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The impact of metabolic reprogramming on tertiary lymphoid structure formation: enhancing cancer immunotherapy

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Abstract

Background Cancer immunotherapy has achieved unprecedented success in the field of cancer therapy. However, its potential is constrained by a low therapeutic response rate.

Main body Tertiary lymphoid structure (TLS) plays a crucial role in antitumor immunity and is associated with a good prognosis. Metabolic reprogramming, as a hallmark of the tumor microenvironment, can influence tumor immunity and promote the formation of follicular helper T cells and germinal centers. However, many current studies focus on the correlation between metabolism and TLS formation factors, and there is insufficient direct evidence to suggest that metabolism drives TLS formation. This review provided a comprehensive summary of the relationship between metabolism and TLS formation, highlighting glucose metabolism, lipid metabolism, amino acid metabolism, and vitamin metabolism.

Conclusions In the future, an in-depth exploration of how metabolism affects cell interactions and the role of microorganisms in TLS will significantly advance our understanding of metabolism-enhanced antitumor immunity.

Keywords Tertiary lymphoid structure, Metabolic reprogramming, Cancer immunotherapy, T follicular helper cell, Germinal center B cell

Background

Tumor immunotherapy has experienced tremendous growth in recent years, due to the groundbreaking work of reshaping the tumor microenvironment [1]. This exciting development has opened new possibilities for treating cancer and offers hope to countless patients. Unfortunately, tumor immunotherapy is currently limited due to the heterogeneity of the individual tumor microenvironment (TME) and the low response rate with immunological agents in most solid tumors [2]. The poor response rate to tumor immunotherapy is attributed to the low immune cell infiltration in some tumors, which belong to the category of immune-excluded and immune-desert tumors, also known as "cold tumors" [3]. Therefore, the key to improving the response rate to immunotherapy is to turn cold tumors into hot tumors with a high degree of immune cell infiltration [4, 5]. Tertiary lymphoid structure (TLS) has been shown to correlate with good prognosis in many cancers [6, 7]. TLS is an ectopic lymphoid organ that develops in non-lymphoid tissue at the site of chronic inflammation [8]. Their structure is like that of lymphoid follicles in secondary lymphoid organs (SLO).

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Mature TLS is characterized by T-cell-rich areas containing dendritic cells (DCs) and B-cell-rich areas containing germinal centers (GCs) [9]. These areas include high endothelial venules (HEVs) and lymphatics that collect antigen and tissue immune cells and release cells. Follicular helper T (Tfh) cells are required and responsible for TLS formation, and can stimulate the differentiation of GC B cells. Research indicates that enhancing Tfh cell and GC activity via anti-PD-1 immunotherapy yields improved outcomes [10]. However, the underlying mechanisms and factors influencing the induction of TLS formation are not clear.

Metabolic reprogramming plays a potential role in inducing TLS formation. Metabolic reprogramming is a hallmark of cancer, involving cells altering metabolic pathways to meet the energy, material, and redox capacity needed for rapid proliferation [11]. Alterations in TME factors like nutrients, hypoxia, extracellular acidity, and secretion of inflammation marker can cause metabolic reprogramming of immune cells. This can lead to either proinflammatory or anti-inflammatory phenotypes, which are associated with a hot or cold TME [11, 12]. This finding has driven extensive researches aiming to convert cold tumors into hot tumors via metabolic pathways, ultimately enhancing the effectiveness of antitumor immunotherapy. Metabolic reprogramming can induce Tfh cell and GC formation, which is significantly associated with TLS. Specifically, glycolysis induces Tfh cell differentiation and promotes GC formation through mTOR and HIF-1α-associated signaling [13, 14]. Additionally, metabolic reprogramming plays an important regulatory role in cytokine release, HEV formation, and activation of inflammatory signaling pathways associated with TLS formation by altering lipid and amino acid metabolism. It is suggested that metabolic reprogramming may indirectly induce TLS formation, but there are few reviews on the correlation between metabolism and TLS. Therefore, providing an overview of the known and unknown correlations between TLS and metabolism is necessary.

This review summarized the metabolic reprogramming of glucose, lipids, amino acids, and vitamins, emphasizing the cells, molecules, and pathways directly involved in TLS induction and the potential connection between metabolic reprogramming and TLS formation (Fig. 1). Meanwhile, the potential relationship between metabolic reprogramming and TLS formation in inflammation and TME was elucidated. Moreover, this review provided an outlook on the mechanisms, strategies, and the role of microorganisms in metabolism-induced TLS formation, and innovatively proposed the hypothesis of inducing TLS formation in TME by regulating metabolic reprogramming. This review will provide a theoretical basis for the future development of novel approaches to induce TLS formation through metabolic modulation, improve TME, and enhance antitumor immunity, and ultimately improve the prognosis of cancer patients.

TLS enhances tumor immunity

The formation mechanism and role of TLS

In recent years, the mechanisms that induce the formation of TLS have become a popular topic. Understanding these mechanisms not only helps to reveal the process of tumor immune response but also provides important clues for the development of new tumor therapeutic strategies.

TLS is induced to form and function as antitumor immunity in TME based on its main constituent structures, including DCs, B cells, Tfh cells, lymphoid tissue inducer (LTi) cells, HEV cells, chemokines, and the STING pathway. The recruitment of immune cells is the basis for the formation of TLS. By expressing lymphotoxins, LTi cells in the TLS region promote lymphoid tissue organizer (LTo) cells to produce cytokines (CXCL12, CXCL13, CCL19, CCL21, etc.), adhesion molecules, and integrins. These molecules are essential for attracting B cells and T cells to the TLS region [15]. In TLS, DCs, M1-polarized macrophages, B cells, $CD8^+$ T cells, and T helper 17 (Th17) cells can initiate TLS occurrence in a similar manner to LTi cells [15, 16]. Vascular endothelial cells, DCs, cancer-associated fibroblasts, and macrophages can act in place of LTo cells. It was found that Tfh cells, $CXCR5^+$ $PD\text{-}1^+$ $CD8^+$ T cells, and $CD20^+$ $CXCR5^+$ B cells in the blood can converge into the tumor TLS under the influence of TLS secretion [17–19]. Tfh cells induce humoral response, GC formation, and immune memory [10, 20], playing a crucial role in TLS formation. $CD8^+$ T cells and $CD4^+$ T cells are activated by DCs through antigen presentation. $CD8^+$ cytotoxic effector T cells and B cells produced in TLS form synergistic interactions that can result in direct killing, antibody-dependent cytotoxicity mediated through macrophages and/or natural killer cells, and localized complement activation to achieve antitumor immunity. Furthermore, the production of memory T and B cells can prevent tumor metastasis [20].

Cytokines that are closely associated with the induction of TLS formation include interleukins (ILs), tumor necrosis factor (TNF) superfamily, chemokines, transforming growth factor-β (TGF-β), interferons (IFNs), colony-stimulating factors, and vascular endothelial growth factors (VEGFs) [21]. These cytokines are released by a wide range of cells and play a crucial role in the recruitment and transportation of immune cells, making them essential for the formation and maintenance of TLS [21].

