9 Lipid Metabolism in Tumor-Associated B Cells

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Abstract

Breakthroughs have been made in the cancer immunotherapy field focusing on utilizing T cells' antitumor immunity, and the lipid metabolism of tumor-associated B cells is not well studied compared to T cells. Accumulating evidence suggested that B cells also play important roles in tumor biology and antitumor immunity, especially the germinal center B cells that present in the tumor-related tertiary lymphoid structures. Due to scarce studies on lipid metabolisms of tumor-associated B cells, this chapter mainly summarized findings on B cell lipid metabolism and discussed B cell development and major transcription factors, tumor-associated B cell populations and their potential functions in antitumor immunity, fatty acid oxidation in germinal center B cells, and tumor microenvironment factors that potentially affect B cell lipid metabolism, focusing on hypoxia and nutrients competition, as well as lipid metabolites that affect B cell function, including cholesterol, geranylgeranyl pyrophosphate, oxysterols, and short-chain fatty acids.

Keywords

B cells · Lipid metabolism · Germinal center Cholesterol · Cancer

9.1 B Cell Development

B cells, derived from bone marrow (BM) hematopoietic stem cells, undergo programmed development firstly from lymphoid progenitors to pre-B cells, which express "B cell receptor (BCR)" composed of immunoglobulin (Ig) heavy chain and a surrogate light chain after Ig gene V(D)J recombination [1]. Then the pre-BCR signaling triggers proliferation and results in an increased amount of resting pre-B cells, among which Ig light-chain gene rearrangement is fulfilled and a functional BCR (IgM usually) presents, indicating development into immature B cells [1]. Accompanied by another kind of BCR (IgD) expression, mature B cells migrate to the periphery surveying for antigens (Ag). Ags and co-stimulatory molecules as toll-like receptor ligands drive the subsequent B cell proliferation and differentiation into the antibody (Ab)-secreting cells. A cohort of B cells further differentiates to memory B cells or long-lived plasma cells [2, 3]. A summary of B cell development is shown in Fig. 9.1.

To fulfill the energy and nutrient demands of humoral immunity, B cells adapt both non-

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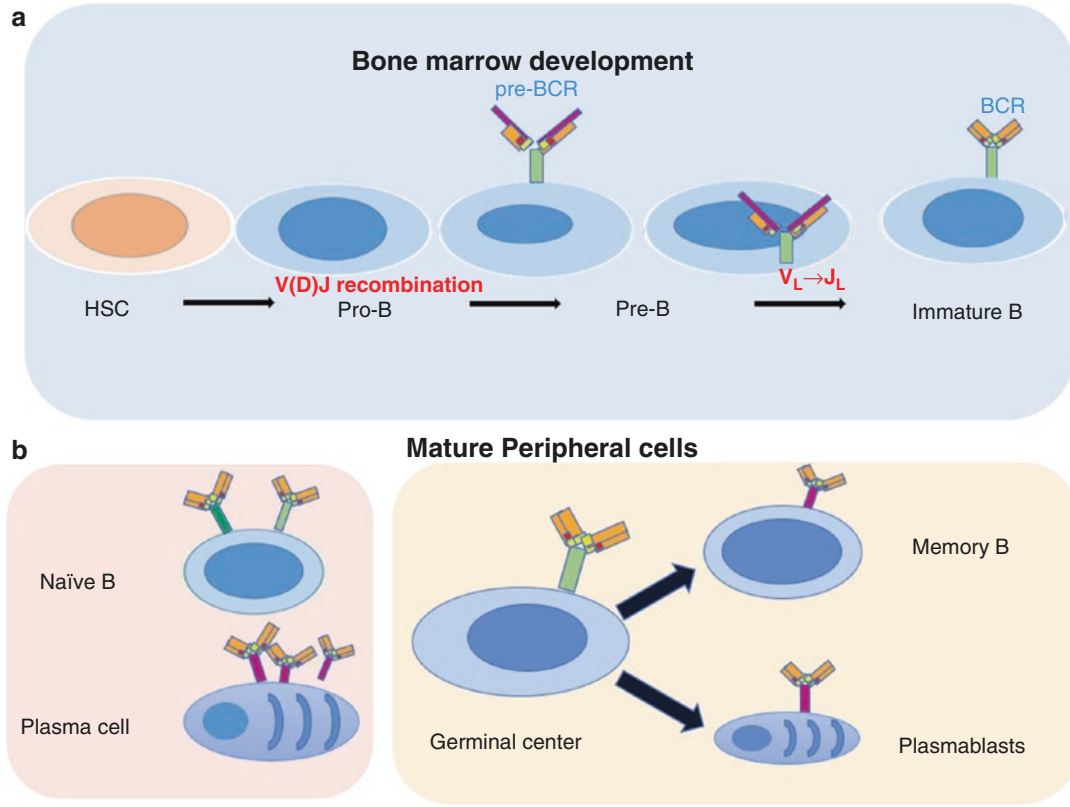

