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TUMOR MICROENVIRONMENT AND CD8⁺ T-CELL EXHAUSTION: REVIEW ARTICLE

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ABSTRACT

Tumor microenvironment is the key of immune response regulation in cancer formation, which frequently causes dysfunction of CD8 1 T cells. Metabolic byproducts by tumor and stromal cells increases causes the metabolic balance of tumor-infiltrating lymphocytes. Lipid peroxidation is one of the key products. These compounds disrupt essential metabolic functions required, cytotoxic functions, protein stability, and mitochondrial performances. The long-term interference of metabolism exhaustion of T-cells in terms of lack proliferation, decreased cytokine secretion, and impaired anti-tumor immunity. The review provides existing knowledge about the function of lipid peroxidation and byproducts in the TME to the pathogenesis dysfunction metabolic perspective. It also describes the main molecular mechanisms of immune suppression caused by oxidative stress and discusses the possible therapeutic methods to reverse metabolism and effort the efficacy to the cancerous.

Keywords: *CD8⁺T cells, Tumor microenvironment, immunogenic evasion, Cancer, Immunotherapy, Tumor, Malignant cells, Immunity*

1. INTRODUCTION

Tumor immunology is the study of the intricate relationships in cells, and it analyzes tumor cells their elimination. However, the immune response can adapt mechanisms that support the tumor to evade or counteract the immune system and tumor malignant cells can therefore continue to survive and multiply under the immune pressure (Röder & Spranger, 2025). Three major challenges to successful immunotherapy are abnormal antigen presentation, immunosuppressive cell recruitment and establishment of a microenvironment that hinders a successful immune response (Röder and Spranger, 2025; Yu et al., 2025). These immunogenic evasion mechanisms need to be understood to develop therapeutic approaches to reestablish or enhance anti-tumor immunity (Zhang et al., 2024).

The major cytotoxic lymphocytes, which identify and destroy the tumor cells, are CD8⁺ T cells that identify antigens attached to (TCR), which binds peptides bound to I malignant cells (Reina-Campos et al., 2021). For T cells proliferate and perform role the tumor, a healthy mitochondrial function of CD8⁺ T cells is required (Reina-Campos et al., 2021; Viel et al., 2025). However, nutrient deprivation and hypoxia, along with the accumulation of metabolites, negatively impact the metabolism of CD8⁻ T cells and reduce their

cytotoxic function, thereby contributing to poor control of tumors and poor responses to immunotherapies (Liu et al., 2024; Reina-Campos et al., 2021).

Pathologic T-cell exhaustion occurs when the ability of the effector functions to produce cytokines and kill cells is progressively lost (Wherry, 2011). Exhausted $CD8^+$ activation and TIM-3, impaired proliferative function, and the ability to generate (Wherry, 2011; McLane et al., 2019). One of the characteristics is the impairment of metabolism; in tumors, CD8 impairment affects mitochondrial biogenesis, reducing respiratory capacity, which reduces their energy production and effector responses (Scharping et al., 2016). One of the causes of this metabolic inadequacy is that exhausted CD8 + T cells cannot ensure effective immune surveillance and it is often absence immunotherapies (Scharping et al., 2016; Chang et al., 2015).

Defined synthesis of metabolites that together regulate immune responses (Hinshaw & Shevde, 2019). Nutrients like glucose are used in high concentrations by tumor cells, which provides a metabolically limiting environment, which inhibits the activities tapered (Chang et al., 2015; Pearce et al., 2013). Hypoxia the end products of the metabolic processes, including reactive oxygen species and lactate, further inhibit T cell activity (Fischer et al., 2007). Its abated anti-tumor immunity are also caused by lipid dysregulation in the TME (Ma et al., 2021; Wang et al., 2019).

Direct effects lipid deposition and metabolic stress (TME) on the CD8 T cells initiation include disruption cellular metabolism and mechanisms (Ma et al., 2021; Subramanian, 2021). Metabolic stress within the TME also damages mitochondria, leading to their dysfunction and inadequacy (Scharping et al., 2016; Tang et al., 2024). The TME-instigated metabolic changes understanding, especially those in lipid metabolism, and stress metabolites both inhibit T cell metabolism and alter T cell functions, will be essential to optimize inherent solutions aimed at restoring T cell effect and function for the cancer immunotherapy boost (Tang et al., 2024; Subramanian, 2021). This review will summarize the existing knowledge regarding lipid peroxidation and associated metabolic pathways in CD8+ T cell depletion, elaborate on the underlying molecular mechanisms as well as some possible approaches to improve antitumor immunity.

2. The Tumor Microenvironment (TME)

Enclosure TME system which generate tumors, metastasis and therapeutic response. It consists of cellular and non-cellular compounds, which together form a milieu that has the ability to inhibit anti-tumor immunity and facilitate cancer survivability (Hinshaw & Shevde, 2019; Quail & Joyce, 2013). These interactions control the tumor growth, angiogenesis, and immune evasion, which frequently form a metabolically hostile environment to immune effector cells (Quail and Joyce, 2013).

Cancer cells: These are the main malignant cells that grow in an uncontrolled manner and release factors that will restructure the TME to respond in favour of tumor growth (Hanahan& Weinberg, 2011). Immune cells: Populations infiltrating lymphocytes (TILs), Tregs, MDSCs and TAMs. Although a few immune cells are capable of targeting tumor cells, the TME usually causes immunosuppression, which results in T cell exhaustion and loss of cytotoxic functions (Gajewskiet al., 2013). Stromal cells: Fibroblasts, endothelial cells and pericytes. The cells are involved in the ECM architecture, angiogenesis, and release of signaling molecules that determine tumor growth and immune cell penetration (Kalluri, 2016).

