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Review

Tumor Microenvironment Stress and Stress Adaptation Mechanisms

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Abstract

The tumor microenvironment (TME) constitutes a highly dynamic and interactive complex ecosystem, whose core components include tumor cells, stromal cells, immune cells, and an intricate network of signaling molecules. A prominent characteristic of this environment is the presence of multiple tumor-intrinsic stress responses, including hypoxia, oxidative stress, endoplasmic reticulum (ER) stress, metabolic stress, and mechanical stress. These stressors do not act in isolation but act synergistically to form a unique microenvironmental stress field, ultimately serving as a key biological engine that drives tumorigenesis, promotes disease progression, and induces therapeutic resistance. Emerging evidence highlights that targeted modulation of TME stress signaling pathways can not only suppress tumor growth but also remodel the immunosuppressive landscape, thereby augmenting anti-tumor immunity and achieving a synergistic “stress induction-immune activation” effect. This review provides a comprehensive synthesis of the molecular mechanisms underlying TME stress, adaptive strategies employed by tumor cells, and recent therapeutic advances centered on stress regulation. By integrating mechanistic insights with translational perspectives, this article aims to offer a foundational framework for developing novel combination therapies in oncology.

1. Introduction

As a multidimensional regulatory system, the tumor microenvironment (TME) comprises the tumor cells themselves, diverse stromal cell populations (e.g., fibroblasts, endothelial cells), immune cell subsets, the three-dimensionally reticular extracellular matrix (ECM), and a dynamically cross-linked signaling molecule network. Far from being a simple cellular assembly, this complex system forms a sophisticated regulatory network through dynamic interactions between cells, matrix, and molecules, acting as an irreplaceable “ecological hub” that governs tumor initiation, malignant progression, and therapeutic response [1]. Within this highly heterogeneous and dynamically evolving ecosystem, tumor cells and the microenvironment engage in continuous and complex interactions, collectively shaping a local milieu characterized by multiple stress features, such as hypoxia, nutrient deprivation, oxidative stress, endoplasmic reticulum stress, metabolic stress, and mechanical stress. Such stress responses not only constitute a core driving force for the malignant progression of tumors, but also profoundly reshape the functional spectrum of immune cells. Through multiple mechanisms including impairing antigen presentation efficiency, lowering the activation threshold of effector cells, and inducing the differentiation shift toward regulatory cells, they ultimately foster an immune-escape microenvironment characterized by disabled immune surveillance and a tolerogenic niche that renders therapeutic intervention ineffective [2,3].

Over the past decade, with breakthrough advances in the multidimensional dissection of the tumor microenvironment, a growing number of scholars have reached a strategic consensus: precisely targeting the endogenous stress response networks and dynamic adaptation modules within the TME can enable multidimensional innovations in antitumor strategies. Such targeted interventions not only effectively curb tumor proliferation by blocking aberrant signaling cascades, but more crucially, can reshape the ecological architecture of the immunosuppressive microenvironment, ultimately remodeling an "active immune microecosystem" that favors host antitumor immune responses. This approach ultimately achieves a "stress induction–immune activation" dual-strike effect [4-9].

While previous reviews have addressed individual stress pathways, there remains a need for an integrated analysis that elucidates how these stresses interact and converge to shape tumor evolution and immune evasion. This review aims to fill that gap by systematically examining the molecular mechanisms of TME stress, the adaptive responses of tumor cells, and emerging therapeutic strategies targeting these pathways. We further highlight the conceptual innovation of combining stress modulation with immunotherapy to achieve dual anti-tumor effects, offering a forward-looking perspective for next-generation combination regimens.

2. Stressors

The TME is essentially formed by the non-tumor cellular components within tumor tissue and the signaling molecules they secrete [10]. This system exhibits the following typical characteristics: a hypoxic microecological niche (abnormally remodeled oxygenation gradient) [11], nutrient deprivation (depletion of metabolic substrates) [12], an oxidative stress–enhanced zone (accumulation of reactive oxygen species) [13], an acidotic microenvironment (imbalanced H^+ concentration) [14], and a domain of interstitial fluid pressure imbalance (abnormally elevated hydrostatic pressure) [15]. These stressors do not act independently; instead, through crosstalk among complex molecular modules including the hypoxia-inducible factor (HIF) signaling axis, lactate shuttle metabolic pathway, vascular endothelial growth factor (VEGF) dynamic gradient, and PD-1/PD-L1 immune checkpoint, they dynamically adjust the stress threshold of the microenvironment at different stages of tumor progression, enabling malignant progression of tumors via stress adaptation [16].

2.1 Hypoxia

Hypoxia constitutes a central and defining feature of the TME. It arises from two primary factors: firstly, the dysfunctional and malformed tumor vasculature fails to provide adequate oxygen delivery; secondly, the rapid proliferation and heightened metabolic demands of tumor cells vastly outstrip the available oxygen supply. This imbalance creates pervasive regions of oxygen deficiency [17-19]. Furthermore, TME remodeling (such as ECM stiffening and elevated interstitial fluid pressure (IFP)) compresses blood vessels, exacerbating hypoxia [20]. Hypoxia alters the expression levels of genes regulating processes like metabolism [21,22]. The interaction of hypoxia signaling with other cellular pathways promotes malignant behaviors, including proliferation, migration, invasion, epithelial-mesenchymal transition (EMT), and enhances resistance to immunotherapy, chemotherapy, and radiotherapy [23-25].

2.2 Nutrient Deprivation

Under normal oxygen tension, mammalian cells primarily rely on mitochondrial oxidative phosphorylation (OXPHOS), the "molecular energy factory", to efficiently synthesize ATP. This process consumes oxygen and releases carbon dioxide, consistent with classic metabolic theory. In contrast, malignant tumor cells exhibit a striking metabolic reprogramming: even under normoxic conditions, they preferentially activate an "aerobic glycolysis engine". Through aberrantly enhanced glycolysis, glucose is converted to lactate at a much higher rate than in normal cells, accompanied by massive ATP production. This seemingly inefficient metabolic strategy actually represents "metabolic wisdom" evolved by tumor cells to adapt to hypoxic microenvironments, resist oxidative stress, and establish an immunosuppressive niche, widely known in biology as the “Warburg effect” [26]. While oxidative phosphorylation generates 36-38 ATP per glucose molecule, glycolysis yields only 2. To compensate and fuel their rapid proliferation, tumor cells exhibit a voracious glucose uptake from the TME [27,28]. However, the abnormal structure and functional insufficiency of the tumor vascular system lead to inefficient delivery of nutrients such as glucose, amino acids, and fatty acids [29]. Simultaneously, the rapid proliferation rate of tumor cells outstrips the nutrient supply speed, and the rapid metabolism driven by the Warburg Effect rapidly depletes local microenvironmental glucose and amino acids, creating a "nutrient desert". Specific cell types further exacerbate nutrient deprivation; for example, tumor cells with high IDO expression degrade tryptophan, and myeloid-derived suppressor cells (MDSCs) deplete arginine via arginase 1 (ARG1), thereby selectively inhibiting T cell functions that depend on these amino acids, while tumor cells can adapt to nutrient deprivation through alternative metabolic pathways [30-32]. Lactate accumulation leads to TME acidification (low pH), which not only inhibits immune cell functions (such as T cells and NK cells) but also promotes the activity of immunosuppressive cells like regulatory T cells (Tregs) and MDSCs, facilitating immune evasion [33]. The acidic environment can also activate matrix metalloproteinases, promoting ECM degradation and thereby enhancing tumor invasion and metastasis [34,35]. Additionally, a glucose-deprived microenvironment prevents T cells from effectively proliferating, secreting cytokines (like IFN-γ), and exerting cytotoxic effects, ultimately leading to the loss of anti-tumor immune function [36].

