Trends in Cancer

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REVIEWS

Review

B-Cell Metabolic Remodeling and Cancer

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Cells of the immune system display varying metabolic profiles to fulfill their functions. B lymphocytes overcome fluctuating energy challenges as they transition from the resting state and recirculation to activation, rapid proliferation, and massive antibody production. Only through a controlled interplay between metabolism, extracellular stimuli, and intracellular signaling can successful humoral responses be mounted. Alterations to this balance can promote malignant transformation of B cells. The metabolic control of B-cell fate is only partially understood. Here, we provide a compelling overview of the current state of the art and describe the main metabolic features of B cells during normal development and oncogenesis, with emphasis on the major B-cell transcriptional and metabolic regulators, including myelocytomatosis virus oncogene cellular homolog (Myc) and hypoxia-inducible factor 1-α (HIF-1α).

Highlights

Energy metabolism has a significant role in immune responses because it sustains signal transduction within and between activated immune cells.

Immune cells continuously experience changing microenvironments and produce metabolites that direct diverse cell functions and differentiation patterns.

The transitions in morphology and function of naïve, activated, and memory B cells are imposed by metabolic regulators and allow the massive production of immunoglobulins.

B-cell lymphoma undergoes metabolic adaptations that may be potentially targeted while sparing nontransformed cells.

Metabolism and Protective Immunity

Over the last ten years, immune functions have been linked with cellular **metabolism** (see Glossary) [1]. The study of metabolic signatures and pathways and their influence on immune function is known as immunometabolism [2] (Box 1 and Figure 1). When triggered, resting immune cells go through transitional stages of activation, proliferation, and differentiation into effector cells. Extensive research revealed much of the transcriptional circuits underlying each stage [3–6] and made clear the roles of antigen receptors, co-receptors, cytokines, and chemokines in lymphocyte development. However, elucidation of how B lymphocytes meet the substantial energy requirements for activation and execution of effector functions has lagged behind.

From a bioenergetic viewpoint, the immune response to a pathogen appears to be rather costly [7]. Changes in B cells initiated by antigen recognition, such as proliferation and differentiation, followed by population contraction and eventually the generation of memory, require a sustained supply of energy that matches the fluctuating cellular needs at different stages. Indeed, several studies showed that, rather than simply being involved in biosynthesis, metabolic regulators such as the myelocytomatosis virus oncogene cellular homolog (**Myc**), **hypoxia-inducible factor 1-α (HIF-1α)**, mechanistic target of rapamycin (mTOR), and the glycogen synthase kinase 3 (Gsk3) can shape the immune response [8–10].

Studies of the energy metabolism of immune cells are beginning to shed light on metabolic mechanisms that sustain disease progression, and have revealed new pathways that can potentially be targeted to treat inflammatory conditions such as autoimmunity, chronic viral infections, and cancer [11,12]. In the tumor settings, for example, uncontrolled cell proliferation together with impaired programmed cell death sets the stage for neoplastic progression and metastasis. Moreover, cell-extrinsic factors may alter cellular metabolism. Indeed, as the cell number increases, the tumor microenvironment is altered, and the pH as well as concentrations

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Box 1. Immunometabolism at a Glance

Immunometabolism links two research areas formerly thought as distinct: immunology and metabolism. Studies of immunometabolism have provided new insights into how lymphocytes perform their functions, including how they mature, migrate, and secrete cytokines. Cells of the immune system are geared to patrolling the body, sensing pathogens, and eliminating them to avoid disease. Immune cells generally detect pathogens using a broad spectrum of intracellular and extracellular sensors. These sensors activate mediators that launch specific molecular pathways, resulting in the downstream activation of effector molecules needed to support the functional state of a given immune cell. This molecular activation necessarily depends on the cell's metabolism, which consists of a highly integrated network of biochemical reactions. A cell's metabolism fuels all its biological programs, but which part of the network is activated at any one time is dictated by the environmental context.

The field of immunometabolism investigates how immune cells adopt a specific metabolic configuration to sustain a particular response, and, conversely, how different inflammatory settings influence metabolic pathways within a cell [7]. The overall outcome of an immune response is thus the result of several factors, including triggering and effector mechanisms that have to be initiated and regulated for a successful response. In addition, various metabolic nuances can either sustain or dampen an immune response, adding a new layer of complexity to the established paradigm of lymphocyte actions during immune responses (Figure 1). These findings open up the possibility of interfering with metabolism as a means of regulating immune cell behavior, thereby potentially uncovering new avenues for innovative therapeutic approaches.

of crucial nutrients such as glucose, glutamine, and oxygen fluctuate and become limiting [13,14]. As a result, the tumor core becomes hypoxic. This dynamic environment affects both the tumor cells and the tumor-infiltrating immune cells.

Multiple metabolic mechanisms provide support for the three basic needs of dividing tumor cells: increased energy supply, sustained biosynthesis of macromolecules, and maintenance of redox balance. Altered metabolism is thus considered to be a hallmark of cancer [15]. The current view in the field is that cancer cells and the immune cells trying to suppress them co-exist in a crowded and nutrient-limited microenvironment that forces them to compete for fuel [16,17]. Highly aggressive tumors are often better equipped for this competition than are the immune cells and end up modulating T-cell functionality in a way that contributes to tumor progression. Thus, controlled manipulation of these altered metabolic programs and changes may uncover new targets for cancer immunotherapy.

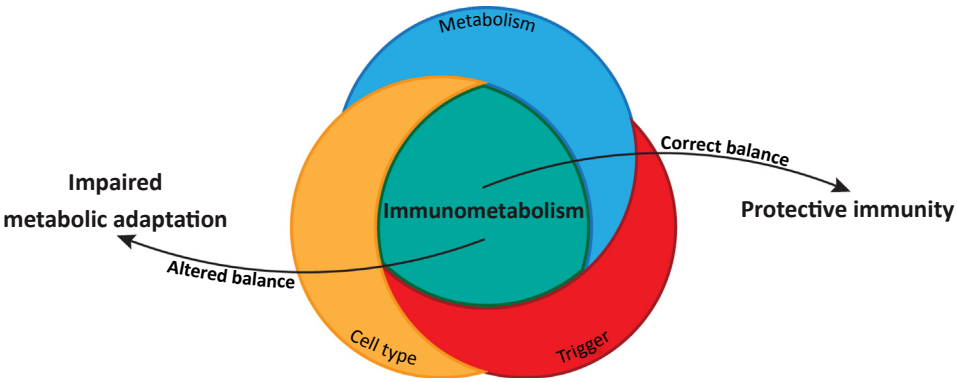

Figure 1. Immune Responses Demand Tight Metabolic Regulation. When immune cells are activated by a pathogen, they respond to clear the infection. The factors invoked to mount protective immunity and inflammation depend on the specific pathogen antigen (trigger) and the cell type involved in the response. Immunometabolism regulates the interplay between metabolic and immunological responses. Dysregulation of these pathways has been associated with aberrant immune responses and/or the development of hematological malignancies.