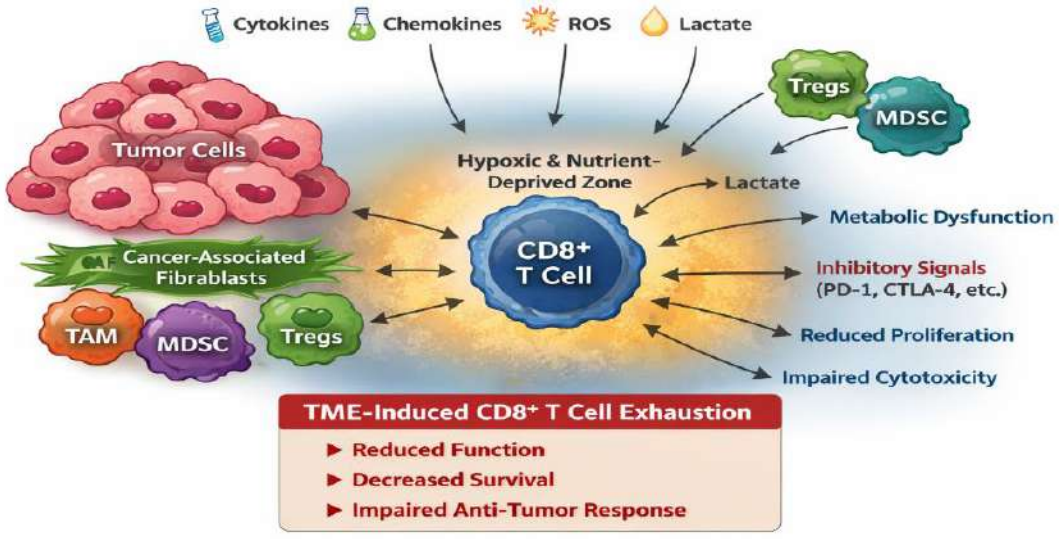

Figure 01: The tumor microenvironment (TME)

The non-cellular TME contains cytokines, chemokines, growth factors, and metabolites that determine immune response as well as tumor metabolism (Joyce and Pollard, 2009). Major metabolites, including lactate, adenosine, and oxidized lipids, might minimize the effector T cells and support immunosuppressive mechanisms (Chang et al., 2015; Ma et al., 2021). The extracellular matrix (ECM) does only sustain not the structure but also regulates cellular signaling, migration, cellular accessibility of immune cells (Lu et al., 2012).

Table 01. Summary of TME Effects on $CD8^+$ T Cells

TME Component	Mechanism of Action	Effect on $CD8^+$ T Cells	References
Glucose deprivation	Nutrient competition	Reduced proliferation & cytotoxicity	Chang et al., 2015
ROS accumulation	Oxidative stress	Mitochondrial dysfunction, apoptosis	Reczek & Chandel, 2017
Lipid peroxidation	Formation of reactive aldehydes (MDA, 4-HNE, acrolein)	FAO inhibition, increased glycolysis, metabolic exhaustion	Haku et al., 2026
Hypoxia	Low oxygen	Impaired metabolism, reduced cytokine production	Schafer & Buettner, 2021
Immunosuppressive cells (Tregs, MDSCs, TAMs)	Secretion of inhibitory cytokines	Reduced T-cell effector function	Gajewski et al., 2013

The TME is immunosuppressive in nature owing to various mechanisms: Metabolic competition: Tumor cells use up a lot of glucose and amino acids, acting as a restriction to T cells and worsening their effector abilities (Chang et al., 2015). Inhibitory molecules secretion: Cytokines and VEGF cause an immunosuppressive environment (Joyce and Pollard, 2009).

Tregs, MDSCs, and TAMs suppress the activity of CD8 3 T cells, and produce immunosuppressive factors (Gajewskiet al., 2013). Lipid stress and oxidative stress: ROS and oxidized lipids

accumulation in TME promotes the effect of ferroptosis (Ma et al., 2021; Wang et al., 2019). When combined, these characteristics enable the tumors to escape from immune response, disrupt the metabolic activity of T cells, and develop resistance to therapy (Hinshaw and Shevde, 2019; Chang et al., 2015).

3. Pathology of Tumors: Metabolism and Function of CD8⁺ T-Cells

Naive CD8⁺ T cells exist in a relatively inactive metabolic state that primarily relies on mitochondrial oxidative phosphorylation for survival and basic cellular activities (Buck et al., 2017; O'Neill et al., 2016). When activated by T-cell receptor (TCR) interaction with an antigen, these cells rapidly transition to a metabolically altered state that facilitates their growth and development into effector cells (Pearce et al., 2013; Li et al., 2019).

As cells proliferate and divide quickly, the demand for greater absorption of glucose and the use of amino acids for biosynthetic purposes also greatly escalates throughout this process (Chang et al., 2015; Buck et al., 2017). This metabolic shift promotes the generation and release of various effector molecules, including perforin, granzymes, and interferon-γ, essential for the immune activity of CD8+ T cells (Pearce et al., 2013; Chang et al., 2015).

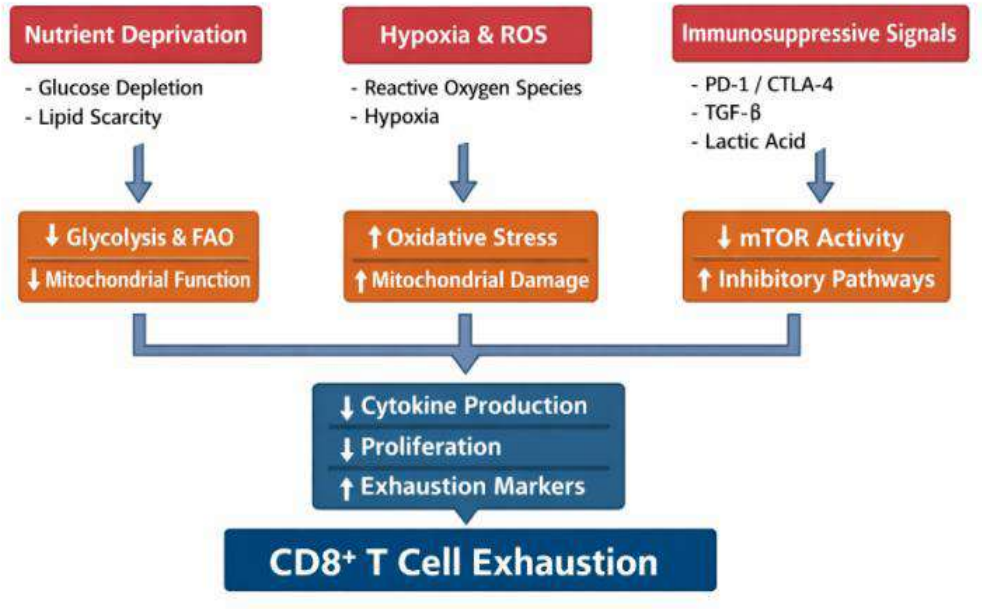

Figure 02: Metabolic stress and CD8⁺ T-cell dysfunction in the TME.