2.3 ROS Imbalance

Within the TME, reactive oxygen species (ROS) form a sophisticated oxidative stress network, whose core components include superoxide anion (O_2^-), hydroxyl radical (·OH), hydrogen peroxide (H_2O_2) [37], and lipid hydroperoxide (LOOH) [38]. These molecules are dynamically balanced through the synergy of multidimensional stressors. The three major sources of ROS are: OXPHOS imbalance caused by metabolic reprogramming in tumor cells, abnormal activation of NADPH oxidase due to disordered signaling pathways, and oxidative bursts triggered by cyclic hypoxia-reoxygenation fluctuations [39]. As the "dual energy-oxidation hub" of tumor cells, mitochondria continuously generate ROS via the OXPHOS pathway, forming a self-reinforcing vicious cycle: ROS burst - mitochondrial DNA (mtDNA) damage-respiratory chain dysfunction-further ROS burst [40]. Meanwhile, cancer-associated fibroblasts (CAFs) secrete oxidative molecules such as H_2O_2, establishing "oxidative stress microdomains" in the extracellular matrix, which directly stimulate tumor cell proliferation, invasion, and activation of the EMT program [41]. The biological effects of ROS display a concentration-dependent biphasic regulation pattern. At moderate to high concentrations, ROS act as a "signaling switch": they drive malignant progression by activating proliferation-related pathways including PI3K/AKT and

MAPK/ERK, while stabilizing HIF-1α to promote angiogenesis and metabolic reprogramming. In contrast, ROS at suprathreshold concentrations function as a "cytotoxic weapon", directly causing cell damage and death by inducing DNA double-strand breaks, protein oxidative modification, and lipid peroxidation.

Simultaneously, they establish a dual barrier of "oxidative suppression and immune escape" by inhibiting T-cell receptor (TCR) signaling, attenuating the cytotoxic activity of natural killer (NK) cells, and inducing regulatory T-cell (Treg) differentiation [42,43]. Such a multidimensional regulatory network, spanning from molecular bursts to cell fate determination, profoundly underscores the core strategic role of ROS in the construction of the tumor niche. The sophistication of the TME lies in maintaining ROS within a "sweet spot" beneficial for tumor cells but detrimental to immune cells. The so-called "imbalance" stems not only from increased ROS production but more crucially from alterations in the antioxidant defense system. Many tumor cells activate the nuclear factor erythroid 2-related factor 2 (NRF2) pathway, upregulating antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), thereby maintaining ROS at levels conducive to proliferation while avoiding toxicity–a form of "pre-adaptation" [44,45]. In contrast, immune cells infiltrating the TME, such as effector T cells, often have insufficient antioxidant capacity and lower NRF2 activity, making them more susceptible to ROS-mediated functional inhibition and apoptosis [46]. When the antioxidant defense of tumor cells surpasses that of immune cells, a ROS imbalance favorable for tumor progression is established.

2.4 Mechanical Stress

Uncontrolled tumor cell proliferation elevates cellular density, generating solid stress through direct physical compression between cells [47]. This direct physical contact and compression between cells constitute a major source of solid stress, directly affecting cell morphology, division processes, and viability [48-50]. Activated CAFs extensively synthesize and secrete ECM components (such as collagen, fibronectin), leading to ECM over-deposition [51]. Enzymes like lysyl oxidase (LOX) promote cross-linking between collagen and elastic fibers, significantly enhancing ECM stiffness and mechanical tension [52,53]. This "stiffening" of the ECM is one of the most representative features of the tumor mechanical microenvironment [54,55]. Simultaneously, the structural arrangement of ECM fibers changes significantly, typically becoming thicker and more linearly aligned, forming a "highway" network conducive to cancer cell migration [56,57]. In terms of vasculature, abnormal tumor vascular structure, increased permeability, coupled with impaired lymphatic drainage, lead to massive leakage and accumulation of plasma components in the tumor interstitium, significantly raising IFP [15]. This sustained high hydrostatic pressure not only severely hinders the effective delivery of anticancer drugs and the infiltration capacity of immune cells but also further drives malignant tumor progression [49,58,59].

Collectively, these stressors do not act in isolation. Instead, they interact TME to form a synergistic milieu that promotes tumor survival, invasion and immune evasion. For instance, hypoxia exacerbates oxidative stress and alters the stiffness of the ECM, while metabolic byproducts such as lactate further acidify the microenvironment and suppress immune function, among other effects. This interconnected stress network highlights the clinical imperative for multi-targeted therapeutic strategies that intervene in the TME as an integrated system, rather than targeting individual signaling pathways in isolation.

3. Stress Responses and Adaptive Strategies

The concept of TME stress encompasses the adaptive and maladaptive reactions elicited within tumor cells and their surrounding milieu when confronted with diverse internal and external challenges. Predominant forms include hypoxic, oxidative, endoplasmic reticulum, metabolic, and mechanical stress. In concert, these stress axes exert profound influence over the entire cancer lifecycle–from inception and local expansion to metastatic dissemination–while also serving as major contributors to the failure of therapeutic interventions [60-63].

3.1 Hypoxic Stress and Adaptive Strategies

Hypoxic stress in the TME is a core feature of malignant tumors, primarily driven by oxygen insufficiency due to aberrant vasculature and high cellular demand (Figure 1). The central adaptive response is orchestrated by hypoxia-inducible factors (HIFs), notably HIF-1α and HIF-2α [5,64]. In normoxia, HIF-α subunits are prolyl hydroxylated by PHDs, marking them for rapid ubiquitination and proteasomal degradation. Under hypoxic conditions, PHD activity is suppressed, leading to HIF-α stabilization, nuclear translocation, and dimerization with HIF-β. This complex then binds to hypoxia response elements (HREs) in DNA, initiating the transcription of a broad program of genes essential for hypoxic adaptation [65,66]. HIF-regulated genes participate in multiple processes: (1) Metabolic reprogramming (Warburg Effect): HIF-1α upregulates glycolytic enzymes (such as hexokinase, phosphofructokinase, LDH), shifting tumor cells towards glycolysis for energy production even when oxygen is sufficient [67]. (2) The angiogenesis regulatory axis: HIFs act as a "molecular switch" that precisely activates pro-angiogenic signaling modules such as VEGF in the hypoxic microecosystem, triggering the remodeling of the neovascular network within tumor tissue. Through dynamic processes including endothelial cell proliferation and migration, basement membrane remodeling, and pericyte recruitment, aberrant vascular loop structures and a leaky vascular bed are formed. This remodeling not only meets the oxygen and nutrient demands for rapid tumor proliferation but also further promotes tumor invasion and metastasis [68,69]. HIF-2α promotes clear cell renal cell carcinoma growth via erythropoietin (EPO) and angiopoietin (ANG); its

inhibitor Belzutifan has received clinical approval [70,71]. (3) Proliferation and Survival: HIFs regulate the expression of cell cycle proteins and apoptosis-related genes, enhancing survival [72]. Hypoxia can induce cells into a quiescent state and confer stem cell-like properties [73,74]. It also promotes EMT, enhancing migration and invasion capabilities [75]. Tumor cells under hypoxia secrete large amounts of hypoxia-induced tumor-derived exosomes (hiTDExs), whose unique cargo (e.g., miRNAs, proteins) mediates intercellular communication within the TME, promoting immune evasion, angiogenesis, and therapy resistance [76-78]. Hypoxia also remodels multiple cell types in the TME, synergistically promoting progression and resistance [79-81]: it inhibits T cell metabolism and function [82]; induces CAF formation (secreting immunosuppressive factors like TGF-β, PGE2, IL-6) [83]; recruits MDSCs and Tregs, exacerbating immune evasion [84]. ECM produced by CAFs forms a physical barrier, impairing NK cell activity [85,86]. Hypoxia also alters ECM components (like collagen, hyaluronic acid), increasing tissue stiffness and forming barriers to drug diffusion and immune cell infiltration [87]. Studies find that hypoxia alters key signature genes of glioma-associated microglia/macrophages (GAMs), enhancing their immunosuppressive properties [88]. While hypoxia can indirectly influence redox balance (e.g., via mitochondrial dysfunction), the primary sources and signaling roles of ROS constitute a distinct stress axis.

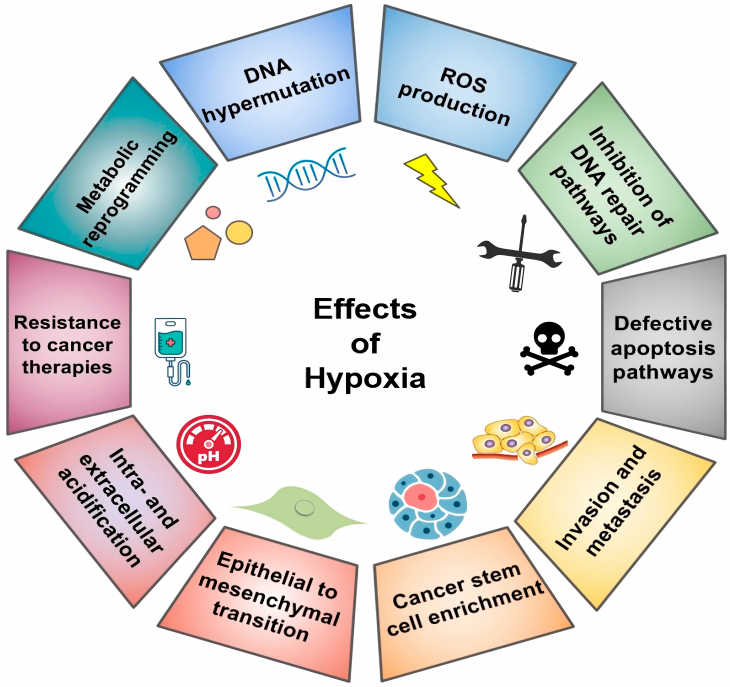

Figure 1. Hypoxia induces multifaceted effects on cancer cells, encompassing alterations in cell fate, genetics, metabolism, and clinicopathological behaviors. It promotes genetic instability and DNA damage, modulates ROS and metabolic pathways, and leads to extracellular acidification. Hypoxia also inhibits apoptosis, enriches cancer stem cells, and drives EMT, thereby enhancing invasion, metastasis, and resistance to therapies [23].

