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Metabolic Reprogramming of T Cells in the Tumor Microenvironment

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Abstract

This paper investigates the impact of oxidative stress on the metabolic reprogramming of CD8+ cytotoxic T cells in the tumor microenvironment (TME) and its implications for cancer immunotherapy. Elevated reactive oxygen species (ROS) disrupt mitochondrial function, leading to impaired energy production and T cell exhaustion, which in turn reduces the efficacy of T cell-based immunotherapies such as immune checkpoint blockade (ICB) and adoptive cell transfer (ACT). The study proposes therapeutic strategies, including antioxidant therapy and metabolic modulators, to restore T cell functionality and enhance their antitumor activity. These findings highlight the potential for metabolic reprogramming to reinvigorate exhausted T cells and improve the effectiveness of cancer immunotherapy.

Keywords: *Oxidative stress, metabolic reprogramming, T cell exhaustion, cancer immunotherapy, CD8+ cytotoxic T cells*

Introduction

The immune system plays a critical role in controlling cancer, with CD8+ T cells being particularly important for eliminating tumors. However, within the tumor microenvironment (TME), these T cells often become dysfunctional due to persistent antigen exposure and immunosuppressive factors, leading to a state known as T cell exhaustion [1]. A key contributor to this exhaustion is oxidative stress, characterized by the accumulation of reactive oxygen species (ROS), which disrupts T cell metabolic processes and impairs their function.

T cells normally rely on a shift from oxidative phosphorylation (OXPHOS) to aerobic glycolysis to meet the energy demands of rapid proliferation during immune responses. However, oxidative stress in the TME severely impairs this metabolic reprogramming, leading to mitochondrial dysfunction and reduced ATP production [2]. This limits the ability of T cells to sustain their effector functions, contributing to tumor immune evasion [3]–[5]. Moreover, oxidative stress promotes T cell exhaustion by upregulating inhibitory receptors like PD-1 and CTLA-4, further diminishing their anti-tumor activity [6]. Efforts to restore redox balance in T cells through the use of antioxidants, such as N-acetylcysteine (NAC) and mitochondrial-targeted agents like MitoTEMPO, have shown promise in reactivating T cell metabolism and enhancing their ability to combat tumors [7].

Targeting metabolic pathways disrupted by oxidative stress has emerged as a promising therapeutic strategy. Metformin, an activator of AMP-activated protein kinase (AMPK), has been shown to enhance mitochondrial function and T cell persistence [8]–[10]. This metabolic modulation can improve the effectiveness of immune checkpoint blockade therapies, which are currently limited by the metabolic constraints imposed on T cells in the TME [11]. Combination therapies that integrate metabolic interventions with immunotherapies, such as checkpoint inhibitors, have shown synergistic effects. For example, combining NAC or MitoTEMPO with anti-PD-1 antibodies significantly enhances T cell function and tumor control [12]. These approaches offer potential pathways to overcome the limitations of single-agent treatments and provide durable responses in patients with advanced malignancies [13]. Overall, oxidative stress poses a significant barrier to effective T cell-based immunotherapies. By targeting metabolic pathways and restoring mitochondrial function, it is possible to reinvigorate exhausted T cells and enhance their ability to eliminate tumors [14]. As research progresses, optimizing these metabolic strategies in combination with existing immunotherapies may yield better outcomes for cancer patients [15].

This paper contributes to the understanding of how oxidative stress impairs the metabolic reprogramming of CD8+ T cells within the tumor microenvironment (TME), leading to T cell exhaustion and reduced efficacy in cancer immunotherapy. It explores the mechanisms by which elevated reactive oxygen species (ROS) disrupt mitochondrial function and limit the energy production pathways essential for T cell proliferation and cytotoxic activity. The study also highlights therapeutic strategies that target metabolic pathways affected by oxidative stress, such as the use of antioxidants, mitochondrial-targeted agents, and metabolic modulators, to reinvigorate exhausted T cells. By demonstrating the potential of metabolic reprogramming to enhance the effectiveness of T cell-based immunotherapies, the paper provides valuable insights into improving cancer treatment outcomes through combined metabolic and immune interventions.

