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Strategies of cancer cell glucose metabolism in determining cd8+ t cell reprogramming in the ovarian cancer tumor microenvironment

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Abstract

Ovarian cancer is the leading cause of death among gynecological neoplasm due to its high proliferation rate and invasive ability. This elevated proliferation rate correlates with increased glycolytic activity, a mechanism also utilized by $CD8^+$ T cells, which serves as the body's primary line of defense against cancer. Elevated glycolysis in ovarian cancer cells is primarily due to *PIK3CA* mutation, one of the most frequently mutated genes in ovarian cancer. Other mutations contributing to elevated glycolysis include *FOXM1*, *SIK2*, and *PTGES3*, all of which lead to increased glucose uptake and upregulation of glycolytic enzyme expression. $CD8^+$ T cell activation results in metabolic reprogramming that enhances glycolytic activity, which is important for maintaining their effector functions. In the scarcity of glucose, GAPDH enzyme binds to IFN-γ mRNA, inhibiting its translation. Lactate accumulation in tumor microenvironment decreases granzyme secretion and inhibits proliferation and infiltration of effector $CD8^+$ T cells. Similar metabolic profiles between ovarian cancer cells and effector $CD8^+$ T cells result in nutrient deficiency and accumulation of lactate in tumor microenvironment, which leads to effector $CD8^+$ T cells' dysfunction, thereby contributing to immune escape. Intervention in T cell metabolic reprogramming may present opportunity to improve their cytotoxicity toward cancer cells.

Keywords: Ovarian cancer; Immunometabolism; Glycolysis; $CD8^+$ T cells

1. Introduction

According to data from GLOBOCAN 2022, ovarian cancer ranked third as the most common gynecological neoplasm worldwide, with an incidence rate of 6,6 per 100.000 population and a mortality rate of 4,2 per 100.000 population [1]. In Indonesia, ovarian cancer is the most prevalent cancer after breast cancer and cervical cancer found in women, with 15.150 new cases and 9.673 total deaths found in 2022 [2]. Factors that influence the risk of ovarian cancer include age, genetic factors such as mutation in BRCA1/2 and KRAS genes, prolonged ovulation cycles such as in early menarche and late menopause, use of hormone replacement therapy, chronic inflammation, environmental exposure such as smoking, as well as diets [3]. These factors can trigger genetic and molecular changes that drive uncontrolled cell growth and proliferation. High proliferation rate in ovarian cancer, particularly in the epithelial type, demands a very high energy intake to sustain cell growth and survival. To meet these energy needs, cancer cells increased the uptake, utilization, and regulation of various nutrient sources, such as glucose, lipids, and amino acids significantly [4, 5]. Over the progression of the disease, ovarian cancer cells experience not only changes in their genetic characteristics but also alterations in metabolic reprogramming. These changes enable cancer cells to survive in less-than-ideal environmental conditions, such as nutrient scarcity, hypoxia, and overcome the cytotoxic effects of therapy, enhancing the cancer aggressivity [5].

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One of the main characteristics of cancer cell metabolism is their ability to utilize glycolysis, even in a normoxic condition. This phenomenon is called Warburg effect or aerobic glycolysis [6]. In normal condition, cell uses oxidative phosphorylation in mitochondria to produce ATP when oxygen is available, while glycolysis is mostly used during hypoxia. The primary use of glycolysis in ovarian cancer cells is not only to give the cell energy they need in a short time period, but also to protect cancer cells from oxidative stress that induces apoptosis [5, 7, 8].

On the other hand, ovarian cancer progression is also determined by the complex interactions between cancer cells and other components within the tumor microenvironment (TME), including immune cells like $CD8^+$ T cells. $CD8^+$ T cells are activated by tumor antigens expressed on the surface of ovarian cancer cells and play a crucial role in eliminating cancer cells by their cytotoxic activity [9, 10]. Upon activation, $CD8^+$ T cells use glycolysis as its primary metabolism pathway, similar to ovarian cancer cells [11]. Competition between cancer cells and $CD8^+$ T cells to obtain glucose from tumor microenvironment may cause nutrient deprivation, resulting in either cancer cells regression or T cells' exhaustion [12, 13].

2. Material and methods

This review is a narrative literature review. A literature research was conducted to retrieve available articles on the role of glucose metabolism in ovarian cancer cells and $CD8^+$ T cells. All papers were identified using several database search engines, namely Pubmed and Scopus, as well as Cochrane Library and ProQuest, using multiple search terms. Search terms were chosen to include 'ovarian cancer', 'metabolism', 'glycolysis', 'glucose', and 'CD8 T cell'. The search and selection of the article were done with no time frame specified. Relevant papers were screened and chosen for relevance by reviewing titles and abstracts according to the study objectives. Full texts of eligible studies were assessed and selected.