3.2 Oxidative Stress and Adaptive Strategies

In contrast to the oxygen deficiency defining hypoxia, oxidative stress in the TME arises from an imbalance between the production and clearance of ROS, encompassing molecules such as superoxide anion (O_2^-), hydroxyl radical (·OH), and hydrogen peroxide (H_2O_2) [37-39]. This state is fundamentally driven by elevated ROS generation–primarily from mitochondrial oxidative phosphorylation, aberrant oncogenic signaling, and stromal cell activity–coupled with altered antioxidant defenses [40,41,89,90]. Due to their rapid proliferation capacity and specific metabolic patterns, tumor cells typically exhibit elevated basal ROS levels [91,92]. The pathological state caused by abnormally high ROS is oxidative stress, accompanied by imbalanced redox signaling and oxidative damage to biomolecules [93]. As a core hallmark of cancer, it is closely related to tumor proliferation regulation and microenvironment remodeling [94]. Elevated ROS levels activate various signaling pathways by oxidizing specific amino acid residues in signaling proteins, promoting tumor cell proliferation and survival [95] (Figure 2). For example, the oxidative microenvironment centered on H_2O_2 triggers the unwinding of the "molecular latch" in the three-dimensional conformation of protein tyrosine phosphatase 1B (PTP1B) by targeting and modifying the Cys215 cysteine residue. This chemical modification leads to dynamic rearrangement of the PTP1B catalytic pocket and markedly attenuates its substrate-binding capacity, initiating a cascade of "phosphatase activity inhibition-signaling pathway activation". Specifically, inactivation of PTP1B releases the dual inhibitory constraints on two critical axes: the survival axis composed of insulin receptor substrate 1 (IRS-1)-phosphatidylinositol 3-kinase (PI3K)-phosphoinositide-dependent protein kinase 1 (PDK1)-AKT, and the proliferation axis consisting of leptin. Janus kinase (JAK)-signal transducer and activator of transcription 3 (STAT3).

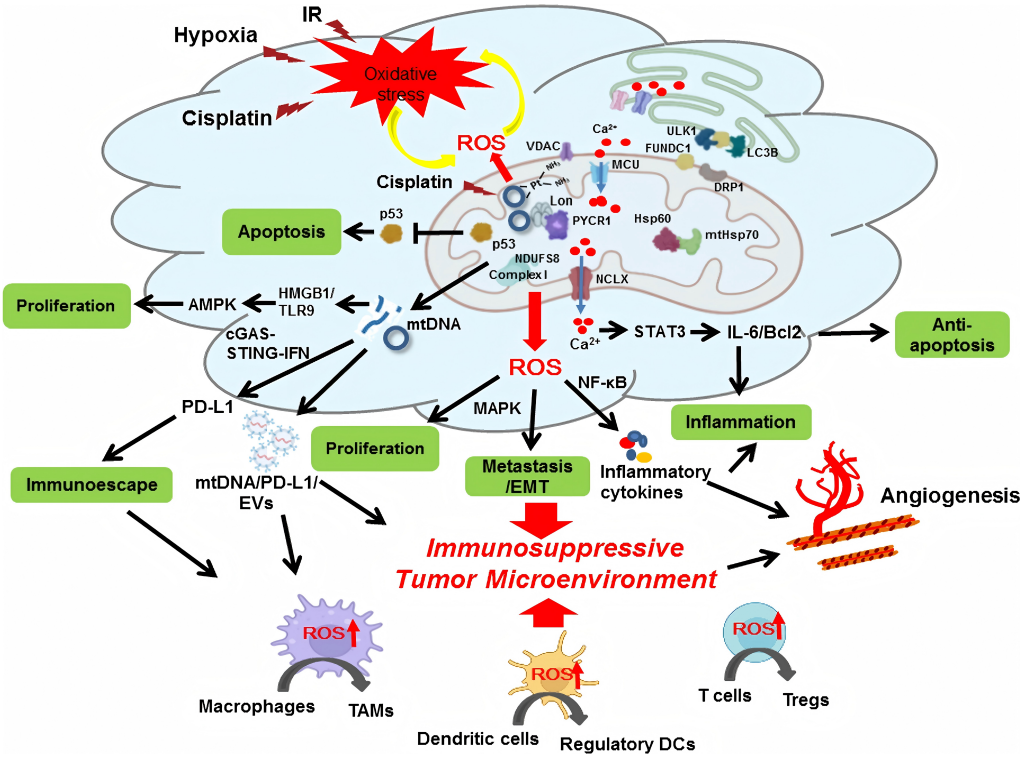

Figure 2. Schematic diagram illustrating how mitochondrial ROS (mtROS) stress promotes cancer cell survival and shapes an immunosuppressive TME to drive tumorigenesis. mtROS are mainly generated by mitochondrial aerobic respiration and metabolic enzymes. The chaperone Lon, a key component of mitochondrial protein quality control, interacts with NDUFS8 in Complex I and with PYCR1 to enhance mtROS production, thereby promoting proliferation and inflammation. The HSP60-mtHSP70-Lon complex sequesters p53 and stabilizes the mitochondrial Na^+/Ca^{2+} exchanger (NCLX), inhibiting apoptosis and increasing cisplatin resistance under ROS stress. mtROS also cause oxidative damage to mtDNA, activating the cGAS–STING–IFN pathway and upregulating PD-L1 expression, which suppresses T-cell activation. ROS and hypoxia upregulate Lon, triggering the release of extracellular vesicles (EVs) carrying mtDNA and PD-L1. These EVs stimulate macrophages to produce IFN and IL-6, further impairing T-cell immunity. Moreover, ROS induce NF-κB-dependent inflammatory cytokines (e.g., IL-6, TGF-β, VEGF), polarizing macrophages, dendritic cells (DCs) and T cells toward immunosuppressive phenotypes (e.g., TAMs, regulatory DCs, Tregs). Ultimately, mtROS establish an immunosuppressive TME that facilitates immune escape, cancer cell survival, and EMT/metastasis [94].

This molecular logic chain of "oxidative modification-conformational unlocking-pathway activation" establishes a "survival signal enhancement loop" and a "proliferation command amplification network" in cancer cells.

Ultimately, through multidimensional effects including enhanced glucose uptake, suppressed apoptotic programs, and promoted ribosome biogenesis, it drives the adaptive survival and malignant proliferation of cancer cells under oxidative stress [96-98]. ROS also inhibits protein tyrosine phosphatase (PTP) activity, preventing epidermal growth factor receptor (EGFR) dephosphorylation, continuously activating EGFR signaling, which then promotes proliferation and inhibits apoptosis via the Ras–RAF–MEK–ERK pathway [99-101]. ROS affects the DNA-binding activity of the NF-κB subunit p50 and regulates RelA (p65) phosphorylation; meanwhile, kinases like p38α MAPK, ATM, ERK mediate p53 phosphorylation, disrupting cysteine clusters in its DNA-binding domain, weakening p53's transcriptional activity, thereby promoting proliferation and inhibiting apoptosis [102,103]. Extensive crosstalk exists between these pathways, enabling tumor cells to integrate multiple stress adaptation signals, driving tumor progression [6]. A key adaptive strategy for tumor cells is to harness this pro-tumorigenic signaling while avoiding cytotoxic ROS levels, achieved by upregulating antioxidant systems such as the NRF2 pathway [44,45]. In contrast, immune cells infiltrating the TME, such as effector T cells, often have insufficient antioxidant capacity and lower NRF2 activity, making them more susceptible to ROS-mediated functional inhibition and apoptosis [46]. When the antioxidant defense of tumor cells surpasses that of immune cells, a ROS imbalance favorable for tumor progression is established.

