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A Review of the Interplay Between ER Stress Responses and T Cell Biology in the Tumor Microenvironment

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Abstract. T cell exhaustion within the tumor microenvironment (TME) is a major barrier to effective cancer immunotherapy. Drawing on a literature review and case analysis, this study explores the emerging role of endoplasmic reticulum (ER) stress and the subsequent unfolded protein response (UPR) as a central driving force behind this exhausted state. It is put forward that the hostile TME induces persistent ER stress not only in tumor cells but also in tumor-infiltrating lymphocytes (TILs). Within T cells, chronic UPR activation directly impairs effector functions by inhibiting key transcription factors, disrupting metabolic fitness, and promoting epigenetic programming associated with exhaustion. On the other hand, tumor cell-intrinsic ER stress fosters a tumor-permissive immunosuppressive microenvironment by secreting factors and exosomes that can directly inhibit T cell activity or indirectly suppress immunity by polarizing myeloid cells toward a tolerogenic phenotype. This bidirectional crosstalk establishes ER stress as a critical regulator of anti-tumor immunity. Finally, the study shows novel therapeutic strategies targeting this axis. Understanding these interactions between ER stress, UPR activation, and anti-tumor immune responses provides a theoretical framework for developing more effective immunotherapies.

Keywords: Endoplasmic Reticulum Stress, T Cell Exhaustion, Tumor Microenvironment, Unfolded Protein Response, Immunotherapy

1. Introduction

In the era of cancer immunotherapy, understanding why T cells infiltrating tumors often lose their effector function is critical for improving therapeutic efficacy [1]. T-cell exhaustion is a state of dysfunction characterized by the progressive loss of effector functions and proliferative capacity, along with high expression of inhibitory receptors after long-term exposure to antigens and inflammatory signals [2]. This is one of the major obstacles in current cancer immunotherapy.

The causes of T cell exhaustion are complex and diverse, involving metabolic reprogramming, epigenetic changes, transcription factor dysregulation, myeloid cell action, and the involvement of a variety of soluble factors and signaling pathways. Recent studies reveal that endoplasmic reticulum Stress (ER stress) and its triggered unfolded protein response (UPR) in the tumor microenvironment (TME) are among the core factors driving T cell exhaustion and immunosuppression [3]. ER stress not only directly impairs T cells but also indirectly weakens anti-tumor immunity by reshaping the

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entire microenvironment. Therefore, understanding the interaction between ER stress and T cells in the TME has profound implications for cancer therapy.

This review aims to explore the impact of ER stress in both T cells and tumor cells on anti-tumor immunity. It aims to explore how ER stress interacts with T cells in the TME to shape the immunosuppressive landscape and determine its potential as a therapeutic target.

2. Origin of endoplasmic reticulum stress in the tumor microenvironment

2.1. The tumor microenvironment as a trigger for ER stress

Multiple stress conditions in TME, a dynamic network of cancer cells, stromal cells, immune cells, and the extracellular matrix, are key drivers of endoplasmic reticulum stress and UPR [4]. This induction occurs not only in the tumor cells themselves but also profoundly affects all the components of the microenvironment, collectively shaping a pathological environment that supports tumor growth, metastasis, and immune escape [4]. Because of its unique pathophysiological state, the TME naturally has the conditions to induce ER stress. A number of studies have shown that TME-driven ER stress is a common feature across multiple cell types rather than an isolated case.

2.2. Key stressors inducing ER stress in the TME

There are many factors that induce endoplasmic reticulum stress in the TME, mainly from the tumor's intrinsic malignant characteristics and external treatment pressure.

2.2.1. Nutrient deprivation and metabolic stress

First, the nutrient demand of rapidly proliferating tumor cells often leads to a shortage of glucose and amino acids in the microenvironment, which affects the protein synthesis and folding ability of the endoplasmic reticulum [5]. For example, in hepatocellular carcinoma, the accumulation of bile acids induces ER stress, and ER stress in T cells can be directly triggered by a high-cholesterol environment in a variety of tumors [6].

2.2.2. Hypoxia and oxidative stress

Regions of inadequate oxygen supply are common within solid tumors. Such hypoxic conditions directly disrupt the normal function of the endoplasmic reticulum [4]. Intermittent hypoxia is an important factor in the induction of UPR in TME, which leads to the production of high levels of reactive oxygen species (ROS), which in turn activate UPR [7]. High metabolic activity and hypoxia-reperfusion generate large amounts of ROS. Since the ER is relatively sensitive to oxidative damage, oxidative stress rapidly disrupts its homeostasis and activates the UPR signaling pathway.