3. Results and discussion

3.1. Glucose Metabolism in Ovarian Cancer Cell

The high proliferation rate of ovarian cancer, especially in epithelial type, leads to an increased energy demand by cancer cells to meet their needs. This results in a high rate of uptake, utilization, and regulation of various nutrient sources such as glucose, lipids, and amino acids [14]. As the cancer progresses, cancer cells undergo metabolic reprogramming in order to overcome issues such as nutrient limitations and resist therapeutic effects. In the early phase of tumorigenesis, cancer cells typically use both glycolysis and oxidative phosphorylation as primary mechanisms to produce ATP. Oxygen limitations due to insufficient vascularization to the TME (tumor microenvironment) cause cancer cells located more than 100–200 μm from the nearest blood vessel to rely more heavily on glycolysis, as they are unable to oxidize pyruvate due to a lack of NAD^+ within the cell. Glycolysis produces only 2 ATP molecules per glucose molecule processed, hence in order to meet energy demands, cancer cells increase glucose uptake from the TME [6]. As the cancer can create a more conducive environment, glycolysis remains as its primary metabolic pathway, even under normoxic and hypoxic conditions. This phenomenon, known as the Warburg effect or aerobic glycolysis, provides advantages by allowing cancer cells to survive in the TME and protecting them from the cytotoxic effects of oxidative stress, which can trigger apoptosis in cancer cells [5]. Approximately 60% of the ATP used by cancer cells is derived from aerobic glycolysis [4]. The glycolytic pathway itself is complex due to its bidirectional metabolic flow, feedback inhibition mechanisms, and involvement of numerous intermediate metabolites that serve as biosynthetic precursors needed for cancer cell proliferation [6]. The metabolic shift toward oxidative phosphorylation occurs in response to lactic acidosis and low glucose levels in the TME, demonstrating the capability of ovarian cancer cells to exhibit dual metabolic phenotypes [5].

The ability of ovarian cancer cells to absorb glucose is influenced by oncogenic mutations that drive tumorigenesis [4]. The *PIK3CA* gene (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) is one of the genes in ovarian cancer that frequently undergoes mutation and is responsible for increasing the proliferation and invasiveness ability of ovarian cancer [15]. Increased expression of PIK3CA leads to overactivation of the PI3K/AKT/mTOR pathway, which plays a role in glucose signaling by enhancing the translocation of GLUT4 to the cancer cell membrane, thus facilitating glucose uptake by cancer cells [4, 16]. Besides the overexpression of PIK3CA, increased expression of FOXM1 (forkhead box protein M1) also contributes to enhance glucose absorption. FOXM1 is a transcription factor that can recognize the promoter region of GLUT1, thereby increasing GLUT1 expression and facilitating glucose uptake. Compared to GLUT4, GLUT1 has a higher affinity to glucose hence comprises its ability to uptake glucose in low-glucose condition [4].

The increase in glycolysis in ovarian cancer cells is mediated by several signaling pathways. HIF-1α, induced by hypoxic conditions in cancer cells, can modulate glucose metabolism in ovarian cancer through several mechanisms: 1) activation of VEGF/RTKs; and 2) activation of HIF-1α/RTK [17–19]. VEGF/RTKs activate the PI3K/AKT pathway, which in turn enhances GLUT1 expression and translocation [5]. Activation of HIF-1α/RTK increases the expression of PDK1 [18]. Pyruvate dehydrogenase kinase (PDK), along with the pyruvate dehydrogenase complex (PDC), regulates the metabolic reprogramming of ovarian cancer cells. PDC functions to convert pyruvate into acetyl-CoA, which enters the tricarboxylic acid (TCA) cycle or Krebs' cycle. PDC activation is regulated by PDK, which phosphorylates PDC, thereby inhibiting its activation and function [5, 6]. In ovarian cancer, increased PDK1 expression via HIF-1α/RTK leads to decreased pyruvate oxidation. This results in the inability to produce ATP even in the presence of oxygen [18]. Salt-inducible kinase (SIK) 1-3 are serine/threonine kinase proteins that are also overexpressed in epithelial ovarian cancer. Activation of SIK through the PI3K/AKT/HIF-1α pathway can increase the transcription of various genes involved in glycolysis, thereby enhancing the Warburg effect in ovarian cancer [20].

Mutation of the tumor-suppressive gene *PTGES3* in ovarian cancer contributes to the invasive and metastatic potential of ovarian cancer through increased glucose metabolism via glycolysis [21]. Under normal conditions, PTGES3, a prostaglandin E2 (PGE2) synthase, can bind to phosphofructokinase liver-type (PFKL) and synthesize PGE2, which inhibits PFKL activity. Suppression of PFKL activity results in a reduction of glycolysis. In ovarian cancer, mutation of *PTGES3* gene causes decreased expression of PTGES3, which prevents the inhibitory pathway of PFKL. This results in increased glucose metabolism via glycolysis, ultimately contributing to the invasive and metastatic potential of ovarian cancer [21].