Fig. 9.1 B cell development. A schematic of B cell development from the bone marrow to the periphery. (**a**) B cells in the bone marrow undergo early stage of differentiation from hematopoietic stem cell (HSC) to immature B cells, which transit to the periphery to develop to mature circulating cells. (**b**) The naïve B cells are activated by antigen and co-stimulatory molecules and become antibody-secreting plasma cells after proliferation and differentiation. A cohort of B cells undergo further differentiation in the germinal center to become memory B cells or long-lived plasmablasts

cycling resting state and rapid proliferation state. The metabolic requirements are high when B cells are the early proliferative progenitors in the BM and fall in the pre-B and immature B cells. For the resting naïve and memory B cells, energy demands are relatively low, but raised during antigen-stimulated proliferation and differentiation, and remain high in the Ab-secreting plasma cells [4].

Glucose, glutamine, and fatty acids are the main carbon sources for B cell metabolism, among which glucose is the main carbon source for both the resting and activated B cells [5]. It is reported that resting B cells in murine spleen require glycolysis as well as oxidative phosphorylation (OXPHOS) [6]. Meanwhile, for the peripheral naïve B cells, there exists a specific loss of mature B cells in response to the absence of glucose transporter GLUT1, indicating that glucose uptake plays an especially important role for peripheral resting B cell homeostasis [6]. On the other hand, the surface expression of GLUT1 is raised after BCR engagement, and the subsequent upregulated glycolysis is PI3K-Akt-dependent [6–8]. BCR engagement also promotes OXPHOS, which is a significant difference between BCR-stimulated B cells and TCR/CD28-stimulated T cells that prefer glycolysis only [6]. Besides, LPS treatment also promotes glycolysis and OXPHOS in naïve B cells, indicated by increased GLUT1 expression and mitochondrial mass [6, 7].

For B cell proliferation and differentiation, glycolysis has been considered the primary driving power [5]. Per the increased energy needs after B cell activation, glucose uptake is elevated to enter glycolysis [6, 9, 10]. Consistently, GLUT1-deficient B cells are defective in Ab production [6]. Similarly, 2-deoxyglucose (2-DG) treatment inhibits LPS-activated B cell proliferation as well as Ab production [8]. The resultant pyruvate derived from glycolysis then enters mitochondria and undergoes Krebs (TCA) cycle and OXPHOS not only to enhance energy production as the form of ATP but also to provide a large pool of citrate for intrinsic lipogenesis catalyzed by ATP citrate lyase (ACLY). The newly produced lipids contribute to membrane synthesis during B cell growth and division [11].

Lipid and protein metabolism also fulfills energy supply and supports B cell function. Fatty acid oxidation also generates pyruvate, which enters the TCA cycle to feed OXPHOS and produce ATP [5]. Proteins can also function as a carbon source. The hydrolyzed individual amino acids participate in parts of the TCA cycle and generate ATP [5]. On the other hand, serine metabolism also contributes to lipid synthesis. Serine is generated from glucose-derived 3-phosphoglyceric acid and enters the one-carbon metabolism pathway, which means a one-carbon unit from serine is processed through methionine and folate cycles to contribute to lipid, nucleotide, and protein synthesis. This pathway also generates products that are crucial for methylation reactions as well as redox reactions. How serine and serine-derived one-carbon metabolism involves the regulation of tumor and immunity is investigated [12, 13].

B1 B cells, tissue-resident and innate-like, display distinct development and metabolic patterns from abovementioned B2 B cells [14], which is the center of humoral immunity and the main source of glycosylated Abs. B1 B cells exist from fetal and neonatal stages, and the subsequent expansion is mainly through self-renewal [15], although there is rare potential that B1 B cells originate from BM B1 progenitors [16]. Similar to B2 cells, B1 cells have a potent requirement for lipogenesis de novo, potentially from glycolytic product citrate by ACLY. However, B1 cells exhibit higher levels of glycolysis as well as OXPHOS and the subsequent TCA cycle-coupled fatty acid synthesis compared to B2 cells [14].

9.1.1 Transcriptional Regulation of B Cell Metabolism

The transcriptional regulation for peripheral B cell destiny still needs further investigation, although for early-stage differentiation, it is relatively well-known.

Among the critical B cell transcription factors, c-Myc plays an important role in B cell proliferation, clonal expansion, and fate determination [17, 18], contributing to an expression of effectors involved in nutrient uptake and mTOR activation [19]. c-Myc is essential for B cell positive selection in the germinal center (GC). c-Myc is expressed in a small portion of B cells in the light zone of the GC [20], where mesenchyme-originated follicular dendritic cells capture immune-complex and facilitate B cell recognition of antigen by B cell receptor [21]. The c-Myc-expressing cells are characterized by upregulated genes critical to glycolysis and nutrient sensing [22]. Also, c-Myc is modestly crucial for LPS-triggered glutamine oxidation increase while antagonizing LPS-mediated downregulation of fatty acid oxidation and pyruvate oxidation [6]. In addition, c-Myc induces transcription factor AP4, which is essential for T-B interaction in the light zone of GC through IL-21 signaling and for the subsequent GC B cell division in the dark zone of the GC [23].

