Metabolic requirements of Th17 cells and of B cells: Regulation and defects in health and in inflammatory diseases

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The immune system protects from infections and cancer through complex cellular networks. For this purpose, immune cells require well-developed mechanisms of energy generation. However, the immune system itself can also cause diseases when defective regulation results in the emergence of autoreactive lymphocytes. Recent studies provide insights into how differential patterns of immune cell responses are associated with selective metabolic pathways. This review will examine the changing metabolic requirements of Th17 cells and of B cells at different stages of their development and activation. Both cells provide protection but can also mediate diseases through the production of autoantibodies and proinflammatory mediators. In health, B cells produce antibodies and cytokines and present antigens to T cells to mount specific immunity. Th17 cells, on the other hand, provide protection against extracellular pathogens at mucosal surfaces but can also drive chronic inflammation. The latter cells can also promote the differentiation of B cells to plasma cells to produce more autoantibodies. Metabolism-regulated checkpoints at different stages of their development ensure that the self-reactive B cells clones and needless production of interleukin (IL-)17 are limited. The metabolic regulation of the two cell types has some similarities, e.g. the utility of hypoxia induced factor (HIF)1α during low oxygen tension, to prevent autoimmunity and regulate inflammation. There are also clear differences, as Th17 cells only are vulnerable to the lack of certain amino acids. B cells, unlike Th17 cells, are also dependent of mechanistic target of rapamycin 2 (mTORC2) to function. Significant knowledge has recently been gained, particularly on Th17 cells, on how metabolism regulates these cells through influencing their epigenome. Metabolic dysregulation of Th17 cells and B cells can lead to chronic inflammation. Disease associated alterations in the genome can, in addition, cause dysregulation to metabolism and, thereby, result in epigenetic alterations in these cells. Recent studies highlight how pathology can result from the cooperation between the two cell types but only few have so far addressed the...
key metabolic alterations in such settings. Knowledge of the impact of metabolic dysfunction on chronic inflammation and pathology can reveal novel therapeutic targets to treat such diseases.

### Metabolic requirements of T and B cells

Over the last decade, it has emerged that throughout their life spans, lymphocytes differentiate and function using distinct metabolic pathways, directed by specific functional needs at each stage of their development, the microenvironment, and the availability of nutrients and oxygen (O₂) tension. Basic metabolic pathways in these cells involve glycolysis and the pentose-phosphate pathway (PPP) that are key for their effector functions. During glycolysis, glucose is actively transported to the cytoplasm and metabolized by a set of 10 enzymes to generate energy-rich pyruvate and NAD⁺. In proliferating T cells that rely on glycolysis for their energy needs, NAD⁺ is reduced to NADH with lactate as a by-product. Low O₂ tension in certain niches, such as the bone marrow, the light zone (LZ) of GCs of B-cell follicles, and the mucosa, activates the transcription factor hypoxia-inducible factor 1α (HIF1α) that regulates genes that control glycolysis. Mechanistic target of rapamycin (mTOR) is a large protein complex located at the endosome of lymphocytes. The subcomponent Raptor associates with mTOR to form mTORC1, while Rictor associates with mTOR to form mTORC2. mTORC1 senses amino acid availability, regulates cell differentiation to effector cells, and determines the selection, or death of B cells in the LZ of GCs. mTORC2 is regulated via phosphatidylinositol 3-kinase (PI3K) and growth factor signaling and promotes the differentiation of Th cells to Th2 cells. mTORC2 also cooperates with mTORC1 in B-cell activation.
activated protein kinase (AMPK), which is localized to the cytoplasm or the lysosomes, is a crucial energy sensor that reduces cellular activity, augments fatty acid oxidation (FAO), and maintains quiescence of cells (7, 10, 11).

The glycolysis in the cytoplasm generates a limited amount of ATP and substrates for amino acid, nucleotide, and fatty acid biosynthesis as well as pyruvate for the more efficient energy producers, the mitochondria. In the mitochondrial compartment, the tricarboxylic acid (TCA) cycle is replenished by β-fatty acid oxidation, pyruvate and imported amino acids in what is called anaplerotic reactions. Pyruvate, which is transported from the cytoplasm, is converted in the mitochondria to TCA substrate acetyl-coenzyme A (acetyl-CoA) by the pyruvate dehydrogenase (PDH1). The TCA cycle provides substrates for the mitochondrial inner membrane-residing electron transport chain (ETC). The resulting conversion of O2 to H2O and NADH to NAD+ generates ATP in what is known as oxidative phosphorylation (OXPHOS). During this process, the ETC transports protons to the intermembrane space, thereby establishing mitochondrial membrane potential (∆Ψm). This potential is essential for the function and metabolism of effector cells and for their early progenitors to develop in the bone marrow (12). During activation, the availability/lack of nutrients and O2 tension influence ∆Ψm. The mitochondria also have a role in Ca2+ homeostasis, with the ion being transported from the endoplasmic reticulum (ER) and from outside of the cell and, therefore, influencing ∆Ψm in the process. TCR and BCR signaling results in increased mitochondrial Ca2+ (13). Metabolites generated through anaplerosis contribute to the biomass but also influence epigenetic regulators and gene transcription (see Table 1 for Th17 cells). The TCA cycle and OXPHOS provide basal functional requirements to all cells and are the only pathways that drive naive and non-activated memory T, B, and Tregs. It is now widely recognized that changes to the metabolic properties of different cell subsets are of fundamental importance to the regulation of the cell-specific transcriptional programs and effector functions.

The focus of this review is on the changing metabolic requirements of Th17 cells and of B cells at different stages of their development and activation. These two cell types have been selected because of their role in promoting chronic inflammation that underpins pathology in most chronic diseases. Generally, metabolism-regulated checkpoints at different stages of lymphocyte development are instilled to prevent the emergence of self-reactive B- and T-cell clones (Table 2 for B cells). Metabolic regulation of B cells and Th17 cells have similarities. For example, both cell types utilize HIF1α during low oxygen tension. In addition, both cells express the anti-inflammatory adenosine-sensing CD73 molecule (4, 5, 29). The two cell types, nevertheless, have differences too. As will be discussed later on, Th17 cells are particularly vulnerable to the lack of certain amino acids. This latter issue has not been reported in B cells (15, 30). B cells, unlike Th17 cells, are dependent on mTORC2 for their functions (9). Although lymphocyte activation following TCR and BCR engagements induce metabolic changes required for immunity against pathogens, it is increasingly recognized that metabolic dysregulation of Th17 cells or B cells relates to the development of autoimmune diseases due to defective tolerance (17, 31). Disease-associated genetic variations might be one cause of metabolism and epigenic dysregulation in these cells (32, 33). Recent reports have highlighted autoimmune pathology-inducing interactions between the two cell types, metabolic alterations resulting in epigenetic changes to Th17 cells.