Beyond autonomous regulation by tumor cells, ROS also plays a key role in the interaction between tumor cells and the microenvironment: excessive ROS causes DNA damage, genomic instability, and oxidative damage to biomolecules, activating oncogenic signals and promoting TME remodeling [6]. Mitochondria-derived ROS are important mediators of tumor initiation and progression, affecting proliferation, migration, invasion, angiogenesis, and inflammatory responses [94]. ROS mediates interactions between cancer cells, stromal cells, and immune cells via signaling pathways. Inflammation and oxidative stress form a complex network jointly influencing tumorigenesis and development [104-106]. Oxidative stress can induce EMT, promoting invasion and metastasis [107]. High levels of ROS directly inhibit T cell proliferation, differentiation, and effector function

[108,109], and promote macrophage polarization towards the M2 phenotype, enhancing immunosuppression, thereby promoting tumor immune evasion [104]. It is noteworthy that hypoxia can modulate the oxidative stress landscape (e.g., by affecting mitochondrial respiration and ROS generation); however, the core mechanisms and consequences of redox imbalance remain a distinct hallmark of the TME, as outlined above.

3.3 Endoplasmic Reticulum Stress and Adaptive Strategies

Protein processing, modification, and folding in the endoplasmic reticulum (ER) are tightly linked regulatory processes determining cell function, fate, and survival [110]. The uncontrolled proliferation of malignant tumor cells creates an unfavorable microenvironment, disrupting calcium/lipid homeostasis for various cells in this environment, impairing ER protein folding capacity in both tumor cells and infiltrating immune cells [111]. This promotes the accumulation of misfolded/unfolded proteins within the ER, triggering the unfolded protein response (UPR), thereby inducing ER stress [112]. The UPR in the endoplasmic reticulum is essentially a homeostatic repair program initiated by cells to restore the protein-folding capacity and secretory function of the ER (Figure 3). This repair program is intelligently regulated: Under transient stress, the UPR re-establishes homeostasis by upregulating the expression of molecular chaperones, suppressing global protein translation, and enhancing the degradation of misfolded proteins. However, when persistent stress exceeds a threshold, the repair network triggers a homeostatic collapse-to-apoptosis switch:via activation of the CHOP transcription factor, opening of the Bax/Bak mitochondrial permeability pore, and amplification of the caspase cascade, it ultimately executes the emergency decision of repair failure followed by programmed cell death [113,114]. The UPR is primarily regulated by three ER-resident sensors: inositol-requiring enzyme 1α (IRE1α), PKR-like ER kinase (PERK), and activating transcription factor 6 (ATF6). These three branches can control multiple pro-tumor characteristics in cancer cells while dynamically reprogramming the functions of innate and adaptive immune cells [115-117]. Therefore, aberrant activation of ER stress sensors has become a key regulator of tumor growth, metastasis, and response to chemotherapy, targeted therapy, and immunotherapy [118,119]. The UPR promotes adaptation and survival through its three branches: (1) IRE1α–XBP1 axis: IRE1α splices XBP1 mRNA to produce the active transcription factor XBP1s, upregulating ER chaperones (like GRP78) and lipid synthesis genes, promoting ER expansion [120]. (2) PERK–eIF2α axis: PERK phosphorylates eIF2α, inhibiting global protein synthesis, while inducing ATF4 transcription, upregulating antioxidant genes (like glutathione synthetase) and autophagy-related genes [121]. (3) ATF6 axis: ATF6 is cleaved in the Golgi apparatus, releasing an active fragment that upregulates chaperones and ER-associated degradation (ERAD) components [122-124]. Persistent and severe stress shifts towards pro-apoptotic pathways such as upregulating CHOP [125]. However, many tumors evade UPR-induced apoptosis by upregulating chaperones/anti-apoptotic proteins, thus utilizing the UPR to promote their own survival [8,126,127]. ER-mitochondria communication is important: ER stress causes abnormal Ca^{2+} release, leading to mitochondrial calcium overload, permeability transition pore opening, cytochrome c release, and apoptosis. ER stress also causes ROS accumulation, impairing mitochondrial function, forming a vicious cycle; mitochondrial ROS can feedback to exacerbate the UPR. This bidirectional regulation enhances the tumor's antioxidant capacity and metabolic plasticity [128-130]. There is crosstalk between mitochondrial UPR (UPRmt) and ER UPR (UPRER); for example, ATF5 (a key regulator of UPRmt) and ATF4 (a downstream molecule of UPRER) share transcriptional regulatory targets, coordinating cellular adaptive responses under metabolic stress [131]. ER stress regulates the immune microenvironment: it induces $CD8^+$ T cell dysfunction and exhaustion (upregulating PD-1, 2B4), induce macrophage polarization (upregulating MRC1, CD206) and regulates NK cell function and dendritic cell maturation via pathways like c-Myc [126,132,133]. It promotes immunosuppression: enhancing the immunosuppressive function of TAMs; potentially affecting immunosuppression by regulating TREM2 in myeloid cells [134,135]. It affects immune checkpoint dynamics: overactivation of immune checkpoint proteins (ICPs) impairs anti-tumor immunity, even induced suppression may impair the efficacy of immune checkpoint inhibitors (ICIs) [136].

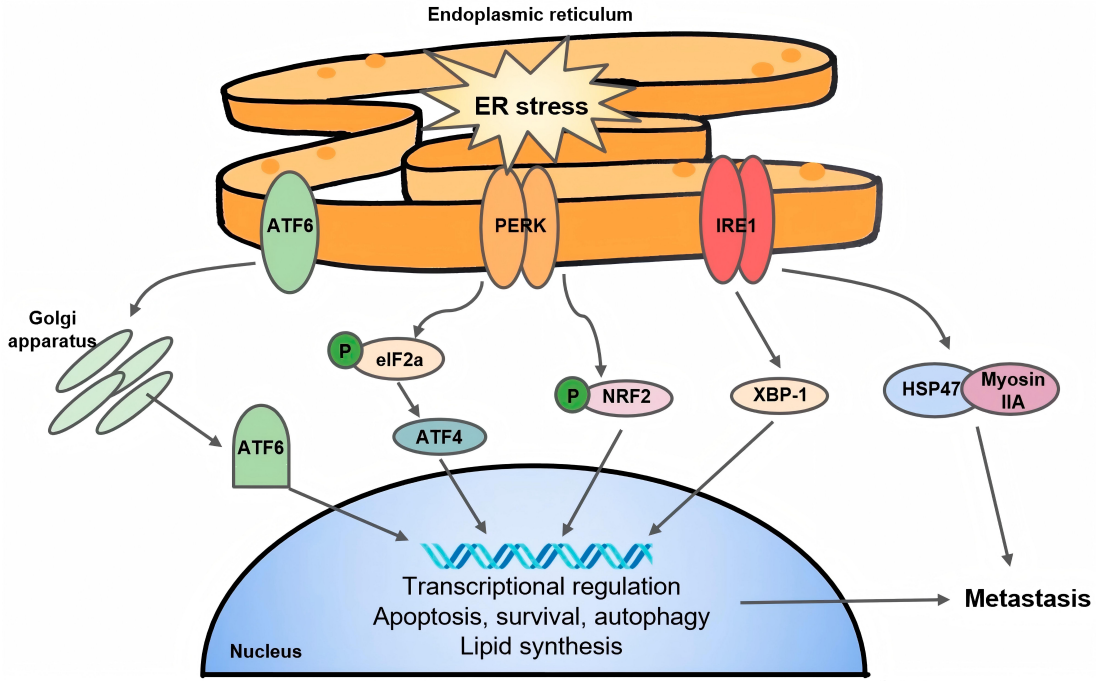

Figure 3. Dynamic regulatory network of the UPR triggered by ER stress. Upon aberrant accumulation of misfolded proteins in the ER lumen, three core sensor modules–ATF6, PERK, and IRE1–are synchronously activated and initiate sophisticated signaling cascades. ATF6 undergoes proteolytic cleavage during its translocation from the ER to the Golgi apparatus, releasing a transcriptionally active cytoplasmic domain. PERK induces the selective translation and activation of ATF4 by catalyzing the phosphorylation of eukaryotic initiation factor 2α (eIF2α), which in turn regulates the expression of downstream targets such as NRF2. IRE1 splices the precursor mRNA of X-box binding protein 1 (XBP1) via its endoribonuclease activity to generate a transcriptionally active spliced isoform, driving the coordinated expression of genes involved in protein folding, quality control, and secretion. These crosstalking signaling pathways converge in the nucleus and regulate the transcriptional program of key effector molecules including heat shock protein 47 (HSP47) and non-muscle myosin IIA, thereby maintaining a dynamic balance in cell fate decisions among apoptosis, survival, and autophagy, while also modulating lipid synthesis and metastasis-related pathways. Through multidimensional signal integration, this adaptive response program initiates homeostatic reprogramming to restore ER function under transient stress, or directs cells toward programmed elimination under persistent ER stress [23].