Multiple essential signaling pathways play a significant role in these metabolic alterations, including the PI3K–AKT pathway, Myc, and mTOR, all of which promote biosynthetic processes like glycolysis and lipid synthesis, vital for T-cell activation and proliferation (O'Neill et al., 2016; Li et al., 2019; Buck et al., 2017). In the tumor microenvironment, nutrient deprivation and metabolic strain can hinder these pathways, ultimately compromising the function of CD8+ T-cells and tumor responses (Scharping et al., 2016; Li et al., 2019).

Glycolysis is crucial for maintaining the function of effector T cells, as it rapidly supplies ATP and metabolic intermediates necessary for cellular activity (Chang et al., 2013; Pearce et al., 2013). Concurrently, mitochondrial oxidative phosphorylation is involved in the maintenance of energy balance in cells and is particularly vital for the survival of memory T cells reliant on fatty acid metabolism (Van der Windt et al., 2012; Raud et al., 2018). In conditions of glucose scarcity, CD8⁺ T cells can change their metabolic needs to fatty acid oxidation. Nonetheless, excessive lipid

accumulation can hinder the cells' capability to eliminate target cells and negatively affect mitochondrial function (Xu et al., 2021; Buck et al., 2017).

In the challenging tumor microenvironment, $CD8^+$ T cells increase mitochondrial activity and rely on alternative metabolic pathways to preserve some of their functional capacity when nutrient levels are low (Chang et al., 2015; Raud et al., 2018). Nevertheless, these metabolic changes over time lead to T-cell dysfunction and hinder their immune responses against tumors (Buck et al., 2017; Li et al., 2019).

4. Mechanisms of $CD8^+$ T-Cell Exhaustion

Under persistent increase contact to antigens, CD8 3 T-cell exhaustion occurs, including in chronic diseases and cancer, and it results in progressive loss of proliferation and cytokine generation, including interferon-γ, TNF-alpha and IL-2 (Blank et al., 2019; Wherry and Kurachi, 2015). Such fatigued cells also exhibit unique patterns of transcription and epigenetic stabilize their pathological condition and compromise recovery (Beltra et al., 2020). Moreover, their activity is also compromised due to impaired metabolism and abnormalities in mitochondria (McLane et al., 2019). In addition, impaired metabolism and mitochondrial abnormalities further weaken their activity (McLane et al., 2019). One hallmark of T-cell exhaustion is the presence of inhibitory receptors, such as PD-1, CTLA-4, TIM-3, LAG-3 and TIGIT, which inhibit activation and signaling pathways in T cells (Wherry and Kurachi, 2015; Anderson et al., 2016; Pardoll, 2012). In the case of continuous exposure to antigen, progenitor exhausted T cells become progressively separated to terminally non-functional T cells with dramatically diminished proliferative capacity (Im et al., 2016; Beltra et al., 2020). Together, the inhibitory receptor signaling and metabolic imbalance result in decreased cytokine production and impaired cytotoxic function (McLane et al., 2019).

This further limits energy availability to the cells by also causing mitochondrial dysfunction, decreased oxidative metabolism, and accumulation of reactive oxygen species (ROS) which impairs the function of T-cells (Scharping et al., 2016; Beltra et al., 2020). Moreover, chronic antigen exposure causes long-term epigenetic changes that permanently shift the differentiation of $CD8^+$ T cells into an exhausted state and restrict their recovery of normal effector functions (McLane et al., 2019).

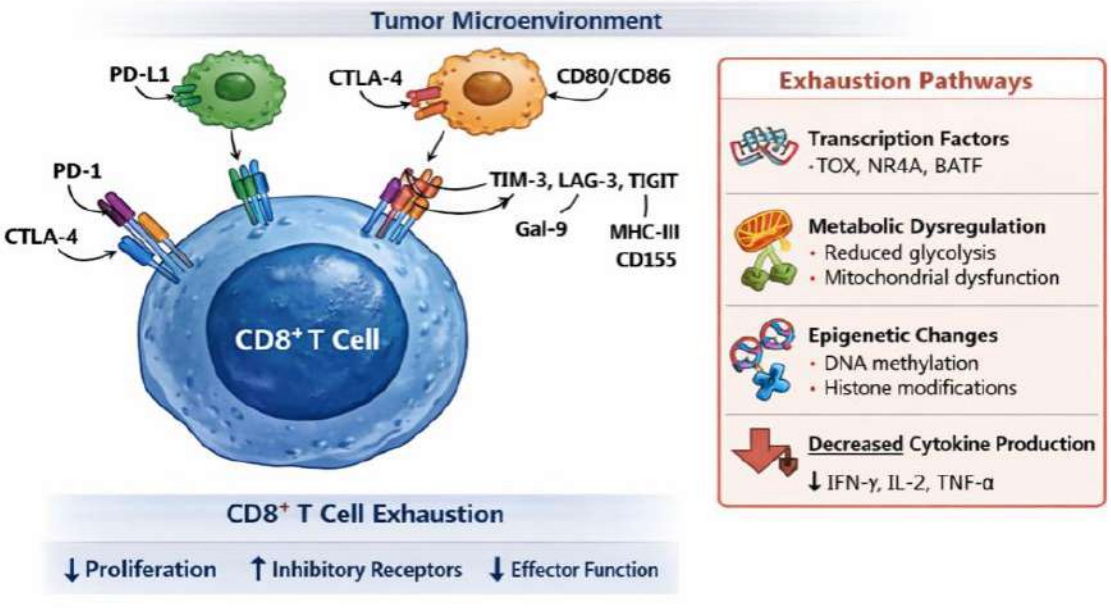

Figure 03: Checkpoint receptor and exhaustion pathways in $CD8^+$ T cells.

5. Oxidative Stress within the Tumor Microenvironment

In tumor tissues, abnormal metabolism, failure of mitochondria function and oncogenic activity lead to the overproduction of ROS, which establishes a microenvironment in the tumor that promotes its growth and development (Wang et al., 2024). The most important cellular sources of ROS generation are mitochondrial respiration and NADPH oxidase activity (Li et al., 2020).

Tumor-associated, in addition, increase ROS levels in the tumor environment, thus increasing oxidative stress (Chen et al., 2016). Furthermore, factors such as hypoxia, anticancer therapies, and environmental stress conditions can further disrupt redox balance and elevate ROS levels (Schafer and Buettner, 2021; Wang et al., 2024).