| Metabolic alteration | Effect | Epigenetic / transcription factor change | Th17/ Treg | Reference |
|----------------------|--------|----------------------------------------|------------|-----------|
| Glutamine intake     | ↓ 2-HG | Methylation of the Fospr3 promoter     | Treg ↓     | (14)      |
| Lack of glutamine    | ↓ ROS  | HJK4 methylation, promoter of genes involved in Th17 cell differentiation; Il17 and Batf and cell cycle | Th17 ↓     | (15)      |
| Lack of methionine   | ↓ SAM  | Acetylation of HJK9Ac and HJK27Ac in the Il17 promoter | Th17 ↑     | (16)      |
| High (GLS1 and)      | ↓ SAM  | DNA demethylation in the Fospr3 promoter | Treg ↓     | (18)      |
| Acetyl-CoA            |        | Foxp3 ↑                                | Th17/ Treg |           |
| Inhibition of        |        | 1) Associate with ROYRy and p300        | Th17/ Treg |           |
| polyamine metabolism |        | 2) Binds FOXP3                          |            |           |
| Pentanoate from      | Histone deacetylase inhibitor           | Th17 ↓     | (21)      |
| SFB                  |        |                                        |            |           |

GLS, glutaminase 1; GOT1, glutamate oxaloacetate transaminase 1; 2-HG, 2-hydroxyglutarate; MTHFD2, bifunctional methylenetetrahydrofolate dehydrogenase/cyclohydrolase; SAM, S-adenosylmethionine; SFB, segmented filamentous bacteria. ↓ increased, ↓ decreased.
Spleen and lymph nodes

Spleen

Tbx21 plays a role in metabolism in these cells, as activation of the chromosomal markers favoring a Th1 gene signature including primed to become Th1 cells (39). This is reflected by the transcription factor in naive T cells, indicates that the cells are primed to become Th1 cells (39). Tbx21 also appears to play a role in metabolism in these cells, as Tbx21−/− mice have increased visceral adiposity but are more insulin-sensitive, exhibiting reduced immune cell numbers and cytokine secretion specifically in the visceral fat depot, perhaps due to altered T-cell trafficking (14). The Th1 program is activated in lymph nodes (LNs) following TCR engagement. This leads to the upregulation of the glucose transporter GLUT1, activation of glycolysis and mTORC1, and differentiation of the cells (15). Th2 cells, in contrast, rely on mTORC2 for their differentiation that also inhibits the Th1 program (16, 41).

TABLE 2  Metabolism at B-cell stages where clones with low antigen specificity or self-reactivity are excluded.

| Bone marrow | Exclusion selection due to self reactivity / low antigen specificity | Metabolism type | Reference |
|-------------|---------------------------------------------------------------|----------------|-----------|
| Large pre-B cells | Autoreactivity of the IgH chain | Glycolysis ↑, OXPHOS ↑, Low O2−, HIF1α ↑ | (22, 23) |
| Immature B cells | Autoreactivity of BCR | Glycolysis ↑, OXPHOS ↓, FOXP3↑ | (23, 24) |
| Spleen | Transitional B cell | Autoreactivity of BCR | Glycolysis ↑, OXPHOS ↑ | (7) |
| Spleen and lymph nodes | Activated B cell | BCR not recognized via CD40 or TLR | Glycolysis ↑, OXPHOS ↑ | (25, 26) |
| Light Zone B cell | Competition for BCR selection, IgH class switch | GSK3↑, Low O2−, HIF1α↑ | (5, 8, 27, 28) |

↑ increased, ↓ decreased.

but only a few have so far assessed altered metabolic properties of the two cell types during such scenarios (34–36).

Metabolism in T cells

T-cell progenitors are produced in the bone marrow. They migrate to the thymus where they undergo development, including rearrangement of their TCR genes, positive recognition of the major histocompatibility complex II, and tolerance to prevent self-reactivity. During these developmental phases, the functioning metabolic pathway changes with high glycolysis and OXPHOS during TCR arrangement followed by low metabolic activity during positive and negative selections (37). Thymic outputs are highest during childhood, continue at a slower rate in adolescence, and are then much reduced after the third decade of life, and these changes are reflected by changes in thymocyte metabolism (38).

After exiting the thymus, naive T cells remain quiescent while circulating through blood and the lymphatics (30). The cells express low amino acid transporter levels, have low glucose transport capacity, and rely on OXPHOS and FAO (30). Expression of the T-bet gene, TBX21, an immune cell transcription factor in naive T cells, indicates that the cells are primed to become Th1 cells (39). This is reflected by chromosomal markers favoring a Th1 gene signature including activation of the IFNG gene locus (40). T-bet also appears to play a role in metabolism in these cells, as Tbx21−/− mice have increased visceral adiposity but are more insulin-sensitive, exhibiting reduced immune cell numbers and cytokine secretion specifically in the visceral fat depot, perhaps due to altered T-cell trafficking (14). The effector Th1 program is activated in lymph nodes (LNs) following TCR engagement. This leads to the upregulation of the glucose transporter GLUT1, activation of glycolysis and mTORC1, and differentiation of the cells (15). Th2 cells, in contrast, rely on mTORC2 for their differentiation that also inhibits the Th1 program (16, 41). nTregs and iTregs rely on OXPHOS and FAO during their resting state but require glycolysis and mTORC1 when activated in LNs or in the periphery (10, 42, 43). Perhaps paradoxically, however, this activation was also shown to reduce their suppressive activity (44). Th1 cells use glycolysis and OXPHOS selectively in response to changes in substrate availability in the GC where they reside (45). Being a focus of the review, Th17-cell metabolism will be described in more detail below. Interestingly, metabolism of activated Th17 cells has many similarities with that of Th1 cells. Antigen presentation in mesenteric LNs induces metabolic changes and the establishment of a Th17 differentiation program in naive T cells (46). Following TCR engagement, just as for Th1 cells, transcription of genes involved in glycolysis, including GLUT1, is upregulated (Figure 1A). Stromal interaction molecule 1 (STIM1) expressed in the ER undergoes conformational changes that augment Ca2+ release from intracellular compartments and its influx through cell membrane channels in Th1 and Th17 cells. These events promote glycolysis and OXPHOS and lead ultimately to IL-17 production, while RORγt level remains unaffected by the change in Ca2+ levels (47). Hence, not only is glycolysis, but also OXPHOS is essential for the early molecular events leading to Th17 differentiation. Induction of the transcription factors BATF and STAT3 are such early events (48). TCR engagement activates mTORC1 via PI3K/Akt, which also promotes cell differentiation (49). Th17 cells lacking Raptor lose the ability to develop effector functions (6). In addition, activated effector Th17 cells have a high ΔΨm (12). Interestingly, among T lymphocytes, Th17 cells are unique in displaying functional flexibility. For example, Th17 cells can transdifferentiate to both Tregs and pathogenic Th17 cells, the latter often associated with the ability to produce Interferon-γ (IFNγ) (Figure 1C) (1, 46). Th17 cells can transdifferentiate to pathogenic Th17 cells in response to severe bacterial and fungal infections (described in the section on Changes in Th17-Cell Metabolism Are Related to Its Physiological Functions) (46, 47).
Th17-cell metabolism