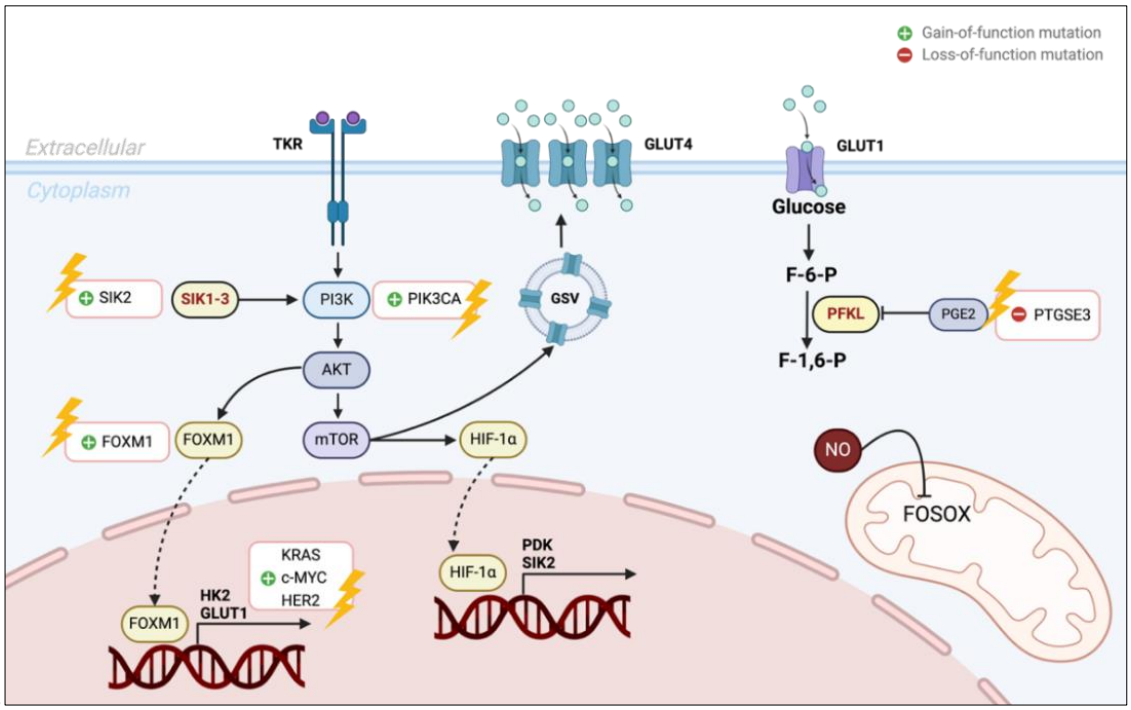

Figure 1 Factors regulating glucose metabolism in ovarian cancer cells. Mutations which cause gain-of-function in *SIK2*, *PIK3CA*, and *FOXM1* genes in ovarian cancer cells contribute to enhance glucose uptake and glycolysis rate. Another mutation in *PTGES3* gene leads to loss of function of PGE2 protein, thereby further increasing glycolysis rate. Additionally, nitric oxide found in ovarian cancer cells prevents inhibition of glycolysis by blocking ATP production through oxidative phosphorylation in mitochondria. AKT, protein kinase B. c-MYC, cellular MYC. F6P, fructose-6-phosphate. F1,6P, fructose-1,6-biphosphate. FOSOX, oxidative phosphorylation. FOXM1, forkhead box protein M1. GLUT, glucose transporter. GSV, glucose-transporter storage vesicle. HER2, human epidermal growth factor receptor 2. HIF-1α, hypoxia inducible factor 1α. HK2, hexokinase 2. mTOR, mammalian target of rapamycin. No., nitric oxide. PDK, pyruvate dehydrogenase kinase. PFKL, phosphofructokinase, liver type. PGE2, prostaglandin E2. PI3K, phosphatidylinositol 3-kinase. PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha. PTGES3, prostaglandin E synthase 3. SIK, salt inducible kinase. TKR, tyrosine kinase receptor

The presence of nitric oxide (NO) in ovarian cancer cells is also known to sustain glycolysis pathways in cells under normoxic conditions [22]. NO can inhibit mitochondrial respiration, leading to the inability of cells to produce ATP

through oxidative phosphorylation, thus pushing cancer cells to rely on glycolysis as their main energy-generating metabolism [22]. NO binds to cytochrome oxidase (COX), or complex IV, in the electron transport chain located on the inner mitochondrial membrane [23]. COX acts as the terminal complex of the electron transport chain, transferring electrons from cytochrome C to oxygen molecules, producing water [6].

The feedback inhibition mechanism in glycolysis is mediated by various enzymes and metabolites involved in glycolysis itself. Hexokinase (HK) is the first enzyme that initiates the glycolysis pathway by converting glucose to glucose-6-phosphate, which can regulate the rate of glycolysis through lactate inhibition of HK [6]. Overexpression of FOXM1 (forkhead box protein M1) in ovarian cancer and induction by IL-6 produced by cancer-associated fibroblasts (CAF) in the ovarian cancer TME disrupts this inhibition mechanism, leading instead to an increase in glycolysis in ovarian cancer by enhancing HK expression [24, 25]. High HK expression is associated with advanced stages and poor patient survival in ovarian cancer.[24] The rate of glycolysis can also be mediated by other enzymes, such as lactate dehydrogenase A (LDHA), which reduces pyruvate to lactate. This reduction requires NADH to be converted into NAD^+, which can then be reused in subsequent glycolysis reactions [6]. Without this mechanism, NAD^+ cannot be regenerated, which would limit the rate of glycolysis in cancer cells [26].

Excessive glycolysis in ovarian cancer cells will lead to the production of large amounts of lactate. The increase of lactate within cancer cells will cause overexpression of monocarboxylate transporters (MCT)-1 and MCT4, a type of solute carrier, which will expel lactate from the cell to prevent intracellular lactic acidosis.[26] This mechanism will lead to increased lactate levels in the TME, which will, in return, affect the immune response against cancer [26]. Additionally, cancer cells utilize lactate to prevent cell death from chemotherapy through lactylation of Nijmegen Breakage Syndrome-1 (NBS1), thereby promoting the formation of the meiotic recombination 11 (MRE11)-radiation sensitive 50 (RAD50)-NBS1 (MRN complex), which plays a role in DNA repair mechanisms through homologous recombination [8].