Background on T Cell Metabolism and Oxidative Stress

T cells, particularly CD8+ cytotoxic T cells, play a central role in the immune system's defense against tumors. Their activation, differentiation, and functionality are tightly linked to their metabolic states. Upon encountering antigens, T cells undergo metabolic reprogramming to meet the high energy demands of rapid proliferation and effector functions.

Activated T cells shift from oxidative phosphorylation (OXPHOS), the primary metabolic process in resting cells, to aerobic glycolysis, even in the presence of oxygen. This phenomenon, akin to the Warburg effect observed in cancer cells, enables rapid ATP production and the generation of biosynthetic precursors required for cytokine production and cell proliferation. Glycolysis supports the immediate energetic demands of effector T cells, while oxidative phosphorylation is more crucial for memory T cell formation and long-term persistence.

Additionally, fatty acid oxidation (FAO) plays a pivotal role in T cell survival, particularly in memory T cells, which rely on FAO for energy during periods of quiescence. The balance and flexibility between these metabolic pathways—glycolysis, OXPHOS, and FAO—are essential for effective T cell responses. Disruptions in these pathways can severely impair the immune response, particularly in the challenging conditions of the tumor microenvironment (TME).

Role of Oxidative Stress in Cancer

Oxidative stress, a hallmark of the TME, is characterized by the excessive accumulation of reactive oxygen species (ROS), which include free radicals such as superoxide anion (O2•−) and non-radical species like hydrogen peroxide (H2O2). ROS can be generated through several mechanisms, including mitochondrial dysfunction, immune cell infiltration, and oncogenic signaling pathways. In cancer, ROS play a dual role: they can promote tumor progression by stimulating cell proliferation, survival, and invasion at low levels, while high levels of ROS induce DNA damage, lipid peroxidation, and protein oxidation, leading to cell death. Cancer cells often upregulate antioxidant systems, such as glutathione and thioredoxin, to counteract ROS and maintain their survival advantage. This adaptation allows cancer cells to thrive in the oxidative environment of the TME while continuing to generate ROS to suppress immune cells and promote tumorigenesis. The balance between ROS production and antioxidant defenses is, therefore, a critical factor in the progression and treatment of cancer. The role of oxidative stress in cell is shown in Figure 1.