3.4 Metabolic Stress and Adaptive Strategies

The confluence of hypoxia, nutrient scarcity, and acidosis–hallmarks of the TME–establishes a pervasive state of metabolic stress [137]. This condition acts as a dual regulator: it drives further metabolic rewiring in tumor cells and imposes profound functional constraints on tumor-infiltrating immune cells, thereby critically determining the efficacy of anti-tumor immunity and therapeutic success [9,138]. Under TME metabolic stress conditions, tumor cells evolve various adaptation mechanisms [139]. For example, facing nutrient deprivation such as glucose deprivation, tumor cells can upregulate glutathione (GSH) synthesis to resist oxidative stress, thereby enhancing their viability and resistance to nutrient starvation therapies [140]. Clinical studies have revealed that high expression of interleukin-1A (IL-1A) activates the glutathione synthesis engine in tumor cells. By upregulating the expression of γ-glutamylcysteine synthetase (γ-GCS) and enhancing the activity of cystine transporters, it drives the abnormal accumulation of GSH and constructs an oxidative defense barrier. This metabolic reprogramming strategy endows oral squamous cell carcinoma (OSCC) cells with potent antioxidant capacity. It not only neutralizes oxidative damage induced by chemotherapeutic agents, but also generates a superimposed survival advantage by inhibiting ferroptosis, maintaining mitochondrial functional stability, and promoting DNA damage repair. Notably, enhanced GSH synthesis is significantly negatively correlated with clinical prognosis. Patients with high GSH levels generally exhibit increased tumor invasion depth, elevated lymph node metastasis rate, and shortened overall survival, making it an independent indicator of poor prognosis [141]. Tumor cells also respond to stress through ECM remodeling and metabolic interdependence with other cells: CAFs exhibit strong survival capabilities under stress conditions, releasing nutrients into the microenvironment via catabolism for tumor cell uptake and utilization, thereby helping tumor cells adapt to the harsh environment [142]. Furthermore, lipid metabolic reprogramming is another important strategy for tumor cells to adapt to TME stress–lipids, as energy sources and cell membrane components, play a key role in tumor initiation and progression [143,144]. Tumor cells typically undergo lipid metabolic reprogramming (Figure 4), characterized by increased lipid uptake, lipid synthesis, fatty acid oxidation (FAO), and lipid storage, to survive and proliferate under hypoxic and nutrient-deprived conditions [145]. Besides supporting tumor development, lipid metabolic reprogramming can alter TME properties by affecting the recruitment, activation, and function of immune cells and stromal cells: on one hand, tumor cells actively modify the TME by secreting signaling molecules and metabolites, regulating the functions of CAFs and immune cells

within it [146]; on the other hand, adaptive changes in cellular lipid metabolism within the TME (such as increased lipid uptake and accumulation, enhanced FAO) promote the transformation of the TME towards an immunosuppressive phenotype that supports tumor progression [147]. For example, upregulated lipid uptake and FAO increase lipid metabolic levels in Tregs, TAMs and MDSCs, facilitating their immunosuppressive functions [148-150]. Elevated CD36 expression leads to excessive intracellular lipid accumulation in $CD8^+$ T cells and NK cells: it inhibits the secretion of anti-tumor factors (IFN-γ and TNF-α) by $CD8^+$ T cells and impairs the tumor-killing activity of NK cells, respectively [151,152]. Moreover, the metabolic stress field within the TME also exerts a systematic remodeling effect on the activation process, differentiation trajectory, and effector function of immune cells, ultimately resulting in a significant attenuation of the efficacy of antitumor immune responses [153]. Nutrient competition exists between tumor cells and immune cells: tumor cells consume large amounts of glucose, leading to reduced glucose levels in the TME, limiting glucose uptake and glycolysis in effector T cells, impairing their function, and ultimately leading to exhaustion [154]. Simultaneously, metabolites produced by tumor cells, such as lactate, prostaglandin E2 (PGE2), and fatty acids, also create an immunosuppressive microenvironment [155]. For instance, lactate accumulation induces TME acidification; this acidic environment directly inhibits anti-tumor immune effector cells (like M1 macrophages, T lymphocytes, dendritic cells, NK cells) while enhancing immunosuppressive components (like M2 macrophages, Tregs), thereby promoting tumor immune evasion [156-159].

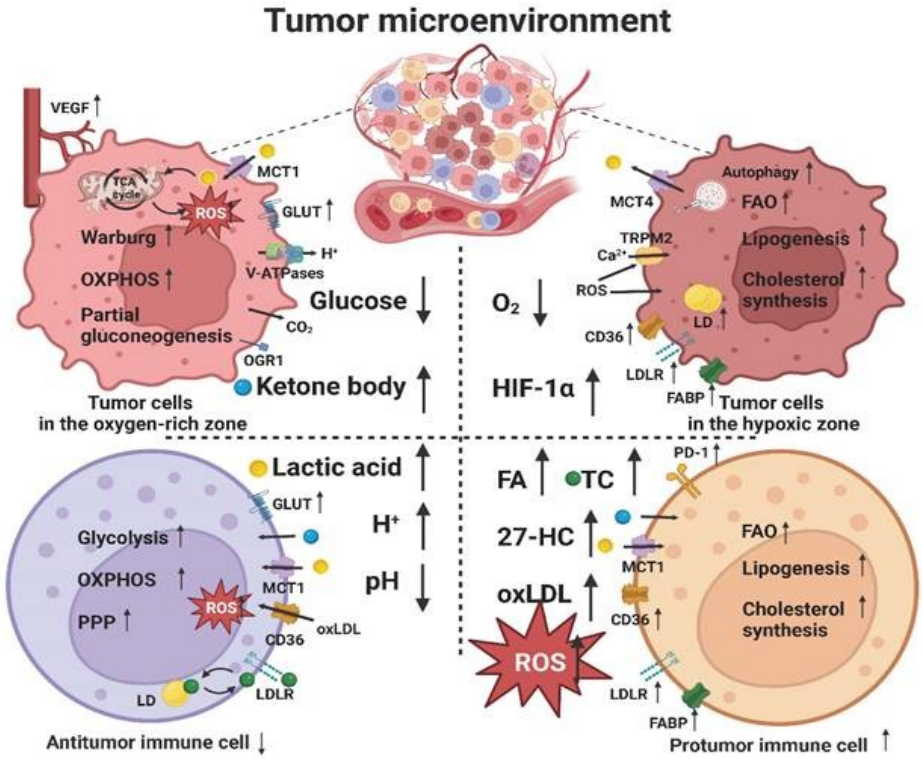

Figure 4. Lipid metabolic reprogramming within the TME driven by metabolic stress. Limitations in glucose and oxygen availability, along with accumulation of lactic acid and lipid peroxidation products, induce adaptive changes in lipid metabolism in both tumor and immune cells, enabling survival and function under nutrient-deprived and acidic conditions [160].

In oxygen-rich zones, tumor cells upregulate VEGF, glucose transporters (GLUT), and monocarboxylate transporter 1 (MCT1), enhancing the Warburg effect and OXPHOS while engaging in partial gluconeogenesis. Acid-sensing receptor OGR1 responds to extracellular H^+, further modulating metabolic flux. By contrast, in hypoxic regions, tumor cells increase glycolysis, OXPHOS, and the pentose phosphate pathway (PPP), while upregulating MCT4 to export lactate. Hypoxia-inducible factor-1α (HIF-1α) promotes fatty acid (FA) uptake via CD36 and induces autophagy, lipogenesis, and cholesterol synthesis to support membrane and energy demands.Concurrently, immune cells such as T cells exhibit reduced lipid droplet degradation and turnover (LDDR), impairing effector functions and antitumor immunity. Elevated lactate and protons in the TME further suppress immune activity through acid-sensing ion channels and PD-1-mediated exhaustion. FAO and ketone body utilization are enhanced across cell types, providing alternative energy sources and contributing to an overall immunosuppressive, pro-survival metabolic landscape that facilitates tumor progression [160].