Glossary

Antibody class switching: exchange of immunoglobulin (Ig) gene segments encoding the constant region of a given Ig heavy chain while retaining its variable region. This process involves a DNA recombination event and changes the effector functions of the resulting antibody.
CD138: transmembrane proteoglycan involved in many cellular functions, including cell–cell adhesion and cell–matrix adhesion. CD138 is a major plasma cell marker.
Chaperones: molecular helpers that assist other proteins with folding. Chaperones are essential for correct protein synthesis and need an oxidative environment in the endoplasmic reticulum to be active.
Glucose transporter 1 (Glut1): the major glucose transporter located in the plasma membrane of mammalian cells.
Hexokinase-2 (HK2): enzyme that catalyzes the irreversible first step of glycolysis by phosphorylating glucose, causing it to be sequestered intracellularly.
Hypoxia-inducible factor-1α (HIF-1α): transcription factor induced in response to low oxygen levels. HIF-1α binds to hypoxia-responsive elements in the cell's DNA to activate the transcription of more than a hundred genes promoting adaptation and survival.
Metabolism: the sum of all biochemical reactions associated with the generation of energy via catabolism and the synthesis of macromolecules via anabolism.
MYC: transcription factor that regulates normal cell cycle progression and apoptosis. Myc overexpression is tightly associated with the initiation of cancer.
Noncanonical NF-κB activation: pathway involving the phosphorylation and processing of the p52 precursor, p100, into the mature protein, followed by the formation of the RelB:p52 heterodimer, and the subsequent translocation of this heterodimer into the nucleus, where it activates expression of NF-κB target genes. Only a small number of receptors (including BAFF) are known to activate noncanonical NF-κB.

Our understanding of the metabolic rewiring in cells of the innate and adaptive arms of the immune system is increasing exponentially. B cells, however, have remained relatively understudied. B cells take on the role of producing and secreting the antibodies critical for humoral immunity. These specialized functions are driven by several mechanisms, including **antibody class switching** and affinity maturation that are exclusive to B cells and impose distinct metabolic demands and warrant further investigation. In this review, we discuss the most recent findings on immunometabolism of B cells and the puzzling questions that remain.

Bioenergetic Profiles of B Cells

Development and Maturation

Naïve B cells develop in the bone marrow, recirculate throughout the spleen and lymph nodes, and eventually head back to the bone marrow until death or encounter with a specific antigen. Binding of an antigen to its B-cell receptor (BCR) triggers B-cell proliferation and differentiation into plasma cells that produce thousands of clone-specific antibodies. B-cell activation requires a massive metamorphosis of cellular architecture and the secretory apparatus to comply with the new function of secretion [18]. It has now become apparent that these changes are likely coupled to the nutritional status of the B cell's immediate microenvironment (Box 2) that influences B-cell metabolism (Figure 2).

Metabolic changes in B cells are triggered by a group of conserved metabolic regulators. One of those regulators is HIF-1α, which triggers homeostatic transcriptional responses to limited oxygen levels, and also mediates the expression of genes encoding glucose transporters and glycolytic enzymes [19]. However, in B cells, Kojima and colleagues [20,21] showed that HIF-1α not only controls transcriptional hypoxic responses, but also functions in a stage-specific manner to regulate B lymphocyte differentiation and proliferation. During early B-cell development in the bone marrow, HIF-1α-mediated glycolytic metabolism is more crucial for some B-cell precursors than others. Specifically, HIF-1α deficiency decreases the expression of glucose transporters (**Glut1** and Glut3) and **phosphofructokinase (Pfkfb3)**, blocking the transition from pro- to the pre-B cell stage [22]. HIF-1α also sustains the metabolic demands of antigen-experienced germinal center (GC) B cells [23], implying that HIF-1α exerts its metabolic modulation at various stages. However, HIF-1α is dispensable for the metabolic reprogramming of naïve B cells triggered by lipopolysaccharide stimulation, suggesting that other metabolic regulators, like Myc, are involved [24].

Tumor necrosis factor (TNF) receptor-associated factor-3 (TRAF3) is another critical regulator of B lymphocyte metabolism. TRAF3-deficient B cells abnormally upregulate key genes involved in the very early stages of the glycolytic cascade, including Glut1 and inducible

Pentose phosphate pathway (PPP): anabolic pathway that utilizes glucose to generate both five-carbon sugars for nucleotide synthesis and reducing equivalents (NADPH) for maintaining optimal redox status.
Phosphofructokinase (Pfkfb3): enzyme that catalyzes the rate-limiting step in glycolysis by adding a phosphate group from ATP to fructose-6-phosphate, producing fructose-1,6-bisphosphate.
Reactive oxygen species (ROS): highly chemically reactive molecules produced mainly by incomplete reduction of O_2 in the mitochondrial electron transport chain.
Somatic hypermutation: process of antibody diversification to generate high-affinity antigen-binding sites through mutations, which are mainly single-base substitutions, with occasional insertions and deletions.
TNFα receptor-associated factor 3 (TRAF3): crucial component of the signalosome formed upon CD40 and BAFF stimulation. TRAF3 is primarily involved in the regulation of noncanonical NF-κB activation.

Box 2. Environment Composition Influences the Immune Response

In the course of an immune response, responding cells migrate through tissues to reach the target site, and in so doing may dramatically change their functional state. In a local microenvironment, the cells are exposed to extremely variable environments, depending on the nature of the pathogen, the inflammatory state of the surrounding tissue and its cellular composition, and the presence of secreted products. Collectively, these factors may alter the nutrients and oxygen availability in the tissue. Because immune cells lack significant storage of substrates such as glucose, amino acids, and fatty acids, their effector functions critically depend on nutrient uptake from the microenvironment [97]. In this scenario, nutrient sensing by the responding cells plays a pivotal role and affects their metabolism, maturation, and effector actions toward the pathogen. Fortunately, immune cells possess the almost unique ability to switch their metabolic configurations, enabling them to cope with changing and challenging metabolic conditions. B cells, for instance, are exposed to different nutrients and oxygen concentration within the GC niche. In addition, B-cell proliferation and anabolic rates differ between the dark and light zones [10]. For this reason, a B-cell metabolic and signaling capacity must be flexible enough to maintain viability and develop further in the GC response to generate memory and plasma cells.

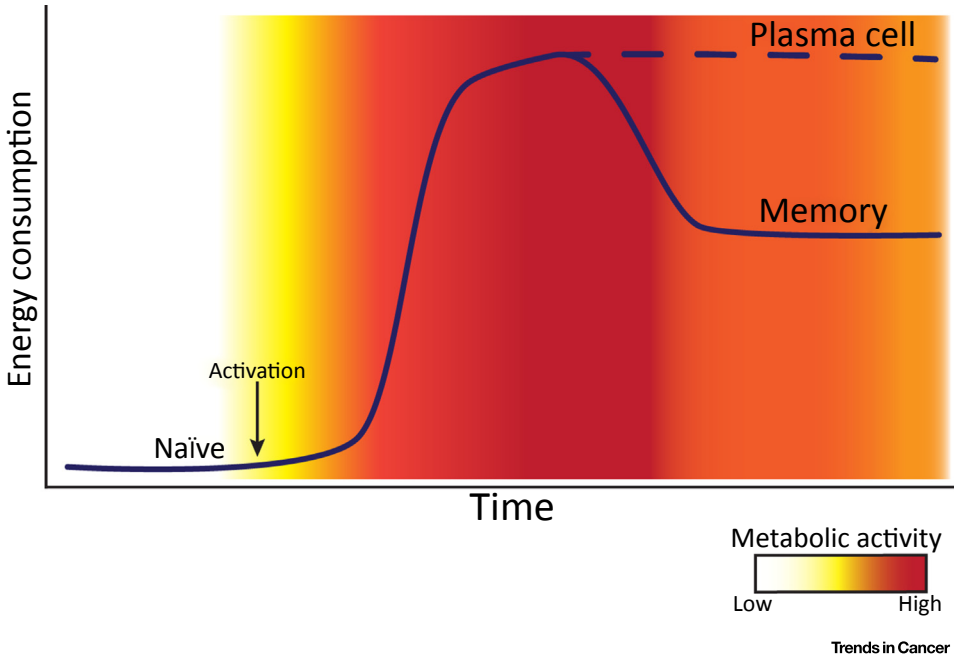

Figure 2. Metabolic Remodeling in B Cells. The metabolic requirements of B cells depend on the state of activation. Naïve B cells expend little energy as they recirculate throughout the body. Antigen challenges induce a structural change in the B-cell energetic profile because the biosynthetic machinery requires ATP generated through glycolysis to support B-cell maturation and differentiation. In particular, energy is consumed in expanding the secretory machinery that will be needed for antibody production by plasma cells. Plasma cell differentiation is a multistep process associated with increased mitochondrial respiration designed to meet maximum energy needs, a process that generates copious reactive oxygen species. At the same time, a few activated B cells differentiate into antigen-experienced memory B cells. Memory B cells persist in a relatively quiescent state until further antigen encounter but retain specific metabolic features that allow them to quickly reactivate when needed.