Nuclear factor-κB (NF-κB), the key regulator of inflammatory immune response and cytokine production, is suggested to be involved in the regulation of B cell metabolism and proliferation via a TRAF3-NIK-NF-κB axis [24]. Tumor necrosis factor (TNF) receptor-associated factor-3 (TRAF3) plays a critical role in B cell metabolism. TRAF3-deficient B cells present unusually increased expression of key genes that are involved in the early phase of glycolysis, such as genes encoding GLUT1 and hexokinase-2. In addition, this kind of B cells increases mitochondrial respi-

ration, but does not increase reactive oxygen species generation [25]. B cell full activation demands co-stimulation through CD40-B-cell activating factor (BAFF) receptor pathway, which triggers the degradation of TRAF3 and the buildup of NF-κB-inducing kinase (NIK) [26]. The latter leads to translocation of NF-κB into the nucleus, where the transcription of target genes is activated. Double knockout of TRAF3 and NIK causes a low level of GLUT1 expression and reduced mature B cell counts [25]. Consistently, when activated by LPS, BAFF-exposed naïve B cells display increased glucose uptake as well as a relatively higher basal mitochondrial activity [6]. The above findings indicate that NF-κB is involved in the regulation of glucose uptake [25] and that B cell co-stimulation plays a role in B cell metabolic reprogramming [24].

The transcription factor Bcl6 is highly expressed in both GC B cells and follicular helper T (Tfh) cells, induced by multiple co-stimulatory molecules between B and T cells, including IL-21 [27–29]. It has been reported that Bcl6 suppresses glycolysis in macrophages [30], therefore may have to be overcome by c-Myc [20, 22, 31] and hypoxia-inducible factor (HIF) in the GC.

The light zone of GC provides a hypoxic environment, which is also related to B cell metabolism [32]. HIF1 and HIF2 evoke glycolysis through aldolase A, M2 isoform of pyruvate kinase, and phosphoglycerate kinase 1 [33]. Although HIF and c-Myc both actuate glycolysis [34], HIF represses c-Myc activity [23, 35]. c-Myc promotes mitochondrial biogenesis [36], while HIF inhibits Krebs cycle and respiration [37]. Given that c-Myc evokes expression of effectors related to mTOR activation [19], HIF also suppresses mTOR1 activity [23, 35]. HIF-1α not only regulates expression of genes associated with glycolysis in response to limited oxygen environment but also controls B cell development and activity in a stage-specific pattern [38, 39]. It is reported that lack of HIF-1α results in decreased expression of phosphofructokinase (Pfkfb3) and glucose transporters, which obstructs the development from pro- to pre-B cell stage in the BM [40]. Also, HIF-1α sustains the energy requirement of the Ag-exposed B cells in the GC [41]. In addition, hypoxia potentially promotes plasma cell fate determination [32], which may be due to the HIF-regulated *lrf4* gene [42].

IRF4 is critical to plasma cell differentiation and GC response [43]. It is expressed in resting B cells at a low level to promote survival, and its expression is elevated inconsistent with the strength of activation signals stimulated by Ag, cytokines, or TLR ligands. The majority of IRF4-targeted genes may be co-regulated by c-Myc since they bear AP1-IRF4 composite sites [42]. A small amount of $IRF4^{+}c\text{-}Myc^{+}$ cells exist in the GC and may be the outcome of asymmetric division to generate plasmablasts [20, 22, 44].

The c-Rel transcription factor is also expressed at a relatively high level upon B cell activation, inducing *lrf4* expression [45]. It is involved in the metabolic regulation that fulfills the energy demands of proliferating GC B cells [46]. c-Rel translocation is PI3K-dependent and only happens in a small amount of GC B cells, which may be the ones facilitated by T cells [47].

Bach2, Foxo1, and Pax5 act similarly to Bcl6 and inhibit plasma cell differentiation [48], while E2A and E2–2 are committed to GC response and plasma cell differentiation [49, 50]. In addition, Pax5 has been reported that it inhibits metabolism in early B cells [51]. The combined findings indicate that the transcription factors regulating B cell metabolism remain to be revealed.

B1 B cells exhibit significantly higher gene expression associated with glycolysis and lipid metabolism as well as lipid storage, compared to B2 B cells [14].

9.2 Tumor-Associated B Cell Populations

B cells are commonly found in tumor-draining lymph nodes, and less commonly at the invasive margin of tumors, or infiltrated into the tumor mass. A closer look at tumor-related B cells revealed that B cells exist in different forms, from nonstructured immune cell aggregates to structured ones, i.e., tertiary lymphoid structures

(TLS). TLS is induced in chronic inflammations including cancer, autoimmunity, and organ transplant and resembles follicles of the second lymphoid organs. In cancer, TLS localizes at the tumor periphery and, less frequently, inside the tumor.