Th17 cells, unlike Th1 cells, divert glycolysis-derived pyruvate away from the TCA cycle as PDH1 is downregulated in the cells (50). PDH1 is Ca$^{2+}$ sensitive, but whether the increased levels of Ca$^{2+}$ in Th17 cells in response to TCR stimulation influence PDH1 differently to Th1 cells has not been addressed (13). In Tregs, however, PDH1 is required for their function and, consequently, limiting autoimmunity, inflammation, and chronic disease (18). Since pyruvate is diverted from OXPHOS, Th17 cells will become dependent on amino acids as substrates for anaplerosis (Figure 1A). The importance of certain amino acids for Th17 functions is highlighted by the fact that only these cells among all T-cell subsets cease to proliferate when the glutamate-proline tRNA ligase EPRS1 is inhibited, or cysteine or methionine is depleted, resulting in phosphorylation of the stress sensor general control nonderepressible 2 (GCN2). The importance of glutamine as a substrate for Th17-cell metabolism is highlighted by that the glutamine transporter SLC1A5 and the glutamine-degrading enzyme glutaminase 1 (GLS1) are being expressed at high levels in these cells. Hence, the culture of Th17 cells in media lacking glutamine, or the ablation of GLS1, inhibits the function of the cells (15). Glutamate, the product of glutamine degradation, is a constituent to the reactive oxygen species (ROS)-scavenging glutathione but can also be metabolized to 2-hydroxyglutarate (2-HG) via $\alpha$-ketoglutarate (51). GLS1 deficiency both increases ROS and alters cells’ epigenetic status by inducing trimethylation of histone H3K27 at many chromosomal locations (Table 1). Inhibition of ROS alters these epigenetic marks, indicating that glutamine supports Th17 cells by inhibiting ROS and its influence on epigenetic gene control. ROS is also an activator of mTORC1, underpinning the importance of this protein complex in Th17-cell functions. In support of this theme, ablation of the catalytic subunit of glutamate cysteine ligase (Gclc) in T cells results in glutathione depletion and impaired mTORC1 activity (52). Th1 cells, in contrast, adapt to GLS inhibition and increase glucose uptake for anaplerotic reactions to maintain cell phenotypes (15). Methionine restriction, in contrast, reduces the production of S-adenosyl methionine (SAM) that is required for histone H3K4 methylation at the promoter regions of Th17 cells, thus, inhibiting their proliferation and IL-17 production (Figure 1B, Table 1) (53).
Cytoplasmic acetyl-coenzyme carboxylase 1 (ACCL) is upregulated in Th17 cells. ACC1 utilizes pyruvate-derived acetyl-CoA as metabolite for lipid synthesis (54). Lipids generated because of this reaction interact with RORγt and increase its activity in driving Th17-cell differentiation. Acetyl-CoA produced from glutamine also regulates IL-17 production by acetylation of histone H3, thereby exposing the IL-17A promoter for RORγt transcriptional activity (17).

In addition, Th17 cells have a unique response pattern to environmental stresses. Thus, these cells cease to proliferate to deficit in specific amino acids (15, 55). In contrast, low O2 tension, both high and low levels of glucose, mannitol-induced osmotic stress, and high levels of NaCl promote Th17-cell proliferation (19, 56, 57). Low glucose levels reduce IL-2 production and STAT5 signaling, which is unfavorable for T cells other than Th17 cells (58). Relevant to these observations is that Th17 cells require a lower TCR signaling strength than Th1 cells to be activated. However, this results in reduced IL-2 production (58, 59). High levels of glucose, in contrast, induce Th17 cells. In this setting, neither glycolysis nor OXPHOS is affected, but high glucose levels induce mitochondrial ROS (mtROS) production. mtROS is released extracellularly where it converts TGFβ from its latent form to its active one that, in turn, supports the development of Th17 cells (57). Mannitol-induced osmotic stress promotes Ca2+ release from Th17 cells’ ER, and this influx augments Th17 cell responses (19). Compared with Th1 cells, Th17 cells are specifically regulated by HIF1α and mTORCl. Of note, in mice, HIF1α did directly associate with RORγt to promote Th17-cell differentiation (20). It is, thus, intriguing to speculate that this reliance of HIF1α reflects the Th17-cell localization to mucosal membranes where the 02 tension can be low and antigen-presenting cells are scarce (4, 22, 29).

As cited in the previous section, Th17 cells can transdifferentiate to Tregs or to pathogenic Th17 cells, and this process manifest metabolic alterations. Such alterations can be induced experimentally, or by disease. Experimentally induced metabolic dysregulation can induce Th17 transdifferentiation to Tregs. One carbon (1C) metabolism is important for T-cell activation (30). The 1C metabolism consists of a series of interlinking metabolic pathways, including the methionine and folate cycles. The methionine/folate pathways, thus, involve folate/methionine providing 1 methyl group for the synthesis of purine nucleotides for DNA synthesis, polyamines, amino acids, creatine, and phospholipids. One of the enzymes in the mitochondrial branch of the 1C pathway, the bifunctional methylenetetrahydrofolate dehydrogenase/cyclohydrolase 2 (MTHFD2), is important for Th17-cell functions. Inhibition of MTHFD2 results in reduced mTORC1 activity, increased OXPHOS, and reduced abundance of succinate and fumarate (60). MTHFD2 deficiency results in increased DNA demethylation including in the FOXP3 promoter-locus, thereby shifting pathogenic Th17 cells to acquire a Treg phenotype (Table 1) (60). Another study revealed that 2-HG produced by glutamate oxaloacetate transaminase 1 (GOT1) facilitated methylation and silencing of the FOXP3 promoter. Inhibition of GOT1 activity on the other hand converted Th17 cells to iTregs (51). Furthermore, chronic infection, malignancy, and T-cell exhaustion are known to upregulate the receptor PD-1 on T cells. PD-1 augmentation promotes FAO and inhibits glycolysis which could impede on Th17-cell effector function and promote a regulatory phenotype shift (61). Along similar lines, TGFβ and IL-6 upregulate CD73 expression on Th17 cells and this renders the cells anti-inflammatory in a tumor microenvironment (23). CD73 is an ecto-5’-nucleotidase that degrades AMP, derived from ATP or from NAD, generating the anti-inflammatory metabolite adenosine (23, 24). Adenosine, in turn, binds receptors on immune cells to trigger anti-inflammatory activities. Intriguingly, CD73 is also expressed on B cells (24).