hexokinase-2 (HK2). Loss of TRAF3 alters B-cell metabolism and increases mitochondrial respiration without increasing **reactive oxygen species (ROS)** production [25]. The full activation of B cells requires costimulation through CD40–B-cell activating factor (BAFF) receptor interaction, which also induces proteasomal degradation of TRAF3 and the accumulation of nuclear factor-κB (NF-κB)-inducing kinase (NIK) in the cytoplasm [26]. NIK activates IkappaB kinase alpha (IKKα) and causes nuclear translocation of NF-κB, leading to transcription of target genes. Loss of both NIK and TRAF3 in double knockout mice results in decreased Glut1 expression and low mature B-cell counts, suggesting that noncanonical NF-κB signaling regulates glucose influx [25]. In line with this finding, BAFF-exposed naïve B cells show enhanced glucose uptake and a higher basal mitochondrial capacity when activated with lipopolysaccharide [24]. These studies suggest that B-cell costimulation is involved in metabolic remodeling. Particularly, the **noncanonical NF-κB pathway** may play a role in B-cell metabolism and proliferation through the TRAF3–NIK–NF-κB axis, a pathway that can contribute to the initiation of B-cell malignancies.

In addition, the transcription factors Pax5 and Ikaros affect B-cell lineage decisions and cellular bioenergetics. Pax5 regulates the transition of lymphoid progenitors to the B lymphoid lineage in the bone marrow [27]; and Ikaros controls the transition from pro-B cell to pre-B cell by promoting pre-BCR signaling, cell migration, and proliferation [28]. Both factors are considered antioncogenes and their loss contributes to the development of B-cell acute lymphoblastic

leukemia (B-ALL) [28,29]. Pax5 and Ikaros partially exert their tumor-suppressor function through alteration of B-cell metabolism [30], which will be discussed in the following sections.

Activation and Differentiation

B-cell activation is a dynamic process that leads to antibody class-switching, **somatic hypermutation**, and plasma cell differentiation. Upon BCR engagement or CD40/interleukin-4 (IL-4) stimulation, activated B cells expand in cell size [23,31–35] and increase the overall protein content and **CD138** expression [35]. Moreover, BCR signaling leads to glucose uptake and Glut1 expression in a phosphoinositide 3-kinase (PI3K)-dependent mechanism [31], and glucose catabolism is diverted from glycolysis to the **pentose phosphate pathway (PPP)** to generate NADPH crucial for the maintenance of proper redox status [31] (Figure 3). As a result, expression of glycolytic enzymes such as glyceraldehyde 3-phosphate dehydrogenase and α-enolase, as well as amino acid-metabolizing enzymes such as ornithine and phosphoserine aminotransferases, steadily increases in newly activated B cells, with peak levels of activity at three days postactivation [35]. Previous studies of primary splenic B cells revealed increased glucose uptake following activation [36], and studies of B-cell metabolome indicated

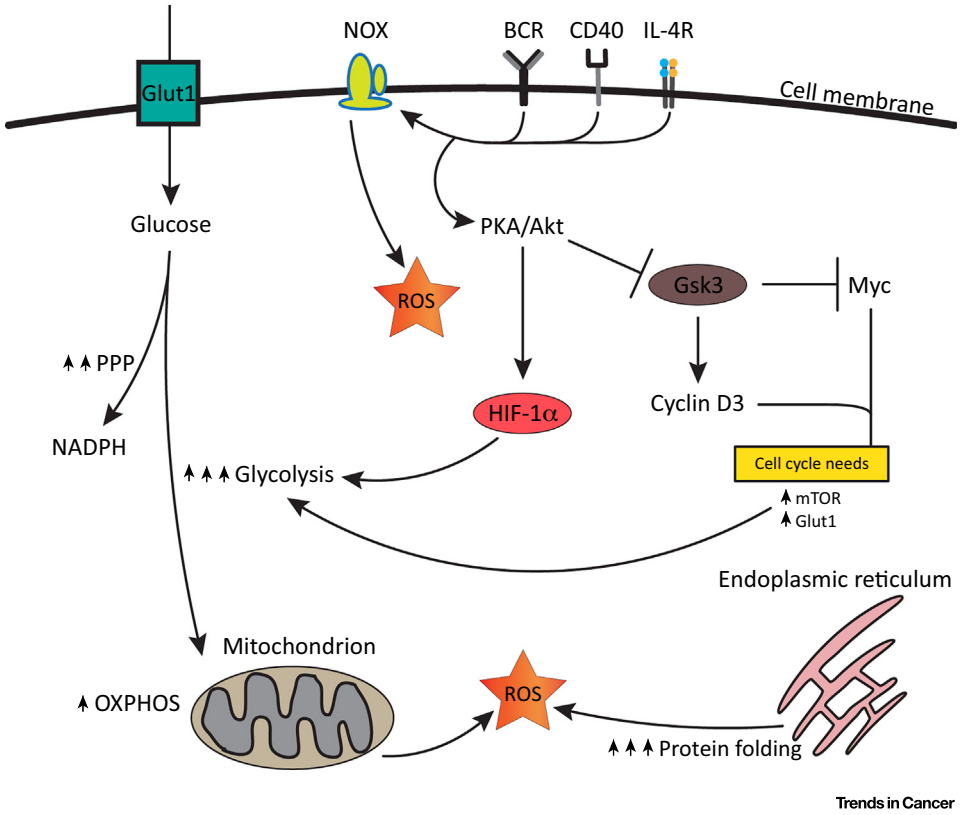

Figure 3. B-Cell Activation Drives Metabolism. B cells require B-cell receptor (BCR) engagement and costimulation via CD40 for proper activation. In addition, interleukin-4 (IL-4) stimulates cell cycle entry [92]. Glycolysis and glucose uptake are boosted as a consequence of hypoxia-inducible factor 1-α (HIF-1α) transcriptional control. Activation is conferred by protein kinase A (PKA) and protein kinase B (Akt) [93], which both repress glycogen synthase kinase 3 (Gsk3) activity [94]. Thus, cyclin D3 and Myc support cell growth and proliferation. Upon activation, reactive oxygen species (ROS) are generated either by mitochondrial activity and/or NADPH oxidase (NOX). GLUT1, glucose transporter 1; mTOR, mechanistic target of rapamycin; Myc, myelocytomatosis virus oncogene cellular homolog; OXPHOS, oxidative phosphorylation; PPP, pentose phosphate pathway.

that glucose oxidation and lactate accumulation are prominent in activated B cells [37]. Amino acid consumption and production of alanine and glutamate are also elevated during B-cell activation [38]. Glucose is needed to support cell activation and is in part used to support *de novo* lipogenesis via the activity of ATP–citrate lyase (ACLY), supplying the activated B cell with enough phospholipids to sustain the morphological change [39]. In addition, glucose flux is diverted to the hexosamine pathway to allow antibody glycosylation in long-lived plasma cells [40]. In addition to glycolysis, the tricarboxylic acid (TCA) cycle plays an important role in the differentiation of naïve B cells in the intestinal compartment. In particular, vitamin B_1 is required as a cofactor for several enzymes within the TCA cycle, and the initiation of the intestinal antibody response [41].