9.2.1 B Cells with Antitumor Function

The presence of certain B cells in the tumor has been associated with a better prognosis. Earlier studies found that in some breast or ovarian cancer patients, tumor infiltrated B cells were associated with a good prognosis [52]. Later, TLS that contains a GC was found to be correlated with improved survival in multiple cancer types. The prognostic significance of the tumor-related TLS was reviewed in depth by Sautès-Fridman et al. [53]. Originally discovered in hepatocellular carcinoma, numerous studies found that B cells/GCs' presence in the TLS correlated with prolonged survival in other types of cancers, including non-small cell lung cancer, colorectal cancer, pancreatic cancer, oral squamous cell carcinoma, invasive breast cancer, etc. Since B cells initiate TLS formation, these discoveries highlighted B cell roles in patients' survival. The two scenarios of tumor-associated B cells are summarized in Fig. 9.2: presence of B cells with mature TLS containing GC, or with less organized cell aggregates without GC (immature TLS). It should be noted that the broad classification of TLS presented here is an oversimplified model, as there are immune "cold" tumors and more variety of tumor-associated B cells.

Very recently, the presence of B cells in the TLS has been found to correlate with immunotherapy success [54–56], indicating that B cells play a critical role in immunotherapy success. In searching for predictors for patients' outcome after immune checkpoint blockade (ICB), the B lineage signature has been found to be the strongest predictor for survival in a cohort of sarcoma patients [56]. Corroborating this finding, in another cohort of melanoma patients treated with ICB, a TLS associated gene signature predicted

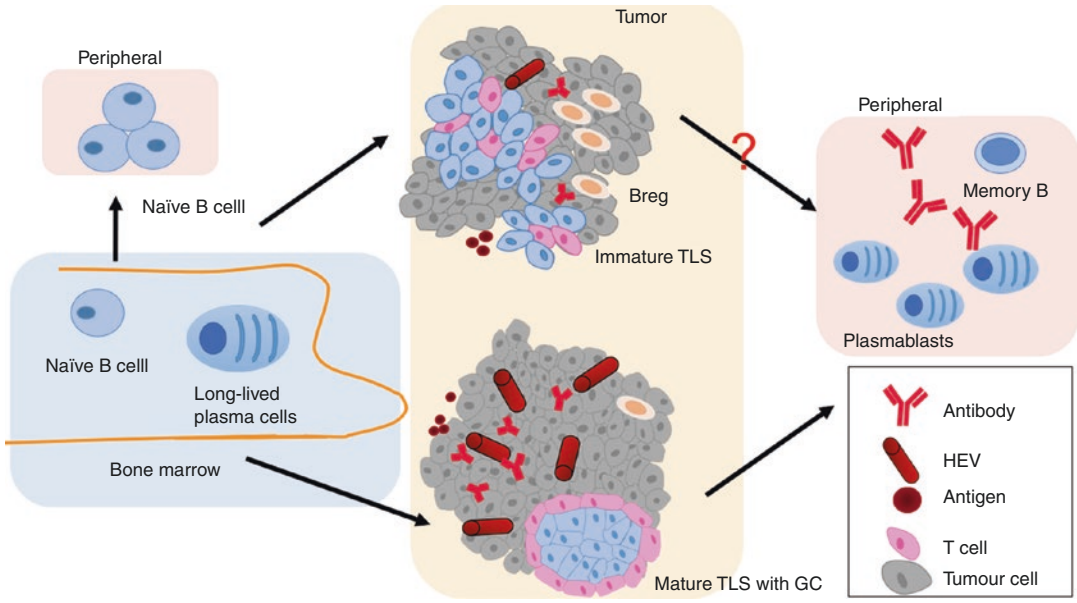

Fig. 9.2 Mature or immature TLS and tumor-associated B cells. A schematic of various tumor-associated B cell populations and TLS. The existence of mature B cells in tumors featuring germinal centers is associated with better prognosis, where B cells are selected and differentiated and correlated with better prognosis in multiple cancers. Immature TLS are unstructured cell aggregates. B cells and TLS signature are more prominent in responders versus nonresponders of immunotherapy. Memory B cells and regulatory B cells are associated with tumor, too

patients' survival [54]. Furthermore, the B cells and TLS signatures are more prominent than T cell signatures for discerning between the responders and the nonresponders to neoadjuvant ICB for melanoma [55]. These findings confirm the critical roles played by B cells/TLS in antitumor immunity and immunotherapy.

Circulating plasmablasts, a type of mature B cells that circulate back to the BM or reside in the chronic inflammation sites, were found increased in patients with metastatic but non-progressing melanoma, lung adenocarcinoma, or renal cell carcinoma. In these non-progressing cancer cases, clonal affinity matured B cells exhibited progressive class switch, and recombinant antibodies from clonal families were able to bind non-autologous tumor tissue/cell lines and caused tumor regression in syngeneic mouse tumor models [57], indicating that B cells contributed to control the disease progression in these patients.