3.5 Mechanical Stress Response and Adaptive Strategies

The TME contains not only metabolic substances but also various abnormal physical signals, such as the aforementioned increased matrix stiffness, solid stress, fluid stress, and abnormal ECM structure [161]. These biophysical changes affect the metabolic behavior of tumor cells and immune cells, thereby regulating tumor initiation, progression, and therapeutic response (Figure

5). Mechanical signals are sensed by tumor cells through mechanotransduction pathways and elicit responses that ultimately affect their proliferation, migration, invasion, and survival [162]. The concept of "cellular mechanical memory" has been proposed, where cells alter their phenotype in response to a specific physical microenvironment, and this phenotype is retained even after the original physical stimulus is removed and the cells are exposed to a new microenvironment [163]. Solid and fluid stresses can confer mechanical memory to tumor cells, enabling them to acquire biophysical adaptations through responses to high matrix stiffness in the primary TME, and potentially retain these properties via mechanical memory to facilitate metastasis. Primary tumor cells are induced by matrix stiffening and adapt by enhancing proliferation, drug resistance, factor secretion, force generation, altered mechanical properties, and migration [164]. Compared to healthy tissues and even benign tumors, solid malignant tumors (such as breast cancer, pancreatic cancer, liver cancer, prostate cancer) typically exhibit higher stiffness [162,165]. This characteristic can serve as a diagnostic marker and predictor for cancer risk, survival rate, and recurrence rate [166,167]. In solid tumors, high solid stress affects cell metabolism, gene expression, and the mechanical properties of the ECM [49,168,169]; elevated IFP hinders the delivery of drugs and oxygen to tumor cells, impairs cell migration [168], and is associated with reduced T cell interactions, which may contribute to an immunosuppressive microenvironment [170]. To further construct a microenvironment conducive to tumor growth and therapy escape, tumor cells adaptively secrete various factors to alter the phenotypes of stromal cells, endothelial cells, and immune cells. A typical example is matrix metalloproteinases (MMPs) degrading ECM proteins to promote tumor growth and invasion [171,172]. Furthermore, increased matrix stiffness can directly promote angiogenesis through mechanosensitive pathways involving endothelial cell MMP activity, or indirectly regulate angiogenesis by inducing tumor cells to secrete pro-angiogenic factors like VEGF, thereby affecting endothelial cell behavior [173].

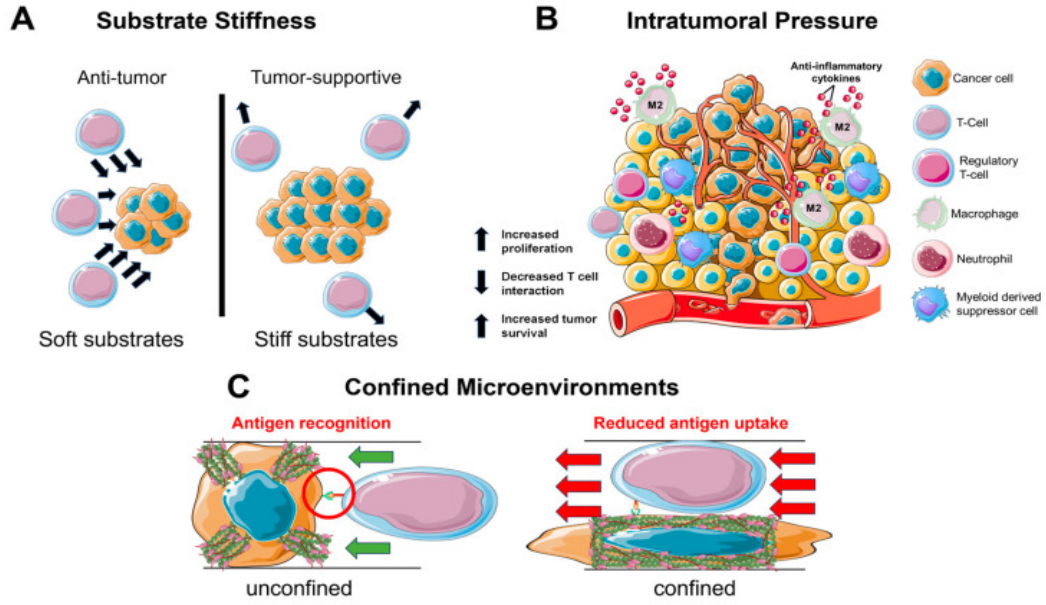

Figure 5. Biophysical properties of the TME impair immune cell-cancer cell interactions and promote an immunosuppressive state. Multiple mechanical cues act in concert to limit immune surveillance and support tumor progression. (A) Substrate stiffness influences immune cell function. On soft substrates, T cells exhibit normal migration and tumoricidal activity. In contrast, stiff substrates-often associated with fibrotic tumor stroma-reduce the motility of T cells and specifically impair the effector functions of $CD8^+$ T cells, thereby weakening anti- tumor immunity. (B) Intratumoral pressure alters immune cell phenotypes. Elevated interstitial pressure within tumors promotes the polarization of macrophages toward a tumor- supportive state, characterized by the secretion of anti- inflammatory cytokines. These cytokines not only inactivate infiltrating effector T cells but also recruit regulatory T cells (Tregs) and other immunosuppressive populations such as MDSCs. The resulting microenvironment favors cancer cell proliferation, limits productive T- cell engagement, and enhances tumor survival. (C) Confined microenvironments limit immune recognition. In densely packed tumor tissue, physical confinement distorts cell shape, disrupts cytoskeletal organization, and reduces the efficiency of antigen uptake and presentation by dendritic cells. Consequently, the chance of successful antigen recognition by T cells is markedly decreased, further compromising adaptive immune responses in the TME. Together, these biophysical barriers-stiffness, pressure, and spatial confinement–cooperatively establish an immune- resistant niche that facilitates tumor evasion and progression [170].

4. Therapeutic Strategies Based on Stress Regulation

4.1 Therapeutic Strategies Targeting Hypoxic Stress

Current core strategies to improve tumor oxygenation and intervene in hypoxia-related mechanisms are mainly divided into five categories: (1) Improving tumor vascular function: Using vascular normalization agents (such as the VEGF/VEGFR inhibitor bevacizumab) to optimize tumor vascular structure and function, improving oxygen delivery efficiency [174]. (2) Inhibition of HIF signaling: Directly targeting the HIF pathway involves developing agents that impair the stability or transcriptional activity of HIF-1α or HIF-2α. For instance, HIF-prolyl hydroxylase inhibitors (HIF-PHIs) such as roxadustat, which stabilize HIF-α by blocking its degradation, are clinically approved for anemia management. Interestingly, in certain tumor

contexts like glioblastoma, this stabilization can paradoxically induce ferroptosis and suppress growth, revealing a context-dependent therapeutic potential [175]; the HIF-2α inhibitor Belzutifan has been approved by the US FDA for VHL disease-associated tumors (including renal cell carcinoma, central nervous system hemangioblastoma, pancreatic neuroendocrine tumors) [176]. (3) Utilizing hypoxia-activated prodrugs: Such as tirapazamine (TPZ) and Evofosfamide (TH-302), which are reduced to cytotoxic substances under hypoxic conditions, selectively killing hypoxic tumor cells [177]. (4) Combination therapy to enhance immunotherapy efficacy: Hypoxia impairs immunotherapy efficacy by inhibiting T cell function and promoting immune evasion, which can be reversed by combination strategies, for example, anti-VEGF antibodies (like bevacizumab) combined with PD-1 inhibitors (like pembrolizumab) can remodel the hypoxic and immunosuppressive TME, enhancing immune cell infiltration [178]. (5) Nanomedicine delivery systems: Using oxygen-carrying nanoparticles to directly deliver oxygen to hypoxic regions or as targeted delivery vehicles; for example, manganese dioxide (MnO_2) NPs can catalytically decompose H_2O_2 in tumors to produce oxygen in situ, alleviating hypoxia [179]; perfluorocarbon (PFC) nanoemulsions can carry oxygen directly to deep tumor tissues [180]; functionalized superparamagnetic iron oxide NPs (SPIONs) construct intelligent delivery systems co-delivering HIF-1α/STAT3 siRNA, significantly inhibiting tumor growth in breast and colon cancer models [181]. Nanomedicine delivery systems are constantly being updated and optimized.

4.2 Therapeutic Strategies Targeting Oxidative Stress

Current therapeutic approaches targeting oxidative stress broadly dichotomize into two paradigms: exacerbating ROS accumulation or augmenting ROS clearance. The “ROS overload” strategy exploits the elevated basal ROS levels in cancer cells relative to normal cells. By disabling antioxidant defenses or directly stimulating ROS production, this approach pushes intracellular ROS beyond a tolerable threshold, collapsing redox balance and triggering lethal oxidative damage. Conversely, the “ROS scavenging” paradigm seeks to dampen oncogenic signaling and protect normal tissue by administering antioxidants, deploying enzymatic ROS-neutralizing agents, or inhibiting primary ROS-generating systems.