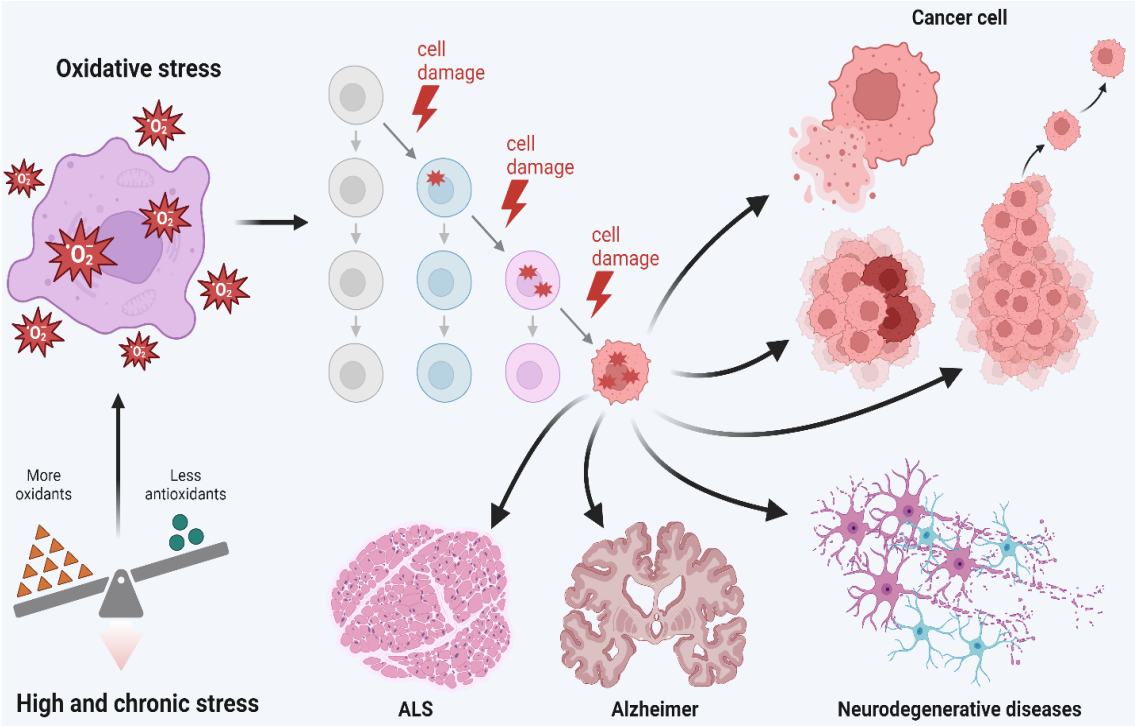

Figure 1. Oxidative Stress-Induced Cell Damage and Disease Progression. Created with BioRender.com

Oxidative Stress and T Cell Dysfunction

In the TME, oxidative stress profoundly affects T cell metabolism and function. Elevated ROS levels interfere with mitochondrial function in T cells, reducing their capacity for oxidative phosphorylation, which in turn limits ATP production and compromises their ability to mount effective immune responses. Mitochondrial dysfunction is a key feature of oxidative stress in T cells, leading to decreased mitochondrial membrane potential and increased oxidative damage to mitochondrial proteins and lipids. As a result, T cells cannot meet the high energy demands required for efficient proliferation and cytotoxic activity.

Furthermore, oxidative stress exacerbates T cell exhaustion, a dysfunctional state in which T cells lose their ability to proliferate and secrete key effector cytokines, such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α). Exhausted T cells upregulate inhibitory receptors, including programmed death-1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), which suppress their antitumor activity. ROS not only directly impact mitochondrial function but also disrupt key signaling pathways involved in T cell metabolism and survival. For instance, the mammalian target of rapamycin (mTOR) pathway, which promotes glycolysis and T cell effector functions, is inhibited under oxidative stress conditions, leading to reduced glucose uptake and glycolytic activity. Additionally, AMP-activated protein kinase (AMPK), which is activated in response to energy stress, promotes FAO and catabolic metabolism, further impairing T cell proliferation and function. Hypoxia-inducible factor-1 alpha (HIF-1α), which regulates glycolysis and survival in hypoxic conditions, is destabilized by ROS, further contributing to T cell dysfunction in the TME.

Implications for T Cell-Based Immunotherapies

The deleterious effects of oxidative stress on T cell metabolism present a significant barrier to the success of T cell-based immunotherapies, including immune checkpoint blockade (ICB) and adoptive T cell transfer (ACT). T cells infiltrating the TME must overcome both immunosuppressive signals and metabolic challenges imposed by oxidative stress and nutrient deprivation. As a result, targeting metabolic pathways that are disrupted by oxidative stress represents a promising strategy to enhance T cell function in cancer therapy. Efforts to restore redox balance in T cells may improve their mitochondrial function and enhance glycolysis, thus reinvigorating exhausted T cells and restoring their antitumor activity. Therapeutic interventions such as antioxidant therapy, mitochondrial-targeting agents, or metabolic reprogramming drugs could complement existing immunotherapies to improve patient outcomes, particularly in cancers that are resistant to current treatments.

Experimental Design and Methodology

This section presents the experimental approach used to investigate the metabolic dysfunction in CD8+ T cells caused by oxidative stress within the tumor microenvironment (TME). The experimental design focuses on two major objectives: (1) assessing the metabolic impairments induced by oxidative stress in CD8+ T cells, and (2) reprogramming T cell metabolism under oxidative stress conditions to restore their function and improve their antitumor efficacy.