Different approaches have been used to probe the heterogeneity of Th17 cells (62). Enrichment of Th17 cells based on their ΔΨm identified high-ΔΨm cells expressing higher levels of IL-17, while cells with low ΔΨm expressed higher levels of the stemness markers TCF1 and LEF1 (12). Furthermore, mice with T cells lacking Raptor produced Th17 cells with low metabolic activity, and expression of TCF1 (Figure 1D) (6). In contrast, Th17 cells with intact mTORC1 showed a capacity to transdifferentiate to pathogenic Th17 cells signified by the ability to produce IFNγ. A study using single-cell RNA sequencing (scRNA-seq) confirmed the Th17 cells’ metabolic heterogeneity. The study revealed that protective Th17 cells accumulate arginine while pathogenic Th17 cells synthesize and recycle polyamines, with putrescine being the mediator that best augments the cells’ activities. Inhibition of polyamine metabolism also promotes FOXP3 expression (Figure 1C) (62). In another study, putrescine was shown to have no impact on Th17 differentiation when added during in vitro cultures (63). These findings highlight the difference between studies of Th17-cell metabolism in vitro and in vivo and the value identifying of specific differences using scRNA-seq (62, 63).

### B-cell metabolism

Early studies have identified two distinct B-cell lineages in mice and, probably in humans. These two B-cell lineages are distinguished phenotypically by the expression of CD5, a primarily T cell-associated membrane protein. The two subsets were designated conventional or CD5- B cells (also called B2 cells) and CD5+ B cells (B1 cells) that produce natural polyreactive IgM antibodies. The developmental pathway of the B2-cell lineage is shown in Figure 2. Cellular metabolism during clonal B2-cell selection/exclusion influenced by their BCR is shown in Table 2 and Figure 2. B1 cells have been
suggested to have diverged during the embryonic stage in mice and have the ability for self-renewal. These cells are endowed with high glycolysis and OXPHOS activity (64). In addition to these two lineage cells, a subset of B cells that regulates immunity and inflammation and promotes differentiation of naïve T cells to iTregs, called Bregs, have been identified. Bregs' functions are contact-dependent and can involve IL-10 production [metabolism reviewed in Iperi et al. (65)].

Conventional B2 cells are produced in the bone marrow from hematopoietic stem cells. B2 precursors undergo gene rearrangements in the bone marrow that ultimately result in the expression of diverse BCR repertoires at the latter stages of pro- and pre-B-cell developments. The progenitor cells localize to different niches in the bone marrow with varying degrees of oxygen tension, thus, influencing the cells' metabolic characteristics. Pro-B cells have the highest Δψm, but this is incrementally diminished during the subsequent stages of their development. OXPHOS activity is similar in pro- and large pre-B-cell stages, but the latter cells have the highest glycolytic activities among the progenitors, accompanied by high levels of ROS. Reflecting a niche with low oxygen tension, HIF1α is active during the pre-B-cell stages, thus, driving glycolysis. When HIF1α is experimentally deleted, B cells switch their metabolism to TCA anaplerosis for their energy needs (66). The Ca<sup>2+</sup>-binding protein Swiprosin-2/EF-hand domain family member D1 (EFhd1) was found to be located to the inner mitochondrial membrane of pro-B cells. Due to the emergence of the pre-BCR in late pro-B cells, Ca<sup>2+</sup> is directed from the ER to the mitochondria. This results in an increased mitochondrial pH and a drop in Δψm and ATP production. Detectable
“mitoflashes,” likely due to a drop in mitochondrial pH, occur in regions with EFhd1 and Ca$^{2+}$. This is likely to be a means to rescue Δψm and increase ATP production in these cells. Ca$^{2+}$ signaling downstream of SYK is important for pre-BCR signaling in pre-B cells and is related to these noted events (27, 67). EFhd1 is downregulated at the pre-B-cell stage consequent to the localization of the pre-BCR to the membrane and the migration of the cells to a niche with low O$_2$. Subsequent anaplerotic reactions provide protection from ROS and growth (67, 68). Glycolysis and OXPHOS are reduced in pre-B cells compared with the B-cells at their earlier developmental stages. Downregulation of PI3K/Akt and ROS-mediated induction of FOXO1 together with the expression of the lineage-defining transcription factor paired box 5 (PAX5) induce cell cycle arrest while light-chain genes are rearranged (69). Provided that the BCR does not bind avidly to self-antigens, a program of maturation follows surface expression of the complete BCR (25).

Immature B cells eventually exit the bone marrow as transitional 1 (T1) B cells. T1 B cells express higher levels of genes involved in ribosome biogenesis, aerobic respiration, and mTORC1 than B cells at later stages of their maturation pathway but, in contrast, express low AMPK levels. Interestingly, studies of mice deficient in the mTORC2 component Sin1 showed a reduction in T1 and T2 B cells. mTORC2 was reported to increase Akt signaling, stabilize mTORC1, and suppress glycogen synthase kinase-3 (GSK3) (9). In vitro treatment with the AMPK agonist 5-Aminomidazole-4-carboxamide ribonucleotide (AICAR) supports the evolution of T1 B cells to conventional B2 cells (7).

In vivo, the progression of T1 to T2 B cells takes place mostly in the spleen where tolerance checkpoints are in place to eliminate residual autoreactive T1 B-cell clones and to prevent their transition to mature B cells (26). B cells that survive peripheral tolerance checkpoints develop either to mature naive B cells or to marginal zone B cells (MZB, see below). Naive B cells are metabolically inactive and circulate through the blood and lymphatics (30). Tonic signaling through the BCR and signals mediated by B-cell activating factor (BAFF) preserve homeostatic mitochondrial signals in naive B cells (70). In contrast, AMPK, GSK3, and PAX5 suppress glucose uptake and maintain quiescence in mature non-activated B cells (7, 71, 72).