Regarding the controversial utility of antioxidants in tumor prevention and treatment, current studies show significant divergence: some experiments have confirmed their definite antitumor activity, while others have revealed potential pro-tumor risks, especially with ambiguity in efficacy evaluation when used in combination with chemotherapy. This contradiction may arise from multidimensional variable differences, including the molecular structure type of antioxidants, dosage gradient, intracellular effective concentration distribution, divergent experimental model designs, and heterogeneity in molecular mechanisms of action [6]. Notably, precise regulation of the spatiotemporal distribution of ROS in the TME can specifically enhance the cytotoxic efficacy of $CD8^+$ T cells and NK cells, and partially reverse the immunosuppressive microenvironment. However, caution is required regarding the significant heterogeneity in ROS concentration thresholds among different cell subsets: tumor cells may achieve ROS tolerance through antioxidant enzyme systems, whereas immune cells may exhibit dual effects of functional activation and inhibition at specific ROS concentrations. This cell-type-specific difference in ROS sensitivity constitutes a key uncertainty in clinical translational application [26,182]. ROS-targeted therapy combined with nanotechnology can improve drug accumulation in tumors, enhance efficacy, and reduce toxicity; it can also promote ROS generation by releasing oxygen, induce immunogenic cell death, or remodel the TME. This technology platform enables combination therapy (such as depleting GSH, degrading lactate) and synergizes with immune checkpoint blockade (ICB) therapy to enhance anti-PD-L1 efficacy [183]. Although strategies targeting oxidative stress continue to emerge, the high interconnectivity of the ROS regulatory network requires more basic and clinical research to accurately assess the potential of different therapeutic strategies. Nanozymes, as an emerging therapeutic strategy, show great potential in cancer therapy mediated by tumor oxidative stress–due to their enzyme-mimicking activity, low cost, good stability, and large-scale production advantages, they are considered promising substitutes for natural enzymes [184]. For example, multi-enzyme mimetic MoCu dual-atom nanozymes (MoCu DAzyme) can amplify tumor oxidative stress through cascade catalysis to improve efficacy [185]; TME-responsive lipid peroxidation amplifiers (e.g., metal-organic framework (MPN)-coated nanohybrids) can enhance ferroptosis-mediated anti-cancer therapy by scavenging GSH and silencing the glutathione peroxidase 4 (GPX4) gene [186]; another study developed TME-specifically regulated Ca-Fe-nanospheres that synergistically promote ferroptosis and tumor immune responses through calcium overload, ROS-mediated CDT, and SDT [187].

4.3 Therapeutic Strategies Targeting Endoplasmic Reticulum Stress

By intervening in ERS-related pathways, tumor cell death can be induced or anti-tumor immune responses enhanced. Various strategies targeting the UPR pathways have been developed: (1) Targeting the PERK-eIF2α-ATF4 pathway: ATP-competitive PERK inhibitors (GSK2606414) can block this pathway, increasing the radiosensitivity of breast cancer cells [188]. (2) Targeting the IRE1α-XBP1 pathway: IRE1α nuclease inhibitors (MKC-8866) can inhibit IRE1α nuclease activity, blocking XBP1s production, enhancing the efficacy of chemotherapeutic drugs (like paclitaxel) against triple-negative breast cancer, inducing pyroptosis and inhibiting tumor recurrence [189]; XBP1 splicing inhibitors (STF-083010) can restore the sensitivity of resistant breast cancer cells to endocrine therapy, suggesting the potential application value of XBP1 inhibitors in ER-positive breast cancer [190]. (3) Targeting the glucose-regulated protein 78 (GRP78)

pathway: GRP78 inhibitors (HHQ-4, Plumbagin) can downregulate GRP78 expression, inhibit tumor cell proliferation, and enhance the sensitivity of ER-positive breast cancer to tamoxifen; the phytoestrogen kaempferol can also trigger cell death by inhibiting GRP78-mediated ERS [191]. Additionally, ERS inducers include: Tunicamycins (inducing ERS by inhibiting DPAGT1, a key enzyme in N-glycan biosynthesis, inhibiting tumor cell proliferation, anti-apoptosis, metastasis, and angiogenesis) [192]; Cucurbitacin B (inhibiting glioblastoma via the STAT3/ROS/ERS pathway) [193]; Usenamine A (UD32-3, a natural compound exerting anti-non-small cell lung cancer (NSCLC) activity by inducing ERS and Notch1-mediated autophagy, and enhancing the cytotoxicity of gemcitabine) [194]. Furthermore, ERS-related molecules can also serve as potential therapeutic targets: Glucose-regulated proteins (GRPs, like GRP78, GRP94, GRP96) are upregulated under ERS and play important roles in cancer cell survival, immune evasion, and therapy resistance, serving as vaccine targets [195]; the ORMDL protein family (ORMDL1/2/3) affects cell proliferation, apoptosis, and metabolic balance by regulating sphingolipid metabolism and maintaining ER homeostasis, and their abnormal expression and function in various tumors make them potential therapeutic targets [196]; Luman/CREB3 regulatory factor (CREBRF) participates in ERS and regulates the UPR, leading to the accumulation of misfolded proteins, garnering significant attention in oncology [197]. Combination therapy strategies are also applicable to ERS-targeted therapy: ERS-targeting drugs can remodel the TME, turning "cold" tumors into "hot" tumors, and enhance the efficacy of ICIs [198]. ERS-targeting nanodrugs (like PPRK@MTO) combined with photodynamic therapy can amplify ERS, induce immunogenic cell death, and improve efficacy [199].

4.4 Therapeutic Strategies Targeting Metabolic Stress

Current intervention strategies focus on a system of precision targeting of metabolic nodes, with specific approaches as follows: (1) Targeting glucose metabolism: Glycolytic pathway inhibitors (such as 2-deoxy-D-glucose (2-DG) and dichloroacetate (DCA)) are employed in an energy-deprivation strategy to block the aberrant aerobic glycolysis (Warburg effect) unique to tumor cells, reduce their energy supply, and enhance chemosensitivity [200]; targeting key glycolytic enzymes: a molecular blockade strategy is implemented against core nodal enzymes in the glycolytic pathway, for example, hexokinase 2 (HK2) inhibitor lonidamine [201], the PKM2 inhibitor Shikonin [202], and the LDHA inhibitor FX-11 [203]. These molecules, by specifically binding to enzyme active sites or interfering with enzyme conformation, exhibit significant tumor growth-suppressive activity in preclinical models [204]. (2) Targeting amino acid metabolism: Developing inhibitors targeting key enzymes in amino acid metabolism, such as glutaminase (GLS) inhibitors (like CB-839) [205], arginase inhibitors (like OAT-1746) [206], and indoleamine 2,3-dioxygenase (IDO) inhibitors (like Epacadostat), to interfere with amino acid utilization by tumor cells and immune cells, thereby regulating the TME [207]. (3) Targeting lipid metabolism: Using fatty acid synthase (FASN) inhibitors (such as TVB-2640) [208], acetyl-CoA carboxylase (ACC) inhibitors (such as ND-646) [209], and fatty acid uptake inhibitors (such as CD36 inhibitors) to disrupt lipid synthesis and uptake in tumor cells, inducing metabolic stress and cell death [210]. (4) Targeting mitochondrial metabolism: Using OXPHOS inhibitors (such as Metformin, IACS-010759) to inhibit the energy metabolism of tumor cells dependent on OXPHOS [211]. (5) Targeting metabolic symbiosis: Disrupting the metabolic symbiosis between tumor cells and stromal cells (such as CAFs), for example, by inhibiting lactate shuttle (using monocarboxylate transporter (MCT) inhibitors like AZD3965) or disrupting glutamine metabolism, to cut off the nutrient supply chain between cells [212]. (6) Targeting metabolic checkpoints in immunotherapy: Combining metabolic modulators with ICIs to improve the efficacy of immunotherapy, for example, using LDHA inhibitors to reduce lactate production, alleviating TME acidification, and restoring T cell function [213]. (7) Nanomedicine-based metabolic intervention: Designing nanocarriers to deliver metabolic inhibitors specifically to tumor tissues, improving drug bioavailability and reducing systemic toxicity, for example, nanoparticles loaded with glycolysis inhibitors can target tumor cells and enhance anti-tumor effects [214]. (8) Dietary intervention: Utilizing specific dietary patterns (such as ketogenic diets, fasting-mimicking diets) to alter systemic metabolism, thereby affecting tumor metabolism and growth, and enhancing the efficacy of conventional therapies [215].

