MEDS Clinical Medicine (2026)
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2026.070220
ISSN 2616-1907 Vol. 7 Num. 2

Metabolic Coupling Mechanisms Between Stromal Cells and Immune Cells in Tertiary Lymphoid Structures

Sirui Song[a,*], Yiang Sun, Tian Xia, Xinmiao Wei, Zhiyi Pan, Chenye Ji

School of Stomatology, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, 310053, China
[a]songsirui321@163.com
**Corresponding author*

Keywords: Tertiary lymphoid structures; Stromal cells; Immune cells; Metabolic coupling

Abstract: Tertiary lymphoid structures (TLS) are ectopic lymphoid tissues formed under pathological conditions such as tumors, chronic inflammation, and autoimmune diseases. Their maturation status is closely associated with the intensity of antitumor immune responses. TLS are composed of B-cell zones, T-cell zones, follicular dendritic cells, fibroblastic reticular cells, and high endothelial venules. Their formation and function are profoundly influenced by the metabolic microenvironment. This review systematically summarizes the metabolic coupling mechanisms between stromal cells and immune cells within TLS, focusing on three levels: key nutrient exchange, metabolite-mediated signal transduction, and the construction of spatial metabolic niches. These mechanisms drive TLS maturation and provide new intervention targets for enhancing antitumor immunity.

1. Introduction

Tertiary lymphoid structures (TLS) are lymphoid-like organs induced under pathological conditions such as chronic inflammation, autoimmune diseases, or the tumor microenvironment. They share functional features with secondary lymphoid organs like lymph nodes, containing B-cell zones, T-cell zones, follicular dendritic cells (FDCs), fibroblastic reticular cells (FRCs), and high endothelial venules (HEVs). Their maturation and composition are heterogeneous across different cancer types and individuals [1]. Compared with secondary lymphoid organs, TLS have the following characteristics: they lack a capsule and are directly exposed to the tumor or inflammatory microenvironment, allowing immune cells within TLS to continuously contact local antigens and inflammatory factors; they exhibit vascular specialization—HEVs not only mediate lymphocyte homing but also regulate the spatial distribution and functional polarization of lymphocytes within TLS; and they show dynamic maturation, classified by their organizational structure into lymphocyte aggregates, primary follicle-like structures, and secondary follicle-like structures [2].

The maturation of TLS is a key determinant of their antitumor efficacy and generally proceeds through the following stages: ① Early TLS, characterized by infiltration of T cells and B cells without evident compartmentalization and lacking germinal centers, FDCs, and HEVs; ② Primary follicle-like TLS, where T and B cells begin to segregate under the induction of FDCs, forming an FDC network within B-cell areas and early HEV formation, but still lacking germinal centers; ③ Secondary follicle-like TLS, defined by distinct B-cell and T-cell zones, FDC networks, and active

germinal centers. In germinal centers, B cells undergo clonal expansion, somatic hypermutation, and affinity selection, eventually differentiating into plasma cells and memory B cells that produce large amounts of antibodies, enabling rapid antibody responses and promoting antitumor immunity [3, 4].

The tumor microenvironment drives a series of changes in cellular metabolism, including alterations in nutrients, oxygen levels, extracellular pH, and inflammatory markers, which lead to metabolic reprogramming in resident cells. This process both promotes tumor progression and facilitates TLS formation [5, 6]. During TLS formation, different stromal and immune cells form metabolic coupling mechanisms through key nutrient exchange, metabolite signal transduction, and the construction of spatial metabolic niches. These mechanisms are part of metabolic reprogramming and, in turn, further promote it, ultimately driving TLS maturation and enhancing antitumor immunity [7].

2. Metabolic Coupling Mechanisms Between Stromal Cells and Immune Cells in TLS

2.1 Key Nutrient Exchange

2.1.1 Glucose and Lactate

Immune cells such as B cells rely on fatty acid oxidation and oxidative phosphorylation for energy in the resting state, but switch mainly to glycolysis upon activation. In germinal centers of TLS, B and T cells are in a state of rapid proliferation and differentiation and have an extremely high demand for glucose [8, 9]. To preferentially support immune responses, stromal cells downregulate their own glucose transporter expression, reducing glucose uptake and indirectly providing an ample glucose supply to immune cells, ensuring sufficient nutrition for clonal expansion and functional execution within TLS [10].

