology, antidepressant therapy improves depressive symptoms overall (152), but direct antitumor survival benefits remain uncertain. In a large breast cancer cohort, SSRI use was shown to be associated with higher mortality (153). This association was likely driven by confounding factors; for example, patients prescribed SSRIs (for example, for more severe depression and related comorbidities) had a higher baseline risk of death, creating a spurious association not attributable to the medication itself. In humans, perioperative short-course RCTs have shown that propranolol combined with a COX-2 inhibitor can downregulate tumor pro-metastatic gene programs and favorably shift inflammatory and immune indices compared with a placebo in early breast cancer and CRC (20,81). A pilot RCT in CRC further reported improved 5-year disease-free survival with a combined regimen, propranolol plus etodolac, warranting phase III confirmation (82). For long-term β-blocker use outside the perioperative window, evidence remains mixed: An updated meta-analysis in breast cancer shows no clear survival benefit (154). Taken together, the strongest translational signal currently lies in the perioperative setting, and routine long-term β-blocker therapy for anticancer benefit will require larger, subtype-stratified RCTs.

Combined protocols. Chronic stress reconfigures the NEI axes and, through them, metabolism, vasculature and antitumor immunity. Accordingly, supportive care should not only treat downstream lesions, but also de-load and recalibrate upstream NEI signaling to establish a more stable physiological baseline. This refers to lower catecholaminergic drive, a restored cortisol diurnal slope, higher HRV and reduced tonic IL-6/CRP, conditions that widen therapeutic windows. Multimodal programs are biologically coherent (Fig. 3): β-adrenergic and glucocorticoid pathways modulate angiogenesis, immunity and invasion under stress, while short-window perioperative blockade can blunt the surgery-evoked surge that amplifies pro-metastatic processes. Evidence also supports a vagal 'braking' pathway and HRV-biofeedback as pragmatic tone-amplifiers for stress regulation.

The present review outlines clinic-facing principles for integrating this framework into routine oncological practice. Combination: Because stress biology drives multiple, coupled pathways, single modalities seldom suffice. Clinicians should use a compact bundle that integrates psychosocial support, structured aerobic-resistance exercise, stress-regulation skills (such as breathing and mindfulness), vagal-tone strategies, and, on surgical pathways, short-window perioperative pharmacology (for example, propranolol plus a COX-2 inhibitor when not contraindicated). Adequate dosing: Clinicians should apply validated frequencies and intensities (for example, ≥150 min/week moderate activity plus two resistance sessions; daily 10-20 min skill practice), track adherence and progressively increase load over time rather than rely on 'light-touch' exposure. Full course: Clinicians should construct a structured 12-week program with interim reviews, embed perioperative bundles into institutional pathways with screening for contraindications (cardiovascular, pulmonary and bleeding risks),