3.2. Glucose Metabolism in $CD8^+$ T Cell

In general, immune cells utilize various forms of metabolism to meet the energy and metabolite requirements needed to support survival, differentiation, proliferation, and other cellular functions [27, 28]. When infection or inflammation occurs, as well as in cancer, immune cells undergo a series of metabolic reprogramming changes to ensure sufficient energy for their effector functions [13]. $CD8^+$ cytolytic T cells utilize glycolysis, the TCA cycle, oxidative phosphorylation, glutaminolysis, and fatty acid oxidation (FAO). The metabolic pathway used depends on their differentiation and metabolic needs of the T cell to support its function at each differentiation stage. This metabolic reprogramming determines the effector function and phenotype of the T cell, including its role as a pro-tumor or anti-tumor cell [29].

Until its activation by an antigen, naive T cells are generally in a resting state as they are not actively proliferating and therefore do not require high energy. The catabolic metabolism that occurs in naive T cells typically involves oxidative phosphorylation to produce ATP. This is because oxidative phosphorylation requires a longer process and the presence of oxygen to produce ATP [13]. In activated $CD8^+$ T cells, T cells undergo reprogramming mediated by TCR together with CD28 costimulation to support $CD8^+$ T cell proliferation and function [30, 31]. Activation of $CD8^+$ T cells through TCR and CD28 costimulation activates various signaling pathways, including PI3K/AKT/mTOR. AKT activation increases the expression of NF-κB and the anti-apoptotic protein BCL-XL, which enhances the synthesis of pro-inflammatory cytokines such as IL-2 and TNF-α, as well as increasing $CD8^+$ T cell proliferation [30]. Further activation of AKT/mTOR increases the expression of 1) MYC, which promotes further T cell proliferation through the synthesis of cyclin-dependent kinase (CDK)-2/4 and cyclin A; and 2) HIF-1α, which plays a role in the synthesis of cytokines such as IFN-γ, TNF-α, and granzyme. TCR activation also activates calcineurin, which in turn activates NFAT, and NFAT plays a role in activating gene expression related to $CD8^+$ T cell proliferation and activation, such as IL-2 and TNF-α [30].

Aside from activating effector functions, AKT/mTOR activation by TCR and CD28 signals increases glycolysis regulation in $CD8^+$ T cells by increasing GLUT1 expression on the $CD8^+$ T cell membrane surface. Increased GLUT1 leads to enhanced glucose uptake, which further increases glycolysis reactions to produce pyruvate and ATP, fulfilling $CD8^+$ T cell energy needs. Increased pyruvate production through glycolysis results in pyruvate conversion to acetyl-CoA, which enters the TCA cycle. The TCA cycle produces alpha-ketoglutarate (α-KG), which serves as an intermediate metabolite for cell proliferation. Increased acetyl-CoA in the cell enhances histone acetyltransferase (HAT) enzyme activity, facilitating chromatin remodeling to allow transcription factors better access to genes involved in glycolysis in $CD8^+$ T cells [30].

MYC activation by the AKT/mTOR pathway increases glycolysis in $CD8^+$ T cells by upregulating miR-17∼92 expression. miR-17∼92 is a polycistronic microRNA complex that enhances the sensitivity of activated $CD8^+$ T cells. MYC also increases the expression of glutamine transporters such as SLC32A1 and SLC32A2 on the $CD8^+$ T cell surface. This

increases glutamine utilization, triggering glutaminolysis mediated by the glutaminase (GLS) enzyme, producing glutamate [13, 30]. Glutamate can be converted back to α-KG through the TCA cycle, which is essential for nucleotide, lipid, and protein synthesis in CD8⁺ T cells. The TCA cycle also produces NADH and FADH2, which serve as electron donors in the oxidative phosphorylation pathway in the inner mitochondrial membrane to produce ATP. This mechanism of using glutamine as an energy source in activated CD8⁺ T cells is an alternative used when CD8+ T cells are in a low-glucose environment. NFAT activation through TCR signaling via calcineurin can increase glycolysis by upregulating GLUT1 and GLUT3 expression [13]. NFAT also upregulates hexokinase expression, which is involved in the glycolysis pathway, and its overexpression enhances glycolysis in CD8⁺ T cells. Further NFAT activation can activate MYC and HIF-1α, increasing glycolysis in CD8⁺ T cells [28, 30]. These data highlight the role of CD28 in modulating the metabolism of activated effector CD8⁺ T cells.