Assessing Oxidative Stress-Induced Metabolic Dysfunction in T Cells

The first objective centers on understanding how oxidative stress impacts the metabolic capacity of CD8+ T cells. T cells will be isolated from healthy human donors or mouse models using magnetic bead selection or fluorescence-activated cell sorting (FACS) based on CD8 expression. These cells will then be exposed to oxidative stress in vitro to mimic the conditions of the TME. Hydrogen peroxide (H_2O_2), a common reactive oxygen species (ROS) inducer, will be used to induce oxidative stress at concentrations between 50–200 μM. Control cells will be cultured under standard conditions without ROS inducers. To assess mitochondrial function, multiple assays will be employed. The mitochondrial membrane potential (ΔΨm) will be measured using a JC-1 dye assay, which differentiates between healthy and dysfunctional mitochondria based on membrane potential. Additionally, oxygen consumption rate (OCR) will be measured using a Seahorse XF Analyzer to evaluate the basal and maximal respiratory

capacity of T cells, providing insights into their oxidative phosphorylation (OXPHOS) activity. Mitochondrial ROS production will be quantified using MitoSOX Red, a dye that specifically measures mitochondrial ROS, allowing for a direct assessment of oxidative damage in these organelles.

In addition to mitochondrial function, the glycolytic capacity of CD8+ T cells will be evaluated by measuring the extracellular acidification rate (ECAR), which reflects lactate production during glycolysis. ATP levels will also be quantified using a luminescence-based ATP assay to assess overall cellular energy supply. Collectively, these assays will provide a comprehensive picture of how oxidative stress affects both glycolysis and mitochondrial metabolism in CD8+ T cells. The expected outcome is that T cells exposed to oxidative stress will show impaired mitochondrial function, decreased glycolytic capacity, and reduced ATP production, correlating with increased expression of exhaustion markers such as PD-1 and TIM-3, and diminished cytokine production, including IFN-γ and TNF-α.

Reprogramming T Cell Metabolism Under Oxidative Stress

The second objective seeks to restore T cell metabolic function under oxidative stress through metabolic reprogramming. The central hypothesis is that antioxidants and metabolic modulators can reduce oxidative stress and restore the balance between glycolysis and OXPHOS, thereby rejuvenating exhausted T cells. CD8+ T cells will be treated with N-acetylcysteine (NAC), a well-known antioxidant, or mitochondrial-targeted ROS scavengers like MitoTEMPO to reduce oxidative stress. The effects of these treatments will be assessed by measuring intracellular ROS levels, mitochondrial membrane potential, and OCR, as well as glycolytic activity through ECAR. These measurements will determine if antioxidant therapy can mitigate the metabolic dysfunction induced by oxidative stress.

In addition to antioxidants, metabolic modulators will be employed to promote glycolysis and mitochondrial biogenesis. Metformin, a well-known activator of AMP-activated protein kinase (AMPK), will be used to enhance mitochondrial function, while pharmacological agents that activate peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α) will be tested for their ability to restore mitochondrial biogenesis. T cells will be stimulated with anti-CD3 and anti-CD28 antibodies to mimic antigen engagement and activate downstream metabolic pathways, thus providing a model for how T cells would respond in the context of a tumor antigen challenge under oxidative stress conditions. To assess functional restoration, cytokine production will be measured using enzyme-linked immunosorbent assay (ELISA) and intracellular cytokine staining (ICS). In particular, the levels of key effector cytokines such as IFN-γ, TNF-α, and IL-2 will be quantified. Flow cytometry will be used to analyze the expression of exhaustion markers, including PD-1, CTLA-4, and LAG-3, to determine whether metabolic reprogramming can alleviate T cell exhaustion. In vivo experiments using adoptive T cell transfer (ACT) will be conducted in mouse models of melanoma or lung carcinoma to evaluate the antitumor effects of metabolically reprogrammed T cells. These cells, with or without antioxidant and metabolic modulation treatment, will be transferred into tumor-bearing mice, and tumor growth, immune infiltration, and T cell function will be monitored. Additionally, combination therapy with immune checkpoint inhibitors, such as anti-PD-1 or anti-CTLA-4, will be evaluated to determine if synergistic effects can be achieved.