Mature naive B cells are activated when they encounter and bind their target antigens through their BCRs, mostly, in the presence of T-cell help. This results in Myc- and PI3K-mediated GLUT1 expression, glycolysis, and glutamine-supplemented anaplerosis for OXPHOS (73). The cells initiate a transcriptional program to remodel the mitochondria and increase their glycolytic activities. To prevent abnormal activation and/or the expansion of residual unswitched autoreactive B cells, the cells require a second stimulation within 24 h that can either be T cell mediated (CD40) or through Toll-like receptor (TLR9) (74). Stimulated B cells upregulate chemokine (C-C motif) receptor 7 (CCR7) and move to nearby secondary lymphoid organs to proliferate inside or outside GCs. Ectopic GCs can be initiated in non-lymphoid organs during chronic inflammation and autoimmunity. Without a second activation signal, increasing intracellular Ca$^{2+}$ levels transported through calcium channels and increasing levels of ROS will ultimately lead to the apoptosis of antigen-primed B cells (74).

In lymphoid organs, on the boundaries between T- and B-cell areas, B cells present fragments of the antigen recognized by their BCRs for cognate Th-cell interaction together with costimulatory signals. These B cells can develop independent of GCs into short-lived extral follicular plasma cells that are important for the initial wave of protective antibodies. Alternatively, these cells can differentiate to unswitched memory B cells. Other B cells will migrate into B-cell follicles to initiate GC reactions and become founders for clones whose antibodies acquire increasing affinity for the antigen in the newly formed GCs. GCs will evolve into two zones, the dark zone (DZ) closest to the T-cell zone in LNs and the LZ that is closest to the capsule in LNs and marginal zones of the spleen and with cells shuffling in-between guided by chemokine signals. B cells actively divide in the LZ and express activation-induced cytidine deaminase (AID) enzyme and mediate somatic hypermutation (SHM). BCR and CD40 are required for Myc-regulated expression of metabolic enzymes and membrane transporters. B cells do not proliferate in the LZ and, instead, compete for selection during interactions with antigens expressed on follicular dendritic cells (FDCs) and obtaining help from ThFB cells. FDCs and ThFB cells regulate positive selection, while TFB cells suppress the output of activated B cells (28). Strength of the B cell/ThFB cell interaction determines later proliferation efficiency in the DZ (75). As the LZ is farthest from the blood supply and oxygen in GCs, HIF1α is activated. This activation prevents AID activity and, thereby, restricts Ig class switching but, interestingly, not SHM. mTORC1 regulates HIF1α and the Von Hippel–Lindau tumor suppressor while GSK3 protects B cells from deprivation of glucose and nutrients (5, 8, 71). Fatty acids (FAs) from other surrounding B cells, dying due to lack of costimulation, supply OXPHOS (76). PKCβ regulates antigen presentation in B cells and, therefore, the development of ThFB cells to support further B-cell proliferation and differentiation (77). Class-switched B cells subsequently undergo repeated expansion in the DZ or exit the GC. Memory B cells and long-lived plasma cells (LLPCs) have exit cues from the GC that correlate with BCR affinity and time since the response began (75). Memory B cells circulate and when reactivated by their target antigens start producing antibodies or initiate another GC reaction for further affinity maturation. Memory B cells are signified by low-level metabolism relying primarily on OXPHOS. LLPCs migrate to the bone marrow and, guided by the transcription factor Blimp-1, mature to cells...
Changes in Th17-cell metabolism are related to its physiological functions

During homeostasis, IL-22-producing Th17 cells are primarily found in the mucosa of the intestine conferring protection and supporting intestinal barriers. DCs present antigens from the intestinal microflora to naïve T cells in mesenteric LNs leading to the expression of RORγt and the gut homing receptor α4β7 by the cells. The cells subsequently proliferate and migrate to Peyer’s patches and intestinal mucosa to start protective activities (21, 46, 82). Infection with the commensal segmented filamentous bacteria (SFB) in mice results in effector Th17 cells in the intestine with elongated mitochondria, relying on OXPHOS to produce Nicotinamide adenine dinucleotide phosphate (NADPH) and glutathione. Infection with the pathogen *Citrobacter rodentium*, in contrast, results in pathogenic Th17 cells that coproduce IL-17 and IFNγ. The latter Th17 cells have fragmented mitochondrial morphology and rely on glycolysis for their metabolic needs. The IFNγ-producing Th17 cells cannot transdifferentiate from resident intestinal Th17 cells but are originated in the LNs. The pathogenic Th17 cells, unlike Th17 cells from SFB-infected mice, can also disseminate to spleens of infected mice (46). The bacterial flora produces short-chain fatty acids (SCFAs) such as pentanoate. These SCFAs act in Th17 cells as a histone deacetylase inhibitor, thereby suppressing IL-17 transcription. Pentanoate from SFB can, therefore, reduce Th17 activity in the intestine (83).

Studies in mice have revealed that Th17 cells differentiate to tissue-resident memory T (Trm) cells to provide protection against bacterial and fungal infections in the lungs and skin (84, 85). These cells provide protection mainly through the recruitment of neutrophils (47). Deletion, or mutations described in patients, of *STIM1* that regulates Ca2+ uptake in Th17 cells leads to impaired fungal defenses, dissemination in kidneys, and eventual death. *In vitro* analyses of non-pathogenic and pathogenic STIM1-deficient Th17 cells showed that the non-pathogenic subset of cells was most dependent on STIM1. Expression of HIF1α target genes, mTORC1 activation, glycolysis, and OXPHOS are reduced in these cells, while the FOXO1 pathway is upregulated. Thus, specifically for non-pathogenic Th17 cells, extracellular Ca2+ is important for effective immunity to fungal infections (47). Hence, non-pathogenic Th17 cells rely on Ca2+ imported via STIM1, glycolysis, and OXPHOS, while pathogenic Th17 cells, stimulated by severe bacterial and fungal infections, utilize glycolysis only (46, 47). Low oxygen tension (activation of HIF1α) may thus, promote a pathogenic phenotype. Such findings are in line with a recent study comparing pathogenic and non-pathogenic Th17 cells in a model of multiple sclerosis (22). This, apparently, is associated with a lack or reduced supply of amino acids (15, 49).