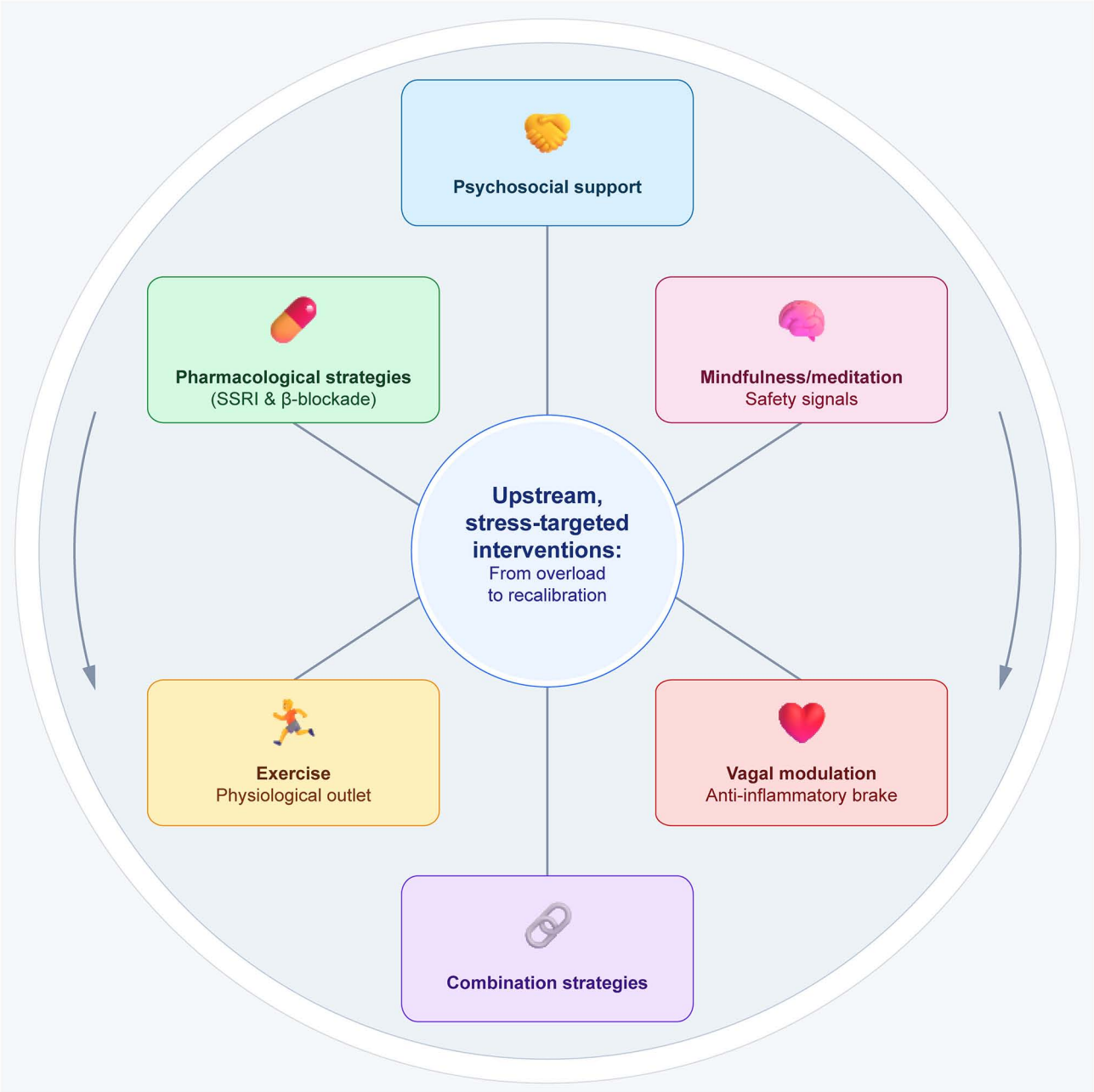

Figure 3. Upstream, stress-targeted interventions: From overload to recalibration. Schematic diagram of six evidence-based neuro-endocrine-immune interventions that shift the system from chronic stress overload to homeostatic recalibration and a tumor-suppressive microenvironment. i) Psychosocial support provides safety signals that downregulate limbic threat processing. ii) Mindfulness/meditation enhances top-down prefrontal control and stress reappraisal. iii) Vagal modulation amplifies cholinergic anti-inflammatory reflexes through heart-rate variability biofeedback or vagus nerve stimulation. iv) Pharmacological strategies (SSRI and β-blockade) modulate the hypothalamic-pituitary-adrenal axis rhythm and blocks β-adrenergic signaling. These interventions work synergistically to reduce systemic stress burden and create a less permissive tumor microenvironment. v) Exercise channels stress mobilization into structured physical activity to harness myokine-mediated benefits. vi) Combination strategies integrate multiple interventions to achieve synergistic effects. SSRI, selective serotonin reuptake inhibitor.

and monitor simple biomarkers (HRV, diurnal cortisol slope and IL-6/CRP) to confirm physiological recalibration.

Clinical endpoints and evidentiary boundaries. Interventions that target chronic stress and NEI, including psychosocial support, structured exercise, mindfulness-based programs, vagal neuromodulation and antidepressant strategies, have shown the most consistent evidence for improving patient-reported outcomes (such as distress, fatigue, sleep and pain) and, in some studies, intermediate biomarkers (for example, inflammatory markers, autonomic indices and neuroendocrine readouts) (126,137,143,148,152). However, it is crucial to distinguish these supportive benefits from disease-modifying effects. Across much of the literature, improvements in quality of life and biomarkers do not necessarily translate into durable tumor control or survival benefit, and survival-related signals, when present, frequently derive from observational datasets that remain susceptible to confounding factors such as baseline health status, treatment adherence, socioeconomic conditions and reverse causality (121,122,124,153,154).