At the same time, lactate produced by immune cells during glycolysis can be internalized by neighboring immune cells and stromal cells as an energy substrate, entering glycolysis via lactate dehydrogenase. However, high lactate concentrations lead to excessive acidification of the microenvironment, inhibiting $CD8^+$ T-cell function and promoting regulatory T-cell (Treg) differentiation [11]. Thus, lactate homeostasis in TLS is critical: moderate lactate may support tissue homeostasis, but excess lactate hinders TLS maturation and antitumor immunity [12].

2.1.2 Amino Acids

In TLS, FRCs highly express glutamine synthetase and can synthesize glutamine (Gln) from glutamate and ammonia. Activated T and B cells highly express glutamine transporters on their membranes during proliferation but lack the ability to synthesize Gln themselves. FRCs release synthesized Gln into the microenvironment, and immune cells take it up via glutamine transporters and channel it through glutaminolysis to generate energy or as precursors for nucleotide and protein synthesis, supporting clonal expansion and antibody secretion [13]. Additionally, other amino acids such as tryptophan, serine, and histidine can promote macrophage polarization, support germinal center reactions, and enhance cytokine expression in immune cells, respectively; stromal cells may also facilitate TLS maturation by delivering these amino acids [14–16].

2.1.3 Lipids

Lipids play an important role in TLS maturation. Lipid metabolism, such as fatty acid oxidation and cholesterol synthesis, supports germinal center B-cell survival and promotes HEV formation, respectively [17, 18]. In TLS, specific stromal cell subsets may regulate immune cell differentiation and function by secreting fatty acids or cholesterol. For example, prostaglandin E2 produced by

cancer-associated fibroblasts (CAFs) can induce $CD4^+$ T-cell differentiation into Tregs and promote macrophage polarization toward the M2 phenotype; CAFs in pancreatic cancer secrete lysophosphatidylcholine, which is metabolized by tumor cells to lysophosphatidic acid, promoting B-cell recruitment [19–21]. Therefore, lipids secreted by stromal cells have a dual role in TLS formation, and certain lipid species can promote TLS maturation.

2.2 Metabolite-Mediated Signal Transduction

In the tumor microenvironment, certain metabolites have transcended their traditional metabolic roles and act as signaling molecules through specific receptors, modulating the functions of immune or stromal cells and thereby promoting TLS formation and maturation.

2.2.1 mTOR/HIF-1α Signaling Pathway

mTOR is a serine/threonine protein kinase composed of two complexes, mTORC1 and mTORC2. mTORC1 can be activated by nutrient signals such as leucine, glutamine, and arginine to promote anabolic metabolism. Some immune cells, like tumor-associated macrophages, may regulate amino acid concentrations in the tumor microenvironment to activate mTOR complexes (especially mTORC1), driving glycolysis and lipid synthesis to provide material and energy support for the proliferation and function of Tfh and $CD8^+$ T cells, maintaining their activity [22, 23].

HIF-1α is a transcription factor that responds to hypoxia. When oxygen is insufficient, it is activated and triggers a series of adaptive responses, including angiogenesis, pro-inflammatory cytokine production, and glycolysis. Studies have found that HIF-1α activation can promote CXCL13 expression in T cells within the tumor microenvironment, suggesting that hypoxic conditions may maintain immune cell energy metabolism and promote B-cell recruitment, thereby driving TLS formation [24].

In addition to direct nutrient activation, mTOR is a downstream target of the PI3K signaling pathway and interacts with HIF-1α. Succinate serves as a key metabolic signaling molecule in this context: immune cells take up succinate from the microenvironment and act on GPR91, activating the PI3K pathway, which in turn initiates mTOR. Activated mTOR further enhances HIF-1α activation by increasing its translational efficiency, thereby promoting TLS formation through the aforementioned mechanisms [25, 26].

2.2.2 STING Signaling Pathway

The STING pathway promotes antitumor immunity by sensing aberrant DNA and is a crucial activator of dendritic cells (DCs) [27]. In TLS, DCs exhibit elevated glycolysis, and ATP produced by glycolysis is essential for activating STING signaling and downstream type I interferon production. Moreover, STING signaling upregulates HIF-1α expression, enhancing glycolysis and further stimulating STING activation, creating a positive feedback loop that augments DC activation [28].