The proliferative burst of activated B cells leads to the synthesis of immunoglobulin (Ig) proteins and the generation of antibody-secreting plasma cells. In parallel with proliferation, B cells reorganize the synthetic machinery to accommodate higher antibody production. In particular, protein trafficking through the endomembrane system is sharply increased (Figure 3). Too much of this trafficking can lead to protein overload and the accumulation of unfolded or misfolded proteins in the lumen of the endoplasmic reticulum (ER), which may ultimately induce an ER stress response. To avoid this, generation of plasma cell relies on the overlapping activities of B lymphocyte-induced maturation protein-1 (Blimp-1, a transcriptional repressor) and X-box binding protein 1 (XBP-1, a transcription factor downstream of Blimp-1) [42]. While Blimp-1 is implicated in the regulation of the mTOR kinase activity and the unfolded protein response [43], XBP-1 plays a central role in defining the B-cell secretory phenotype [32]. Furthermore, the folding of newly synthesized Ig proteins often requires disulfide bond formation, which generates a flux of ROS [44]. Because the ER greatly expands during plasma cell generation [32], B cells become more oxidative, which affects their overall intracellular redox equilibrium. Hence, it is not surprising that B cells control oxidative stress by linearly upregulating proteins involved in proteostasis and the redox system, including cytosolic and mitochondrial **chaperones** [heat shock protein 90α (HSP90α) and β, HSP70] [35] and NF-E2-related factor-2 (NRF2) [45].

Proteins function normally when ROS production and detoxification are tightly controlled to maintain appropriate redox homeostasis. Alterations in ROS balance are implicated in hematopoietic malignancies and are associated with resistance to treatment [46]. It was shown that mitochondrial mass, membrane potential, and ROS are strongly associated with B-cell fate determination [33]. For example, class-switch recombination in activated B cells and plasma cell differentiation have different requirements for the depicted mitochondrial activity [33]. On a molecular level, Gsk3 has been linked to ROS accumulation and B cell's metabolic activity [23]. Gsk3 has an important role in glycogenesis and its dysfunction correlates with progression of solid tumors [47]. Nonactivated Gsk3-deficient B cells displayed the metabolic phenotype of their activated wild-type counterpart, exhibiting increases in cell size, protein content, and glucose consumption [23–25,48]. Gsk3-deficient B cells are characterized by elevated mitochondrial mass and ROS levels. However, when humoral responses were assessed in GCs *in vivo*, Gsk3-deficient B cells were prone to apoptosis and the mutant mice could not mount a robust immune response. GCs contain a broad collection of functionally diverse immune and nonimmune cells [49], where metabolites and metabolic by-products likely influence cell differentiation [50] and oxygen tension alters B-cell physiology and function [51] (Box 2). Hypoxia in GCs increases the rate of glucose consumption [51], implying that oxygen availability represents a stringent threshold during GC responses that regulate B-cell survival. Jellusova and coworkers [23] showed that the survival of B cells in GCs was most likely dependent on the availability of high levels of glucose needed for vigorous glycolysis and to sustain the PPP and

the viability of Gsk3-deficient B cells was impaired when the cells were cultured in glucose-free medium. As mentioned earlier, the metabolism of a newly activated B cell adapts to support its ensuing proliferation and funnels glucose to the PPP to produce NAPDH to offset ROS [31], which correlates with the Pax5/Ikaros-mediated upregulation of the glucose-6-phosphate dehydrogenase (G6PD) [30]. Consequently, activated B cells that lack Gsk3 in a glucose-limited environment cannot counterbalance the high levels of ROS generated by proliferation, which in turn leads to cell death [52]. When Gsk3 is present, it promotes cell cycle progression [53] and acts as a sensor of the metabolic status of B cells, switching from proliferation to death depending on the oxygen levels in the surrounding microenvironment. Interestingly, BCR signaling inhibits Gsk3 [23,54], which enhances Myc expression to support cell growth, proliferation, and metabolic adaptation. Gsk3 inhibition upon BCR stimulation has been studied in the context of Myc-driven lymphoma by Casola *et al*. [54]. In this study, the authors showed that BCR^+ lymphoma cells outgrow the BCR^- counterparts. This effect is promoted by Gsk3, as its pharmacologic inhibition abolished the competitive advantage of the BCR^+ cells [54]. Thus, restraining Gsk3 activity upon BCR engagement (along with PI3Kδ signaling [54]) supports Myc-transformed B cells. These studies underline the importance of Gsk3 in the control of Myc-dependent proliferation in B cell and its intimate connection with B-cell pro-tumorigenic transformation. We will discuss the significance of Myc-dependent oncogenic transformation in the next paragraph. Overall, metabolic control in B-cell subsets depends on specific metabolic regulators and the picture of metabolic adaptation in activated B cells is far from complete (Figure 4).

Dysfunctional Metabolism in B-Cell Malignancies

To support rapid proliferation, cancer cells exhibit a hypermetabolic phenotype that is distinct from that of nontransformed cells [55]. This metabolic adaptation is closely linked to genetic mutations and oncogenic signaling pathways, which often include PI3K/protein kinase B (Akt), HIF-1α, Myc, Pax5, and Ikaros [30,56]. These tumorigenic signals often initiate a vicious loop by directing metabolic reprogramming, which in turn generates metabolites that positively support these metabolic pathways [57].

Myc is the dominant oncogene associated with B-cell malignancies, and its dysregulation by gene rearrangement (including translocation and amplification) in B cells leads to its upregulation and overcomes the inhibitory effect of physiological repressors such as B-cell lymphoma 6 (BCL6) in GC B cells or Blimp-1 in differentiated B cells [58,59]. Myc is a transcription factor that promotes cell cycle entry in almost all dividing cells and is triggered downstream of multiple signaling pathways promoting cell growth, survival, and metabolism. Although Myc overexpression alone does not cause lymphomagenesis, it is classified as oncogenic driver because of its pleiotropic effect on many cellular functions [60].

Early studies of the role of Myc in the regulation of normal B-cell proliferation during the GC reaction produced conflicting results [61–63]. These contradictions were attributed to differences in the experimental detection systems, target subpopulations analyzed, and/or the transient stability of Myc. More recently, Myc function was investigated at the single B-cell level [64,65]. Studies of small numbers of proliferating Myc^+ B cells in both mature and immature GCs showed that these cells expressed both cyclin D2 and D3 mRNAs, which likely contributed to the proliferative phenotype. Within a GC, light zone Myc^+ B cells represent those cells that undergo positive selection and survive to interact with cognate T cells and follicular dendritic cells. These activated B cells then migrate to the GC's dark zone (DZ), proliferate, and establish DZ proliferation foci. During this transition, the B cells activate BCL6 and lose Myc expression [65], although they maintain a high rate of proliferation [64]. Why Myc