Table II. Clinical trial evidence for targeting stress-information flow in cancer.

Intervention	Cancer setting	Trial-level evidence	Main result	(Refs.)
Psychosocial support	Breast cancer	RCTs with long-term follow-up	Improved long-term psychological outcomes; selected breast cancer trials also reported favorable biological changes and signals for reduced recurrence/breast cancer mortality	(121,122)
Structured exercise	Colon cancer; perioperative surgical oncology	Phase III RCT; perioperative RCT	Colon cancer: A 3-year structured exercise program initiated after adjuvant chemotherapy prolonged disease-free survival, with signals suggesting a possible overall survival benefit Perioperative setting: Prehabilitation improved functional capacity, but definitive oncological benefit has not been established	(124,139)
Mindfulness-based interventions	Mainly survivors of breast cancer	RCTs; supportive meta-analysis	Reduced anxiety, depression, cancer-related distress and sleep burden; improved quality of life. Biomarker-related benefits, including telomere preservation, have also been reported. Survival benefit has not been established	(125,126, 140,141)
Vagal stimulation	Cancer populations overall	No cancer-specific endpoint-driven RCT; prognostic and exploratory translational evidence only	Higher HRV was associated with more favorable cancer outcomes. Vagal modulation and HRV-oriented strategies remain exploratory adjuncts, and cancer-specific randomized trials are still lacking. Evidence for anti-inflammatory effects in humans is inconsistent	(127,148)
Perioperative propranolol + COX-2 inhibitor	Early breast cancer; CRC	Phase II biomarker RCTs; pilot RCT with 5-year follow-up	Improved pro-metastatic, inflammatory and immune biomarkers; pilot CRC trial showed improved 5-year DFS	(20,81,82)
Antidepressant-based management	Patients with cancer and depression	Evidence synthesis of randomized trials	Improved depressive symptoms overall in patients with cancer and depression; direct antitumor survival benefit remains uncertain	(152)

CRC, colorectal cancer; DFS, disease-free survival; HRV, heart-rate variability; RCT, randomized controlled trial.

Thus, the current review presents stress-targeted interventions primarily as strategies that may optimize the host adaptive landscape, potentially improving treatment tolerance, adherence and resilience during high-stress clinical windows, including diagnosis, perioperative periods and intensive therapy. Whether these approaches can influence hard oncological endpoints likely depends on tumor type, disease stage and the presence of NEI-responsive phenotypes. Demonstrating such effects will require adequately powered, stratified randomized trials with prespecified survival or recurrence endpoints. For clarity, the available trial-level clinical evidence for interventions targeting stress-information flow in cancer is summarized in Table II (20,81,82,121,122,124-127,139-141,148,152).

5. Discussion

A systemic perspective on stress-response capacity. The present review interprets cancer progression partly through the lens of chronic stress adaptation and NEI dysregulation. Within this framework, an important conceptual query arises: To what extent is stress-response capacity best understood as a distributed property of individual tissues vs. a coordinated property of organism-level regulatory systems? Traditional models often describe stress responses in terms of discrete functions of genes, cells, organs or local microenvironments (6,10,14). However, the evidence synthesized in the current review is also consistent with a broader systems perspective in which stress-related outcomes emerge from coordinated NEI circuit activity rather than from any single biological unit in isolation.