B1a cells, an innate-like B cell population, were essential for protection induced by toll-like receptor and C-type lectin receptor agonist pairing of monophosphoryl lipid A (MPL) and trehalose-6,6′-dicorynomycolate (TDCM) treatment in a mouse model. MPL/TDCM treatment effectively inhibited tumor growth and ascites development in this mouse model of aggressive mammary cancer-induced peritoneal carcinomatosis. B1a cells were enriched in the peritoneal cavity and deficient in mice lacking CD19. MPL/TDCM treatment effects were not observed in mice lacking CD19, and adoptive transfer of B1a cells restored the protective effects [58].

Atypical B cell populations with protective effects are found in breast cancers, too. ICOSL^{+}B cells (ICOSL + CR2highIL – 10 – CD20 + CD38 + CD27 + IgA – IgD-) emerged after chemotherapy in breast cancer patients and correlated with better therapeutic effect and prognosis [59]. CD40 signals in GC B cells upregulated ICOSL in these cells, which in turn promoted interaction with follicular T cells and the GC selection process, forming a feed-forward loop [60].

All the abovementioned pieces of evidence point to certain B cell function in antitumor immunity. Producing antibodies, secreting antitumor cytokines, and serving as antigen-presenting cells are examples of how B cells can help to improve antitumor immunity. Moreover, B cells can secrete granzyme and directly kill tumor cells. The field of B cells' role in antitumor immunity is wide open and booming, and more findings on B cells' function are sure to be revealed.

9.2.2 B Cells with Pro-tumor or Unknown Function

Regulatory B cells expressing IgA and IL-10 were discovered in certain mouse cancer models. Liver-resident cells producing IgA, expressing IL-10, and PD-L1 directly suppressed CD8^{+} T cell activity [61]. Plasmocytes accumulation in this model depended on PD-L1-PD1 interaction, indicating that follicular T cells were involved, probably in TLS GC. B cells expressing IgA, IL-10, PD-L1, and FasL have been shown to suppress antitumor immunity induced by the chemotherapy drug oxaliplatin in mouse prostate cancer models with large tumors, and removal of these cells restores oxaliplatin's activity [62].

B cells accumulated in tumor-draining lymph nodes in a mouse breast cancer model and facilitated tumor metastasis to the lymph nodes. In this spontaneous metastasis model, these B cells produced IgG specifically targeting glycosylated membrane protein HSPA4. This IgG bound to HSPA4 and activated the HSPA4-binding protein ITGB5, which in turn evoked downstream Src/NF-κB pathway in tumor cells, promoting CXCR4/SDF1α-axis-mediated metastasis. High serum anti-HSPA4 IgG correlated with high tumor HSPA4 expression and poor prognosis of breast cancer subjects [63].

How B cell populations affected antitumor immunity varies in different types of cancers. Analysis of the RNA sequencing data from The Cancer Genome Atlas database revealed that gene expression signatures of B cells correlated with good prognosis in melanoma, lung adenocarcinoma, pancreatic adenocarcinoma, and head

and neck squamous cell carcinoma patients, but with poorer survival in renal tumor patients [64]. A recent review on B cells, plasma cells, and cancer was published by Sharonov et al. and provided a comprehensive summary of B cell involvement in cancers [65].

In the complex tumor microenvironment (TME), B cell populations with unknown functions have been discovered. Mature $CD27^{-}IgG^{+}$ memory B cells were found in human ovarian and liver cancer samples, expressing antigen-presenting cells surface markers (MHC Class II, CD40, CD80, and CD86), and cooperated or co-localized with $CD8^{+}$ T cells [66, 67]). Circulating memory B cells significantly increased in breast cancer patients [68], with unknown prognostic significance. In glioblastoma, lymphocytes with both T and B markers were detected [69], corroborating that the tumor microenvironment promoted aberrant immune cell development.

9.3 Fatty Acid Oxidation in Germinal Center B Cells

Just as our understanding of B cells' function in tumors is limited, our knowledge of their lipid metabolism is even scarce. Lipid metabolism in tumor-related B cells is an ongoing research topic with few published studies. To provide the readers with some clues in this subject, here we summarized mainly discoveries on normal B cell lipid metabolism, focusing on fatty acid oxidation in germinal center B cells. Cautions shall be taken when postulates from observations made in normal B cells, as tumor microenvironment poses unique challenges for B cells, including but not limited to hypoxia, possible acidosis, limited nutrients, etc. [70].

In healthy people, B cells can be activated in the secondary lymphoid organs including the spleen, lymph node, Peyer's patches, mucosal-associated lymphoid tissue, etc. In these organs, B cells are activated upon antigen binding in the primary follicles; start to proliferate, forming a secondary follicle; and then become a GC.

Quiescent B cells (Naive B, memory B, and long-lived plasma B cells) have a low energy demand and mainly adopt OXPHOS. Once activated, B cells start proliferation and greatly increase their energy demand. Glucose uptake is increased and mainly used for the synthesis of ribonucleotides. Glutamine contributes to the TCA cycle and subsequently provides building blocks by connecting to the pentose phosphate pathway. An earlier study has discovered that in the terminal differentiation phase, murine B cells express CD36, a fatty acid importer under control of the transcription factor Oct2, indicating the importing of fatty acids at the final stage of B cell differentiation [71].