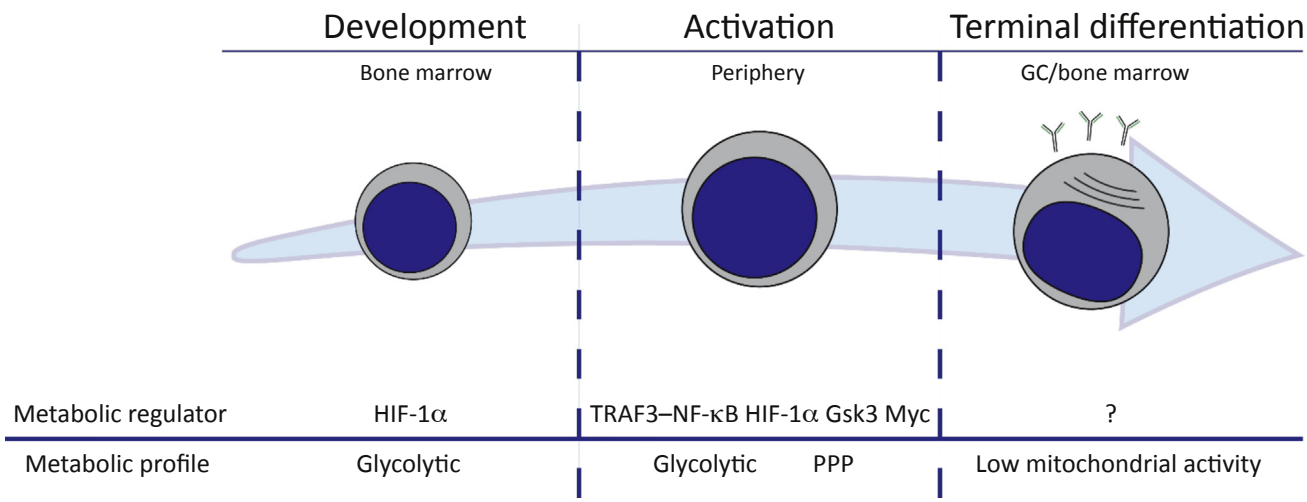

Figure 4. Metabolic Profiles of B Cells at Different Stages. B cells display changing functional, structural, and energetic configurations throughout their life span. B-cell development takes place in the bone marrow, where B cells feed their energetic requirements through glycolysis guided in part by hypoxia-inducible factor 1-α (HIF-1α). However, given the energy demands associated with selection and proliferation, it is likely that glucose is further oxidized in the respiratory chain. Naïve mature B cells in the periphery maintain their metabolic balance through the glycolytic pathway driven by nuclear factor-kappa B (NF-κB) and HIF-1α. Upon activation by antigen, the ensuing metabolic rewiring is mainly orchestrated by myelocytomatosis virus oncogene cellular homolog [Myc; particularly in the germinal center (GC) reaction], with glycogen synthase kinase 3 (Gsk3) also playing an important role. Glycolysis is upregulated together with the pentose phosphate pathway (PPP) to counterbalance the oxidative stress generated by the expansion of the endomembrane system needed to support antibody production. Differentiated B cells can become either memory cells or plasma cells. Although the longevity and persistence of these cells is controversially discussed [95,96], they are both able to produce and secrete massive amounts of antibodies. B-cell dormancy is maintained in part by low mitochondrial activity and slow fatty acid oxidation. The aforementioned scheme is necessarily oversimplified and compresses the main phases of B-cell development and maturation while ignoring several other important B-cell subpopulations (such as regulatory B cells) and metabolic regulators [mechanistic target of rapamycin (mTOR) complexes, Forkhead box protein O1 (FOXO1), and others]. Thus, much more research on the metabolic restructuring of B cells at all stages and in all subsets is required. TRAF3, Tumor necrosis factor (TNF) receptor-associated factor-3.

expression is lost in normal dividing DZ B cells is a puzzling question since Myc is thought to be ubiquitously expressed in proliferating cells.

Myc also influences several metabolic pathways. Genomic studies established that Myc regulates genes involved in glycolysis [66] and Myc is crucial for the induction of Glut1 during B-cell activation [24]. In Burkitt lymphoma cells, upregulated Myc and HIF-1α induce expression of HK2 and pyruvate dehydrogenase kinase-1, enzymes which favor aerobic glycolysis [67]. This induction of glycolytic proteins by Myc suggests a functional correlation and preference toward the upregulation of the glycolytic pathway in B cells, which fits with previously published work [58,68]. However, although Myc^+ B cells have enhanced glycolytic activity, they are more susceptible to mitochondrial perturbation than to glycolytic inhibition [69]. Oncogenic Myc also promotes constitutive expression of lactate dehydrogenase A [70], which diverts glucose-derived pyruvate into lactate, thereby preventing its conversion to acetyl-CoA and its further oxidation in the TCA cycle. Despite this diversion, Myc-transformed cells display increased mitochondrial mass and O_2 consumption [71,72], which is consistent with the finding that several Myc targets are involved in mitochondrial biogenesis and function [73].

Myc activity is also associated with increased glutamine metabolism [24]. Although glutamine is not usually used by tumor cells for ATP generation under non-glucose-limiting conditions, it is critical for biosynthetic reactions and for feeding the TCA cycle [74]. In addition, cell viability is impaired in an Myc-dependent manner under conditions of glutamine starvation [69,74,75],

indicating a strong metabolic addiction to this essential amino acid. Myc induces the expressions of glutamine transporters and glutaminase that accelerate the flux of glutamine to glutamate and upregulate glutamine catabolism [73]. Because glutamate cannot passively exit the cell through the plasma membrane, this amino acid either promotes TCA cycle anaplerosis or is used by the cystine antiporter xCT for cystine intake. This cystine is then reduced to cysteine via the glutathione buffer system, and the resulting cysteine is used for protein biosynthesis [76].

As reported, Myc levels are negatively controlled by phosphorylation through Gsk3 [23]. By contrast, cyclin D3 counteracts Gsk3 by increasing Myc expression in GC B cells [64]. Cyclin D is also negatively regulated by phosphorylation at Thr283 by Gsk3, and this site is frequently mutated in patients with Burkitt lymphoma [77], leading to the conclusion that gain-of-function mutation of cyclin D might cause Myc-driven lymphomagenesis. Many other types of B-cell lymphomas, which include diffuse large B-cell lymphoma (DLBCL) and plasmablastic lymphoma, overexpress Myc as a result of translocation events. DNA breaks in the Myc locus that lead to translocation of Myc into the Ig gene *loci* are thought to be caused by activation-induced cytidine deaminase, an enzyme that usually participates in Ig gene somatic hypermutation [59]. The prominent role of Myc in the regulation of metabolic features of cancer might help to develop new treatment options or a more detailed classification of Myc-associated cancers.

Another important metabolic sensor of relevance to B-cell lymphomas is mTOR. Within any cell, the mTOR protein resides in two distinct complexes: mTOR complex 1 (mTORC1), whose signaling is triggered by nutrient conditions and helps to drive protein synthesis enhancing cellular metabolism, and mTOR complex 2 (mTORC2), which is activated independently of nutrients and regulates cell survival/metabolism and the cytoskeleton. The absence of mTORC1 results in early inhibition of murine B-cell development and defective antibody response, with the cells displaying decreased proliferation and reduced glycolytic and mitochondrial capacities [78,79]. Interestingly, inhibition of PI3K in splenic B cells was reported to completely arrest B-cell growth [80]. In addition, a functional deficiency of mTORC2 results in impaired NF-κB1 and NF-κB2 nuclear induction [81] and enhanced IL-7-dependent survival [82], although it does enhance Ig recombination [82]. Mechanistically, this increase was attributed to loss of mTORC2 normal ability to activate Akt2 and thereby inhibit Forkhead box protein O1 (FOXO1) [82,83]. These studies show that mTORC2, by modulation of FOXO1, is involved in the control of B-cell development.