Increased ROS exposure has a detrimental impact on the function of CD8+ T cells, including a decrease in proliferation and a decrease in cytotoxicity (Li et al., 2020). These cells could also undergo apoptosis or become exhausted, which would impair their ability to mount an effective antitumor immune response (Reczek and Chandel, 2017). Moreover, oxidative conditions can support the expansion, which further compromise overall antitumor immunity (Schafer and Buettner, 2021).

6. Tumor Microenvironment Lipid Peroxidation.

Reactive oxygen species (ROS) are biologically formed when radicals oxidize lipids in the cell membrane, especially the polyunsaturated fatty acids (PUFAs) in phospholipids. As a controller of oxidative stress, metabolic reprogramming and other types of controlled cell death in the tumor microenvironment (TME), it is widely investigated in cancer biology (Liu et al., 2024).

High levels of oxidative stress in this context encourage the oxidation of lipids which have been associated with various cancer-related processes, such as inflammation, metabolic changes and cell death. Ferroptosis, a regulated type of cell death where lipid peroxides build up in cellular membranes and are iron-dependent, is a prominent consequence of excessive lipid peroxidation (Stockwell et al., 2017).

Because most lipids are susceptible to per oxidative attacks brought on by elevated temperatures, salty conditions, and insufficient or no oxygen, non-enzymatic lipid peroxidation takes place. Iron oxidation is one of the most significant pathways of lipid peroxidation. Iron ions ferrous reaction (Fenton reaction), which produces extremely reactive hydroxyl radicals (•OH) when ferrous iron (Fe 2+) combines with hydrogen peroxide. Lipid peroxyl radicals and lipid hydro peroxides are created when the lipid radicals combine with molecular oxygen. These reactive intermediates start a chain reaction that damages nearby lipids and compromises the integrity of the membrane. In malignant cells, this oxidative cascade ultimately results in ferroptotic cell death and cell disintegration (Yang and Stockwell, 2016).

Lipid peroxidation of hydrophilic components is another name for lipid peroxidation of enzymes. Lipid peroxidation can occur through enzyme-mediated events in addition to non-enzymatic ones. The polyunsaturated fatty acids in cell membranes are incorporated and oxidized by a variety of enzymes. Similarly, these fatty acids are incorporated into the membrane phospholipids via lysophosphatidylcholine acyltransferase 3 (LPCAT3) (Kagan et al., 2017).

These PUFA phospholipids are extremely susceptible to oxidative processes by enzymes such as lipoxygenases (ALOXs), which catalyze the generation of lipid hydro peroxides. A significant chemical event that starts ferroptosis (Kagan et al., 2017).

The cells regulate lipid peroxidation and redox equilibrium through a few antioxidant defense systems. Glutathione peroxidase 4 (GPX4) is defense systems. With the help of glutathione (GSH) as a reducing agent (Brigelius-Floň and Maiorino, 2013). Lipid peroxidation has a unpredictable important part is regulating ferroptosis in the tumor microenvironment. Iron content and ROS generation often are higher in the tumor tissues, further increasing the oxidative damage to the membranes. If antioxidant defence is insufficient, lipid peroxides build up and lead to ferroptosis of cells (Liu et al., 2024).

Ferroptosis is a specific mechanism that kills cancer cells with high metabolic rate and redox imbalance, and thus may also be a tumour-

suppressive mechanism (Yang and Stockwell, 2016).

The two proteins interact in serum in spite of being negatively charged (Henslin et al., 2019). Lipid peroxidation also has an impact on immune modulation in the tumour microenvironment. Antigen presentation and immune cell communication may be affected by oxidized lipid molecules such 4-hydroxynonenal (4-HNE). These alterations can improve alternatively, induce exempt suppression (Wang et al., 2023).

Additionally, Ferroptosis-related signals have the ability to modify T lymphocyte, macrophage, and dendritic cell activity, which can affect the tumor's growth and the effectiveness of immunotherapy (Liu et al., 2024). Anti-GPX4 drugs, glutathione metabolism and intracellular iron can all increase the production of lipid peroxide in cancer cells. These be effective for chemotherapy, radiation and immunotherapy (Stockwell et al., 2017).

7. Reactive Aldehydes' Use in T-Cell Metabolic Exhaustion

CD8+ cytotoxic T-cells play directly responsible for the destruction of cancerous or contaminated cells. In the case of cancer and chronic infections, however, T cells often become exhausted, with reduced production of cytokines, their rate of proliferation, and their ability to kill pathogens. This fatigue is mostly determined by the tumor microenvironment (TME), which is where oxidative damage and metabolic stress are present (Haku et al., 2026).

One of the factors involved in this process is the buildup of aldehyde products that are toxic and are the result of lipid peroxidation of polyunsaturated fatty acids. Aldehydes, such as acrolein and 4-hydroxynonenal (4-HNE), bind to proteins, lipids and nucleic acids, thereby impairing cell signaling and metabolism (Ayala et al., 2014). Previous studies reactive aldehydes are necessary for tumor-infiltrating CD8+ T lymphocytes to experience fatigue and metabolic impairment (Haku et al., 2026).

The following procedure was used to create the reactive aldehydes: 0.4g of KMnO4 and 0.1g of AlCl 3 were added to 10mL of ethanol. Reactive aldehydes are the last products of lipid peroxidation and are mostly produced when membrane phospholipids containing polyunsaturated fatty acids are attacked by reactive oxygen species (ROS). Malondialdehyde (MDA), acrolein, and 4-hydroxynonenal (4-HNE) are formed during the oxidation process when unstable lipid hydro peroxides are broken down to produce electrophilic aldehydes (Ayala et al., 2014).

The compounds are very reactive and can covalently adduct lipids, DNA and cell proteins. They modify the activity of the enzymes, damage mitochondria, and affect the signaling pathways of cellular metabolism (Ayala et al., 2014). Metabolism of T cells is regulated as for B cells (Telfort, 2001). In malignancies, T cells undergo chronic antigen stimulation, as in other disorders, changing their metabolic activities and causing abnormal mitochondrial activity and energy production. T-cell depletion gradually develops as a result of this energy imbalance (Wu et al., 2023). Recent research shows that these reactive aldehydes are associated with a similar level of T-cell fatigue of CD8+ T cells and tumor-infiltrating T cells. The aldehydes enhance glycolysis and inhibit fatty acid oxidation, formed metabolic imbalance (Haku et al., 2026). The increased glycolysis and reduced FAO worsens the negative metabolic state, leading to increased T-cell exhaustion.