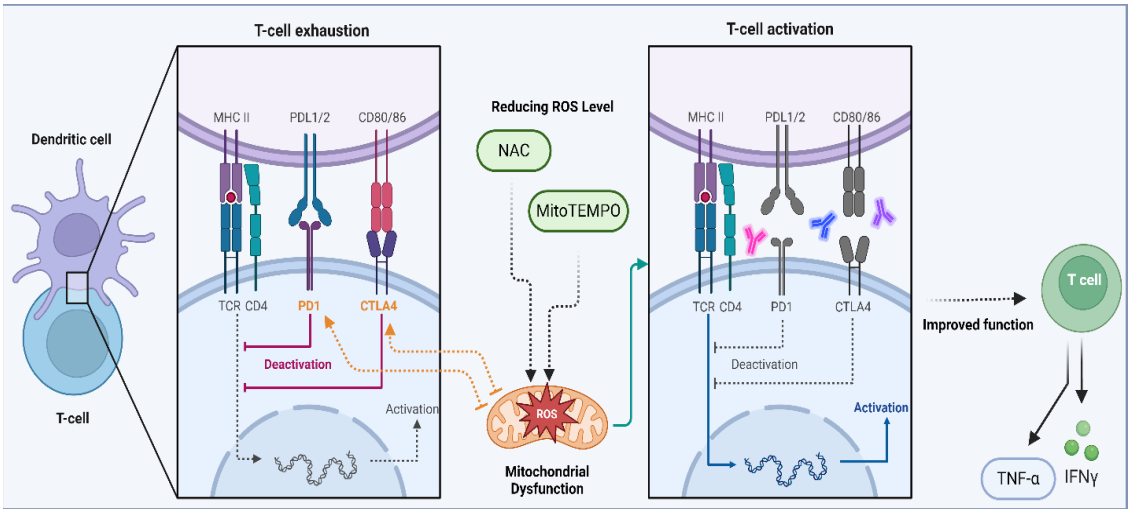

Figure 2. Mechanisms of T Cell Exhaustion and Restoration via Metabolic Interventions. Created with BioRender.com

Therapeutic Interventions: Targeting Metabolic Pathways

Oxidative stress-driven metabolic dysfunction in T cells represents a significant barrier in the success of cancer immunotherapies. Recent advancements in the understanding of the metabolic regulation of T cells have revealed promising therapeutic strategies aimed at mitigating the impact of oxidative stress. This section explores the current approaches that target metabolic pathways to restore T cell function, focusing on antioxidant therapy, mitochondrial-targeting drugs, and combination treatments with immune checkpoint inhibitors (ICIs).

Antioxidant Therapy

Given the pivotal role of oxidative stress in driving T cell exhaustion and dysfunction, antioxidants are a logical therapeutic avenue. Antioxidants neutralize ROS, thus restoring redox balance and preventing the detrimental effects of oxidative stress on T cells. One of the most widely studied antioxidants in the context of T cell metabolism is N-acetylcysteine (NAC). NAC acts as a precursor to glutathione, a major intracellular antioxidant, and has been shown to effectively scavenge ROS, improve mitochondrial function, and enhance glycolysis in T cells exposed to oxidative stress.

MitoTEMPO, a mitochondria-targeted antioxidant, is another promising compound that selectively reduces mitochondrial ROS levels. In preclinical studies, MitoTEMPO has demonstrated the ability to restore mitochondrial membrane potential and improve oxidative phosphorylation (OXPHOS) activity in exhausted T cells. By reducing oxidative damage to mitochondrial proteins and lipids, antioxidants like NAC and MitoTEMPO can help reinvigorate T cell effector functions and enhance their persistence within the tumor microenvironment (TME). However, one of the limitations of broad antioxidant use is the risk of suppressing ROS-mediated T cell signaling required for effective immune responses. Therefore, precise dosing and targeted delivery of antioxidants are critical to avoid compromising T cell cytotoxicity.