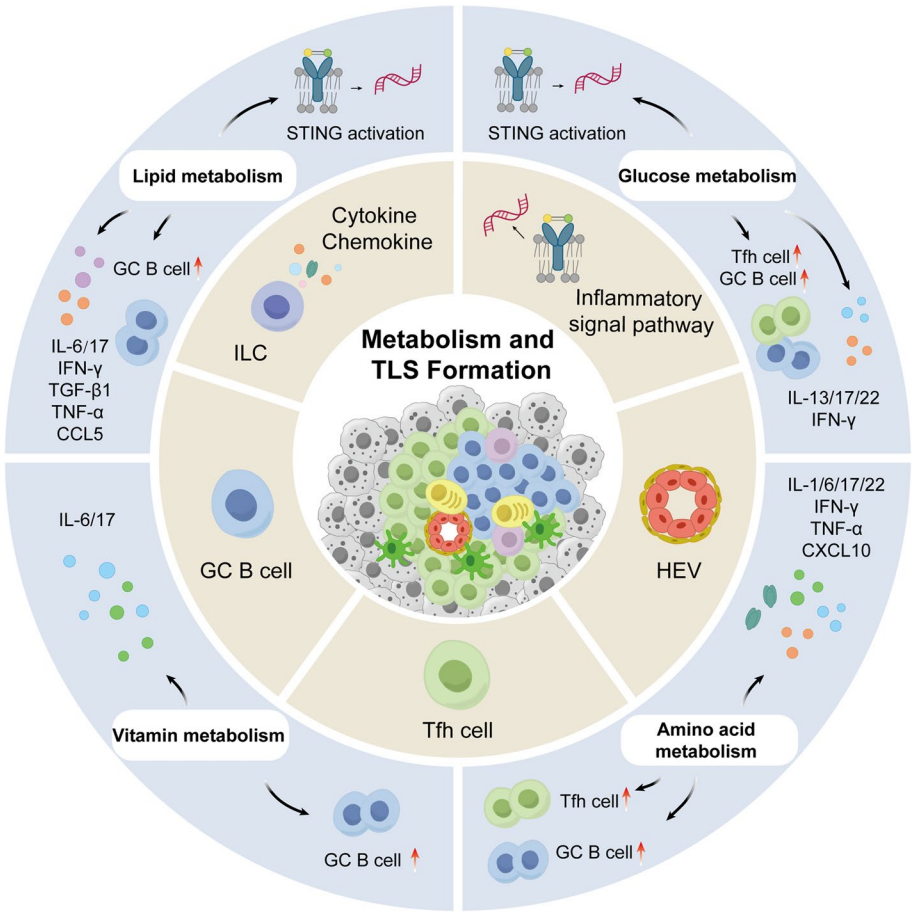

Fig. 1 A schematic of factors and potential strategies for inducing tertiary lymphoid structure (TLS) through metabolism. Follicular helper T (Tfh) cell, germinal center (GC) B cell, innate lymphoid cell (ILC) and cytokine, high endothelial venule (HEV), and inflammatory signaling pathway may play a role in TLS formation. Alterations in glucose metabolism, lipid metabolism, amino acid metabolism, and vitamin metabolism may indirectly induce TLS formation in tumors by promoting the release, infiltration, or activation of these components

The HEV is central to TLS formation, creating a pipeline that allows lymphocytes to enter the TLS. It is composed of endothelial cells and fibroblast reticulocytes [22]. Immune cells (such as $CD8^+$ T cells and DCs), and some signaling pathways (such as LT/LTβR signaling pathway and TNFR1 signaling pathway) play a role in the formation of HEVs in TME [23]. STING serves as the primary mediator in activating the type I IFN (IFN-I) pathway [24, 25]. The binding of cGAS to cytosolic DNA produces cGAMP, which then binds to STING, triggering it to facilitate the phosphorylation of IRF3 via TBK1. Once phosphorylated, IRF3 translocates to the nucleus to initiate the transcription of inflammatory genes. This entire sequence is known as the STING pathway. Activation of the intra-tumoral STING pathway induces TLS formation by upregulating the expression of TLS-promoting factors. These factors include LTα, IL-36, IFN-I, inflammatory chemokines, the LTβR agonists, and Tnfsf14/Light through the activation of mDCs [24]. Furthermore, the expression of STING facilitates the infiltration of lymphocytes and $CD8^+$ T cells [26], and upregulates the expression of TNF-α and IL-6 [27, 28], which in turn produces IFN-γ [29], creating conditions for TLS formation.

TLS promotes antitumor immunity

TLS plays a key role in antitumor immunity, and its structure and function are of great significance for regulating immune cell activity, promoting immune cell infiltration, and forming immune memory. This section introduces the composition of TLS and its role in antitumor immunity.

In tumor immunity, TLS serves as the primary site for interaction between immune cells, and its regulation is crucial in effectively combating tumor cells by helping to regulate the activity of T cells and B cells [30]. Moreover, TLS is the main site of antigen processing and presentation, which can effectively activate immune cells and

form long-term immune memory. TLS also helps regulate the infiltration of immune cells in tumor tissues and promote antitumor immune responses. It activates and spreads immune cells by using its structural characteristics, thereby enhancing immune responses to tumor cells [16]. Furthermore, the presence of tumor-infiltrating lymphocyte aggregates, particularly $CD8^+$ and $CD4^+$ T cells and $CD20^+$ B cells, has been linked to a positive prognosis in cancer patients [31, 32]. TLS has been identified as an independent prognostic factor, regardless of tumor stage or other survival factors [20]. It is suggested that TLS could serve as an effective predictor of tumor prognosis.

Metabolic reprogramming and TLS

Metabolic reprogramming occurs in tumor tissues, and its metabolites and signaling molecules have a significant impact on regulating TLS formation. The regulatory role of the immune system is closely related to the metabolism of immune cells [33]. Metabolism can provide energy for immune cells and promote or inhibit the immune escape of tumor cells. The metabolic characteristics of tumor cells can also affect the metabolism of immune cells [34]. Metabolic reprogramming influences tumor progression by modulating the immune response, which may become a promising target for cancer treatment. Current researches have demonstrated that alterations in metabolism can directly or indirectly impact the development of immune cells, cytokines, as well as HEVs (Table 1). Therefore, this section focuses on investigating the generation of B cells and T cells, chemokines and cytokines, LTi cells, and STING pathway through the lens of glucose metabolism, lipid metabolism, amino acid metabolism, and vitamin metabolism (Fig. 2). A comprehensive review is provided to explore the correlation between metabolic reprogramming and TLS formation.