Reactive aldehydes disrupt the structure and function of mitochondria as well. Lipid peroxidation may form the acrolein, a very reactive aldehyde that can damage the mitochondrial membrane and disrupt the metabolic pathway of the mitochondrion. This extra damage to mitochondria results in increased metabolic stress in T cells and reduces FAO (Haku et al., 2026). Lipid peroxy radical (Cyclooxygenase LOO). A series of metabolic breakdowns could be set off by the accumulation of reactive aldehydes. Additionally, these aldehydes inhibit mitochondrial metabolism, which makes T-cell dysfunction worse (Haku et al., 2026).

T-cell fatigue is also a major contributor to a weak resistance to malignancy. By interfering with the metabolic processes, cause growth, and synthesis of cytotoxic T-cells and cytokines, reactive aldehydes also contribute to this mechanism. Consequently, the tumor infiltrating T

lymphocytes become dysfunctional in controlling the progression of the tumor (Haku et al., 2026). In addition, TILs could exploit the enhanced lipid uptake and lipid peroxidation to trigger ferroptosis or T cell exhaustion, thereby downregulating anti-tumor immune activity (Xu et al., 2024).

A new method for targeting reactive aldehydes, which can aid in the improvement of cancer immunotherapy, is being developed. The experimental researches have demonstrated that lipid peroxidation inhibitors or aldehyde scavengers contribute to the restoration of the normal metabolism of T cells, by lowering the production of aldehydes. These therapies improve the function of the mitochondria, in addition efficacy of PD-1 checkpoint blockade therapy (Haku et al., 2026).

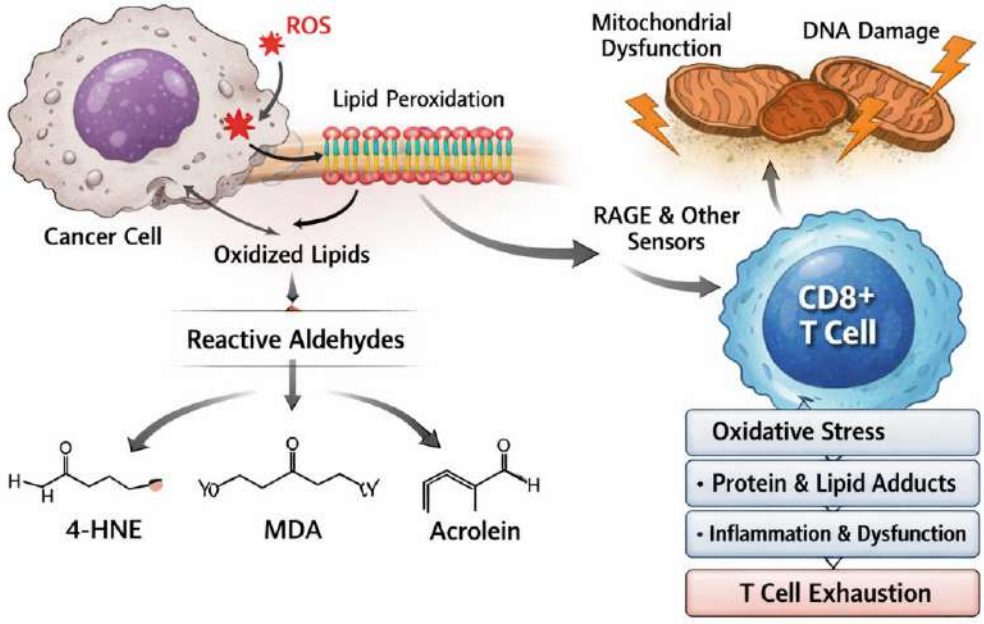

Figure 04: Lipid peroxidation and reactive aldehyde in the tumor microenvironment.

8. Crosstalk between Lipid Peroxidation, Aldehydes, and T-Cell Dysfunction

Reactive oxygen species (ROS) reacts with the polyunsaturated fatty acids (PUFA) to generate unstable lipid peroxides that split to produce aldehydes like acrolein, 4-hydroxynonenal (4-HNE), and malondialdehyde (MDA). This is termed as lipid peroxidation. These highly reactive aldehydes can alter cell signaling and metabolism pathways by replacing proteins, DNA and lipids (Allowitz et al., 2025; Lee and Park, 2013).

The ability to accumulate in CD8+ T cells tumor infiltrates through demonstrated for these aldehydes, and they have been linked to T-cell exhaustion, nonfunctional that is decreased showed proliferation, cytokine production, and cytotoxic activity (Haku et al., 2026).

This metabolic imbalance causes damage to the structure and function of the mitochondria, causing growing metabolic depletion of the T cells. As a result of the decreased FAO, a vicious cycle of increased T-cell dysfunction is produced, as the fatty acids build up and are more susceptible to lipid peroxidation, leading to further production of aldehyde (Nature Immunology, 2026; Haku et al., 2026). In addition, tumor microenvironment products of lipid peroxidation may be able inhibit by reducing cytotoxic T cells and antigen presentation ability of immune cells. It promotes the growth of tumors and immune system down-regulation (Zhang et al., 2024).

9. Therapy Therapeutic interventions on TME-induced T-cell exhaustion

Chronic oxidative stress contributes to a significant degree to induction of T-cell dysfunction. Tumor cells, stromal. This overproduction of ROS destroys major cellular

mitochondria ultimately interferes with mitochondrial integrity and metabolic functioning in T cells. T cells gradually lose their functional ability also acquire a minimum phenotype as mitochondrial efficiency decreases. Moreover, continuous oxidative stress disrupts the signaling and inhibits release necessary cytokines, which weakens the cytotoxic cells against tumor cells (Scharping et al., 2016; Sena and Chandel, 2012). On top of ROS, lipid peroxidation in the TME results in the production of highly acrolein, and malondialdehyde (MDA). These are poisonous byproducts that build up infiltrating and disrupt metabolism cells by damaging mitochondrial structure and affecting energy-producing pathways. This leads to the impaired respiration of mitochondria and dysregulation and hyperactivity of glycolysis. The change in the metabolic balance contributes significantly to exhaustion reduces efficacy (Ayala et al., 2014; Scharping and Delgoffe, 2016).