The contribution of dysregulated Th17-cell metabolism to disease pathogenesis

Th17-cell metabolism in psoriasis

Psoriasis is the consequence of uncontrolled proliferation of dermal keratinocytes. The disease affects 2%–3% of populations worldwide and manifests in scaly plaques that in the disease’s severe form cover more than 10% of the body. Th17 cells, present in the dermis of patients as IL-17-producing Trm cells, contribute to psoriasis pathology, evidenced by therapeutic efficacy of treatment with anti-IL-17 antibody in reducing plaques (86). Th17-cell metabolism was studied in an animal model of psoriasis and discovered that the production of the mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) was dysregulated in Th17 cells. MALT1 stabilizes c-jun that could then bind and activate GLS1 expression, resulting in increased glutaminolysis in Th17 cells. GLS1’s overexpression in patients’ Th17 cells leads to high levels of acetyl-CoA production. This metabolite, in turn, induces histone H3 acetylation; specifically, H3K9Ac and H3K27Ac marks in the IL-17A gene promoter region resulting in increased IL-17 production leading to pathology (Figure 3A). This investigation revealed that GLS, or MALT1 inhibitors, previously considered as cancer therapy, can be a potential treatment for psoriasis (17).

Th17-cell metabolism in rheumatoid arthritis

Rheumatoid arthritis (RA) is a debilitating disease mainly affecting joints in 0.5%–1% of populations worldwide. The synovial lining of RA joints is targeted by an immune
response that causes juxta-articular and generalized bone loss. The level of IL-17 is reduced at disease onset compared with before onset (87). Naive CD4+ T cells in patients with established RA are, however, prone to differentiate to Th17 cells (39). Naive T cells from RA patients manifest defective glycolysis resulting in diminished levels of ATP, low ROS, and an overall defective mitochondrial function (88). The GDP-forming β subunit of succinate-CoA ligase (SUCLG2), part of the TCA, was reported suppressed, resulting in reversal of the cycle. This reversal induces IL-17- and IFNγ-mediated inflammation, as shown by the transfer of patient peripheral blood mononucleated cells (PBMCs) to immune compromised NOD Scid gamma mice that harbor patient synovium transplants. Overexpression of SUCLG2 in these PBMCs reduced IL-17 production. As a consequence of the SUCLG2 defect, citrate was transported out of mitochondria and converted to acetyl-CoA, clustering mitochondria perinuclear and increasing T-cell invasiveness (31). Inflammation and migratory properties suggest that mTORC1 activation and efficient OXPHOS are involved. However, the above-cited studies suggest that these pathways are dysregulated in RA. AMPK was found to be displaced and, thereby, could not regulate mTORC1, resulting in high-level production of IL-17 and IFNγ. This AMPK defect could, therefore, explain the inflammation caused by the cells (Figure 3B) (11). Indeed, an appropriately located AMPK is able to drive FAO favoring Tregs instead of Th17 cells (10). In arthritic joints, there is an enrichment of Th17 cells that can promote arthritis by inducing the production of pro-inflammatory cytokines and receptor activator of nuclear factor κB ligand (RANKL) while inhibiting apoptosis in synoviocytes. Hypoxia in the inflamed synovium favors both the development of Th17 cells and T cells with defective OXPHOS. Furthermore, levels of glutamine and glutamate are high in the synovial fluid of RA patients (89). In a study using an animal model of RA, mTORC1 and glutamine metabolism were simultaneously suppressed using rapamycin and 6-diazo-5-oxo-L-norleucine (DON). This combination reduced Th17 proliferation and arthritic scores. Rapamycin, but not DON, also increased Tregs. Although prior usage of DON as therapy for malignancy was hampered by side effects, inhibition of autoreactive immune cells’ utility of glutamine might be worth considering (90, 91). The inflammatory environment increases the level of lactate in patients’ synovial fluid. One study observed that Th17 cells that took up lactate might be worth considering (90, 91). The inflammatory environment increases the level of lactate in patients’ synovial fluid. One study observed that Th17 cells that took up lactate were unable to migrate, therefore, residing in the synovium (92). It should be pointed out, however, that although Th17 cells are a prominent part of RA pathology, treatment using anti-IL-17 has not shown strong beneficial effects at a level comparable to anti-TNFα (93). A better characterization of these heterogeneous cells and stratification of patients can, potentially, provide better understanding of when anti-IL-17 therapy would be of optimal therapeutic benefit. In that context, a recent study has shown that T cells from RA patients, already as naive, have a dysregulated malate-aspartate cycle, resulting in elevated levels of NAD+ and the expansion of the ER where TNFα was produced. T cells were noted to be a major producer of TNFα compared with monocytes/macrophages (94, 95). Anti-TNFα is currently used as an efficacious therapy in RA patients, but the targeting of the mitochondria-ER cross talk might be a novel more specific therapeutic option (94). Studies have shown that non-responsiveness to anti-TNFα is, however, associated with a Th17-cell signature, potentially, indicating that T cells from

![Image](https://via.placeholder.com/150.png?text=Figure3.png)
these individuals suffer from a metabolic disorder that is distinct from anti-TNFα responder patients (96). Better understanding of such disease-associated defective metabolism might prove useful for the development of therapeutics to induce durable tolerance in anti-TNFα non-responders (60, 62).

### Th17-cell metabolism in systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is another autoimmune disease that affects 20–70 individuals per 100,000 of the population. Patients suffer a range of symptoms; skin and kidneys are affected, probably, due to a defective removal of apoptotic bodies leading to the accumulation of cell debris of nuclear, cytosolic, and membrane origins. This debris activates autoreactive B cells in GCs and elsewhere to proliferate and activate autoreactive T cells leading to the production of anti-nuclear autoantibodies that form complement- and phagocyte-activating immune complexes. Th17 cells in SLE are signified by increased mTORC1, glycolysis, and OXPHOS. Mitochondria from lymphocytes in SLE patients are elongated, have high ΔΨm, and produce mtROS (97). Excessive elongation of mitochondria can be explained by increased degradation of Drp1, which regulates mitochondrial fission. High levels of oxidative stress lead to overexpression of the regulator of endocytic recycling Rab4A, Rab4A, which is genetically associated with SLE, therefore, recycles Drp1 leading to the elongated mitochondria phenotype (32). A long terminal repeat polymorphism in the RAB4A promoter has, moreover, been identified and shown to be associated with SLE. This induces mTORC1 activity in T cells in the patients (98). The protein phosphatase 2A (PP2A) is another protein genetically associated with SLE and is shown to be reduced in Th17 cells in the patients. This finding is related to the PP2A ability to induce the expression of the Th17-inhibiting mitochondrial protein PDK1 (Figure 3C) (33, 50). Th17 cells directly promote GC reactions, or produce IL-21 that can influence Tfh, and animal studies have indicated that the cells can transdifferentiate to Tfh cells (1, 34, 99). It is currently unknown whether the overactive Th17 cells associated with SLE can influence Tfh and Tfr present in GC and that are involved in the regulation of B-cell proliferation.