4.5 Therapeutic Strategies Targeting Mechanical Stress

Targeting the mechanical stress of the TME is an emerging field in cancer therapy. By intervening in the mechanical properties of the TME, drug delivery efficiency can be improved, tumor growth and metastasis can be inhibited, and the efficacy of other treatments can be enhanced [211,216]. Current strategies mainly include: (1) Targeting ECM stiffness: It can inhibit ECM synthesis and remodeling by targeting molecules such as LOX, transforming growth factor-β (TGF-β) and CD44, degrade core ECM components like hyaluronic acid and collagen, or weaken the supportive effect of CAFs on tumor growth and progression by targeting targets including sonic hedgehog (SHH) and fibroblast activation protein (FAP), thereby disrupting the tumor-supportive microenvironment and restricting tumor growth and invasion [216]. (2) Targeting solid stress: Using angiotensin receptor blockers (ARBs, such as Losartan) to reduce solid stress by inhibiting the renin-angiotensin system (RAS), thereby improving blood perfusion and drug delivery [217]; developing tumor-penetrating peptides (such as iRGD) to enhance drug penetration into tumor tissues [218]. (3) Targeting IFP: Using vascular normalization agents (such as bevacizumab) to reduce IFP by normalizing tumor blood vessels or promoting lymphatic drainage, thereby improving drug delivery [219]. (4) Combination therapy:

Combining mechanical stress-targeting strategies with other treatments (such as chemotherapy, immunotherapy) to achieve synergistic effects; for example, using Losartan combined with chemotherapy or immunotherapy can improve drug delivery and enhance anti-tumor immune responses [220]. Although interventions targeting the mechanical microenvironment are still in the early developmental stage, their translational medical value is particularly remarkable–especially in optimizing drug delivery efficiency and blocking the metastatic pathways of cancer cells. This "mechanical microenvironment regulatory framework" reshapes the mechanical signature of the physical space within tumor tissue. It not only breaches the fibrotic stromal barrier to enable efficient penetration of nanocarriers, but also blocks the "mechanotaxis" machinery that guides cancer cell migration along mechanical gradients by inhibiting mechanosensitive ion channels and integrin signaling pathways, thus achieving a dual synergistic effect of enhanced delivery and suppressed metastasis.

However, critical challenges still exist for clinical translation. There is a need to develop tissue-specific mechanical-targeting carriers to avoid collateral damage to normal tissues. Meanwhile, "spatiotemporal synergistic" strategies with existing regimens such as immunotherapy and targeted therapy should be explored to realize the leap from single-mechanism intervention to multimodal therapy [7,221,222].

5. Outlook and Summary

In summary, the TME is a multifaceted ecosystem where tumor, stromal, and immune cells interact under a constellation of stresses–including hypoxia, nutrient lack, oxidative and ER stress, metabolic derangement, and mechanical force. These stresses act as potent drivers of malignancy and architects of therapy resistance by fostering adaptive survival mechanisms. Consequently, therapeutic interception of these stress pathways and their downstream adaptations has emerged as a pivotal frontier in cancer treatment. Current research has made significant progress in targeting various TME stresses, including improving tumor oxygenation, regulating redox balance, inducing endoplasmic reticulum stress, intervening in metabolic pathways, and modulating mechanical properties. These strategies have shown promising results in preclinical studies and some clinical trials. However, challenges remain, such as the complexity and plasticity of the TME, the potential side effects of targeted therapies, and the need for effective combination strategies.

This review synthesizes recent advances in understanding how interconnected stress pathways in the TME, cooperatively drive tumor progression and immune evasion. We highlight the novel concept of "stress induction–immune activation" as a dual-targeting strategy to overcome therapy resistance. Unlike previous reviews focusing on single stress types, this work provides an integrated perspective on the crosstalk between different stress responses and their collective impact on the TME.

Future investigations should prioritize the following directions: First, elucidating the interactive networks and integrated effects of different stress signals within the tumor microenvironment, in order to uncover the systemic principles through which they collectively drive tumor progression and therapy resistance. Second, developing targeted drugs or interventions with greater specificity and efficacy, thereby minimizing off-target effects on normal tissues. Third, exploring optimized combination strategies that integrate stress-targeting therapies with immunotherapy, chemotherapy, or radiotherapy to achieve synergistic antitumor outcomes. Fourth, leveraging cutting-edge technologies – including nanomedicine, artificial intelligence, and advanced imaging–to enhance drug delivery, dynamically monitor treatment responses, and guide personalized therapeutic regimens. Moving forward, several concrete pathways can be pursued: establishing integrated multi-omics platforms to systematically map stress-pathway interactions in patient tumors; designing intelligent nanocarriers capable of sequentially targeting multiple TME stressors; and launching clinical trials that evaluate the synergistic potential of combining mechanical modulators (e.g., Losartan) with immune-checkpoint inhibitors. These efforts will help translate mechanistic insights into clinically effective, precision-based combination therapies.

In conclusion, the strategic targeting of TME-associated stresses and the adaptive programs they engage presents a highly promising avenue for overcoming therapeutic resistance. As research uncovers deeper mechanistic insights and technologies for precise intervention advance, the development of more effective and tailored combination therapies is anticipated, offering renewed hope for improving outcomes in cancer patients.

Abbreviations

ACC: Acetyl-CoA carboxylase

ANG: Angiopoietin

ARG1: Arginine via arginase 1

ATF6: Activating transcription factor 6

CAFs: Cancer-associated fibroblasts

CAT: Catalase

CREBRF: CREB3 regulatory factor

DCA: Dichloroacetate

DCs: Dendritic cells

ECM: Extracellular matrix

EGFR: Epidermal growth factor receptor

eIF2α: Eukaryotic initiation factor 2α

EMT: Epithelial-mesenchymal transition

EPO: Erythropoietin

ER: Endoplasmic reticulum

ERAD: ER-associated degradation

EVs: Extracellular vesicles

FA: Fatty acid

FAO: Fatty acid oxidation

FAP: Fibroblast activation protein

FASN: Fatty acid synthase

GAMs: Glioma-associated microglia/macrophages

GLS: Glutaminase

GLUT: Glucose transporters

GPx: Glutathione peroxidase

GPX4: Glutathione peroxidase 4

GRP78: Glucose-regulated protein 78

GSH: Glutathione

HIF: Hypoxia-inducible factor

HIF-1α: Hypoxia-inducible factor-1α

HIFs: Hypoxia-inducible factors

hiTDExs: Hypoxia-induced tumor-derived exosomes

HK2: Hexokinase 2

HREs: Hypoxia response elements

HSP47: Heat shock protein 47

ICB: Immune checkpoint blockade

ICIs: Immune checkpoint inhibitors

ICPs: Immune checkpoint proteins

IFP: Interstitial fluid pressure

IL-1A: Interleukin-1A

IRE1α: Inositol-requiring enzyme 1α

IRS-1: Insulin receptor substrate 1

JAK: Janus kinase

LDDR: Lipid droplet degradation and turnover

LOX: Lysyl oxidase

MCT: Monocarboxylate transporter

MCT1: Monocarboxylate transporter 1

MDSCs: Myeloid-derived suppressor cells

MMPs: Matrix metalloproteinases

mtDNA: Mitochondrial DNA

NK: Natural killer

NRF2: Nuclear factor erythroid 2-related factor 2

NSCLC: Non-small cell lung cancer

OSCC: Oral squamous cell carcinoma

OXPHOS: Oxidative phosphorylation

PDK1: Phosphoinositide-dependent protein kinase 1

PERK: PKR-like ER kinase

PFC: Perfluorocarbon

PGE2: Prostaglandin E2

PI3K: Phosphatidylinositol 3-kinase

PPP: Pentose phosphate pathway

PTP: Protein tyrosine phosphatase

PTP1B: Protein tyrosine phosphatase 1B

ROS: Reactive oxygen species

SHH: Sonic hedgehog

SOD: Superoxide dismutase

SPIONs: Superparamagnetic iron oxide NPs

STAT3: Signal transducer and activator of transcription 3

TCR: T-cell receptor

TH-302: Evofosfamide

TME: Tumor microenvironment

TPZ: Tirapazamine

UPR: Unfolded protein response

XBP1: X-box binding protein 1

Conflict of Interest

All authors declared there is no conflict of interest in this work.

Generative AI Statement

The authors declare that no generative artificial intelligence technologies were used in the preparation of this manuscript.

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