Glucose metabolism

Glucose metabolism in TME

The TME is frequently characterized by inflammation, hypoxia, and glucose deficiency. Although the relationship between glucose metabolism and tumor TLS formation is not directly proven, most studies have demonstrated that glucose metabolism activates the formation of B cells in GCs with key cells such as Tfh cells, which potentially induce TLS formation [35]. Hepatocellular carcinoma (HCC) exhibits aberrant glycolysis and a higher infiltration rate of immune cells such as $CD4^+$ naïve T cells, $CD4^+$ memory T cells, Tfh cells, M0 macrophages, resting and activated myeloid DCs, and activated mast cells [36]. The lack of infiltration of GC B cells among them may be determined by their metabolic characteristics. The life cycle of B cells begins with naïve B cells, which first differentiate into GC B cells and then into plasma cells [35]. The metabolism of different B cell subtypes is completely different [37]. For example, GC B cells primarily use fatty acid oxidation (FAO), with minimal glycolysis [35]. Early GC B cells are mainly dependent on endogenous fatty acid (FA) while later in the GC reaction, GC B cells are mostly dependent on exogenous FA [37]. After differentiation into plasma cells, the metabolism changes to high glucose consumption to aid in antibody production [37]. Glucose deficiency and slowed glucose metabolism in B cells in TME lead to a significant reduction in the number of IgG-producing B cells and diminished antitumor effects [38]. Therefore, restoring glucose supply to B cells may enhance the antitumor effect by promoting the differentiation and aggregation of IgG-producing B cells to form TLS. Children with pre-B cell acute lymphoblastic leukemia have elevated levels of 1,5-anhydroglucitol (1,5-AG), a compound structurally similar to glucose. The research suggests that 1,5-AG increases cellular ROS levels by enhancing glycolysis and oxidative stress, and promotes $CD19^+$ B cell proliferation [39]. These studies suggest that glucose metabolism can regulate the number and differentiation of different subtypes of B cells, thus providing the possibility to induce TLS formation.

Exosomal enolase 2 (ENO2) released by diffuse large B-cell lymphoma cells accelerates glycolysis through the GSK3β/β-catenin/c-Myc signaling pathway, and finally promotes macrophages to M2-like phenotype [40]. Bioinformatics analysis shows that the high expression of ENO2 is positively correlated with the M2/M1 ratio of macrophages [40]. Therefore, it is possible to induce macrophage M1 polarization by regulating the expression of ENO2 in the future, which provides a potential strategy for the formation of TLS. Since STING-mediated DC activation can induce TLS formation [41], enhanced glycolysis of STING-signaling pathway-mediated DC activation [42] may play a role in TLS formation.

Glucose metabolism in inflammation

Studies on inflammatory diseases have shown that regulation of glycolysis affects the number and response of Tfh cells. Specifically, inhibiting glycolysis reduces the number of Tfh cells [43], while a high level of glycolysis promotes Tfh cell responses [44]. This indicates that abnormal glycolysis in TME may enable the formation of Tfh cells aggregate at certain sites, creating conditions for TLS formation. Activation of mTOR and HIF-1α signaling can lead to increased glycolysis, which is critically required for MST1 deficiency-directed Tfh cell differentiation [45]. Furthermore, a partial defect in glycolysis results from deficiency of the mitogen-activated protein kinase phosphatase DUSP6. Studies have shown that deficiency

Table 1 Main way and potential impact of metabolism on promoting TLS formation

Metabolism	Factor affected	Impact on TLS formation	Diseases	Ref
Glucose metabolism	**T cell**	Abnormal glycolysis/gluconeogenesis increases Tfh cell infiltration	HCC	[36]
	B cell	Enhanced glycolysis promotes proliferation of $CD19^+$ B cell	Pre-B ALL	[39]
	Macrophage	ENO2 accelerates glycolysis to induce M2 polarization of macrophage	DLBCL	[40]
	STING	Glycolysis activates STING signaling in DC	NSCLC	[42]
Lipid metabolism	**T cell**	Lipid metabolism in TME regulates $CD8^+$ T cell activation	-	[57]
		LPC activates T cell	HBV-related HCC	[58]
		Abnormal lipid metabolism activates Th17 cell differentiation	Leukemia	[61]
		Malignant Tfh cell differentiation is dependent on choline lipid metabolism	AITL	[150]
	B cell	Changes in lipid metabolism genes resulting from epithelial-adipose tissue interactions affect the number of local $CD20^+$ B cell	Breast cancer susceptible tissues	[112]
	Cytokines	Altered lipid metabolism reduces IFN-γ secretion	HBV-related HCC	[58]
		GM-CSF regulates lipid metabolism	LUAD	[59]
	Macrophage	TME regulates lipid metabolism to polarize macrophage from M1 to M2	-	[60]
	STING	PUFA peroxidation activates cGAS-STING	HCC	[64]
	HEV	SOAT1 regulates lipid synthesis to promote the expression of VEGF-C	Gastric cancer	[62]
Amino acid metabolism	**T cell**	The renal GLS inhibitor 968 increase the infiltration of $CD3^+$ T cell	Ovarian cancer	[79]
		Increased activity of genes involved in glutamine metabolism in $CD34^+$ pre-B cell	AML	[80]
		Inhibition of glutamine metabolism promotes $CD8^+$ T cell proliferation	HCC	[105]
	B cell	Upregulation of a functional serine synthesis pathway is a metabolic hallmark of B cell activation and the germinal center reaction	Lymphoma	[81]
		Vitamin E metabolism and vitamin A metabolism alter in GC B cell	DLBCL	[92]
		Glutamine metabolism in the tumor cell is significantly associated with $CD20^+$ B cell	Lymphoma	[159]
	Cytokines	Tryptophan metabolites inhibit IFN-I secretion	BLCA	[82]
		IFN-γ leads to tryptophan depletion and kynurenine accumulation	Cervical cancer	[83]
		Low serum histidine and glutamine levels and high serum phenylalanine levels correlate with high serum IL-6 and IL-8 levels	Colorectal cancer	[84]
		Glutamine metabolism in the tumor cell promotes IL-23 secretion	ccRCC	[160]
		GLS inhibitor 968 promotes the secretion of chemokines CXCL10 and CXCL11 in the tumor cell	Ovarian cancer	[79]
		Arginine metabolism in the tumor cell induces macrophage M1 polarization and secretion of IL-1β and TNF-α	Neuroblastoma	[165]
		Active one-carbon metabolism inhibits CXCL10 production in the tumor cell	HCC	[166]
	Macrophage	Tryptophan metabolism is positively correlated with M1 macrophage scores	BRCA	[85]
		$1,25(OH)_2D_3$ promotes cell polarization to M2 and inhibits polarization to M1	-	[100]

Table 1 (continued)

Metabolism	Factor affected	Impact on TLS formation	Diseases	Ref
Vitamin metabolism	**B cell**	Vitamin A metabolism and vitamin E metabolism alter in GC B cell	Large B-cell lymphoma	[92]
	T cell	T cell differentiation is regulated by vitamin A metabolism	Leukemia	[89]
		Vitamin B6 metabolism is required for $CD8^+$ T cell proliferation and effector differentiation	Melanoma	[90]
	Cytokines	Vitamin D3 regulates cytokine production	BRCA	[94]
	Macrophage	Vitamin D3 regulates macrophage polarization	BRCA	[94]