The GC is a microstructure found in all secondary lymphoid organs, composed of the light zone and dark zone. In the light zone, B cells encounter the follicular dendritic cells that capture immune-complex associated antigen and compete for antigen stimulation based on their BCR affinity, followed by a competition for a limited pool of follicular T cells. B cells successfully passing the light zone selection move into the dark zone, proliferate, and induce the enzyme activation-induced cytosine deaminase (AID), and the BCR locus undergoes a high rate of somatic mutation (SHM). B cell clones with a high affinity for antigens emerge and further mature into plasmablasts or memory B cells.

Previously GC B cells have been thought to mainly adopt glycolysis pathway to fulfill their energy needs; however, a recent discovery identified fatty acids as the major fuel for GC B cells [72]. GC B cells adopted fatty acid oxidation for energy and minimally glucose uptake compared to activated splenic B cells, GC follicular T cells, and activated $CD4^{+}$ T cells. When palmitate was supplied in the culture medium, GC B cells produced a large amount of acetyl-CoA with little lactate. Cancer GC B cells are associated with better prognosis and immunotherapy success, and whether they rely on fatty acid oxidation warrants further investigation.

As introduced in Sect. 10.1, GC can be divided into the more hypoxia light zone and the less hypoxia dark zone. It's reported that FOXO1

plays a critical role in the formation and/or maintenance of the dark zone where B cells proliferate and undergo somatic hypermutation [2]. FOXO1 promotes fatty acid oxidation in cells, and whether FOXO1 also exerts similar effects in GC B cells warrants further investigation.

9.4 Factors that May Affect Tumor-Associated B Cell Lipid Metabolism

B cells adapt to the environment by responding to various factors, such as direct interaction with other immune cells, cytokines, hypoxia, and signaling molecules like oxysterols, just to name a few. Tumor microenvironment challenges B cells to differentiate and function normally: hypoxia and local deprivation of nutrients like glutamine, glucose, tryptophan, arginine, etc. could interfere with B cell maturation.

9.4.1 Hypoxia

Hypoxic gradients in GC are important for normal B cell maturation, and accumulating evidence indicate the Goldilocks conditions applied to GC B cell requirement of hypoxia: the hypoxia gradient in the GC has to be "just right" for successful B cell maturation. The main hypoxia sensors in the cell are transcription factors named hypoxia-inducible factors (HIFs). HIFs regulate multiple cellular pathways including cellular metabolisms to adapt to hypoxia stress. It's known that consistent HIF1α stabilization by B cell-specific VHL deletion results in B cell proliferation, decreased antigen-specific GC B cells, and impaired the generation of high-affinity IgG antibodies [73]. Whether/how the "right" GC hypoxia gradient is achieved in the tumor microenvironment is unknown.

HIF1α is known to induce glycolysis; increase fatty acid uptake, lipogenesis, and storage; and reduce its oxidation in cells. In the hypoxia tumor microenvironment, sustained activation of HIF1α in cancer cells inhibits fatty acid oxidation [74]. It has been reported that GC B cells increase glycolysis and mitochondria biogenesis via HIF and GSK3B, respectively [32]. The very recent discovery of fatty acid oxidation as the major energy fuel in GC B cells indicated that other transcription factors regulated the metabolic reprogramming. Both FOXO1 and Bcl6 could regulate this metabolic reprogramming, for FOXO1 is known to activate fatty acid oxidation, while Bcl6 is known to repress glycolysis in other cell types [30].

9.4.2 Nutrients Competition

Fatty acids in the tumor microenvironment are taken up by cells expressing fatty acid importers, for example, B cells and cancer cells with metastasis potential. Metabolic symbiosis exists in colon-rectal cancer regarding fatty acids: cancer-associated fibroblast stock up fatty acids and release them into the extracellular space, which are then taken up by cancer cells [75]. For GC B cells, a possible source of fatty acids is for the B cells, which undergo apoptosis due to insufficient receptor affinity. The relatively enclosed GC environment might provide some insulation for GC B cells against the metabolic competition in the tumor microenvironment. In contrast, tumor infiltrated T cells could face bigger metabolic challenges as activated T cells rely on glycolysis and must compete for glucose in the tumor microenvironment.

As an integral part of the metabolism network, fatty acid oxidation is affected by other metabolism pathways, and one of them is glutamine deficiency. Regional glutamine deficiency often occurs in tumor core and leads to a lack of α-ketoglutarate, which in turn leads to hypermethylation of histones in cancer cells, because histone demethylase JMJD3 requires α-ketoglutarate as a cofactor for removing methyl groups on H3k27 [76]. Whether this glutamine deficiency impairs the fatty acid oxidation in B cells is unknown.