2.2.3 Lactate Signaling

Beyond serving as an energy substrate, lactate itself acts as a signaling molecule via GPR81, inhibiting lipolysis and favoring glucose metabolism. Lactate can also stabilize HIF-1α by competitively inhibiting prolyl hydroxylase activity, promoting HIF-1α activation and upregulating cytokines such as IL-1β, VEGF, and CXCL13. This pathway not only provides energy for immune cells but also directly promotes HEV formation and lymphocyte homing [29].

2.2.4 Redox Signaling

Recent studies have revealed the cystine/glutathione signaling pathway in TLS. During the formation and activity of renal TLS, highly proliferating lymphocytes produce large amounts of reactive oxygen species (ROS), leading to local oxidative stress. Stromal cells such as DCs and fibroblasts selectively upregulate the cysteine transporter xCT to enhance glutathione synthesis, counteracting oxidative stress and maintaining TLS homeostasis, thereby allowing proper immune function [30].

2.3 Construction of Spatial Metabolic Niches

High endothelial venules, fibroblastic reticular cells, and FRC-like cancer-associated fibroblasts are the main stromal cells in the T-cell zone, while follicular dendritic cells are the principal stromal cells in the B-cell zone. These stromal cells actively create a spatial microenvironment favorable for immune cell homing, survival, and function by promoting immune cell migration, secreting specific chemokines, providing survival and metabolic signals, and establishing information exchange networks, thus offering metabolic support for TLS maturation.

2.3.1 Metabolic Niche Construction in the T-Cell Zone

2.3.1.1 High Endothelial Venules and Immune Cells

Tumor HEVs arise from transdifferentiation of post-capillary venules and are surrounded by FRC-formed sheaths, serving as the main passage for lymphocyte migration. Lymphocytes, especially $CD8^+$ T cells and NK cells, induce mature HEV formation through expression of lymphotoxin α1β2 (LTα1β2) and LIGHT. HEVs regulate the extravasation of naive, memory, and activated lymphocytes, directly affecting the cellular composition within TLS. Recent evidence suggests that HEVs may create a specific metabolic microenvironment within TLS, enriching $TCF\text{-}1^+PD\text{-}1^+$ stem-like $CD8^+$ T cells (pTex) that proliferate around HEVs and differentiate into terminal effector cells with high granzyme B and perforin expression, thereby displaying potent cytotoxicity and enhancing antitumor immunity [31, 32].

2.3.1.2 Fibroblastic Reticular Cells and Immune Cells

FRCs are highly specialized immunomodulatory fibroblasts in secondary lymphoid organs, mainly located in the T-cell zone, forming a scaffold structure that supports efficient immune cell interactions. FRCs are therefore representative stromal cells in TLS [33].

The main functions of FRCs are to provide a suitable microenvironment for T-cell recruitment, positioning, survival, and interactions. First, FRCs specifically express and secrete chemokines CCL19 and CCL21, establishing chemical gradients that actively recruit and retain $CCR7^+$ naive T cells and DCs in the T-cell zone, creating a space where T cells and antigen-presenting cells can efficiently meet. Second, FRCs extend into a three-dimensional reticular network within the T-cell zone; these networks may colocalize with DCs, and their associated extracellular matrix fibers form functional “conduits.” This 3D network provides scaffolds and tracks for T-cell and DC migration and interaction, while the conduit system delivers small antigens, cytokines, and nutrients from blood vessels or interstitial spaces deep into the T-cell zone, ensuring efficient distribution of antigens, signals, and nutrients within the niche. Finally, FRCs secrete IL-6, which induces metabolic reprogramming of $CD8^+$ T cells, increasing mTORC1 activity and metabolic rate, ultimately enhancing cytokine production, metabolic activity, and in vivo persistence, and promoting differentiation into memory T cells [34, 35].

2.3.1.3 FRC-like Cancer-Associated Fibroblasts and Immune Cells

In the tumor microenvironment, quiescent fibroblasts are activated into functionally diverse CAFs, including myofibroblastic CAFs (myCAF), inflammatory CAFs (iCAF), and antigen-presenting CAFs (apCAF). They have complex functions and a dual role in tumor development, and their beneficial or detrimental effects are not fully clarified [36].