Abbreviations: STING Stimulator of interferon genes, *HEV* High endothelial venule, *TME* Tumor microenvironment, *HCC* Hepatocellular carcinoma, *ALL* Acute lymphoblastic leukaemia, *DLBCL* Diffuse large B-cell lymphoma, *NSCLC* Non-small cell lung cancer, *LPC* Lysophosphatidylcholine, *AITL* Angioimmunoblastic T-cell lymphoma, *LUAD* Lung adenocarcinoma, *AML* Acute myeloid leukemia, *BLCA* Bladder cancer, *BRCA* Breast cancer, *ccRCC* Clear-cell renal cell carcinoma, *GLS* Glutaminase

in DUSP6 promotes the induction of Tfh cells and GC response [46]. Compared with Tfh cells, GC B cells have higher Glut1 expression and exhibit higher glycolytic activity, especially GC B cells with high branched-chain fatty acid expression [35]. B cells poised to undergo a GC response require lactate dehydrogenase A, a key enzyme in glycolysis [47]. These findings suggest that glycolysis is most likely required for the formation and production of GC reactions in GC B cells. However, some studies have found that in autosomal recessive hyper-IgE syndrome,

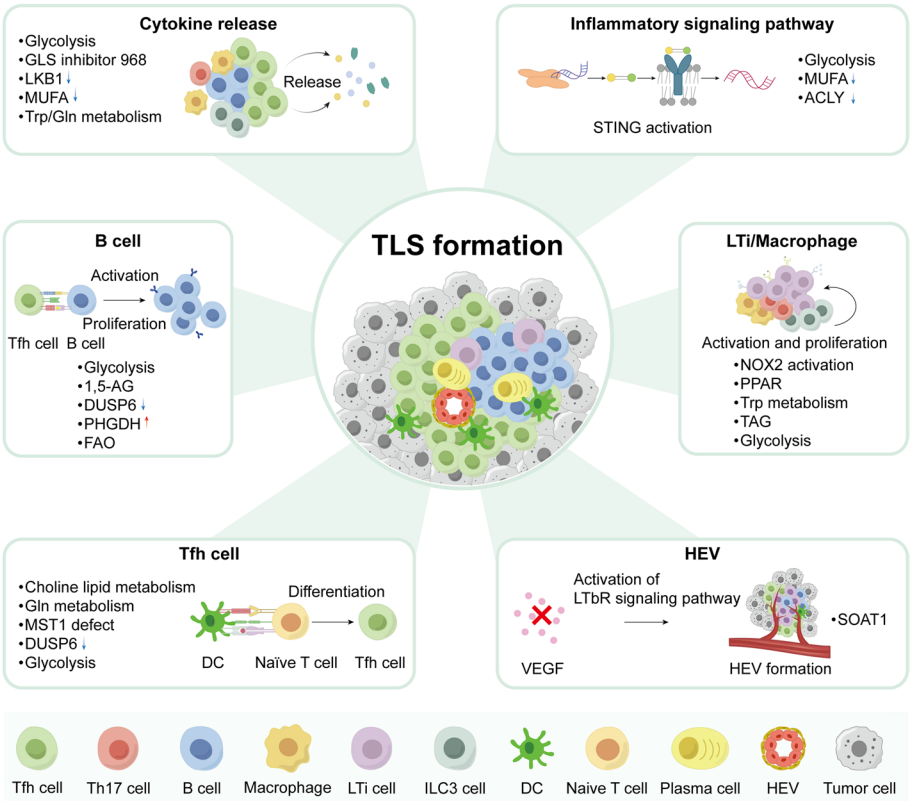

Fig. 2 Potential pathways to induce TLS through metabolic alterations. Abnormal expression of metabolism-related genes caused by metabolic disorders, and alterations in the levels of metabolites and enzymes favor the release of cytokine, the activation of the inflammatory signaling pathway, the activation and proliferation of lymphoid tissue inducer (LTi)/macrophage, the formation of HEV, and the differentiation and proliferation of Tfh cell and GC B cell. These metabolic changes may contribute to the formation of TLS via cytokine, inflammatory pathway, LTi/macrophage, HEV, Tfh cell, and GC B cell. Tfh, follicular helper T; Th17, T helper 17; LTi, lymphoid tissue inducer; ILC3, group 3 innate lymphoid cell; DC, dendritic cell; HEV, high endothelial venule

DOCK8 mutation may inhibit GC B cell formation and immune response by increasing glycolysis [48].

The role of glucose metabolism in inducing cytokines for TLS formation has received significant attention in glycolysis. Glycolysis plays a regulatory role in inducing cytokine production [49]. Dependent on glycolysis, IFN-γ^+ γδ T cells produce IFN-γ [50]. IFN-γ activates group 3 innate lymphoid cells (ILC3s) to secrete IL-22 and IL-17 [51] and activates group 2 innate lymphoid cells to proliferate and produce IL-13 [52]. This suggests that glycolysis plays an important role in the process of cytokine secretion. Glucose supplementation induces glycolysis in cells, which could be an effective pathway to produce cytokines and induce TLS formation. In a mutant cell context, serine/threonine kinase liver-associated kinase B1 deficiency restores IL-17 secretion from mitochondrial membrane-damaged Th17 cells by affecting the tricarboxylic acid cycle [53]. These findings create a potential promotion that induces cytokine secretion and efficiently induces TLS formation through regulating TME glucose metabolism. During early inflammation, both the cytokine and the NOX2 induction promote macrophage M1 polarization by enhancing glycolysis [54]. Increased M1 infiltration is associated with TLS formation. NOX2, a key enzyme involved in glycolysis, may be a potential target for inducing TLS formation by affecting immune cell aggregation.

Lipid metabolism

Lipid metabolism in TME

TME-driven hypoxia, acidosis, and nutritional alterations lead to increased lipid uptake, synthesis, FAO, and storage. This reprogramming of lipid metabolism affects immune cells in TME, especially macrophages and neutrophils, leading to their dysfunction [55]. The survival of GC B cells has been shown to be FAO-dependent [56], so this environment seems to be conducive to GC B cell proliferation. It is important to understand the mechanisms regulating the induction of TLS formation by GC B cells through more detailed studies. Lipid metabolism has different effects on the immune function of $CD8^+$ T cells in TME through different pathways. In the future, the development of antitumor therapy can restore or enhance the immune function of $CD8^+$ T cells by targeting lipid metabolism reprogramming [57, 58]. In tumors, granulocyte–macrophage colony-stimulating factor (GM-CSF) stimulates the proliferation of tumor-associated alveolar macrophages [59]. Due to the high plasticity of tumor-associated macrophages, the hypoxia and hypoglycemia environment of TME switches from the M1 antitumor phenotype to the M2 pro-tumor phenotype by regulating lipid metabolism [60]. Leukemia patients with abnormal lipid metabolism and increased plasma triglycerides exhibit stimulation of Th17 cell differentiation [61]. Therefore, lipid metabolism increases the infiltration of GC B cells, $CD8^+$ T cells, M1 macrophages, and Th17 cells, which play an important role in TLS formation.