2.2.3. Extracellular acidosis

At the same time, tumor cells tend to undergo glycolysis and produce a large amount of lactic acid, which leads to the acidic TME. This low pH environment similarly interferes with the proper folding of proteins, triggering ER stress [5]. It is worth noting that external treatments such as chemotherapy and radiotherapy are themselves a form of cellular stress that can further aggravate ER stress already present in TME.

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3. Direct modulation of T cell function by intrinsic ER stress

3.1. From physiological response to pathological dysfunction

When the T-cell receptor (TCR) is activated, the cell needs to rapidly synthesize large numbers of effector molecules and cytokines, placing transient but substantial stress on the ER [8]. It has been shown that TCR activation directly induces upregulation of GRP78, an ER stress chaperone protein, signaling the initiation of UPR [9]. This stress response is essential for the normal activation and function of T cells. For example, the ER lumen chaperone gp96 (encoded by the Hsp90b1 gene) plays a central role in the activation of $CD4^+$ T cells. Gp96-deficient $CD4^+$ T cells fail to effectively mobilize ER calcium(Ca^{2+}) after TCR activation, resulting in an insufficient cytosolic calcium concentration and an inability to initiate activation-induced glycolysis, ultimately preventing normal T-cell activation [8].

However, within the TME, this adaptive pathway is subverted. Persistent stressors (e.g., nutrient deprivation, hypoxia) lead to chronic, unresolved ER stress. Unlike the transient UPR supporting activation, sustained ER stress directly leads to T-cell dysfunction, including activation of exhaustion-related pathways, impairing their antitumor and immunomodulatory capacity [9,10].

How chronic ER stress reprograms T cells into a dysfunctional state is a core question. Emerging evidence delineates three interconnected mechanistic axes. It includes three interconnected aspects: the induction of functional exhaustion, suppression of key transcriptional networks, and disruption of core metabolic pathways. The following sections will discuss how these axes collectively mediate the failure of anti-tumor immunity.

3.2. Activation of exhausion-associated pathways

Persistent, unrelieved endoplasmic reticulum stress eventually initiates an apoptotic program, an important pathway for T-cell depletion.

The function of cytotoxic T lymphocytes (CTLs) is often inhibited within tumors. Hepatoma cells induce ER stress in CTLs in two ways: by depleting glutamine (Gln) in the microenvironment and downregulating the expression of glutaminase 2 (GLS2) and the amino acid transporter SLC1A5 in CTLs [10]. The resulting ER stress severely damages CTLs' ER architecture. This damage leads to the upregulation of exhaustion markers Programmed cell death protein 1, (PD-1) and TIM-3 and decreases CTLS' ability to secrete granzyme B and perforin, resulting in functional exhaustion [10]. The restoration of CTL function by ER stress inhibitors demonstrates that ER stress is directly responsible for this dysfunction.

Conversely, T cells have evolved specific adaptive mechanisms to survive and maintain function under chronic stress. RNA-binding protein CPEB4 constitutes a new branch of the UPR in effector CD8+ T cells [9]. Triggered by ER stress during T-cell activation and effector phases, it uncouples from the terminal pro-apoptotic signals of the conventional UPR. CPEB4-mediated adaptation to chronic stress is essential for maintaining cellular fitness, producing effector molecules, and maintaining cytotoxic activity. Disruption of this pathway severely impairs the antitumor effector function of T cells and accelerates tumor growth [9].

When chronic ER stress remains unresolved, it can initiate the apoptosis program through the mTOR-Akt-IRE1α-JNK-Caspase signaling cascade [11]. Excessive production of reactive oxygen species (ROS) induces ER stress, and the mTOR pathway plays a key regulatory role in the process. Blockade of mTOR signaling reduces ROS-mediated endoplasmic reticulum stress, thereby reducing apoptosis and improving survival of $CD4^+$ T cells [11].

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3.3. Suppression of key transcription factors

ER stress, primarily through its IRE1α and PERK signaling branches, profoundly inhibits the transcriptional networks essential for T cell effector function, with the ATF6 pathway playing a more context-dependent role.

A key mechanism involves the persistent endoplasmic reticulum stress, which disrupts intracellular calcium homeostasis and consequently activates kinases such as JNK. These signaling events further impair the activation and nuclear translocation of nuclear factor of activated T-cells while suppressing the transcriptional activity of activator protein 1 (AP-1). This process fundamentally obstructs the initiation of the T cell effector program.