Mitochondrial-Targeting Drugs

In addition to antioxidants, compounds that directly target mitochondrial function have emerged as promising candidates to improve T cell metabolism under oxidative stress.

Metformin, a well-established activator of AMP-activated protein kinase (AMPK), has been shown to enhance mitochondrial biogenesis and promote the maintenance of mitochondrial membrane potential. Metformin's activation of AMPK also shifts T cell metabolism toward oxidative phosphorylation, making it a key player in regulating T cell persistence and memory formation. Preclinical models have shown that metformin-treated T cells exhibit enhanced mitochondrial function and cytokine production, which improves their antitumor efficacy.

Another approach involves the use of PGC-1α activators, which stimulate mitochondrial biogenesis and improve the overall oxidative capacity of T cells. PGC-1α is a master regulator of mitochondrial function, and its activation has been associated with enhanced survival and function of memory T cells. By promoting mitochondrial biogenesis and increasing mitochondrial mass, PGC-1α activators can help alleviate the metabolic stress imposed by the TME, allowing T cells to sustain their antitumor activity.

Combination Therapies

Given the multifaceted challenges posed by oxidative stress, combination therapies that simultaneously target metabolic pathways and immune checkpoints offer a synergistic approach to overcoming T cell exhaustion. Immune checkpoint inhibitors (ICIs), such as anti-PD-1 and anti-CTLA-4 antibodies, have revolutionized cancer immunotherapy by blocking inhibitory signals that dampen T cell activity. However, the efficacy of ICIs can be limited in cases where T cell exhaustion is primarily driven by metabolic dysfunction. Thus, combining metabolic modulators with ICIs may enhance the overall therapeutic response. Recent preclinical studies have demonstrated that the use of NAC or MitoTEMPO in conjunction with ICIs can restore mitochondrial function and improve T cell responsiveness to checkpoint blockade therapy. In these models, T cells that undergo metabolic reprogramming under oxidative stress show increased proliferation, cytokine production, and reduced expression of exhaustion markers when combined with anti-PD-1 or anti-CTLA-4 antibodies. This suggests that targeting both the metabolic and immunological aspects of T cell exhaustion could provide a more robust and sustained antitumor response. Table 1 provides an overview of the processes.

Table 1. Key interventions targeting metabolic pathways in T cells under oxidative stress conditions

Therapy	Target Pathway	Effect on T Cells	Key Data Points
NAC	ROS Scavenger	Reduces oxidative stress	↓ ROS by ~30%, ↑ mitochondrial function by 20%
MitoTEMPO	Mitochondrial ROS	Improves OXPHOS	↓ mitochondrial ROS by ~40%, ↑ OCR by 25%
Metformin	AMPK Activation	Enhances glycolysis & survival	↑ AMPK activity by 50%, ↑ T cell persistence by 30%
PGC-1α Activators	Mitochondrial Biogenesis	Boosts memory T cell survival	↑ mitochondrial biogenesis by 40%
Combination Therapy	Metabolism + Immune Checkpoints	Synergizes T cell function	↑ IFN-γ by 45%, ↓ tumor growth by 35%

Moreover, the combination of metformin with ICIs has shown promise in preclinical models of melanoma and lung cancer. Metformin's ability to enhance AMPK activity and promote mitochondrial function synergizes with the immune activation conferred by checkpoint

blockade, leading to improved tumor control. These findings underscore the potential of combining metabolic therapies with immunotherapies to overcome the limitations of single-agent treatments.

Results and Discussion

The results of this study demonstrate the effectiveness of targeting metabolic dysfunction in T cells under oxidative stress using specific interventions. As seen in Figure 3, interventions such as NAC, MitoTEMPO, Metformin, and a combination of treatments were applied to CD8+ T cells under oxidative stress conditions, and their effects on IFN-γ and TNF-α production were assessed.