Sterol O-acyltransferase 1 (SOAT1) is a rate-limiting enzyme in gastric cancer that regulates the expression of cholesterol metabolism genes, which could increase VEGF-C expression [62]. Given that antiangiogenic therapies, such as VEGF/VEGFR2 inhibitors, can promote HEV formation by activating the LTbR signaling pathway [63], this may provide a potential pathway for HEV formation in TME. Lipid metabolism affects IFN-γ secretion by T cells [58]. Adenosine 5'-triphosphate citrate lyase (ACLY) is a cytoplasmic enzyme used in the biosynthesis of FA and cholesterol. ACLY inhibition leads to peroxidation of polyunsaturated FA and mitochondrial damage, which trigger the leakage of mitochondrial DNA to activate the cGAS-STING innate immunity pathway [64]. The above finding proposes a novel approach to activate the STING pathway via lipid metabolic pathways, which induces TLS formation in TME.

Lipid metabolism in inflammation

Studies have shown that airway epithelial cells of patients with chronic obstructive pulmonary disease significantly express CH25H and CYP7B1, which activate oxysterol metabolism, lead to 7α,25-OHC secretion, and promote B cell migration to the bronchus and the formation of broncho-associated lymphoid tissue [65]. In addition, in studies of chronic kidney disease, high-fat diet was found to increase the level of cholesteryl ester (CE) in the kidney by activating SOAT1, which promoted the production of renal TLS [66]. This indicates that lipid metabolism is closely related to the formation of TLS.

The generation of memory $CD8^+$ T cells requires metabolic reprogramming, characterized by enhanced intracellular mitochondrial FAO [67]. Lipid metabolism regulates cytokine secretion through metabolites in metabolic cycles, enzymes, or stimulation by other cellular secretions [68]. IL-17^+ γδ T cells and mucosal-associated invariant T cells (MAITs) exhibit high lipid uptake and storage [50, 69]. In cholesterol metabolism, cholesterol metabolites and metabolizing enzymes influence the release of inflammation-associated cytokines, such as TNF-α and IL-17 [70, 71]. In turn, cytokines have been shown to affect cholesterol and lipid metabolism [70–72]. Activation of PPAR and NOX2 pathways can polarize toward M1 macrophages by affecting lipid metabolism [73–75]. There is an interaction between the cGAS-STING pathway and lipid metabolism [76]. After influenza virus infection, lipid metabolism is altered, and

monounsaturated fatty acids in $CD4^+$ T cells are reduced. This activates the cGAS-STING pathway to produce IFN-I-induced antiviral responses [77].

Amino acid metabolism

Amino acid metabolism in TME

Reprogramming of glutamine metabolism is considered a vital aspect of metabolic reprogramming in tumors [78]. It also affects the expression of immune checkpoint proteins in tumor cells. The renal glutaminase (GLS) inhibitor 968 was shown to increase the infiltration of $CD3^+$ T cells into the tumor and improve therapeutic efficacy against ovarian cancer [79]. The increased activity of glutamine metabolism-related genes in $CD34^+$ pre-B cells in acute myeloid leukemia (AML) will regulate the immune response. This regulatory effect may produce different effects under different immune microenvironments through a variety of mechanisms and pathways. In the future, it is expected to form TLS by directional induction of GC B cell formation [80].

Additionally, upregulation of serine synthesis is a metabolic hallmark of the GC response [81]. Phosphoglycerate dehydrogenase (PHGDH) is the first rate-limiting enzyme in the serine synthesis pathway [81]. Overexpressing PHGDH to promote the GC response in TME has emerged as a possible strategy to induce TLS formation [81].

Tryptophan metabolism inhibits STING pathway-induced IFN-I expression through aryl hydrocarbon receptor activation [82]. IFN-γ drives tryptophan breakdown, altering endothelial glucose metabolism, leading to enhanced FAO. This disrupts tryptophan catabolism, and promoting kynurenine accumulation and depletion of citrulline and tryptophan [83]. Low serum histidine and glutamine levels and high serum phenylalanine levels are associated with high serum levels of IL-6 and IL-8 in colorectal cancer [84]. Tryptophan metabolism promotes macrophage M1 polarization in breast cancer [85]. This provides a possible strategy for increasing M1 macrophage-induced TLS by modulating amino acid metabolism.

Briefly, there is a complex interaction between the metabolic activities of different amino acids and the secretion of cytokines. It is possible to produce a variety of cytokines to enhance the induction effect of TLS by regulating the quantity of amino acid metabolites, the gene expression activity of key enzymes, and the metabolic features of the cellular microenvironment.

Amino acid metabolism in inflammation

Glutamine metabolism is required for Tfh cells to perform optimally and interact with GC B cells [43]. In oral lichen planus, epithelial cells promote CCL5 production by upregulating glutamine uptake mediated by glutamine transporter alanine-serine-cysteine transporter 2 [86]. IL-6 and IL-21 in the bone marrow of Waldenstrom's macroglobulinemia patients can regulate glutathione metabolism via increasing the expression of amino acid transporter genes that mediate glutathione metabolism [87]. TSC2-deficient lymphangioleiomyomatosis patient-derived cells reveal high levels of IL-6 and IL-6 regulates serine metabolism [88].

Vitamin metabolism

Vitamin metabolism in TME

T cell differentiation and activity are regulated by the metabolism and signaling of vitamin A [89], vitamin B6 [90], and vitamin B5 [91]. In diffuse large B-cell lymphoma, the metabolism of vitamin A and vitamin E in GC B cells is altered [92]. Vitamin D can regulate innate and adaptive immune cells to exert anti-cancer effects [93]. Vitamin D3 regulates macrophage polarization and cytokine production, thereby affecting its role in tumors [94].

Vitamin metabolism in inflammation

Vitamin A and vitamin D-induced activation of nuclear hormone receptors has an effect on B cell differentiation [95], which provides potential strategies for the directional differentiation of B cells to generate TLS. There is a significant positive correlation between IL-17A and IL-23 serum levels and vitamin D3 serum levels in osteoarthritis patients [96]. Vitamin D is required for the early production of IL-22 by ILC3s [97]. Studies have shown that $1,25(OH)_2D_3$, the active form of vitamin D, effectively stimulates the expression of IL-33 in a time-dependent manner [98]. Vitamin B metabolites can be recognized by MAITs in the oral cavity to produce IL-17 [99]. Treatment with $1,25(OH)_2D_3$ increases the expression of T cell immunoglobulin mucin-3 (Tim-3) in macrophages, polarizes the cells to M2, and inhibits polarization to M1. Therefore, silencing the *HAVCR2* gene (encoding Tim-3) induces M1 polarization of macrophages, providing a method for TLS formation [100].

Multiple metabolisms

Multiple metabolisms in TME

The above sections describe the relationship between specific metabolism and the production of cells or molecules. However, the metabolic processes of different nutrients are not independent, but interact with each other. Moreover, the metabolism of various nutrients is collectively regulated by cells or molecules.