One CAF subtype, FRC-like fibroblasts, plays a positive role in TLS construction. These FRC-like fibroblasts are mainly located in the T-cell zone and also possess lymphoid tissue organizer (LTo) characteristics. Their formation is driven by lymphotoxin signals: intratumoral $CD8^+$ T cells may provide initial TNFR signals via TNF, driving CAFs to acquire an LTo-like phenotype; then immune cells such as LTi cells, B cells, and T cells secrete LTα1β2, which acts on the LTβR of CAFs, activating non-canonical NF-κB signaling to drive CAF proliferation and formation of reticular networks. FRC-like fibroblasts express chemokines CCL19, CCL21, and CXCL13, recruiting T lymphocytes, DCs, and B lymphocytes to TLS; they also express cytokines such as IL-7, IL-15, TNFSF13B (BAFF), TNFSF13, TNFSF14 (LIGHT), and adhesion molecules VCAM-1/ICAM-1, sustaining T- and B-cell survival, aggregation, proliferation, and differentiation [37, 38].

2.3.2 Metabolic Niche Construction in the B-Cell Zone

FDCs are mainly located in the B-cell zone, especially within germinal centers, and are the core organizers of the B-cell niche. First, FDCs highly express CXCL13, which acts on B cells and Tfh that express its receptor CXCR5. By secreting CXCL13, FDCs define the boundaries of germinal centers, recruiting and aggregating B cells and Tfh into specific areas, thus constructing a niche dedicated to B-cell activation and antibody responses. Second, FDCs are the main source of B-cell activating factor (BAFF). By providing BAFF, FDCs directly sustain the survival of germinal center B cells and prevent their apoptosis. Finally, FDCs express Fc receptors and complement receptors, allowing them to display native antigens in the form of immune complexes on their surface for long periods, forming an “antigen depot.” In the light zone of germinal centers, FDCs present antigens and collaborate with Tfh to drive affinity maturation and positive selection of B cells, promoting high-affinity antibody production [34].

Recent studies have shown that FDCs and B cells can form gap junctions via specific channel proteins, allowing sharing of metabolites such as ATP, amino acids, and nucleotides between FDC networks and B cells. This pathway may enable FDCs to provide biosynthetic precursors or survival signals to rapidly proliferating B cells. Critical second messengers like Ca^{2+} and inositol triphosphate (IP_3) can also diffuse rapidly through gap junctions, synchronizing the entire FDC network and the connected B-cell population, which is essential for the coordinated function of the germinal center as a whole [39]. Additionally, upon contact with B cells through their reticular network, FDCs secrete epidermal growth factor-related molecules that tag apoptotic germinal center B cells, mediating macrophage clearance of apoptotic cells and preventing local inflammatory responses caused by cell lysis, thereby establishing a metabolic environment conducive to B-cell function [34, 40].

3. Summary and Perspectives

This review systematically outlines the metabolic coupling mechanisms between stromal cells and immune cells within tertiary lymphoid structures, revealing that TLS are not merely organized aggregations of immune cells but are dynamic metabolic ecosystems actively regulated by stromal cells. Through nutrient exchange, metabolite signaling, and functional metabolic niche construction, immune cells and stromal cells collectively promote TLS maturation and enhance antitumor immune mechanisms. These insights deepen our understanding of TLS formation and offer new avenues for targeting metabolic pathways to boost TLS-mediated antitumor immunity. Future research should

further explore the heterogeneity of TLS metabolic niches across different tumor types, clarify the spatiotemporal regulatory mechanisms of key metabolic pathways, and evaluate the synergistic effects of metabolic interventions with immunotherapies. Integrating single-cell omics, spatial metabolomics, and functional imaging holds promise for delineating a fine-scale map of TLS metabolic coupling and laying a theoretical foundation for developing novel cancer immunotherapeutic strategies.