The PERK-ATF4-CHOP is another key switch. Moderate PERK-ATF4 signaling induces protective autophagy and promotes T-cell memory formation and antitumor function. Under the chronic ER stress of the TME, this pathway shifts toward a dominant pro-apoptotic and inhibitory signal mediated by CHOP. In the TME, cytotoxic T lymphocytes (CTCS) cocultured with hepatoma cells can repress the expression of genes encoding effector molecules and elevate the up-regulation of failure markers like PD-1 and TIM-3 [12]. A direct transcriptional pathway from sustained UPR signaling to the exhausted phenotype.

3.4. Disruption of metabolic reprogramming

T cells undergo profound metabolic reprogramming after activation, shifting from oxidative phosphorylation to aerobic glycolysis to support rapid proliferation and effector functions. Subsequently, a partial return to oxidative metabolism supports memory functions. Endoplasmic reticulum stress directly attacks the core link of this metabolic remodeling process.

Lipid metabolism is essential for the function of effector and memory T cells. The cytoskeletal protein TAGLN2 enhances fatty acid uptake and mitochondrial respiration, which are necessary for the anti-cancer activity of CD8+ T cells, by interacting with the fatty acid-binding protein FABP5 to facilitate its cell surface localization [4].

ER stress induced by the TME suppresses TAGLN2 expression, thereby impairing lipid uptake and mitochondrial respiration in CD8+ T cells, leading to a state of dysfunction. Similarly, inhibition of stearyl coenzyme A desaturase 1 (SCD1) enhances CD8+ effector T cell function by alleviating endoplasmic reticulum stress in T cells [13].

XBP1 is a key transcription factor in the UPR. Moderate XBP1 signaling during early T-cell activation manages the endoplasmic reticulum load from increased protein synthesis. However, under prolonged or intense stress, such as in the ovarian cancer malignant ascites, sustained XBP1 activation switches to an inhibitory signal. ER stress induced by the TME was confirmed to activate the IRE1α-XBP1 axis in T cells. This activation inhibits mitochondrial respiration and IFN-γ production. Inhibition occurs because upregulation of XBP1 reduces glutamine transporter expression, limiting glutamine influx essential for mitochondrial respiration in glucose-deprived T cells. In ovarian cancer-infiltrating CD8+ T cells, increased XBP1 correlates with reduced T-cell infiltration and decreased IFN-γ mRNA expression.

Limiting glutamine utilization through the IRE1α-XBP1 axis is a primary way by which ER stress inhibits mitochondrial respiration in T cells. In the glucose-deprived TME, elevated protein synthesis demands activate the UPR. This response cannot be properly sustained and leads to impaired mitochondrial function. Inhibiting this pathway restores T-cell metabolism and increases the expression of proteins involved in glycolysis and mitochondrial bioenergetics, thereby enhancing effector function and response to PD-1 immunotherapy [14].

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4. Indirect modulation of T-cell function by tumor cell ER stress

4.1. Transduction of ER stress in tumor cells

Endoplasmic reticulum oxidoreductase-1α (ERO1α) in tumor cells is a key molecule. It transmits their own ER stress to neighboring T cells, triggering CHOP-dependent apoptotic pathways in T cells and leading to the formation of immune-rejecting Tmes [12]. Knockout of ERO1α gene in tumor cells promotes $CD8^+$ T cell infiltration and enhances the efficacy of anti-PD-1 therapy [12]

4.2. Immune regulation mediated by tumor-derived exosomes

ER stressed tumor cells actively secrete exosomes as key messengers for their crosstalk with the immune system. MicroRNA (miRNA) miR-23a-3p is abnormally enriched in exosomes released from hepatoma cells treated with ER-stress-inducing agents (e.g., tunicamycin). High expression of this miRNA in tumor tissue is also predictive of shorter overall survival [15].

These exosomes loaded with specific molecular cargo are released into the TME and can be taken up by surrounding immune cells, particularly myeloid cells (e.g., macrophages), thereby conveying ER stress signals from tumor cells to the immune system [15].

4.3. Suppression of T cells via myeloid cell reprogramming

In vitro and in vivo studies show that tumor ER-stress-derived exosomes carrying miR-23a-3p significantly upregulate programmed death ligand 1 (PD-L1) in macrophages. Bioinformatics analysis and functional studies demonstrate that exosomal miR-23a-3p drives PD-L1 expression by targeting and inhibiting PTEN in macrophages, thereby activating the PI3K-AKT pathway.

PD-L1-high macrophages may exert a suppressive effect on T-cell function. Coculture experiments reveal that incubation with these exosome-stimulated macrophages results in a significant decrease in the proportion of CD8+ T cells and interleukin-2 production, along with an increase in T-cell apoptosis. This directly shows that tumor cells inhibit the function of CD8+ T cells, the core executors of anti-tumor immunity, through the “ER stress-exosome-macrophage” axis.