Future work is required to elucidate the precise roles of Myc, mTOR, and FOXO1 in normal B-cell metabolism, as well as in the genomic instability and malignant transformation of GC B cells leading to B-cell lymphoma. The molecular hierarchy, if any, is not yet fully understood and these factors all alter each other's activity. For instance, Myc overexpression alone is unable to sustain B-cell growth and proliferation independently of mTORC1 [23], and other work has suggested that Myc is required for the activation of mTOR-dependent phosphorylation of a translational repressor [4E-binding protein 1 (4EBP1)], promoting protein translation [84]. In addition, gain-of-function mutations that induce mTORC1 caused increased Ig secretion in non-B cells [44], but the molecular details of how mTORC1 contributes to Ig secretion in B cells are not clear.

As mentioned previously, B-ALL is frequently associated with genetic aberrations in Pax5 and Ikaros. Chen *et al*. [30] proposed a model in which these B-lymphoid transcription factors act as metabolic gatekeepers by repressing energy metabolism in early B cells. Indeed, reconstitution

of Ikaros and Pax5 diminished Akt activation and decreased protein levels of glucose transporters (Glut1, Glut3, and Glut6) and effectors of glucose and antioxidant metabolism such as HK2 and G6PD [30]. As a consequence of the metabolic repression, Pax5 and Ikaros sustain the activation of the energy sensor AMPK, which regulates the metabolic response by balancing catabolic and anabolic processes depending on the AMP-to-ATP ratio [30,85]. Thus, B-ALL cells sustain proliferation due to an altered Pax5/Ikaros/AMPK metabolic barrier. More details are needed to unravel the complex molecular and metabolic circuits that are crucial for lymphogenic transformation.

Manipulating B-Cell Metabolism as a Therapeutic Strategy

Despite the metabolic heterogeneity of B-cell lymphomas [86], therapeutic targeting of a common metabolic crossroad may provide a way to inhibit uncontrolled proliferation or deviate cell adaptation, perhaps fostering a favorable antitumor immune response. However, because all cells rely on the same housekeeping metabolic machinery for self-maintenance, it has been assumed that any druggable metabolic target would adversely affect normal tissues. Therefore, finding a therapeutic window in which a drug kills lymphoma cells while sparing normal proliferating cells has been a major barrier to the development of successful therapies. Another attractive approach is to compare metabolic fluxes in cancer cells versus normal cells. Rather than blocking individual pathways or metabolites, it might be worthwhile to therapeutically restrict metabolic fluxes that are exacerbated in malignant cells so that they are restored to normal levels. Defining these metabolic profiles and unique adaptations of cancer cells is thus crucial. Recently, AMPK has been revealed as a novel target for B-cell malignancies. Pharmacological targeting of AMPK by BML275 in pre-B-ALL cells abolished its enzymatic activity (thus mimicking the metabolic firewall imposed by Pax5/Ikaros) and Akt signaling and had a synergistic effect with glucocorticoids, which are routinely administered to pre-B-ALL patients [30].

In general, cancer cells rely on the engagement of aerobic glycolysis and increase their glucose consumption even in the presence of oxygen, which is known as the Warburg effect [87]. However, DLBCL were found to upregulate genes that are involved in oxidative phosphorylation (OXPHOS) and displayed enhanced mitochondrial activity coupled with better antioxidant defenses [88]. These DLBCLs were efficiently killed by inhibition of the nuclear receptor peroxisome proliferator-activated receptor gamma, which regulates the expression of many genes encoding mitochondrial proteins [89].

Moreover, few studies have examined the metabolic profiles of chronic lymphocytic leukemia B cells and found that OXPHOS correlated with the aggressiveness of the disease [90]. OXPHOS is associated with PI3K activation, although the stromal microenvironment might play a role in shaping B-cell bioenergetics [91]. Overall, tumors that rely on OXPHOS display a good cellular fitness compared with glycolytic tumors, and this may guide the development of a better classification and new treatments.

Concluding Remarks

Recent studies have advanced our understanding of the complexity of B-cell metabolism and signaling. Nevertheless, many questions remain unanswered (see Outstanding Questions). For example, what are the metabolic features of memory B cells and regulatory B cells? Although we know that activated B cells consume more glucose and glutamine than do resting B cells, the metabolic states of memory and regulatory B cells are unclear and the nature of the metabolic switch between them (if any) is far from being understood. How do B cells control intracellular reorganization and the rise of ROS upon activation? One possibility is that

Outstanding Questions

How is BCR signal transduction influenced by the cell metabolic state at various stages of its life cycle?

What is the role of the mitochondria in supporting and/or regulating the functions of memory B cells and regulatory B cells?

How are ROS and ER stress kept in check during the structural rewiring that characterizes B-cell activation?

To what extent is costimulation involved in the immunometabolic reprogramming of B cells?

costimulatory activity mediated, for example, by CD40/BAFF has an effect on the metabolism of activated B cells that compensates for ROS accumulation. Most of our current knowledge is derived from *in vitro* analyses. While these studies represent a good starting point, the dissection of how metabolic alterations influence cancer progression *in vivo* is necessary to truly uncover druggable pathways. A combination therapy taking different concepts into account might be necessary; that is, inducing metabolic stress in malignant B cells followed by a drug targeting the metabolic adaptation to the induced stress. This might increase specificity and widen the therapeutic window to minimize toxicity to normal tissues. Thus, defining the particular metabolic profiles of malignant B cells and then exploiting this knowledge with rational drug targeting may serve as an exciting new approach for the treatment of hematological malignancies.