### Defective B-cell metabolism and role in chronic inflammatory diseases

B cells differentiate to plasma cells that produce antibodies conferring humoral immunity against infectious pathogens and to memory cells. As cited in the B-cell section, metabolism is continuously regulated and changes selectively during B-cell development and activation, so they can develop a highly variable antibody repertoire that does not react with self (Figure 2, Table 2). In addition to phases of B-cell development, factors such as severity and chronicity of an infection and the age of an individual also influence B cells’ metabolic properties. Aberrant regulation of cellular metabolism in B cells can lead to chronic inflammation and autoimmunity (100–102).

In RA and SLE, it is widely recognized that a breach in B-cell tolerance is an initiating step for disease development (103). In RA, B cells produce autoantibodies that recognize citrullinated antigens (anti-CCP) or the Fc part of IgG [rheumatoid factors (RFs)], the presence of which is associated with a more severe disease (104). In SLE, autoantibodies are mostly specific for nuclear antigens. Research is ongoing to understand how alteration to the B-cell metabolism in these diseases leads to immune dysregulation and autoimmunity. Assessment of the B-cell subset present in synovial tissues and synovial fluids has identified switched memory and double-negative memory B cells. These cells produce inflammatory cytokines when cultured in hypoxic conditions that mimic the synovial microenvironment. A proportion of these cells express PD1 and have active mTORC1 and a glycolytic gene signature. Assessment of intracellular NAD+ levels confirmed that the cells are primarily driven by glycolysis (105). As cited earlier, active glycolysis is a feature of activated antibody-producing B cells.

In SLE, B-cell metabolic dysregulation can take place during the GC reaction and in B cells that produce antibodies independent of the GC reaction. One study noted increased mTORC1 activity in B cells from patients with SLE, and the presence of cells with this activity correlated to plasmablast accumulation (106). Unswitched memory B cells develop independently of GC reactions (107). The study showed that in vitro stimulation of unswitched memory B cells with CpG/TLR9 and IFNα led to the development of plasmablasts dependent on mTORC1. CpG-only stimulation of the unswitched memory cells on the other hand induced a memory cell phenotype that was promoted by AMPK augmentation (106). Specific stimulation and mTORC1 upregulation can, therefore, promote B-cell pathology independent of GCs. The potential involvement of GC reactions in SLE pathology has, on the other hand, been proposed based on observations that autoantibodies in the disease are generated because of defects in the clearance of apoptotic cells within the LZ of GCs leading to BCR-mediated internalization of nuclear antigens and TLR-mediated activation. B cells that undergo GC reactions express high levels of the anti-inflammatory adenosine generating ecto-5’-nucleotidase CD73. A study noted inefficient functions of B cells from patients due to defective CD73’s nucleotidase activity (24). The authors suggested that the CD73 defect may promote autoimmunity due to two factors. First, there is the lack of adenosine that can render Th cells to differentiate to pro-inflammatory cells. This enables the Th cells to promote the survival of autoreactive B cells. Second, the accumulation of undegraded AMP prompts inflammation through augmenting IL-6 production by B cells (24). In GCs, mTORC1 activity is required for the selection of B
cells in the LZ (8). A study using the Roquin lupus mouse model 
reported that treatment of mice with metformin reduced the number 
of GC B cells. Furthermore, Th1 and Th17 cells were inhibited, while 
Tregs were increased by treatment with metformin. Inhibition of 
immune cells was associated with an increase in AMPK levels (108). 
The study, therefore, concluded that therapeutic targeting of 
metabolic pathways might be a strategy to suppress autoimmune 
GC reactions. Th17 cells may also be involved, as they play an 
important role in the GC reactions (34). The interaction between B 
cells and Th17 cells changes the metabolism of Th17 cells and leads to 
their activation. After TCR engagement, naive B cells prompt IL-17 
production by Th17 cells through the inducible T-cell costimulator 
(ICTC) and the inducible T-cell costimulator ligand (ICOSL) interaction 
(94). Intriguingly, naive B cells appear to be better inducers of T- 
cell responses than memory B cells. This interaction induces 
mTORC1 and glycolysis in the Th17 cells and IFNy production 
(36, 109). T cells in patients with RA and SLE express ICOS, and the 
level appears to be associated with RA patients’ plasma anti-CCP and 
RF levels. In line with the dysregulated Th17-cell phenotypes 
described earlier, naive B cells induce higher levels of IL-17 in RA 
and SLE patients’ Th17 cells than Th17 cells from healthy 
controls (36).

Conclusions and prospects

Metabolic activity is intertwined with the functional status and 
stage of development and activation of immune cells and is 
impacted by disease. Th17 cells differentiate in response to 
various stresses but they do not utilize pyruvate for anaplerosis. 
Thus, while protective Th17 cells are reliant on glycolysis and 
OXPHOS, pathogenic Th17 cells only utilize glycolysis and produce 
putrescine that may reflect the environment in which they reside. 
Th17 cells are vulnerable to deficiency of certain amino acids or to 
deregulation of their processing in mitochondria. Stress increases 
Δψm, leading to ROS production, that would be sensed by 
mTORC1, and this will favor pathogenic Th17 
transdifferentiation during low oxygen tension. Furthermore, 
deprivation from amino acids reduces survival but also influences 
epigenetic regulation to favor Th17 to Treg transdifferentiation. The 
tumor microenvironment can promote such transdifferentiation. 
Further studies are required to understand the physiological 
relevance of such transdifferentiation and whether this has a role 
in protection from disease or a break of tolerance. Disturbances in 
the transcription of genes involved in metabolism can render Th17 
cells hyperactive in patients with psoriasis, RA, and SLE. 
Furthermore, inherited genetic changes can contribute to immune 
hyperreactivity. It remains to be determined, however, whether such 
hyperreactivity directly influences/promotes the expansion of B-cell 
autoreactivity too, directly or indirectly Th17 cells.