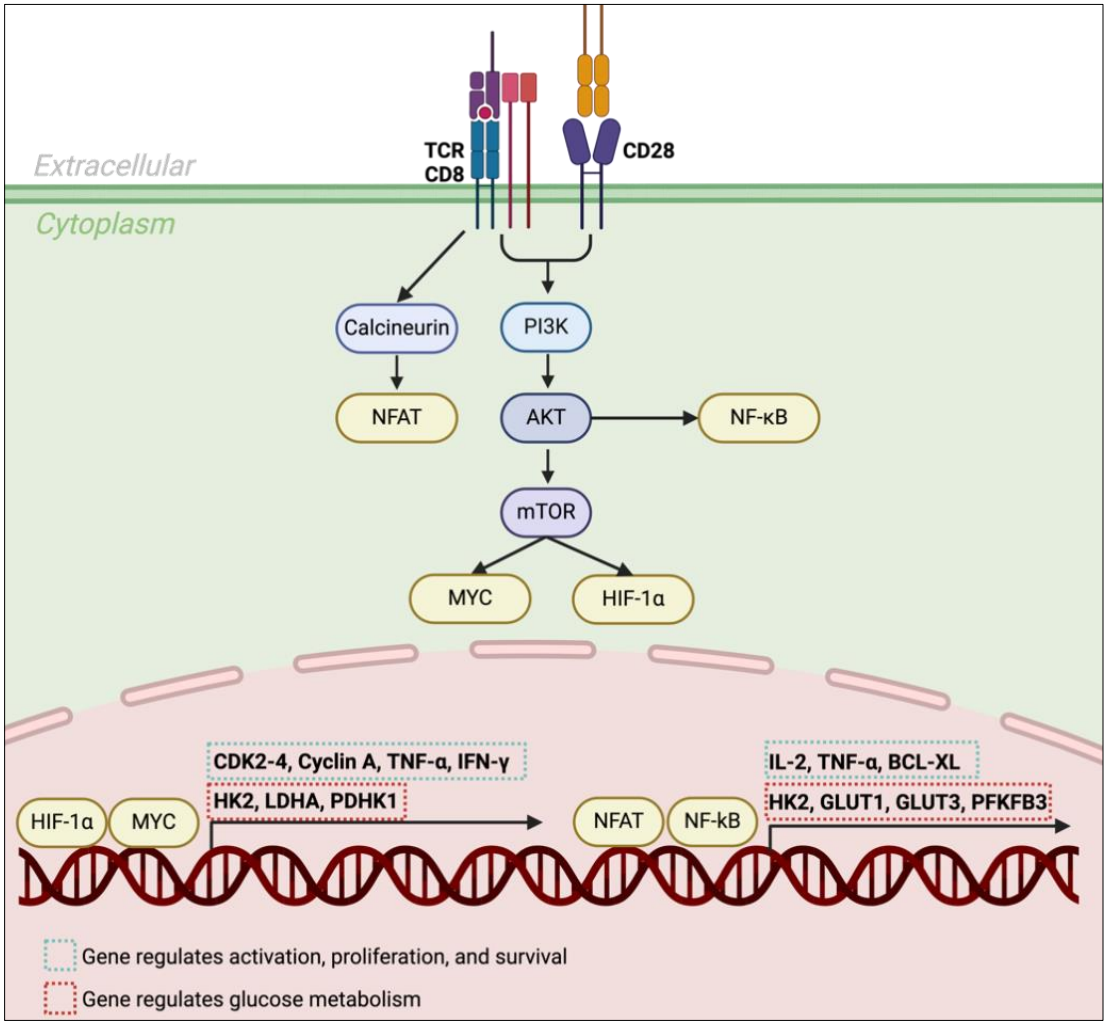

Figure 2 Factors regulating glucose metabolism in CD8⁺ T cells. Activation of CD8⁺ involving CD28 triggers a cascade of intracellular signaling pathways that eventually activate protein responsible for increasing glycolysis rate. This metabolic reprogramming supports CD8⁺ T cell activation and survival, characterized by the production of cytokines and other proteins essential for cells survival. CD, cluster of differentiation. CDK, cyclin-dependent kinase 2. HIF-1α, hypoxia inducible factor 1α. HK, hexokinase. LDHA, lactate dehydrogenase A. PDHK1, pyruvate dehydrogenase kinase 1. mTOR, mammalian target of rapamycin. NFAT, nuclear factor of activated T-cells. PFKB3, phosphofructokinase-2/fructose-2,6-bisphosphatase 3. TCR, T-cell receptor

CD8⁺ T cell reprogramming can also occur through pathways that do not involve the CD28 co-stimulator. TCR signaling can activate PDHK1 (pyruvate dehydrogenase kinase 1) associated with LAT (linker for activation of T cell family member 1). PDHK1 activation inhibits PDH (pyruvate dehydrogenase), which converts pyruvate to acetyl-CoA to enter the TCA cycle. This results in pyruvate accumulation, inducing its conversion to lactate by lactate dehydrogenase (LDH) [11]. The increased glucose requirement is necessary to meet the demands for ATP, intermediate metabolites, and cytokine production. Intermediate metabolites from glycolysis, such as glucose-6-phosphate, are used in the pentose

phosphate pathway for nucleotide synthesis. Like cancer cells, activated CD8+ T cells rely heavily on glycolysis as the primary metabolic pathway, even in the presence of oxygen [32]. Excess lactate production in effector $CD8^+$ T cells is then expelled from the cell. The inefficiency of oxidative phosphorylation in effector $CD8^+$ T cells may be due to mitochondrial fragmentation and the loosening of mitochondrial cristae areas in these T cells. Consequently, mitochondria's ATP production role is replaced by glycolysis and glutaminolysis, while mitochondria play a more supportive role in facilitating various signaling pathways required for T cell proliferation, migration, and cytokine synthesis. For example, mitochondria-derived ROS are used as secondary signals for IFN-γ synthesis induced by IL-12/IL-18 signaling and post-antigen activation proliferation [33].