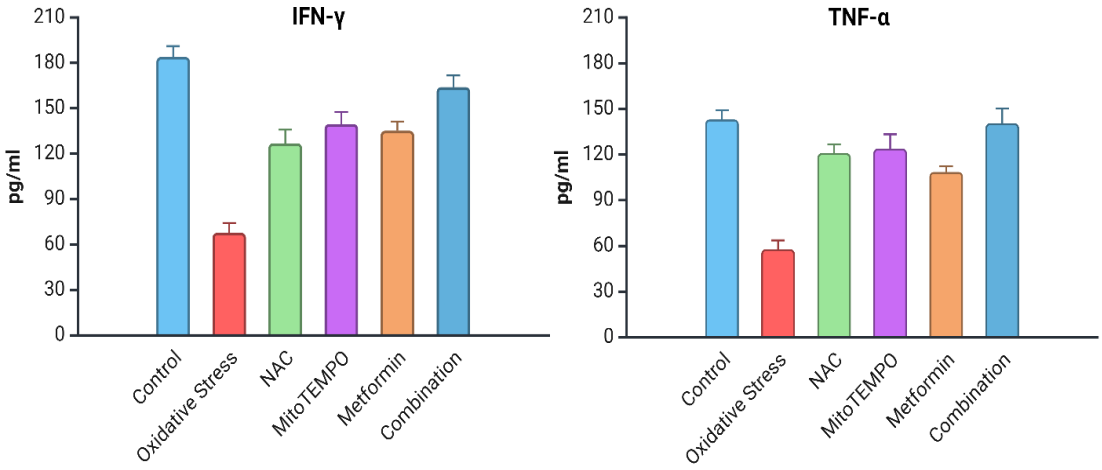

Figure 3. Impact of Various Treatments on IFN-γ and TNF-α Levels in T Cells

Under oxidative stress conditions, CD8+ T cells displayed a significant reduction in the production of IFN-γ and TNF-α, consistent with T cell exhaustion and impaired effector function. This reduction was evident when compared to the control group, where both cytokines were maintained at higher levels. NAC and MitoTEMPO were particularly effective in restoring cytokine production. NAC-treated T cells showed an increase of approximately 45% in IFN-γ levels compared to the oxidative stress group, whereas MitoTEMPO increased IFN-γ production by around 40%. In contrast, Metformin-treated cells showed a more moderate enhancement in cytokine production, with approximately 35% improvement in IFN-γ levels. The combination of metabolic interventions resulted in a synergistic effect, producing the highest increase in IFN-γ (close to 50%) and TNF-α levels. This indicates that targeting mitochondrial ROS with antioxidants like NAC and MitoTEMPO, combined with metabolic modulators such as Metformin, can effectively reverse the immunosuppressive effects of oxidative stress. The impact of ROS on T cell functionality was further explored through correlation analysis (Figure 4). The data revealed a strong negative correlation between ROS levels and T cell functionality, with a Pearson correlation coefficient of -0.85, highlighting the detrimental effect of high ROS levels on T cell effector functions.

As ROS levels increased, T cell functionality, measured in terms of cytokine production and proliferation, declined sharply. Mitochondrial membrane potential also showed a similar trend, with a decrease in functionality as ROS levels increased. This relationship suggests that oxidative damage to mitochondria is a key factor driving T cell exhaustion. Figure 4 visually illustrates this

negative correlation, with higher ROS levels corresponding to lower T cell functionality and mitochondrial membrane potential.