9.5 Lipid Metabolites that Affect B Cell Function

9.5.1 Cholesterol

Cholesterol is synthesized in the liver and transported to other tissues as low-density lipoprotein, taken up by the cells via lipoprotein receptors. Cholesterol can be synthesized from HMG-CoA derived from acetyl-CoA, via the cholesterol biosynthesis pathway. Mevalonate is synthesized from HMG-CoA, and then farnesyl pyrophosphate (FPP) is synthesized and further converted into different signaling metabolites: (1) FPP is converted into geranylgeranyl pyrophosphate (GGPP), which prenylates important protein targets including small GTPase Rac, Rho, Rab, etc. (2) FPP is further metabolized to cholesterol and eventually generates either steroids or oxysterols, both are important signaling molecules. A summary of cholesterol metabolism and related B cell functions is shown in Fig. 9.3.

9.5.2 Geranylgeranyl Pyrophosphate

GGPP regulates cellular processes via posttranslational modification of important protein targets in B cells. GGPP drives the IL-10 production of regulatory B cells via PI3K-Akt signaling, revealing the critical roles played by cholesterol metabolism in regulatory B cells [77]. On the contrary, in autoimmunity-related disease and graft-versus-host disease, GGPP is important for CD40-mediated B cell activation [78]. How GGPP regulates tumor-associated B cells is an intriguing question, especially when considering potential cancer therapy with mevalonate pathway inhibition.

Mevalonate pathway is an important cancer therapy target as cancer cells rely on it for survival (reviewed by [79, 80]). Very recently, it's found that PTEN mutates cancer cells and *t*(4;14)-positive multiple myeloma cells generate GGPP via the mevalonate pathway, and statin kills these cells by decreasing GGPP [81, 82].

While statin starves cancer cells by decreasing GGPP, it also interferes with B cell activation [83]. Given that B cell expresses increased cholesterol biosynthesis enzymes upon activation by CD40-CD40L, and the important role of GGPP in CD40-mediated cell activation, statin's inhibitory effects in B cells might not be a direct consequence of reduced cellular cholesterol level, but of reduced GGPP. Treatment schemes have to be carefully designed to avoid statins' immune-suppressive effects when combining statin and immunotherapy in cancer treatment.

9.5.3 Oxysterol

Oxysterols are oxygenated derivatives of cholesterol and can be generated by cholesterol metabolism pathway or ingested from the diet. Oxysterols affect many cellular functions by binding to different proteins such as liver X receptors, oxysterol-binding proteins, ATP-binding cassette, etc. Accumulating evidence suggests that oxysterols play roles in cancers, including breast, prostate, colon, and bile duct cancers, which is nicely reviewed by Kloudova et al. [84].

Two oxysterols, 7α,25-dihydroxycholesterol (7a,25-HC) and 7α,27-dihydroxycholesterol (7a,27-HC), are ligands for a G protein-coupled receptor EBI2, also named as GPR183. Various immune cells express EBI2, including B cells. Oxysterols direct B cell migration via binding to EBI2 [85], and the oxysterol gradient generated by lymphoid stromal cells guides activated B cell migration [86]. EBI2 and 7α,25-HC deficiency both cause defective antibody responses. The function of the oxysterol-EBI2 axis in immune cells is comprehensively reviewed by Cyster et al. [87].

Recently, it's found that the EBI2-oxysterol axis promotes the development of intestinal lymphoid structures and colitis [88]. Since TLS resemble follicles of secondary lymphoid organs,