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References

1. O'Neill, L.A. *et al.* (2016) A guide to immunometabolism for immunologists. *Nat. Rev. Immunol.* 16, 553–565
2. Mathis, D. and Shoelson, S.E. (2011) Immunometabolism: an emerging frontier. *Nat. Rev. Immunol.* 11, 81
3. Grossman, Z. *et al.* (2004) Concomitant regulation of T-cell activation and homeostasis. *Nat. Rev. Immunol.* 4, 387–395
4. Evans, C.M. and Jenner, R.G. (2013) Transcription factor interplay in T helper cell differentiation. *Brief. Funct. Genomics* 12, 499–511
5. Zhong, B. *et al.* (2006) Innate immune responses: crosstalk of signaling and regulation of gene transcription. *Virology* 352, 14–21
6. Shaffer, A.L. *et al.* (2001) Signatures of the immune response. *Immunity* 15, 375–385
7. Kominsky, D.J. *et al.* (2010) Metabolic shifts in immunity and inflammation. *J. Immunol.* 184, 4062–4068
8. Wahl, D.R. *et al.* (2012) Distinct metabolic programs in activated T cells: opportunities for selective immunomodulation. *Immunol. Rev.* 249, 104–115
9. O'Neill, L.A. and Pearce, E.J. (2016) Immunometabolism governs dendritic cell and macrophage function. *J. Exp. Med.* 213, 15–23
10. Jellusova, J. and Rickert, R.C. (2017) A brake for B cell proliferation: appropriate responses to metabolic stress are crucial to maintain B cell viability and prevent malignant outgrowth. *Bioessays* 39, 201700079
11. Smallwood, H.S. *et al.* (2017) Targeting metabolic reprogramming by influenza infection for therapeutic intervention. *Cell Rep.* 19, 1640–1653
12. Freitag, J. *et al.* (2016) Immunometabolism and autoimmunity. *Immunol. Cell Biol.* 94, 925–934
13. Anastasiou, D. (2017) Tumour microenvironment factors shaping the cancer metabolism landscape. *Br. J. Cancer* 116, 277–286
14. Molon, B. *et al.* (2016) T cells and cancer: how metabolism shapes immunity. *Front. Immunol.* 7, 20
15. Pavlova, N.N. and Thompson, C.B. (2016) The emerging hallmarks of cancer metabolism. *Cell Metab.* 23, 27–47
16. Chang, C.H. *et al.* (2015) Metabolic competition in the tumor microenvironment is a driver of cancer progression. *Cell* 162, 1229–1241
17. Franchina, D.G. *et al.* (2018) Survival of the fittest: cancer challenges T cell metabolism. *Cancer Lett.* 412, 216–223
18. Wiest, D.L. *et al.* (1990) Membrane biogenesis during B cell differentiation: most endoplasmic reticulum proteins are expressed coordinately. *J. Cell Biol.* 110, 1501–1511
19. Iyer, N.V. *et al.* (1998) Cellular and developmental control of O_2 homeostasis by hypoxia-inducible factor 1 alpha. *Genes Dev.* 12, 149–162
20. Kojima, H. *et al.* (2002) Abnormal B lymphocyte development and autoimmunity in hypoxia-inducible factor 1alpha-deficient chimeric mice. *Proc. Natl. Acad. Sci. U. S. A.* 99, 2170–2174
21. Kojima, H. *et al.* (2003) HIF-1 alpha deficiency perturbs T and B cell functions. *Curr. Pharm. Des.* 9, 1827–1832
22. Kojima, H. *et al.* (2010) Differentiation stage-specific requirement in hypoxia-inducible factor-1alpha-regulated glycolytic pathway during murine B cell development in bone marrow. *J. Immunol.* 184, 154–163
23. Jellusova, J. *et al.* (2017) Gsk3 is a metabolic checkpoint regulator in B cells. *Nat. Immunol.* 18, 303–312
24. Caro-Maldonado, A. *et al.* (2014) Metabolic reprogramming is required for antibody production that is suppressed in anergic but exaggerated in chronically BAFF-exposed B cells. *J. Immunol.* 192, 3626–3636
25. Mambetsariev, N. *et al.* (2016) TRAF3 deficiency promotes metabolic reprogramming in B cells. *Sci. Rep.* 6, 35349
26. Xiao, G. *et al.* (2004) Induction of p100 processing by NF-kappaB-inducing kinase involves docking IkappaB kinase alpha (IKKalpha) to p100 and IKKalpha-mediated phosphorylation. *J. Biol. Chem.* 279, 30099–30105
27. Busslinger, M. (2004) Transcriptional control of early B cell development. *Annu. Rev. Immunol.* 22, 55–79
28. Schwickert, T.A. *et al.* (2014) Stage-specific control of early B cell development by the transcription factor Ikaros. *Nat. Immunol.* 15, 283–293
29. Heltemes-Harris, L.M. *et al.* (2011) Ebf1 or Pax5 haploinsufficiency synergizes with STAT5 activation to initiate acute lymphoblastic leukemia. *J. Exp. Med.* 208, 1135–1149
30. Chan, L.N. *et al.* (2017) Metabolic gatekeeper function of B-lymphoid transcription factors. *Nature* 542, 479–483
31. Doughty, C.A. *et al.* (2006) Antigen receptor-mediated changes in glucose metabolism in B lymphocytes: role of phosphatidylinositol 3-kinase signaling in the glycolytic control of growth. *Blood* 107, 4458–4465
32. Shaffer, A.L. *et al.* (2004) XBP1, downstream of Blimp-1, expands the secretory apparatus and other organelles, and increases protein synthesis in plasma cell differentiation. *Immunity* 21, 81–93
33. Jang, K.J. *et al.* (2015) Mitochondrial function provides instructive signals for activation-induced B-cell fates. *Nat. Commun.* 6, 6750