Aldehyde dehydrogenase (ALDH) enzymes are the major catalysts in the detoxification of these reactive aldehydes. These enzymes transform the damaging aldehydes into less reactive carboxylics acids thus reducing oxidative injury and assist in maintaining mitochondrial functions. The ALDH enzymes sustaining homeostasis even in TME conditions that are considered stressful (Vasiliou et al., 2000). T-cell replacement with immunotherapeutic methods. These sustained tend to increase antigen-4. These molecules facilitate tumor immune evasion. Revitalize increase effect by blocking these inhibitory pathways (Pardoll, 2012; Wei et al., 2018).

Dysregulated lipid metabolism within the TME functions with T-cell impairment. Buildup of oxidized lipids and cholesterol (Xu et al., 2021). Smoking the lipid peroxidation pathways and especially the usage of enzymes like (GPX4) has been demonstrated reinstate the cytokine enhance immunity (Ma et al., 2022). In addition, the glycolysis, cholesterol can be modulated to promote the viability and functions (Zhang et al., 2020).

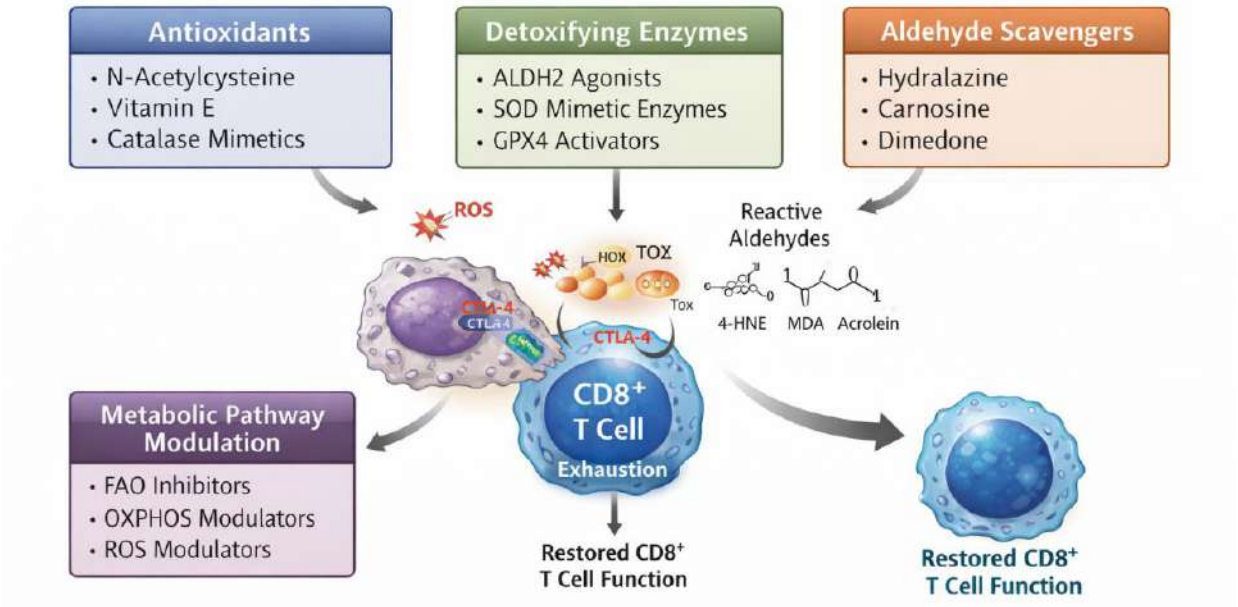

Figure 05: Therapeutic strategies to target lipid peroxidation and reactive aldehyde-mediated CD8⁺ T-cell dysfunction.

10. Current Challenges and Knowledge Gaps

Despite significant progress that has been achieved in understanding the connection between oxidative stress, lipid peroxidation and tumor micro environment, there are still some crucial issues and gaps that are not resolved yet. These obstacles are essential to cancer immunotherapy and making it more successful. The metabolic

properties, oxygenation as well as the population of immune cells and lipids of tumors differ considerably. These variations also influence the extent of oxidative stress and lipid peroxidation, which restrict generalization of the results in different types of cancer (Hinshaw and Shevde, 2019; Quail and Joyce, 2013). The other significant loose end is the limited knowledge of the molecular pathways by which products of lipid peroxidation change T-cell metabolism. The precise mechanism of these compounds to signal and interact with other molecules in mitochondria to cause mitochondrial impairment and metabolic depletion in CD8 + T cells is not fully understood yet (Ayala et al., 2014; Haku et al., 2026).

The therapeutic dilemma is also a complex issue of lipid peroxidation vs ferroptosis. Although ferroptosis may be advantageous in that the immune cells may be killed leading to the death of cancer cells, too much lipid peroxidation can also destroy the immune cells, thus weakening their anti-tumor effect. Such dual action highlights the necessity of finding therapeutic solutions that can be able to selectively affect tumor cells without affecting the work of immune cells (Stockwell et al., 2017). Further characterize how affect the metabolism and functional processes. New technologies such as proteomics and metabolomics are available to serve as powerful tools for identifying molecular targets of reactive aldehydes in T cells. These strategies can assist in metabolic imbalances, discover new objects of therapeutic intervention (Haku et al., 2026; Ayala et al., 2014).

The other important point of interest is the elaboration of strategies to protect T cells against oxidative damage. Possible solutions include the use of compounds that neutralize reactive aldehydes, enhancement of intrinsic systems of detoxification and reinforcement of the antioxidant defense of the cell. In general, a better appreciation of these processes will be essential to come up with measures that would reinstate.

11. Future Perspectives

Future studies will be geared towards a more precise definition of effects induced by oxidative stress and lipid peroxidation control activity, CD8+ T. Proteomics and other emerging technologies like metabolomics can be used to identify certain molecular targets of reactive aldehydes in T cells. The methods can help identify metabolic imbalances, find new objects of pharmacotherapy (Haku et al., 2026; Ayala et al., 2014).

The other area of interest is developing strategies to protect T cells from oxidative damage. The possible solutions involve neutralizing reactive aldehydes with compounds, boosting the cellular defenses against antioxidants, and improving the intrinsic detoxification processes. Such interventions may help maintain functions (Scharping et al., 2016; Vasiliou et al., 2000). Altogether, combining metabolic and immunological approaches can be a promising way to recover and enhance use in immunotherapy for cancer.