Metabolic changes of lipids and amino acids in TME can drive the polarization of γδ T cells into an IL-17-producing subset [101]. Metabolic dysfunction of

the kynurenine pathway, citric acid cycle, and mitochondrial respiratory chain has been demonstrated to result in mitochondrial dysfunction and ROS overproduction, activating $CD3^+$ T cell-dependent chronic inflammatory response [102]. Regulation of VDR Taq and MAO-A polymorphisms may increase $CD3^+$ T cell infiltration, which may serve as a potential factor affecting TME and TLS.

There is a complex metabolic crosstalk between tumor cells and immune cells, which affects each other's function and phenotype [103]. Tumor cells compete for glucose and oxygen in order to produce energy through aerobic glycolysis. This leads to the accumulation of lactate in TME, which supports tumor growth and metastasis and inhibits T cell function [103, 104]. In addition, the distribution of glutamine was imbalanced between HCC cells and $CD8^+$ T cells, and the expression of glutamine metabolism genes was significantly higher in tumor cells than that in $CD8^+$ T cells [105]. JHU083, an inhibitor of glutamine metabolism, was found to promote the proliferation of $CD8^+$ T cells [105, 106]. Inducing TLS formation by breaking the distribution imbalance of important nutrients between tumor cells and immune cells to enhance immune cell infiltration and function in TME seems to be a potential strategy in the future. Inhibitory cytokines in TME act on immune cells and inhibit their antitumor ability by regulating immune cell metabolism [107]. The secretion of some inhibitory metabolites, such as lactate [108, 109], succinic acid [110], and ammonium [111], will lead to the formation of an immunosuppressive environment, affecting the function of immune cells and promoting tumor invasion. The mammary epithelial cells that are susceptible to breast cancer show a significant up-regulation of genes involved in FA uptake/transport of CD36 and AQP7, lipolysis of lipase E, and lipid peroxidation of AKR1C1 [112]. Additionally, there is a decrease in $CD20^+$ B cells compared to healthy mammary tissue. The findings indicate that metabolites released from the interaction between epithelial and adipose tissues in the mammary microenvironment affect the number of local $CD20^+$ B cells [112]. It can be concluded that immunosuppressive TME is formed through complex metabolic crosstalk between tumor cells and immune cells. This could explain the abnormal function of immune cells in TME, and therefore understanding these mechanisms is crucial for the development of new therapeutic strategies.

Multiple metabolisms in inflammation

Previous studies have found metabolic changes in lymphocyte cytosolic protein 1 (LCP1) ^{high} monocytes/macrophages were manifested as FA enrichment and enhanced glycolytic metabolism. Moreover, $LCP1^{high}$ cells showed enhanced chemotaxis and migration ability. In the future, elucidating the exact molecular mechanism of the interaction between LCP1 in metabolic regulation and immune cell function may promote the generation of immune cells [113]. Studies on polycystic ovary syndrome have suggested a relationship among IL-22 and the metabolism of amino acid, glucose, and lipid [114]. The disruption of glycolysis, amino acid, and FA metabolism seen in gingivitis will lead to the destruction of the Th17/regulatory T cell balance, which is manifested as an increase in TGF-β and IL-17 concentrations [115]. Abnormal T cell metabolism in patients with systemic lupus erythematosus includes increased glycolysis, active synthesis of fatty acid synthesis and cholesterol, and increased degradation of glutamine. These metabolic changes contribute to the differentiation and function of Th17 cells [116, 117], suggesting that targeting glycolysis or FA metabolism may promote Th17 cell infiltration and TLS formation.

Microbiota-derived metabolites

Microbes colonize tumors and affect tumor progression [118]. Intratumoral microbiota affects T-cell-dominated immune cell aggregation and function in TME by producing metabolites, which has been observed in colon cancer [119], colorectal cancer [120, 121], and melanoma [122, 123]. Microbial metabolites affect the homeostasis of M1/M2 macrophages [124–127]. *Fusobacterium nucleatum* produces short-chain fat acids that bind to GPR43 to increase Th17 cell infiltration in the colon [128]. Antibiotic-induced gut flora increases serum secretion of IFN-γ, IL-13, and IL-17 by altering lipid and amino acid metabolism and promotes the inflammatory response [129]. Tryptophan metabolism in the gut microbiota activates T cells to produce IL-17 [130]. Intestinal dysbiosis during inflammatory arthritis causes altered tryptophan catabolism and elevated serum levels of IL-6 and IL-1β [131]. Microorganisms in vivo affect arginine and histidine metabolism, and changes in metabolism affect the expression of TNF-α and IFN-γ [132]. The findings demonstrate an association between the microbiota, metabolite levels, and changes in response to stimulation.

Tumor cell metabolism in TME

Glucose metabolism

Tumor cells undergo a metabolic reprogramming known as aerobic glycolysis, which includes an increase in glucose uptake and consumption, and the conversion of glucose to lactate in the presence of oxygen [133]. This change can alter the way cells metabolize carbohydrates and reduce oxygen consumption in the face of nutrient deprivation, thereby facilitating the adaptation of tumor

cells to unfavorable environment and promoting cancer progression [133]. Studies have shown that glycolysis is positively correlated with metastasis, drug resistance, and malignancy of tumors [134]. The pentose phosphate pathway (PPP) is another important pathway in glucose metabolism. The highly activated PPP in cancer cells reduces damage to cancer cells and is essential for the survival and growth of cancer cells [34, 135].

Tumor cells achieve high glucose uptake and increased aerobic glycolysis through a variety of pathways, which promote tumor cell invasion and migration [136–140]. During this process, integrin αvβ3 appears to be activated as an important mediator acting on a downstream signaling axis to induce enhanced aerobic glycolysis, as found in both glioblastoma [141] and triple-negative breast cancer [142] cells. Hexosamine biosynthesis pathway (HBP) is a branch of glycolysis, and the activation of its key enzymes, such as glutamine-fructose-6-phosphate transaminase 2 and glucosamine 6-phosphate N-acetyltransferase, can promote tumor cell proliferation and migration by activating HBP [143–145]. However, it has also been shown that increased HBP flux can lead to decreased cell movement and migration of melanoma cells [146]. This may be due to the different effects of HBP flux on different tumor cell species. Overall, this suggests that HBP activation may serve as a cancer biomarker, suggesting that HBP activation is associated with cancer progression [147]. It could be a feasible strategy to inhibit tumor progression by developing drugs targeting HBP in the future.