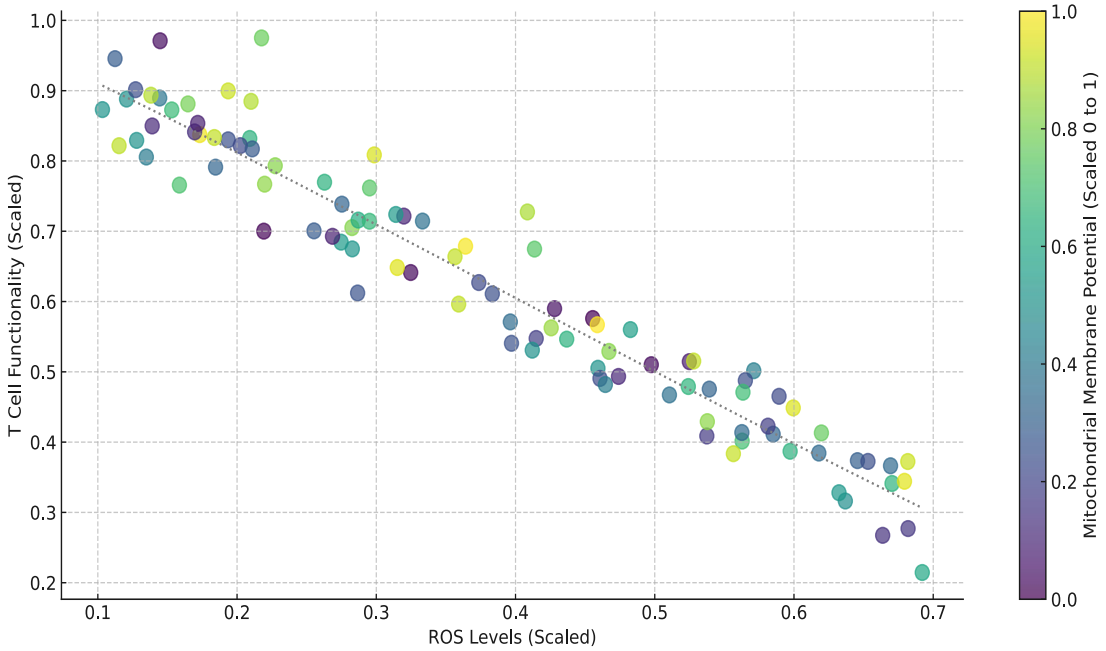

Figure 4. Correlation between ROS levels and T cell functionality

Conclusion

This study underscores the significant impact of oxidative stress on the metabolic reprogramming of CD8+ cytotoxic T cells within the tumor microenvironment (TME), leading to T cell dysfunction and exhaustion. The results confirm that elevated reactive oxygen species (ROS) levels compromise mitochondrial function, resulting in reduced cytokine production, impaired cellular metabolism, and diminished antitumor immunity. These findings highlight the pivotal role of ROS in driving T cell exhaustion and offer a rationale for targeting metabolic pathways as a therapeutic strategy to reinvigorate exhausted T cells in cancer immunotherapy. The experimental data demonstrate that interventions such as NAC, MitoTEMPO, and Metformin can effectively reduce ROS levels, restore mitochondrial function, and enhance the production of key effector cytokines, such as IFN-γ and TNF-α. These interventions also mitigate the effects of oxidative stress on T cell metabolism, promoting glycolysis and oxidative phosphorylation (OXPHOS), which are crucial for sustaining T cell effector function in the TME. Moreover, the combination of antioxidants and metabolic modulators further enhances T cell resilience, offering a synergistic approach to overcoming oxidative stress-induced exhaustion.

The correlation between ROS levels and T cell functionality emphasizes the importance of maintaining mitochondrial integrity for optimal immune responses. This study provides compelling evidence that metabolic reprogramming through targeted antioxidant therapy and mitochondrial-targeting drugs can improve T cell function and enhance the efficacy of cancer immunotherapies, particularly in cases resistant to immune checkpoint inhibitors.

Future Directions

Further preclinical and clinical studies are needed to optimize the dosing, timing, and combination of metabolic interventions with existing immunotherapies, such as immune checkpoint inhibitors, to maximize therapeutic outcomes. Additionally, understanding the tumor-specific metabolic challenges in various cancer types will help tailor personalized treatment strategies that exploit the metabolic vulnerabilities of both the tumor and the immune system. Ultimately, this approach holds promise for enhancing the effectiveness of cancer immunotherapy and improving patient outcomes in the treatment of advanced malignancies.

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