5. Targeting strategy for immunotherapy

5.1. Targeting the alleviation of endoplasmic reticulum stress in immune cells

Chronic, intense ER stress leads to T-cell dysfunction and exhaustion, an important cause of tumor immune escape and immune checkpoint inhibitors (ICIs) [16]. Remission of ER stress with the chemical chaperone tauroursodeoxycholic acid (TUDCA) enhances the infiltration of peripheral-blood mononuclear cells (PBMCS) into tumor spheroids and enhances their antitumor activity in preclinical models of kidney and ovarian cancer [16]. This suggests that pharmacologic mitigation of TME-induced ER stress may improve the survival and function of T cells, thereby enhancing the efficacy of immunotherapy.

5.2. Targeted inhibition of tumor cell stress signal transduction

M2 macrophages tend to accumulate in hypoxic regions of tumors, where their IRE1α-XBP1 pathway is activated to maintainthe M2 phenotype [17]. Co-inhibiting ER stress and oxidative stress

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can effectively reprogram M2 macrophages into proinflammatory M1. It combines with PD-1 antibodies to improve treatment efficacy [17].

Tumor cell ER stress can impair tumor-infiltrating lymphocytes. Knocking down or inhibiting ERO1α in T cells can block this stress transmission, promote CD8+ T cell infiltration, and enhance PD-1 inhibitors' response. High ERO1α expression correlates with poor immunotherapy response and survival in non-small-cell lung cancer patients [12]. Therefore, targeting molecules that mediate stress transmission, such as ERO1α, is a new target to alleviate ER stress of immune cells and improve immunotherapy..

5.3. Exploiting endoplasmic reticulum stress to induce immunogenic antitumor responses

ER stress triggers ICD, releasing Damage-Associated Molecular Patterns (DAMPs) to activate Dendritic Cells and initiate cytotoxic T lymphocyte (CTL) responses. Nanotechnologies are designed to specifically induce tumor cell ER stress and Immunogenic Cell Death.

DNA tetrahedral nanomodulators target tumor cell ER, trigger intense ER stress through glucose depletion and reactive oxygen species (ROS) generation, promote DC maturation and T-cell infiltration. It is remarkably efficacious when combined with PD-1 inhibitors [18]. Nanoimmuno-activators (nanoIA) induce ICDs by targeting the ER, co-delivering immunomodulators (e.g., JQ1, NLG919) to activate immunity and reverse immunosuppression [19]. GCT@CM NPs effectively induce tumor growth and ER stress to trigger ICD, thereby inhibiting tumor growth and enhancing the efficacy of PD-L1 antibodies.

Amplifying ER stress activates the cGAS-STING pathway. ER-targeting calcium peroxide nanoparticles disrupt calcium homeostasis, amplify ER stress, trigger cGAS-STING, promote PD-L1 degradation, and reverse systemic antitumor immunity. Inhibiting PERK induces paraptosis (a form of ICD), stimulating DCs to produce type I interferons and drive CD103+ DC differentiation, thereby triggering robust T-cell responses.

6. Conclusion

In summary, this review elucidates the critical, multifaceted roles of endoplasmic reticulum (ER) stress and the UPR in shaping the immunosuppressive landscape of the TME. ER stress acts as a bidirectional regulator of anti-tumor immunity: intrinsically, chronic UPR activation in T cells impairs effector functions, disrupts metabolic fitness, and promotes exhaustion-associated transcriptional and epigenetic programs. Extrinsically, tumor cell-derived ER stress signals—conveyed via soluble factors and exosomes—reprogram myeloid cells toward a tolerogenic phenotype, further dampening T cell activity. This crosstalk underscores ER stress as a pivotal mechanism underlying T cell dysfunction and immunotherapy resistance.

Emerging therapeutic strategies that target ER stress pathways—such as chemical chaperones, UPR kinase inhibitors, and nanotechnologies that induce immunogenic cell death—hold promising potential to reinvigorate anti-tumor immunity. This study exhibits certain limitations. For instance, it overlooks the potential feedback effects of T-cell phenotypic heterogeneity on endoplasmic reticulum stress and lacks an in-depth exploration of its clinical applications in oncology. Furthermore, no discussion is provided regarding potential risks, such as immunosuppression, nor are concerns regarding biotechnological safety and medical ethics addressed. Ultimately, a deeper understanding of ER stress-immune interactions will provide a rational foundation for next-generation cancer treatments.

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