12. Conclusion

This habitat, stress, oxidative damage and perturbations in lipid homeostasis, all negatively affect the metabolic efficiency and cytotoxic activity of tumor-infiltrating lymphocytes. Specifically, lipid peroxidation causes the formation of adversely impact mitochondrial activity, disrupts cellular metabolism and eventual development of T-cell exhaustion. Such metabolic changes compromise and maintain successful immunity and restrict the overall effectiveness of the existing immunotherapeutic strategies. Meanwhile, an increasing amount of evidence indicates that anti-oxidative stress, lipid metabolism regulation, and aldehyde detoxification enhancement could play a role in restoring metabolic stability in T cells and increasing their functional competency.

13. REFERENCES

Allowitz, K., Taylor, J., Harames, K., Yoo, J., & Ramana, K. (2025). Oxidative stress-mediated lipid peroxidation-derived lipid aldehydes in disease pathophysiology. Current Neuropharmacology.

Ayala, A., Muñoz, M. F., & Argüelles, S. (2014). Lipid peroxidation: Production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. *Oxidative Medicine and Cellular Longevity*, 2014, 360438.

Bailis, W., Shyer, J. A., Zhao, J., et al. (2019). Distinct metabolic programs in effector and regulatory T cells. *Immunity*, 51(1), 102–114. https://doi.org/10.1016/j.immuni.2019.05.008

Beltra, J. C., Manne, S., Abdel-Hakeem, M. S., et al. (2020). Developmental relationships of four exhausted CD8$^+$ T cell subsets reveals underlying transcriptional and epigenetic landscape control. *Immunity*, 52(5), 825–841.e8. https://doi.org/10.1016/j.immuni.2020.03.008

Brigelius-Flohé, R., & Maiorino, M. (2013). Glutathione peroxidases. Biochimica et Biophysica Acta (BBA)-General Subjects, 1830(5), 3289-3303.

Buck, M. D., O'Sullivan, D., & Pearce, E. L. (2017). T cell metabolism drives immunity. *Journal of Experimental Medicine*, 214(5), 1245–1260. https://doi.org/10.1084/jem.20151159

Buck, M. D., Sowell, R. T., Kaech, S. M., & Pearce, E. L. (2017). Metabolic instruction of immunity. Cell, 169(4), 570-586.

Chang, C. H., Qiu, J., O'Sullivan, D., Buck, M. D., Noguchi, T., Curtis, J. D., ...& Pearce, E. L. (2015). Metabolic competition in the tumor microenvironment is a driver of cancer progression. Cell, 162(6), 1229-1241.

Chen, D. S., & Mellman, I. (2017). Elements of cancer immunity and the cancer-immune set point. *Nature*, 541, 321–330.

Fischer, K., Hoffmann, P., Voelkl, S., Meidenbauer, N., Ammer, J., Edinger, M., ...& Kreutz, M. (2007). Inhibitory effect of tumor cell–derived lactic acid on human T cells. Blood, 109(9), 3812-3819.

Gajewski, T. F., Schreiber, H., & Fu, Y. X. (2013). Innate and adaptive immune cells in the tumor microenvironment. Nature immunology, 14(10), 1014-1022.

Haku, Y., Kitaoka, K., et al. (2026). Active aldehydes accelerate CD8$^+$ T-cell exhaustion by metabolic alteration in the tumor microenvironment. Nature Immunology.

Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: the next generation. cell, 144(5), 646-674.

Hinshaw, D. C., &Shevde, L. A. (2019). The tumor microenvironment innately modulates cancer progression. Cancer research, 79(18), 4557-4566.

Joyce, J. A., & Pollard, J. W. (2009). Microenvironmental regulation of metastasis. Nature reviews cancer, 9(4), 239-252.

Kalluri, R. (2016). The biology and function of fibroblasts in cancer. Nature Reviews Cancer, 16(9), 582-598.

Khan, O., Giles, J. R., McDonald, S., et al. (2019). TOX transcriptionally and epigenetically programs CD8$^+$ T cell exhaustion. *Nature*, 571, 211–218. https://doi.org/10.1038/s41586-019-1325-x

Lee, S. E., & Park, Y. S. (2013). Role of lipid peroxidation-derived α,β-unsaturated aldehydes in vascular dysfunction. Oxidative Medicine and Cellular Longevity.

Li, H., Chi, H., & Song, Y. (2022). Modeling T-cell exhaustion in cancer: Limitations of preclinical studies. *Frontiers in Immunology*, 13, 875309.

Li, X., Song, Y., & Chi, H. (2021). Metabolic regulation of T-cell function in the tumor microenvironment. *Trends in Immunology*, 42(9), 771–783.

Lim, W. A., June, C. H., &Sadelain, M. (2020). The principles of engineering immune cells to treat cancer. *Cell*, 181(2), 301–316. https://doi.org/10.1016/j.cell.2020.03.035

Liu, H., Yang, W., & Jiang, J. (2025). Targeting tumor metabolism to augment CD8+ T cell anti-tumor immunity. Journal of pharmaceutical analysis, 15(5), 101150.

Lu, P., Takai, K., Weaver, V. M., &Werb, Z. (2011). Extracellular matrix degradation and remodeling in development and disease. Cold Spring Harbor perspectives in biology, 3(12), a005058.

Ma, X., Xiao, L., Liu, L., et al. (2022). GPX4 regulates lipid peroxidation and T-cell function in tumors. *Nature Immunology*, 23, 45–56.

Ma, X., Xiao, L., Liu, L., Ye, L., Su, P., Bi, E., ...& Yi, Q. (2021). CD36-mediated ferroptosis dampens intratumoral CD8+ T cell effector function and impairs their antitumor ability. Cell metabolism, 33(5), 1001-1012.

Maj, T., Wang, W., Crespo, J., Zhang, H., Wang, W., Wei, S., ...Zou, W. (2017). Oxidative stress controls regulatory T cell apoptosis and suppressor activity and PD-L1-blockade resistance in tumor. *Nature Immunology*, 18(12), 1332–1341. https://doi.org/10.1038/ni.3868

McLane, L. M., Abdel-Hakeem, M. S., &Wherry, E. J. (2019). CD8 T cell exhaustion during chronic viral infection and cancer. Annual review of immunology, 37(1), 457-495.

Nature Immunology. (2026). Active aldehydes drive metabolic exhaustion in CD8⁺ T cells.