Lipid metabolism

Lipid reprogramming is observed in tumors to enhance the biological behavior of tumor cells. Tumor cells utilize lipid metabolism for energy, proliferation, biofilm production, signaling molecule generation, and homeostasis across various biological processes [148, 149]. In angioimmunoblastic T cell lymphoma, malignant Tfh cell differentiation is dependent on choline lipid metabolism [150]. PPAR is a member of the nuclear receptor superfamily, which regulates metabolic homeostasis and multiorgan function. GM-CSF was shown to support tumor growth by acting on the GM-CSF-PPARγ signaling pathway in tumor cells [59]. Carnitine palmitoyltransferase 2 (CPT2) induces FAO in tumor cells and inhibits tumor proliferation, invasion, and migration by inhibiting ROS/PPARγ/NF-κB pathway. In vitro and in vivo studies have demonstrated that the high expression of CPT2 in clear-cell renal cell carcinoma (ccRCC) is associated with higher sorafenib sensitivity, which is a potential therapeutic target for increasing sorafenib sensitivity in ccRCC [151]. Increased FA metabolism due to aberrant expression of molecules within tumor cells can promote tumor cell proliferation, migration, and invasion. This has been reported in esophageal squamous cell carcinoma [152, 153], ccRCC [154], colon cancer [155] and HCC [156]. Increased de novo lipogenesis in tumor cells can also promote tumors. Diminishing acetyl-CoA carboxylase 1, a rate-limiting enzyme of de novo lipogenesis, in cholangiocarcinoma will reduce de novo lipogenesis through the AMPK-NF-κB-snail axis, ultimately reducing cell growth and cell migration [157].

Amino acid metabolism

Glutamine metabolism has various effects on tumor cell function, including macromolecular synthesis, energy production, mTOR activation, maintenance of ROS homeostasis, and autophagy [158].

Alterations of the glutamine pathway in breast cancer cells lead to the infiltration of specific subtypes of inflammatory cells. Specifically, there was a significant correlation between the changes in glutamine metabolism on tumor cells and $CD20^+$ B cells [159]. Glutamine metabolism in ccRCC cells can promote IL-23 secretion to coordinate immune escape [160]. SIRT4 is a protein located in the mitochondria. It inhibits the proliferation, migration, and invasion of BCPAP, a human thyroid cancer cell line, by inhibiting glutamine metabolism, blocking the G0/G1 cell cycle, and inducing apoptosis [161]. Glutamine metabolism plays an important role in the proliferation of tumor cells in AML. In the future, targeting glutamine metabolism could probably provide a potential therapeutic strategy for AML [162]. The renal GLS inhibitor 968 can promote the secretion of chemokines CXCL10 and CXCL11 in tumor cells and improve the efficacy of anti-ovarian cancer treatment [79]. Tryptophan metabolism is closely related to tumor immunity. Tryptophan metabolism disorders can cause an immunosuppressive microenvironment and promote the occurrence and development of HCC. Studies have found that overexpression of ALDH2, a differentially expressed gene in tryptophan metabolism in HCC, can reduce HCC cell proliferation and migration [163]. Kruppel-like factor 7 (KLF7) promotes the proliferation and migration of HCC cells by up-regulating tryptophan metabolism through SLC1A5. The newly discovered KLF7/SLC1A5 axis in HCC may represent a potential target for HCC treatment [164]. Arginase 2 regulates arginine metabolism to drive neuroblastoma cell proliferation. The cells induce macrophages M1 polarization, leading to the secretion of IL-1β and TNF-α [165]. In HCC, one carbon (1C) metabolism is active and phosphoserine phosphatase is an upstream enzyme of the 1C pathway. The key enzyme reduces the recruitment of $CD8^+$ T cells by inhibiting

CXCL10 production in TNF-α-conditioned cancer cells [166].

In conclusion, the behavior of tumor cells is regulated by amino acid metabolism. Targeting the regulatory pathway of amino acid metabolism in tumor cells to induce TLS formation is a potential antitumor therapy in the future.

Vitamin metabolism

Vitamin D can influence cancer cell growth, differentiation, and apoptosis through various mechanisms in TME. Calcitriol (1,25-dihydroxyvitamin D-3), the bioactive form of vitamin D, inhibits glycolysis and cell growth in human colorectal cancer cells [167], indicating that tumor cell growth may be inhibited by activated vitamin D. In breast, colorectal and prostate cancers, CYP24A1, a vitamin D metabolic enzyme, may promote tumor growth by reducing the level of activated vitamin D [168]. Therefore, therapies targeting CYP24A1 seem to promote antitumor effects. The vitamin B6 pathway maintains glioblastoma (GBM) cell survival in vitro cultures, and inhibition of the vitamin B6 pathway is a potential target for therapies in GBM [169].

Multiple metabolisms

In hypoxia, tumor cells use reductive carboxylation to produce citric acid and FA and synthesize dihydroorotic acid to mitigate ammonia's detrimental effects on the tumor cells [34]. Low-grade IFN-I was found to promote HCC development by regulating glucose homeostasis and lipid metabolism [170].

Potential strategies for inducing TLS formation

There are potential advantages in achieving TLS formation and treating tumors by modulating metabolism and improving immunosuppressed TME to enhance immune cell infiltration and function and simultaneously inhibit tumor cells. At present, there is limited evidence that lipid metabolism is related to TLS formation. Recent studies suggest that cholesterol metabolism promotes the production of 7α,25-OHC and CE in immune cells, thereby recruiting cells to form TLS