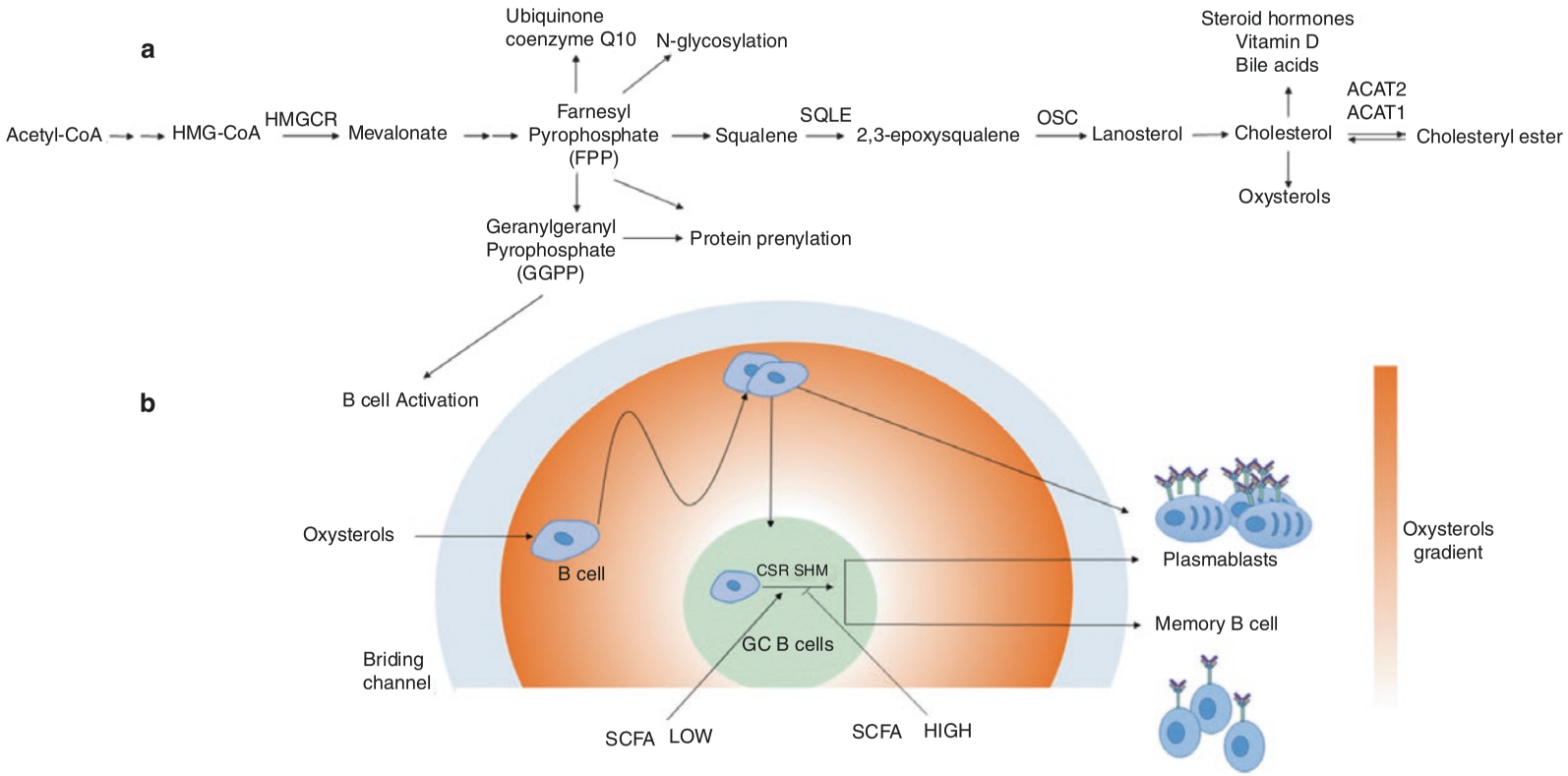

Fig. 9.3 GGPP, oxysterols, and short-chain fatty acids regulate B cell function. (**a**) Cholesterol biosynthesis and metabolism pathway generate GGPP and oxysterols. (**b**) A schematic of B cell regulation by GGPP, oxysterols, and short-chain fatty acids. GGPP regulates B cell activation; oxysterol gradient in TLS regulates B cell migration; short-chain fatty acids regulate GC B cell maturation: low dosage moderately enhances CSR, while high dosage reduces CSR, SHM, and plasma cell differentiation

the control of TLS development in cancer could be affected by oxysterols, too.

9.5.4 Short-Chain Fatty Acids

Butyrate and propionate are short-chain fatty acids generated by gut microbiota when fermenting dietary fibers, and both serve as histone deacetylase inhibitors. Previously it's reported that short-chain fatty acids increase acetyl-CoA production, glycolysis, mitochondrial respiration, and the production of lipid droplets in primary mouse B cells, indicating that these metabolic changes may aid in antibody production [89]. Recently, it's reported that by acting as HDAC inhibitors, butyrate and propionate can enhance or impair B cell antibody responses [90] in human and mouse B cells, depending on the doses. Low-dosage short-chain fatty acids moderately enhance class-switch DNA recombination (CSR), while higher doses of SCFAs decrease AID and Blimp1 expression, CSR, somatic hypermutation, and plasma cell differentiation.

9.6 Future Directions

Contrary to T cells, researches on the function and metabolisms of tumor-associated B cells only now start to gather momentum. Many questions remain open. What are the regulatory mechanisms controlling GC initiation/development in the tumor? How does the immune checkpoint blockade therapy affect tumor-associated B cells in metabolism reprogramming? In the often nutrient-depleted tumor microenvironment, how does TLS secure enough substrate to sustain its energy symbiosis? Do tumor-associated GC B cells utilize fatty acid oxidation to fulfill their energy needs? If so, how does it maintain redox balance and prevent lipid peroxidation/ferroptosis?

Technology advances have paved the way for answering these questions. Single-cell mass spectrometry (SCMS) can be applied for detecting lipid metabolites in a minimal amount of tissue/cell samples. For measuring metabolites in tumor-associated B cells, it's crucial to main the target cells in its native environment, i.e., tumor-associated GC/TLS, and quenching of the fresh cancer samples followed by mass imaging is an option. For peripheral B cells in cancer patients, MS methods established for circulating tumor cells shall be easily adopted [91]. Emphasis should be put on the metabolic symbiosis of the tumor-associated GC/TLS, as these microstructures determine immunotherapy success.

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