3.3. $CD8^+$ Metabolic Reprogramming in Tumor Microenvironment

In light of the previous explanation, ovarian cancer cells and $CD8^+$ T cells share similar metabolic profiles and nutrient requirements, with both increasing aerobic glycolysis to support proliferation and each cell's respective functions. Other studies using DEG (differentially expressed gene) analysis have shown a common increase in the expression of genes involved in glycolysis in ovarian cancer cells and genes involved in glucose uptake and glycolysis in T cells co-cultured with ovarian cancer cells [27]. This allows competition between them for nutrients, especially glucose, present in the TME. The high metabolic rate and nutrient demands of cancer cells can suppress T cell metabolism, potentially contributing to exhaustion in $CD8^+$ T cells. The limited glucose availability results in a lower glycolytic metabolic rate in T cells, leading to the loss of intermediate metabolites that are crucial for maintaining $CD8^+$ T cell effector function [34]. Over time, this condition can result in irreversible $CD8^+$ T cell dysfunction, one example being the impaired ability of $CD8^+$ T cells to produce IFN-γ [30]. Glucose scarcity in the TME due to competition between cancer and $CD8^+$ T cells can cause dysfunction in enzymes involved in glycolysis, such as GADPH (glyceraldehyde-3-phosphate dehydrogenase), preventing $CD8^+$ T cells from producing IFN-γ. GADPH can bind to IFN-γ mRNA, interfering with translation and reducing IFN-γ synthesis [27, 35].

The presence of lactate in the ovarian cancer TME can impair $CD8^+$ T cell motility, affecting their infiltration into ovarian cancer tumors. Lactate acts as an inhibitor of the enzymes HK and phosphofructokinase (PFK), which regulate the glycolytic rate in T cells. This can disrupt ATP production needed by $CD8^+$ T cell, thus decreasing their migratory capacity [36]. Extracellular lactate acidosis in the ovarian cancer TME has been shown to reduce the cytotoxic activity of $CD8^+$ T cell [37]. $CD8^+$ T cell relies on the enzyme pyruvate carboxylase (PC) to convert pyruvate to oxaloacetate, allowing it to enter the TCA cycle and produce essential metabolic intermediates for $CD8^+$ T cell. Through this reaction, succinate is not converted to fumarate and can be secreted by T cells. Succinate secretion has an autocrine effect on $CD8^+$ T cell through succinate receptor 1 (SUCNR1), enhancing the cytotoxic activity of $CD8^+$ T cell in synthesizing perforin and granzyme. Excess lactate in the TME can alter pyruvate metabolism to enter the TCA cycle, typically by activating the PDH enzyme to produce acetyl-CoA, which then converts succinate to fumarate, thereby reducing succinate secretion [37].

Moreover, the lactate production generated by cancer cells in the TME can lead to acidosis, which may promote stromal cell transitions, particularly the transformation of adipocytes into cancer-associated fibroblasts (CAFs). CAFs can secrete activin, which reduces the expression of CXCL9, CXCL10, and CXCL11 by various cells in the TME, leading to the loss of recruitment signals for $CD8^+$ T cells CAFs can also express Presenilin 1 (PS1), which enhances the secretion of IL-1β through the activation of β-catenin in ovarian cancer cells. IL-1β can decrease the proliferation capacity and effector function of $CD8^+$ T cell via the EPAS1/iNOS-NO pathway [38]. Interestingly, lactate along with increased potassium and hydrogen levels in the TME, can induce metabolic changes that restore stemness characteristics in T cells. This is particularly attributed to the effects of these three factors on the expression of TCF1 (T-cell factor 1). TCF1 has histone deacetylase (HDAC) activity, which can maintain T cell stemness by inhibiting genes involved in T cell differentiation. Modulating T cell stemness functionality may allow for a better anti-tumor response from the T cell population [39].

The expression of immune checkpoints, such as CTLA-4, PD-1, and TIM-3, on the surface of $CD8^+$ T cells is often exploited by cancer cells to suppress the cytotoxic activity of $CD8^+$ T cells through metabolic reprogramming. The PD-1/PD-L1 interaction can shift the metabolic pathway from glycolysis to fatty acid oxidation (FAO) through STAT3 activation. Both PD-1 and CTLA-4 can suppress glycolysis, ultimately reducing the anti-tumor capabilities of $CD8^+$ T cells [40].

3.4. Therapeutic Potential of $CD8^+$ Metabolic Reprogramming

The metabolic changes occurring in solid tumors, including ovarian cancer, are one of the factors that contribute to the limited effectiveness of immunotherapy in treating solid tumors. Additionally, the scarcity of nutrients in the TME leads to impaired effector function in $CD8^+$ T cells. Considering the metabolic reprogramming mechanisms in $CD8^+$ T cells and the interactions between the metabolic pathways of cancer cells and $CD8^+$ T cells within the TME, it suggests the potential for metabolic intervention as a therapeutic target in ovarian cancer.

A study about metabolic reprogramming of $CD8^+$ T cells was conducted by Markowitz et al. [41], shifting their dominant pathway from glycolysis to the pentose phosphate pathway by inhibiting the enzyme PKM2. PKM2-/- $CD8^+$ T cells, when introduced into cancer organoids, demonstrated improved infiltration ability and cytotoxic activity. These cells exhibited a $CD8^+$ T cell phenotype similar to progenitor cells, with peak characteristics, responsiveness to PD-1 inhibitor therapy, and the maintenance of a population of $CD8^+$ T cells with constant cytotoxic activity [41].

The development of immune checkpoint inhibitors (ICI) in cancer immunotherapy, which modulate the metabolism of $CD8^+$ T cells, has been widely explored to enhance the anti-tumor capabilities of $CD8^+$ T cells. PD-1 inhibitors can increase glycolysis in $CD8^+$ T cell, improve oxidative phosphorylation pathways, reduce the risk of apoptosis in $CD8^+$ T cells through upregulation of anti-apoptotic proteins like Bcl-2 and Cpt1, and enhance $CD8^+$ T cell infiltration in the TME by increasing the expression of CXCL9 and CXCL10 in tumor cells and CXCR3 expression in $CD8^+$ T cells [40].