O'Neill, B. C., Tebaldi, C., Van Vuuren, D. P., Eyring, V., Friedlingstein, P., Hurtt, G., ... & Sanderson, B. M. (2016). The scenario model intercomparison project (ScenarioMIP) for CMIP6. Geoscientific Model Development, 9(9), 3461-3482.

Pardoll, D. M. (2012). The blockade of immune checkpoints in cancer immunotherapy. *Nature Reviews Cancer*, 12(4), 252–264. https://doi.org/10.1038/nrc3239

Patsoukis, N., Bardhan, K., Chatterjee, P., Sari, D., Liu, B., Bell, L. N., ... & Boussiotis, V. A. (2015). PD-1 alters T-cell metabolic reprogramming by inhibiting glycolysis and promoting lipolysis and fatty acid oxidation. Nature communications, 6(1), 6692.

Pauken, K. E., Sammons, M. A., Odorizzi, P. M., et al. (2016). Epigenetic stability of exhausted T cells limits durability of reinvigoration by PD-1 blockade. *Science*, 354(6316), 1160–1165.

Pearce, E. L., Poffenberger, M. C., Chang, C. H., & Jones, R. G. (2013). Fueling immunity: insights into metabolism and lymphocyte function. Science, 342(6155), 1242454.

Philip, M., Fairchild, L., Sun, L., et al. (2017). Chromatin states define tumour-specific T cell dysfunction and reprogramming. *Nature*, 545, 452–456. https://doi.org/10.1038/nature22367

Postow, M. A., Callahan, M. K., &Wolchok, J. D. (2015). Immune checkpoint blockade in cancer therapy. Journal of clinical oncology, 33(17), 1974-1982.

Postow, M. A., Chesney, J., Pavlick, A. C., et al. (2015). Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *New England Journal of Medicine*, 372(21), 2006–2017. https://doi.org/10.1056/NEJMoa1414428

Quail, D. F., & Joyce, J. A. (2013). Microenvironmental regulation of tumor progression and metastasis. Nature medicine, 19(11), 1423-1437.

Reina-Campos, M., Scharping, N. E., &Goldrath, A. W. (2021). CD8+ T cell metabolism in infection and cancer. Nature Reviews Immunology, 21(11), 718-738.

Ribas, A., & Wolchok, J. D. (2018). Cancer immunotherapy using checkpoint blockade. *Science*, 359(6382), 1350–1355. https://doi.org/10.1126/science.aar4060

Ribas, A., & Wolchok, J. D. (2018). Cancer immunotherapy using checkpoint blockade. *Science*, 359(6382), 1350–1355. https://doi.org/10.1126/science.aar4060

Roerden, M., &Spranger, S. (2025). Cancer immune evasion, immunoediting and intratumour heterogeneity. Nature Reviews Immunology, 25(5), 353-369.

Scharping, N. E., & Delgoffe, G. M. (2016). Tumor microenvironment metabolism: A new checkpoint for anti-tumor immunity. *Vaccine*, 34(40), 4742–4747. https://doi.org/10.1016/j.vaccine.2016.07.046

Scharping, N. E., Menk, A. V., Moreci, R. S., Whetstone, R. D., Dadey, R. E., Watkins, S. C., ... &Delgoffe, G. M. (2016). The tumor microenvironment represses T cell mitochondrial biogenesis to drive intratumoral T cell metabolic insufficiency and dysfunction. Immunity, 45(2), 374-388.

Scharping, N. E., Rivadeneira, D. B., Menk, A. V., et al. (2021). Mitochondrial stress induced by metabolic competition promotes T-cell dysfunction in tumors. *Immunity*, 54(2), 337–352. https://doi.org/10.1016/j.immuni.2020.12.021

Sena, L. A., &Chandel, N. S. (2012). Physiological roles of mitochondrial reactive oxygen species. *Molecular Cell*, 48(2), 158–167. https://doi.org/10.1016/j.molcel.2012.09.025

Sharma, P., & Allison, J. P. (2015). The future of immune checkpoint therapy. *Science*, 348(6230), 56–61. https://doi.org/10.1126/science.aaa8172

Stockwell, B. R., Angeli, J. P. F., Bayir, H., Bush, A. I., Conrad, M., Dixon, S. J., ... & Zhang, D. D. (2017). Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease. cell, 171(2), 273-285.

Subramanian, M., &Marelli-Berg, F. M. (2021). CD36 pumps fat to defang killer T cells in tumors. Cell metabolism, 33(8), 1509-1511.

Tang, Y., Chen, Z., Zuo, Q., & Kang, Y. (2024). Regulation of CD8+ T cells by lipid metabolism in cancer progression. Cellular & Molecular Immunology, 21(11), 1215-1230.

Van der Windt, G. J., Everts, B., Chang, C. H., Curtis, J. D., Freitas, T. C., Amiel, E., ... & Pearce, E. L. (2012). Mitochondrial respiratory capacity is a critical regulator of CD8+ T cell memory development. Immunity, 36(1), 68-78.

Viel, S., Vivier, E., Walzer, T., &Marçais, A. (2025). Targeting metabolic dysfunction of CD8 T cells and natural killer cells in cancer. Nature Reviews Drug Discovery, 24(3), 190-208.

Wang, W., Green, M., Choi, J. E., Gijón, M., Kennedy, P. D., Johnson, J. K., ...&Zou, W. (2019). CD8+ T cells regulate tumourferroptosis during cancer immunotherapy. Nature, 569(7755), 270-274.

Wherry, E. J. (2011). T cell exhaustion. Nature immunology, 12(6), 492-499.

Wherry, E. J., & Kurachi, M. (2015). Molecular and cellular insights into T cell exhaustion. Nature reviews immunology, 15(8), 486-499.

Yu, J., Fu, L., Wu, R., Che, L., Liu, G., Ran, Q., ...& Zhao, G. (2025). Immunocytes in the tumor microenvironment: recent updates and interconnections. Frontiers in immunology, 16, 1517959.

Zhang, H., Li, S., Wang, D., Liu, S., Xiao, T., Gu, W., ...& Chen, P. (2024). Metabolic reprogramming animmune evasion: the interplay in the tumor microenvironment. Biomarker research, 12(1), 96.

Zhang, X., et al. (2024). Lipotoxicity, lipid peroxidation and ferroptosis in cancer therapy. Cancer Research Review.