References

[1] SCHUMACHER T N, THOMMEN D S. Tertiary lymphoid structures in cancer. Science, 2022, 375(6576): eabf9419.
[2] HAN Xiaoqing, SHEN Da, SUN Jiwei, et al. Research progress of tertiary lymphoid structures in oral squamous cell carcinoma: from basic features to clinical significance. Journal of Huazhong University of Science and Technology (Medical Edition), 2025, 54(04): 579-586.
[3] WANG Congying, LIU Haiyan. Research progress on the relationship between tumor-associated tertiary lymphoid structures and anti-tumor immune responses. Modern Oncology, 2025, 33(12): 2177-2185.
[4] GUILLAUME S M, BECCARIA C G, IANNACONE M, et al. Tertiary Lymphoid Structures Across Organs: Context, Composition, and Clinical Levers. Immunol Rev, 2025, 335(1): e70063.
[5] OHSHIMA K, MORII E. Metabolic Reprogramming of Cancer Cells during Tumor Progression and Metastasis. Metabolites, 2021, 11(1).
[6] EL SAYED R, HAIBE Y, AMHAZ G, et al. Metabolic Factors Affecting Tumor Immunogenicity: What Is Happening at the Cellular Level? Int J Mol Sci, 2021, 22(4).
[7] ROSSI A, BELMONTE B, CARNEVALE S, et al. Stromal and Immune Cell Dynamics in Tumor Associated Tertiary Lymphoid Structures and Anti-Tumor Immune Responses. Front Cell Dev Biol, 2022, 10: 933113.
[8] XIAO C, XIONG W, XU Y, et al. Immunometabolism: a new dimension in immunotherapy resistance. Front Med, 2023, 17(4): 585-616.
[9] ZHANG M J, WEN Y, SUN Z J. The impact of metabolic reprogramming on tertiary lymphoid structure formation: enhancing cancer immunotherapy. BMC Med, 2025, 23(1): 217.
[10] KONG D, WILLSONSHIRKEY M, PIAO W, et al. Metabolic Reprogramming of Fibroblastic Reticular Cells in Immunity and Tolerance. Eur J Immunol, 2025, 55(1): e202451321.
[11] PENG Yiman, LUO Xiangmeng, CHEN Jingyao. Research progress on tumor microenvironment metabolism and novel immunotherapy strategies. Journal of Sichuan University (Medical Sciences), 2023, 54(03): 505-509.
[12] LI Dongquan, HUANG Shanhe, HUANG Hai, et al. Research progress on metabolic reprogramming mediated by tumor microenvironment in prostate cancer. Lingnan Modern Clinical Surgery, 2024, 24(06): 398-409.
[13] TEILLAUD J L, HOUEL A, PANOUILLOT M, et al. Tertiary lymphoid structures in anticancer immunity. Nat Rev Cancer, 2024, 24(9): 629-646.
[14] XUE L, WANG C, QIAN Y, et al. Tryptophan metabolism regulates inflammatory macrophage polarization as a predictive factor for breast cancer immunotherapy. Int Immunopharmacol, 2023, 125(Pt B): 111196.
[15] SIRNIÖ P, VÄYRYNEN J P, KLINTRUP K, et al. Alterations in serum amino-acid profile in the progression of colorectal cancer: associations with systemic inflammation, tumour stage and patient survival. Br J Cancer, 2019, 120(2): 238-246.
[16] D'AVOLA A, LEGRAVE N, TAJAN M, et al. PHGDH is required for germinal center formation and is a therapeutic target in MYC-driven lymphoma. J Clin Invest, 2022, 132(9).
[17] ZHU T, WANG Z, ZOU T, et al. SOAT1 Promotes Gastric Cancer Lymph Node Metastasis Through Lipid Synthesis. Front Pharmacol, 2021, 12: 769647.
[18] WEISEL F J, MULLETT S J, ELSNER R A, et al. Germinal center B cells selectively oxidize fatty acids for energy while conducting minimal glycolysis. Nat Immunol, 2020, 21(3): 331-342.
[19] BARATELLI F, LIN Y, ZHU L, et al. Prostaglandin E2 induces FOXP3 gene expression and T regulatory cell function in human CD4+ T cells. J Immunol, 2005, 175(3): 1483-1490.
[20] BHATTACHARYYA S, OON C, DIAZ L, et al. Autotaxin-lysolipid signaling suppresses a CCL11-eosinophil axis to promote pancreatic cancer progression. Nat Cancer, 2024, 5(2): 283-298.
[21] KAY E J, ZANIVAN S. The tumor microenvironment is an ecosystem sustained by metabolic interactions. Cell Rep, 2025, 44(3): 115432.
[22] ZENG H, COHEN S, GUY C, et al. mTORC1 and mTORC2 Kinase Signaling and Glucose Metabolism Drive Follicular Helper T Cell Differentiation. Immunity, 2016, 45(3): 540-554.
[23] LV Y, LI M, WENG L, et al. Ginseng-derived nanoparticles reprogram macrophages to regulate arginase-1 release for ameliorating T cell exhaustion in tumor microenvironment. J Exp Clin Cancer Res, 2023, 42(1): 322.