4. Conclusion

Ovarian cancer cells adapt by altering their metabolic programming, utilizing glycolysis to generate energy even in normoxic conditions, a phenomenon known as the Warburg effect. These cancer cells not only compete with $CD8^+$ T cells for glucose in the tumor microenvironment (TME) but also induce dysfunction in $CD8^+$ T cells, diminishing the effectiveness of the immune response against the tumor. Understanding these complex interactions and the associated metabolic changes offers new insights for developing more effective cancer therapies, including immunotherapy strategies that address metabolic barriers within the TME.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have no conflict of interest to disclose.

References

[1] Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024; 74: 229–263.

[2] World Health Organization (WHO). Indonesia: fact-sheet Globocan 2022. International Agency for Research on Cancer (IARC) 2022; 1–2.

[3] Ali AT, Al-ani O, Al-ani F. Epidemiology and risk factors for ovarian cancer. Menopausal Review 2023; 22: 93–104.

[4] Murali R, Balasubramaniam V, Srinivas S, et al. Deregulated Metabolic Pathways in Ovarian Cancer: Cause and Consequence. Metabolites; 13. Epub ahead of print 2023. DOI: 10.3390/metabo13040560.

[5] Wang M, Zhang J, Wu Y. Tumor metabolism rewiring in epithelial ovarian cancer. Journal of Ovarian Research; 16. Epub ahead of print 2023. DOI: 10.1186/s13048-023-01196-0.

[6] Nelson DL, Cox MM. Lehninger Principles of Biochemistry. 2005.

[7] Andreucci E, Fioretto BS, Rosa I, et al. Extracellular Lactic Acidosis of the Tumor Microenvironment Drives Adipocyte-to-Myofibroblast Transition Fueling the Generation of Cancer-Associated Fibroblasts. Cells; 12. Epub ahead of print 2023. DOI: 10.3390/cells12060939.

[8] Chen H, Li Y, Li H, et al. NBS1 lactylation is required for efficient DNA repair and chemotherapy resistance. Nature 2024; 631: 663–669.

[9] Chraa D, Naim A, Olive D, et al. T lymphocyte subsets in cancer immunity: Friends or foes. Journal of Leukocyte Biology; 105. Epub ahead of print 2019. DOI: 10.1002/JLB.MR0318-097R.

[10] Hao J, Yu H, Zhang T, et al. Prognostic impact of tumor-infiltrating lymphocytes in high grade serous ovarian cancer: a systematic review and meta-analysis. Therapeutic Advances in Medical Oncology; 12. Epub ahead of print 2020. DOI: 10.1177/1758835920967241.

[11] Reina-Campos M, Scharping NE, Goldrath AW. CD8+ T cell metabolism in infection and cancer. Nat Rev Immunol 2021; 21: 718–738.

[12] Jorgovanovic D, Song M, Wang L, et al. Roles of IFN-γin tumor progression and regression: A review. Biomarker Research; 8. Epub ahead of print 2020. DOI: 10.1186/s40364-020-00228-x.

[13] Amitrano AM, Kim M. Metabolic Challenges in Anticancer CD8 T Cell Functions. Immune Network; 23. Epub ahead of print 2023. DOI: 10.4110/in.2023.23.e9.

[14] Shang W, Xu R, Xu T, et al. Ovarian Cancer Cells Promote Glycolysis Metabolism and TLR8-Mediated Metabolic Control of Human CD4+ T Cells. Front Oncol; 10. Epub ahead of print 2020. DOI: 10.3389/fonc.2020.570899.

[15] Maioru OV, Radoi VE, Coman MC, et al. Developments in Genetics: Better Management of Ovarian Cancer Patients. International Journal of Molecular Sciences; 24. Epub ahead of print 2023. DOI: 10.3390/ijms242115987.

[16] Rinne N, Christie EL, Ardasheva A, et al. Targeting the PI3K/AKT/mTOR pathway in epithelial ovarian cancer, therapeutic treatment options for platinum-resistant ovarian cancer. Cancer Drug Resistance; 4. Epub ahead of print 2021. DOI: 10.20517/cdr.2021.05.

[17] Lieberman M, Peet A. Marks' Basic Medical Biochemistry: A Clinical Approach. 6th ed. Philadelphia, USA: Wolters Kluwer, 2022.

[18] Siu MKY, Jiang Y xin, Wang J jing, et al. PDK1 promotes ovarian cancer metastasis by modulating tumor-mesothelial adhesion, invasion, and angiogenesis via α5β1 integrin and JNK/IL-8 signaling. Oncogenesis; 9. Epub ahead of print 2020. DOI: 10.1038/s41389-020-0209-0.

[19] Dou X, Campisi J, Sun Y. Abstract LB274: Senescent cells develop PDK4-dependent hypercatabolism and form an acidic microenvironment to drive cancer resistance. Cancer Res; 83. Epub ahead of print 2023. DOI: 10.1158/1538-7445.am2023-lb274.

[20] Gao T, Zhang X, Zhao J, et al. SIK2 promotes reprogramming of glucose metabolism through PI3K/AKT/HIF-1α pathway and Drp1-mediated mitochondrial fission in ovarian cancer. Cancer Lett 2020; 469: 89–101.

[21] Chen S, Wu Y, Gao Y, et al. Allosterically inhibited PFKL via prostaglandin E2 withholds glucose metabolism and ovarian cancer invasiveness. Cell Rep; 42. Epub ahead of print 2023. DOI: 10.1016/j.celrep.2023.113246.