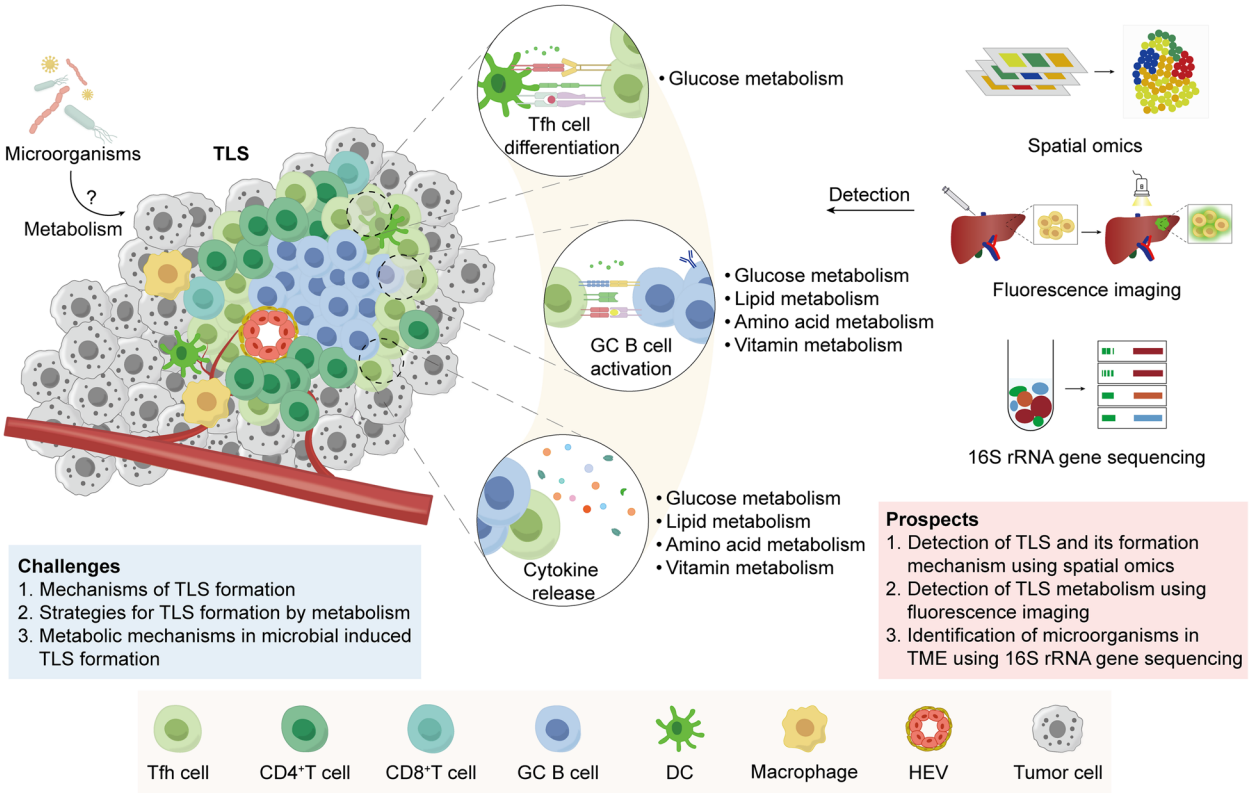

Fig. 3 Challenges and prospects in metabolic and microbial induction of TLS. Tfh cell differentiation, GC B cell activation, and cytokine release can influence TLS formation, but the mechanism by which they directly induce TLS formation is unknown. Some bacteria and viruses have been shown to induce TLS, yet the role of metabolism in this process remains unclear. In the future, significant challenges remain in studying the mechanisms of TLS formation, inducing TLS via microorganisms, and understanding the role of metabolism in TLS formation. Further research will be conducted on mechanisms, strategies, and microorganisms. Tfh, follicular helper T; GC, germinal center; DC, dendritic cell; HEV, high endothelial venule

[65, 66]. However, the blank space is still large. Potential strategies for inducing TLS formation through other metabolisms should be proposed based on sufficient evidence.

Side effects of metabolic interventions

The induction of 7α,25-OHC and CE has been proposed as a potential strategy to promote TLS formation [65, 66]. However, studies have found that CE also promotes tumor cell proliferation [171]. Knockdown of CE transfer protein will lead to the reduction of CE level in tumor cells and inhibit tumor growth [172]. Increased levels of SOAT1 and CE in tumor tissues are displayed by later stage, more invasive tumors with poor prognosis [173]. This suggests that increased CE, while inducing TLS, also promotes tumor cells. Consequently, targeting lipid metabolism in immune cells to increase CE levels becomes a potential strategy for TLS formation.

Conclusions

TLS plays an important role in the treatment of various diseases, particularly tumors. Compared with TLS, metabolism in SLO has been more extensively studied. Studies have shown that in diseases such as tumors and inflammation, immune cells undergo metabolic reprogramming [174, 175], which plays a role in the formation of SLO [176]. In addition, microorganisms have been found to mediate the structural composition of spleen immune cells [177]. Research that has examined metabolism in traditional SLO will be instructive in the study of metabolically induced TLS formation. Current reviews on the role of metabolism in TLS formation have mainly focused on its potential to induce Tfh cells, GC B cells, and cytokines. Therefore, it is crucial to continue exploring the relationship between metabolism and TLS formation, focusing on the mechanisms, strategies, and microbiological factors of metabolic induction of TLS (Fig. 3).

The molecular and cellular mechanisms underlying the formation of TLS and their role in TME are currently unknown. In the future, multi-omics analysis, including spatial omics, will be used to verify the formation of metabolism-induced TLS and the mechanisms by which metabolism affects cell interactions in TLS.

Additionally, current strategies for targeted regulation of metabolism-induced TLS formation are still limited. Metabolism plays a key role in TME, which not only affects the growth and survival of tumor cells and immune cells, but is also closely related to tumor aggressiveness, immune escape, treatment response, and prognosis [178, 179]. Therefore, it is of great importance to regulate TLS formation through metabolism. In the future, imaging techniques and targeted delivery systems provide potential strategies for in vitro and in vivo tracing of the role of metabolism in inducing TLS formation [180, 181].

Most studies have demonstrated that microorganisms, including viruses and bacteria, are associated with TLS formation [41, 182, 183]. However, direct evidence of microbial-derived metabolism and TLS formation is lacking. Microbes can regulate host metabolism [184], and play a potential role in promoting the release of TLS-associated cytokines. Investigating this regulation on TLS formation using metagenomics and 16S rRNA gene sequencing is crucial for harnessing microbes to enhance tumor immunotherapy, with broad potential applications [185].

Abbreviations

TME	Tumor microenvironment
TLS	Tertiary lymphoid structure
DCs	Dendritic cells
GCs	Germinal centers
HEVs	High endothelial venules
Tfh	Follicular helper T
PD-1	Programmed cell death 1
mTOR	Mammalian target of rapamycin
HIF-1α	Hypoxia inducible factor-1α
LTi	Lymphoid tissue inducer
STING	Stimulator of interferon genes
Th17	T helper 17
LTo	Lymphoid tissue organizer
ILs	Interleukins
TNF	Tumor necrosis factor
TGF-β	Transforming growth factor-β
IFNs	Interferons
VEGFs	Vascular endothelial growth factors
LT	Lymphotoxin
cGAMP	Cyclic GMP-AMP
IRF3	Interferon regulatory factor 3
TBK1	TANK binding kinase 1
HCC	Hepatocellular carcinoma
FAO	Fatty acid oxidation
FA	Fatty acid
1,5-AG	1,5-anhydroglucitol
ROS	Reactive oxygen species
ENO2	Enolase 2
MST1	Mammalian sterile 20-like kinase 1
DUSP6	Dual-specificity phosphatase 6
ILC3s	Group 3 innate lymphoid cells
NOX2	NADPH oxidase 2
GM-CSF	Granulocyte-macrophage colony-stimulating factor
SOAT1	Sterol O-acyltransferase 1
ACLY	Adenosine 5′-triphosphate citrate lyase
cGAS	Cyclic GMP-AMP synthase
7α,25-OHC	7α,25-dihydroxycholesterol
CE	Cholesteryl ester
MAIT	Mucosal-associated invariant T cell
PPAR	Peroxisome proliferator-activated receptor
TSC2	Tuberous sclerosis complex 2
GLS	Glutaminase
AML	Acute myeloid leukemia
PHGDH	Phosphoglycerate dehydrogenase
Tim-3	T cell immunoglobulin mucin-3
AQP7	Aquaporin 7
LCP1	Lymphocyte cytosolic protein 1
PPP	Pentose phosphate pathway
HBP	Hexosamine biosynthesis pathway
CPT2	Carnitine palmitoyltransferase 2
ccRCC	Clear-cell renal cell carcinoma

AMPK	AMP-activated protein kinase
NF-κB	Nuclear factor kappa-B
KLF7	Kruppel-like factor 7
1 C	One carbon
GBM	Glioblastoma

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Authors' contributions
MJZ: writing, review & editing, writing original draft, conceptualization. YW: writing, review & editing, writing original draft, conceptualization. ZJS: writing, review & editing, funding acquisition, conceptualization. All authors read and approved the final manuscript.

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Declarations

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