This interpretation should be regarded as a conceptual model rather than an established conclusion. Current evidence suggests that diverse external stressors, including infection, tissue damage, metabolic strain and psychosocial adversity, can converge on partially shared physiological outputs, such as sympathetic activation, HPA axis signaling, vagal modulation and inflammatory responses. What remains uncertain,

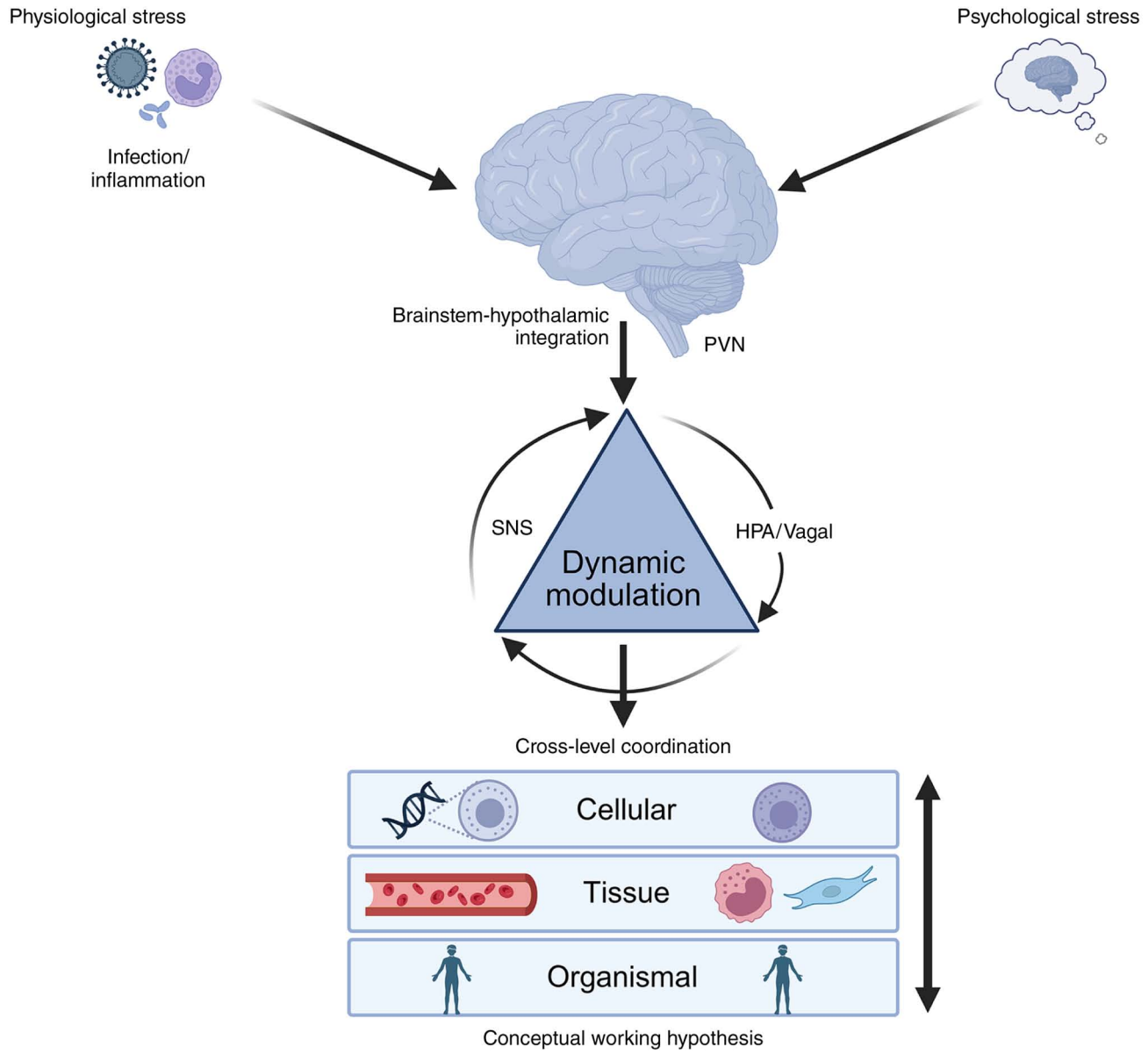

Figure 4. A working hypothesis of coordinated stress regulation. Conceptual schematic diagram showing how physiological and psychological stress signals converge on brainstem-hypothalamic integration and engage coordinated sympathetic and HPA/vagal modulation across cellular, tissue and organismal levels. HPA, hypothalamic-pituitary-adrenal; PVN, paraventricular nucleus; SNS, sympathetic nervous system.

however, is whether these convergent outputs reflect a unified 'stress capacity' that can be measured as a single organism-level property or instead represent partially overlapping and context-dependent regulatory processes. Thus, the present framework is intended to organize existing evidence and generate testable questions rather than to assert that a unified systemic stress capacity has already been conclusively demonstrated in oncology.