[24] WANG J, LIANG Y, XUE A, et al. Intratumoral CXCL13(+) CD160(+) CD8(+) T cells promote the formation of tertiary lymphoid structures to enhance the efficacy of immunotherapy in advanced gastric cancer. J Immunother Cancer, 2024, 12(9).
[25] XIE S, ZHAO J, ZHANG F, et al. Dehydrodiisoeugenol inhibits PDGF-BB-induced proliferation and migration of human pulmonary artery smooth muscle cells via the mTOR/HIF1-α/HK2 signaling pathway. Toxicol Appl Pharmacol, 2025, 495: 117212.
[26] ATALLAH R, GINDLHUBER J, HEINEMANN A. Succinate in innate immunity: linking metabolic reprogramming to immune modulation. Front Immunol, 2025, 16: 1661948.
[27] WANG X, HUANG Z, XING L, et al. STING agonist-based ER-targeting molecules boost antigen cross-presentation. Nature, 2025, 641(8061): 202-210.
[28] HU Z, YU X, DING R, et al. Glycolysis drives STING signaling to facilitate dendritic cell antitumor function. J Clin Invest, 2023, 133(7).
[29] BROOKS G A. Lactate as a fulcrum of metabolism. Redox Biol, 2020, 35: 101454.
[30] ARAI H, SUGIURA Y, YANAGITA M. Elucidating Metabolic Microenvironment of Tertiary Lymphoid Structures in the Kidney: FR-PO1180. Journal of the American Society of Nephrology, 2024, 35(10S): 10.1681/ASN.2024fnt042cn.
[31] VELLA G, HUA Y, BERGERS G. High endothelial venules in cancer: Regulation, function, and therapeutic implication. Cancer Cell, 2023, 41(3): 527-545.
[32] HUA Y, VELLA G, RAMBOW F, et al. Cancer immunotherapies transition endothelial cells into HEVs that generate TCF1(+) T lymphocyte niches through a feed-forward loop. Cancer Cell, 2022, 40(12): 1600-1618.
[33] PEREZ-SHIBAYAMA C, GIL-CRUZ C, LUDEWIG B. Fibroblastic reticular cells at the nexus of innate and adaptive immune responses. Immunol Rev, 2019, 289(1): 31-41.
[34] BARONE F, GARDNER D H, NAYAR S, et al. Stromal Fibroblasts in Tertiary Lymphoid Structures: A Novel Target in Chronic Inflammation. Front Immunol, 2016, 7: 477.
[35] BROWN F D, SEN D R, LAFLEUR M W, et al. Fibroblastic reticular cells enhance T cell metabolism and survival via epigenetic remodeling. Nat Immunol, 2019, 20(12): 1668-1680.
[36] LV K, HE T. Cancer-associated fibroblasts: heterogeneity, tumorigenicity and therapeutic targets. Mol Biomed, 2024, 5(1): 70.
[37] JENKINS B H, TRACY I, RODRIGUES M, et al. Single cell and spatial analysis of immune-hot and immune-cold tumours identifies fibroblast subtypes associated with distinct immunological niches and positive immunotherapy response. Mol Cancer, 2025, 24(1): 3.
[38] RODRIGUEZ A B, PESKE J D, WOODS A N, et al. Immune mechanisms orchestrate tertiary lymphoid structures in tumors via cancer-associated fibroblasts. Cell Rep, 2021, 36(3): 109422.
[39] RAJNAI H, TELEKI I, KISZNER G, et al. Connexin 43 communication channels in follicular dendritic cell development and in follicular lymphomas. J Immunol Res, 2015, 2015: 528098.
[40] KRANICH J, KRAUTLER N J, HEINEN E, et al. Follicular dendritic cells control engulfment of apoptotic bodies by secreting Mfge8. J Exp Med, 2008, 205(6): 1293-1302.