During their maturation, B cells are censored at several 
checkpoints. At each of these developmental stages, B cells 
manifest different metabolic signatures. The activity of mTORC1/2 
in B cells is associated with effector functions and antibody 
production, while AMPK promotes B cells to become memory 
cells. Furthermore, unlike Th17 cells, B cells display a metabolic 
plasticity and can replenish anaplerosis through glycolysis. Recent 
studies have revealed that metabolism-associated activation, stress, 
and exhaustion can promote B cell-mediated pathology through the 
bréath of their tolerance. Such aberrant metabolism seems to 
fluence both B cells involved in GC reactions and the ones that 
mature extrafollicularly. Furthermore, Bregs affected by aberrant 
metabolism lack suppressive abilities leading, potentially, to 
autoimmune pathology. However, knowledge on how altered 
metabolism influences B-cell tolerance at epigenetic levels is 
currently lacking.

Although Th17 cells and B cells are part of different lineages, 
there are similarities with their cellular metabolic responses due to 
similarities in microenvironments in which they can reside and are 
activated. In addition, disease-associated polymorphisms are known 
to alter metabolism in both cell types leading to the breach to 
immunological tolerance and the transdifferentiation of Th17 to 
pathogenic cells. Furthermore, Th17 cells contribute to GC 
reactions and the production of autoantibodies by contribution to 
B-cell differentiation to plasma cells. However, the metabolic status 
of B cells and/or Th17 cells during their interactions, leading to 
disease, has not yet been thoroughly examined (34, 35). Bregs, on 
the other hand, regulate Th17 cells. Better understanding of 
metabolic properties of the distinct functional subsets of B cells 
and T cells and how they influence each other can be of profound 
importance in understanding the pathogenesis of inflammatory 
diseases. Such information can potentially lead to the discovery of 
new therapeautic strategies. As overviewed in this review, such 
therapeutic strategies could involve inhibition of glutaminolysis, 
or supplementation with the SCFA pentanoate to alter cell 
metabolism. Future studies may need to define at what cell stage/ 
type is modulation of metabolism most beneficial for disease 
amelioration while retaining the immune system intact and functional.

Author contributions

JB, TT and RM wrote the first draft which was critically 
scrutinized by SH and DG. RM finalized the manuscript which 
was then approved by all the co-authors.

Conflict of interest

The authors declare that the research was conducted in the 
absence of any commercial or financial relationships that could 
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### Glossary

| Abbreviation | Full Form |
|--------------|-----------|
| 2-HG         | 2-hydroxyglutarate |
| ACC1         | acetyl-coenzyme carboxylase 1 |
| acetyl-CoA   | acetyl-coenzyme A |
| AID          | activation-induced cytidine deaminase |
| APC          | antigen-presenting cell |
| anti-CCP     | anti-cyclic citrullinated peptide antibody |
| ATP          | adenosine triphosphate |
| Akt          | Ak strain transforming (also known as protein kinase B or PKB) |
| AICAR        | 5-Aminoimidazole-4-carboxamide ribonucleotide |
| AMPK         | AMP-activated protein kinase |
| BAFF         | B-cell activating factor |
| BATF         | basic leucine zipper ATF-like transcription factor |
| Bcl-6        | B-cell lymphoma 6 |
| BCR          | B-cell receptor |
| Breg         | regulatory B cell |
| CCR7         | chemokine (C-C motif) receptor 7 |
| ΔΨm         | mitochondrial membrane potential |
| DC           | dendritic cell |
| DON          | 6-diazo-5-oxo-L-norleucine |
| Drp1         | dynamin-related protein 1 |
| EF-hand D1   | EF-hand domain family member D1 |
| ETC          | electron transport chain |
| FAO          | fatty acid oxidation |
| FDC          | follicular dendritic cell |
| FOXO1        | forkhead box protein O1 |
| FOXP3        | forkhead box P3 |
| GATA-3       | GATA-binding protein 3 |
| GC           | germinal center |
| GLS1         | glutaminase 1 |
| GLUT1        | glucose transporter 1 |
| GOT1         | glutamate oxaloacetate transaminase 1 |
| GSK3         | glycogen synthase kinase-3 |
| HIF1α        | hypoxia-inducible factor 1α |
| ICOS         | inducible T-cell costimulator |
| ICOSL        | inducible T-cell costimulator ligand |
| LEF1         | lymphoid enhancer-binding factor 1 |
| LLPC         | long-lived plasma cell |
| LN           | lymph node |
| LZ           | light zone |
| MALT1        | mucosa-associated lymphoid tissue lymphoma translocation protein 1 |
| MTHFD2       | bifunctional methylenetetrahydrofolate dehydrogenase/cyclohydrolase |
| mTORC        | mechanistic target of rapamycin |
| mROS         | mitochondrial reactive oxygen species |
| MZB          | marginal zone B cell |
| NADH         | nicotinamide adenine dinucleotide |
| NADPH        | Nicotinamide adenine dinucleotide phosphate |
| OXPHOS       | oxidative phosphorylation |
| PAX5         | paired box 5 |
| PDH1         | pyruvate dehydrogenase 1 |
| PI3K         | phosphatidylinositol 3-kinase |
| PKCβ         | protein kinase Cβ |
| PP2A         | protein phosphatase 2A |
| PPP          | pentose-phosphate pathway |
| Rab4A        | Ras-related protein Rab-4A |
| RANKL        | receptor activator of nuclear factor kappa-β ligand |
| RF           | rheumatoid factor |
| RORγt        | RAR-related orphan receptor γt |
| ROS          | reactive oxygen species |
| SAM          | S-adenosylmethionine |
| SCFAs        | short-chain fatty acids |
| SFB          | segmented filamentous bacteria |
| SHM          | somatic hypermutation |
| SUCLG2       | GDP-forming β subunit of succinate-CoA ligase |
| STAT3        | signal transducer and activator of transcription 3 |
| STIM1        | stromal interaction molecule 1 |
| SYK          | spleen-associated tyrosine kinase |
| T1/2 B cell  | transitional 1/2 B cell |
| TACI         | transmembrane activator and CAML interactor |
| T-bet        | T-box expressed in T cells |
| TCA          | tricarboxylic acid |
| TCF1         | T-cell factor 1 |
| TCR          | T-cell receptor |
| Th           | follicular helper T cell |
| Tfr          | follicular regulatory T cell |
| TGFβ         | transforming growth factor β |
| TLR          | Toll-like receptor |
| Treg         | regulatory T cell |
| Trm          | tissue-resident memory T cell |

(Continued)