A working hypothesis of coordinated stress regulation. Based on the three-layer model outlined in the present review, a working hypothesis is proposed in which stress regulation in humans may involve partially integrated organism-level properties in addition to local tissue-specific responses. At present, this hypothesis remains conceptual and requires direct validation in cancer-related settings. Nevertheless, it may provide a useful heuristic for interpreting how chronic stress reshapes tumor biology across biological scales. This conceptual working hypothesis is summarized in Fig. 4.

Three provisional components may be considered within this hypothesis. First, information-integration capacity. The hypothalamic PVN is widely recognized as a major integrative node within brainstem-hypothalamic networks; receiving and coordinating signals derived from peripheral immune activity, visceral sensory pathways and limbic appraisal. From this perspective, interindividual variation in this integrative function may influence how proportionately the organism responds to sustained stress exposure. However, the extent to which this property can be operationalized as a stable and clinically meaningful 'capacity' in patients with cancer remains unclear.

Second, dynamic modulatory capacity. Under physiological conditions, sympathetic activation, HPA feedback and vagal restraint interact dynamically to support adaptation and recovery. Chronic stress appears to bias this balance toward

sustained mobilization and reduced regulatory restraint, a pattern broadly consistent with the aforementioned NEI literature. Evidence that β-adrenergic blockade, behavioral stress-reduction approaches, exercise or vagal-targeted interventions can influence selected biomarkers provides indirect support for this interpretation, although such findings do not establish the existence of a unified regulatory construct.

Third, cross-level coordination. The multilevel patterns discussed in the present review, from genomic instability and epigenetic remodeling to microenvironmental inflammation, vascular remodeling and systemic dissemination, suggest that chronic stress may influence cancer biology across cellular, tissue and organismal scales simultaneously. One interpretation is that these changes are linked by dysregulated cross-level coordination within NEI signaling networks; however, this interpretation should be regarded as an explanatory model rather than a demonstrated causal principle, because direct evidence connecting all levels within a single integrated framework is absent.

Collectively, this working hypothesis does not assert that a single unified stress-regulatory system has already been established as a formal oncological construct. Rather, it proposes that viewing stress regulation as a coordinated multiscale process may help bridge currently fragmented observations across neurobiology, immunology, endocrinology and tumor biology, while also identifying priorities for future mechanistic and clinical investigation.

Clinical implications for host-directed oncology. If the aforementioned systemic perspective is considered alongside current oncological knowledge, it may have implications for how cancer prevention and treatment strategies are conceptualized. Notably, this perspective is not intended to replace established tumor-directed therapies but rather to complement them by incorporating host NEI regulation into therapeutic frameworks.

In the context of current paradigms, current cancer treatment focuses on eliminating tumor cells through surgery, chemotherapy, radiotherapy and other tumor-directed approaches, including targeted therapies. These strategies remain the foundation of oncological care. At the same time, the evidence reviewed in the present review suggests that upstream NEI dysregulation may influence the biological context in which tumors progress, recur or respond to treatment. Thus, even when tumor burden is reduced, persistent chronic stress states may contribute to a host environment permissive for inflammation, immune dysregulation and metastatic progression.

Regarding the potential role of system recalibration, the multimodal interventions discussed in the present review, including psychosocial support, structured exercise, mindfulness-based approaches, vagal modulation and short-window pharmacological strategies, may converge on a shared therapeutic objective: Improving the regulation of stress-related NEI signaling. In this context, their potential value may lie not only in reducing perceived stress, but also in helping restore adaptive flexibility across interconnected autonomic, endocrine and immune pathways. These approaches should therefore be regarded as supportive host-directed strategies rather than direct anticancer treatments in themselves.

Regarding implications for precision medicine, future individualized cancer care may benefit from integrating tumor characteristics with selected indicators of host regulatory state. Candidate measures may include HRV, diurnal cortisol rhythm and systemic inflammatory markers. Although these measures have not yet been validated as routine oncological biomarkers, they may provide an initial basis for developing more comprehensive frameworks to assess how host physiological state interacts with tumor biology and treatment response.