[22] Caneba CA, Yang L, Baddour J, et al. Nitric oxide is a positive regulator of the Warburg effect in ovarian cancer cells. Cell Death Dis; 5. Epub ahead of print 2014. DOI: 10.1038/cddis.2014.264.

[23] Timón-Gómez A, Nývltová E, Abriata LA, et al. Mitochondrial cytochrome c oxidase biogenesis: Recent developments. Seminars in Cell and Developmental Biology; 76. Epub ahead of print 2018. DOI: 10.1016/j.semcdb.2017.08.055.

[24] Siu MKY, Jiang YX, Wang JJ, et al. Hexokinase 2 regulates ovarian cancer cell migration, invasion and stemness via FAK/ERK1/2/MMP9/NANOG/SOX9 signaling cascades. Cancers (Basel); 11. Epub ahead of print 2019. DOI: 10.3390/cancers11060813.

[25] Liu C, Barger CJ, Karpf AR. Foxm1: A multifunctional oncoprotein and emerging therapeutic target in ovarian cancer. Cancers (Basel); 13. Epub ahead of print 2021. DOI: 10.3390/cancers13123065.

[26] Wang ZH, Peng WB, Zhang P, et al. Lactate in the tumour microenvironment: From immune modulation to therapy. EBioMedicine; 73. Epub ahead of print 2021. DOI: 10.1016/j.ebiom.2021.103627.

[27] Chang CH, Qiu J, O'Sullivan D, et al. Metabolic Competition in the Tumor Microenvironment Is a Driver of Cancer Progression. Cell; 162. Epub ahead of print 2015. DOI: 10.1016/j.cell.2015.08.016.

[28] Makowski L, Chaib M, Rathmell JC. Immunometabolism: From basic mechanisms to translation. Immunological Reviews; 295. Epub ahead of print 2020. DOI: 10.1111/imr.12858.

[29] Ramalho R, Rao M, Zhang C, et al. Immunometabolism: new insights and lessons from antigen-directed cellular immune responses. Seminars in Immunopathology; 42. Epub ahead of print 2020. DOI: 10.1007/s00281-020-00798-w.

[30] Gupta SS, Wang J, Chen M. Metabolic Reprogramming in CD8+ T Cells During Acute Viral Infections. Front Immunol; 11. Epub ahead of print 22 May 2020. DOI: 10.3389/fimmu.2020.01013.

[31] Beckermann KE, Hongo R, Ye X, et al. CD28 costimulation drives tumor-infiltrating T cell glycolysis to promote inflammation. JCI Insight; 5. Epub ahead of print 2020. DOI: 10.1172/jci.insight.138729.

[32] Cao J, Liao S, Zeng F, et al. Effects of altered glycolysis levels on CD8+ T cell activation and function. Cell Death and Disease; 14. Epub ahead of print 2023. DOI: 10.1038/s41419-023-05937-3.

[33] Rackov G, Tavakoli Zaniani P, Colomo del Pino S, et al. Mitochondrial reactive oxygen is critical for IL-12/IL-18-induced IFN-γ production by CD4+ T cells and is regulated by Fas/FasL signaling. Cell Death Dis; 13. Epub ahead of print 2022. DOI: 10.1038/s41419-022-04907-5.

[34] Gemta LF, Siska PJ, Nelson ME, et al. Impaired enolase 1 glycolytic activity restrains effector functions of tumor-infiltrating CD8+ T cells. Sci Immunol; 4. Epub ahead of print 2019. DOI: 10.1126/sciimmunol.aap9520.

[35] Lin Y, Zhou X, Ni Y, et al. Metabolic reprogramming of the tumor immune microenvironment in ovarian cancer: A novel orientation for immunotherapy. Frontiers in Immunology; 13. Epub ahead of print 2022. DOI: 10.3389/fimmu.2022.1030831.

[36] Haas R, Smith J, Rocher-Ros V, et al. Lactate Regulates Metabolic and Pro-inflammatory Circuits in Control of T Cell Migration and Effector Functions. PLoS Biol 2015; 13: e1002202.

[37] Elia I, Rowe JH, Johnson S, et al. Tumor cells dictate anti-tumor immune responses by altering pyruvate utilization and succinate signaling in CD8+ T cells. Cell Metab; 34. Epub ahead of print 2022. DOI: 10.1016/j.cmet.2022.06.008.

[38] Zhang H, Jiang R, Zhou J, et al. CTL Attenuation Regulated by PS1 in Cancer-Associated Fibroblast. Front Immunol; 11. Epub ahead of print 2020. DOI: 10.3389/fimmu.2020.00999.

[39] Liu Y, Wang T, Ma W, et al. Metabolic reprogramming in the tumor microenvironment: unleashing T cell stemness for enhanced cancer immunotherapy. Front Pharmacol; 14. Epub ahead of print 19 December 2023. DOI: 10.3389/fphar.2023.1327717.

[40] Zhang L, Zhang W, Li Z, et al. Mitochondria dysfunction in CD8+ T cells as an important contributing factor for cancer development and a potential target for cancer treatment: a review. Journal of Experimental & Clinical Cancer Research 2022; 41: 227.

[41] Markowitz GJ, Ban Y, Tavarez DA, et al. Deficiency of metabolic regulator PKM2 activates the pentose phosphate pathway and generates TCF1+ progenitor CD8+ T cells to improve immunotherapy. Nat Immunol 2024; 25: 1884–1899.