34. Vene, R. *et al.* (2010) Redox remodeling allows and controls B-cell activation and differentiation. *Antioxid. Redox Signal.* 13, 1145–1155
35. van Anken, E. *et al.* (2003) Sequential waves of functionally related proteins are expressed when B cells prepare for antibody secretion. *Immunity* 18, 243–253
36. Woodland, R.T. *et al.* (2008) Multiple signaling pathways promote B lymphocyte stimulator dependent B-cell growth and survival. *Blood* 111, 750–760
37. Garcia-Manteiga, J.M. *et al.* (2011) Metabolomics of B to plasma cell differentiation. *J. Proteome Res.* 10, 4165–4176
38. Crawford, J. and Cohen, H.J. (1985) The essential role of l-glutamine in lymphocyte differentiation *in vitro*. *J. Cell Physiol.* 124, 275–282
39. Dufort, F.J. *et al.* (2014) Glucose-dependent *de novo* lipogenesis in B lymphocytes: a requirement for ATP-citrate lyase in lipopolysaccharide-induced differentiation. *J. Biol. Chem.* 289, 7011–7024
40. Lam, W.Y. *et al.* (2016) Mitochondrial pyruvate import promotes long-term survival of antibody-secreting plasma cells. *Immunity* 45, 60–73
41. Kunisawa, J. *et al.* (2015) Mode of bioenergetic metabolism during B cell differentiation in the intestine determines the distinct requirement for vitamin B_1. *Cell Rep.* 13, 122–131
42. Shaffer, A.L. *et al.* (2002) Blimp-1 orchestrates plasma cell differentiation by extinguishing the mature B cell gene expression program. *Immunity* 17, 51–62
43. Tellier, J. *et al.* (2016) Blimp-1 controls plasma cell function through the regulation of immunoglobulin secretion and the unfolded protein response. *Nat. Immunol.* 17, 323–330
44. Aronov, M. and Tirosh, B. (2016) Metabolic control of plasma cell differentiation – what we know and what we don't know. *J. Clin. Immunol.* 36, 12–17
45. Bertolotti, M. *et al.* (2009) B- to plasma-cell terminal differentiation entails oxidative stress and profound reshaping of the antioxidant responses. *Antioxid. Redox Signal.* 13, 1133–1144
46. Panieri, E. and Santoro, M.M. (2016) ROS homeostasis and metabolism: a dangerous liason in cancer cells. *Cell Death. Dis.* 7, e2253
47. McCubrey, J.A. *et al.* (2014) GSK-3 as potential target for therapeutic intervention in cancer. *Oncotarget* 5, 2881–2911
48. Dufort, F.J. *et al.* (2007) Cutting edge: IL-4-mediated protection of primary B lymphocytes from apoptosis via Stat6-dependent regulation of glycolytic metabolism. *J. Immunol.* 179, 4953–4957
49. De Silva, N.S. and Klein, U. (2015) Dynamics of B cells in germinal centres. *Nat. Rev. Immunol.* 15, 137–148
50. Boothby, M. and Rickert, R.C. (2017) Metabolic regulation of the immune humoral response. *Immunity* 46, 743–755
51. Cho, S.H. *et al.* (2016) Germinal centre hypoxia and regulation of antibody qualities by a hypoxia response system. *Nature* 537, 234–238
52. Blaser, H. *et al.* (2016) TNF and ROS crosstalk in inflammation. *Trends Cell Biol.* 26, 249–261
53. Cato, M.H. *et al.* (2011) Cyclin D3 is selectively required for proliferative expansion of germinal center B cells. *Mol. Cell. Biol.* 31, 127–137
54. Varano, G. *et al.* (2017) The B-cell receptor controls fitness of MYC-driven lymphoma cells via GSK3beta inhibition. *Nature* 546, 302–306
55. Vander Heiden, M.G. *et al.* (2009) Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* 324, 1029–1033
56. Schulze, A. and Harris, A.L. (2012) How cancer metabolism is tuned for proliferation and vulnerable to disruption. *Nature* 491, 364–373
57. Ward, P.S. and Thompson, C.B. (2012) Metabolic reprogramming: a cancer hallmark even Warburg did not anticipate. *Cancer Cell* 21, 297–308
58. Dang, C.V. (2013) MYC, metabolism, cell growth, and tumorigenesis. *Cold Spring Harb. Perspect. Med.* 3, a014217
59. Cai, Q. *et al.* (2015) MYC-driven aggressive B-cell lymphomas: biology, entity, differential diagnosis and clinical management. *Oncotarget* 6, 38591–38616
60. Sander, S. *et al.* (2012) Synergy between PI3K signaling and MYC in Burkitt lymphomagenesis. *Cancer Cell* 22, 167–179
61. Klein, U. *et al.* (2003) Transcriptional analysis of the B cell germinal center reaction. *Proc. Natl. Acad. Sci. U. S. A.* 100, 2639–2644
62. Martinez-Valdez, H. *et al.* (1996) Human germinal center B cells express the apoptosis-inducing genes Fas, c-myc, p^{53}, and Bax but not the survival gene bcl-2. *J. Exp. Med.* 183, 971–977
63. Cutrona, G. *et al.* (1997) The propensity to apoptosis of centrocytes and centroblasts correlates with elevated levels of intracellular myc protein. *Eur. J. Immunol.* 27, 234–238
64. Calado, D.P. *et al.* (2012) The cell-cycle regulator c-Myc is essential for the formation and maintenance of germinal centers. *Nat. Immunol.* 13, 1092–1100
65. Dominguez-Sola, D. *et al.* (2012) The proto-oncogene MYC is required for selection in the germinal center and cyclic reentry. *Nat. Immunol.* 13, 1083–1091
66. Dang, C.V. *et al.* (2008) The interplay between MYC and HIF in cancer. *Nat. Rev. Cancer* 51–56
67. Kim, J.W. *et al.* (2007) Hypoxia-inducible factor 1 and dysregulated c-Myc cooperatively induce vascular endothelial growth factor and metabolic switches hexokinase 2 and pyruvate dehydrogenase kinase 1. *Mol. Cell. Biol.* 27, 7381–7393
68. Wang, R. *et al.* (2011) The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation. *Immunity* 35, 871–882
69. Fan, Y. *et al.* (2010) Akt and c-Myc differentially activate cellular metabolic programs and prime cells to bioenergetic inhibition. *J. Biol. Chem.* 285, 7324–7333
70. Osthus, R.C. *et al.* (2000) Deregulation of glucose transporter 1 and glycolytic gene expression by c-Myc. *J. Biol. Chem.* 275, 21797–21800
71. Kim, J. *et al.* (2008) Global identification of Myc target genes reveals its direct role in mitochondrial biogenesis and its E-box usage *in vivo*. *PLoS One* 3, e1798
72. Scarpulla, R.C. (2008) Transcriptional paradigms in mammalian mitochondrial biogenesis and function. *Physiol. Rev.* 88, 611–638
73. Gao, P. *et al.* (2009) c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism. *Nature* 458, 762–765
74. Yuneva, M. *et al.* (2007) Deficiency in glutamine but not glucose induces MYC-dependent apoptosis in human cells. *J. Cell Biol.* 178, 93–105
75. Fagone, P. *et al.* (2007) Phospholipid biosynthesis program underlying membrane expansion during B-lymphocyte differentiation. *J. Biol. Chem.* 282, 7591–7605
76. Conrad, M. and Sato, H. (2012) The oxidative stress-inducible cystine/glutamate antiporter, system x (c) (-): cystine supplier and beyond. *Amino Acids* 42, 231–246
77. Schmitz, R. *et al.* (2014) Oncogenic mechanisms in Burkitt lymphoma. *Cold Spring Harb. Perspect. Med.* 4, a014282
78. Iwata, T.N. *et al.* (2016) Conditional disruption of Raptor reveals an essential role for mTORC1 in B cell development, survival, and metabolism. *J. Immunol.* 197, 2250–2260
79. Jones, D.D. *et al.* (2016) mTOR has distinct functions in generating versus sustaining humoral immunity. *J. Clin. Invest.* 126, 4250–4261
80. Grumont, R.J. *et al.* (2002) B cell growth is controlled by phosphatidylinosotol 3-kinase-dependent induction of Rel/NF-κB regulated c-myc transcription. *Mol. Cell* 10, 1283–1294
81. Lee, K. *et al.* (2013) Requirement for Rictor in homeostasis and function of mature B lymphoid cells. *Blood* 122, 2369–2379
82. Lazorchak, A.S. *et al.* (2010) Sin1-mTORC2 suppresses rag and il7r gene expression through Akt2 in B cells. *Mol. Cell* 39, 433–443

83. Dengler, H.S. *et al.* (2008) Distinct functions for the transcription factor Foxo1 at various stages of B cell differentiation. *Nat. Immunol.* 9, 1388–1398
84. Pourdehnad, M. *et al.* (2013) Myc and mTOR converge on a common node in protein synthesis control that confers synthetic lethality in Myc-driven cancers. *Proc. Natl. Acad. Sci. U. S. A.* 110, 11988–11993
85. Garcia, D. and Shaw, R.J. (2017) AMPK: mechanisms of cellular energy sensing and restoration of metabolic balance. *Mol. Cell* 66, 789–800
86. Sengupta, D. and Pratx, G. (2016) Imaging metabolic heterogeneity in cancer. *Mol. Cancer* 15, 4
87. Warburg, O. (1956) On the origin of cancer cells. *Science* 123, 309–314
88. Monti, S. *et al.* (2005) Molecular profiling of diffuse large B-cell lymphoma identifies robust subtypes including one characterized by host inflammatory response. *Blood* 105, 1851–1861
89. Caro, P. *et al.* (2012) Metabolic signatures uncover distinct targets in molecular subsets of diffuse large B cell lymphoma. *Cancer Cell* 22, 547–560
90. Vangapandu, H.V. *et al.* (2017) B-cell receptor signaling regulates metabolism in chronic lymphocytic leukemia. *Mol. Cancer Res.* 15, 1692–1703
91. Vangapandu, H.V. *et al.* (2017) The stromal microenvironment modulates mitochondrial oxidative phosphorylation in chronic lymphocytic leukemia cells. *Neoplasia* 19, 762–771
92. Rush, J.S. and Hodgkin, P.D. (2001) B cells activated via CD40 and IL-4 undergo a division burst but require continued stimulation to maintain division, survival and differentiation. *Eur. J. Immunol.* 31, 1150–1159
93. Bullen, J.W. *et al.* (2016) Protein kinase A-dependent phosphorylation stimulates the transcriptional activity of hypoxia-inducible factor 1. *Sci. Signal.* 9, ra56
94. Fang, X. *et al.* (2000) Phosphorylation and inactivation of glycogen synthase kinase 3 by protein kinase A. *Proc. Natl. Acad. Sci. U. S. A.* 97, 11960–11965
95. Manz, R.A. and Radbruch, A. (2002) Plasma cells for a lifetime? *Eur. J. Immunol.* 32, 923–927
96. Gatto, D. *et al.* (2006) Regulation of memory antibody levels: the role of persisting antigen versus plasma cell life span. *J. Immunol.* 178, 67–76
97. Siska, P.J. *et al.* (2016) Suppression of Glut1 and glucose metabolism by decreased Akt/mTORC1 signaling drives T cell impairment in B cell leukemia. *J. Immunol.* 197, 2532–2540