Limitations and future directions. First, most human evidence in this field is observational or based on intermediate biomarkers (such as CTRA, HRV, diurnal cortisol, IL-6/CRP), leaving substantial room for residual confounding and reverse causation. Second, phenotyping of stress-related host states remains insufficiently standardized, with variation in sampling windows, posture and respiration control, assay preprocessing and analytic pipelines limiting comparability across studies. Third, intervention effects are likely to be time-, dose- and context-dependent, yet existing trials rarely prespecify perioperative vs. early systemic-therapy windows, or ensure adequate intensity and duration of multimodal interventions. Fourth, NEI dysregulation is likely heterogeneous across cancer types, disease stages, treatment settings and comorbidity profiles, which limits generalizability from single-center or highly selected cohorts. Fifth, host-directed strategies, including β-blockade, vagus-targeted approaches and exercise prescriptions, may be associated with context-specific risks, contraindications and drug-drug interactions that require careful prospective evaluation.

To further evaluate the stress-informed framework proposed in the present review, future studies should prioritize standardized assessment of host NEI-related states using a core battery, potentially including HRV measured under controlled conditions, diurnal cortisol slope, systemic inflammatory markers, such as IL-6/CRP, and transcriptional readouts, such as CTRA, where appropriate. Such phenotyping could be incorporated into prospective trials to identify stress-susceptible subgroups before randomization and to test whether intervention timing influences outcome, for example by comparing perioperative vs. early systemic-therapy initiation of multimodal supportive strategies. Parallel mechanistic studies, including multi-omics approaches, may help clarify whether distinct tumors differ in the relative contribution of stress-related host regulation vs. tumor-intrinsic molecular drivers. In addition, real-world datasets could be analyzed using stronger causal-inference methods, including target-trial emulation, propensity-based approaches and negative controls, with multi-center replication and long-term safety follow-up where feasible. Finally, integrative studies should examine interactions between NEI state and epigenetic regulation, the microbiome and circadian rhythms, while implementation-focused research should aim to address adherence, feasibility and equity across diverse oncological settings.

6. Conclusion

The framework discussed in the present review provides a conceptual perspective for understanding how chronic stress

and NEI interactions may influence cancer biology. Rather than attributing disease processes solely to tumor-intrinsic mechanisms, this perspective highlights the potential contribution of organism-level regulatory states shaped by interactions between external stressors and host physiological responses.

This interpretation should be regarded as a complementary perspective rather than a replacement for established oncological paradigms. The evidence summarized in the current review suggests that chronic stress-related NEI dysregulation may contribute to tumor progression, immune modulation and treatment response in selected contexts, although the magnitude and generalizability of these effects remain to be fully established.

From a clinical standpoint, integrating tumor-directed therapies with strategies that support host regulatory balance may represent a promising direction for future research. Interventions targeting stress-related physiological pathways, including behavioral, lifestyle and selected pharmacological approaches, may potentially improve the systemic environment in which conventional cancer therapies operate. However, rigorous prospective studies will be required to determine whether such strategies can meaningfully influence clinical outcomes.

Overall, considering cancer within a broader host-environment regulatory context may help generate new frameworks linking stress biology, systemic physiology and tumor progression, while also encouraging interdisciplinary research across oncology, neuroscience, endocrinology and immunology.

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Authors' contributions

ZZ and XZ conceptualized the study and designed the methodology. ZZ, JY, MW, YL, WZ, HG, AZ and XZ performed the literature review and evidence appraisal. JY, WZ and HG were responsible for reference management and extraction. ZZ, JY and XZ performed framework synthesis and critical evaluation. MW, YL and AZ obtained resources. YL, AZ and XZ generated figures and tables. ZZ and XZ wrote the original draft. All authors reviewed and edited the manuscript. XZ was responsible for supervision and project administration. JY and MW performed validation (fact-checking and assessing terminology consistency). As the guarantor, XZ accepts overall responsibility for the integrity of the work. Data authentication is not applicable. All authors read and approved the final manuscript.

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, AI tools (ChatGPT and OpenAI) were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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