

Sirtuins in B lymphocytes metabolism and function

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Abstract

Sirtuins (SIRT6) are NAD⁺-dependent histone deacetylases and play a role in virtually all cell biological processes. As SIRT6 functions vary according to their subtypes, they can either activate or inhibit signaling pathways upon different conditions or tissues. Recent studies have focused on metabolic effects performed by SIRT6 in several cell types since specific metabolic pathways (*e.g.*, aerobic glycolysis, oxidative phosphorylation, β -oxidation, glutaminolysis) are used to determine the cell fate. However, few efforts have been made to understand the role of SIRT6 on B lymphocytes metabolism and function. These cells are associated with humoral immune responses by secreting larger amounts of antibodies after differentiating into antibody-secreting cells. Besides, both the SIRT6 and B lymphocytes are potential targets to treat several immune-mediated disorders, including cancer. Here, we provide an outlook of recent studies regarding the role of SIRT6 in general cellular metabolism and B lymphocytes functions, pointing out the future perspectives of this field.

Key words: B cells; Metabolic sensors; Histone deacetylases; Cancer

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Core tip: Current studies have focused on understanding which intracellular molecules coordinate the metabolic flux within the cells. In addition to metabolism, sirtuins play a role in virtually all cell biological processes, but they have not been properly described in B lymphocytes function and metabolism, despite the importance of these immune cells in health and disease. Here we discuss studies that associate sirtuins and B lymphocytes, highlight the gaps found in the literature and point out the future research

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INTRODUCTION

Over the past decade, studies have focused on understanding which intracellular molecules coordinate the metabolic flux within the cells, mainly those belonging to the immune system^[1-3]. Under activation, immune cells suddenly shift their metabolic profile to achieve their cell fates. These changes provide sufficient energy and generate a diversity of metabolic intermediates to allow rapid proliferation, perform specific functions and thus successfully combat the inflammatory insult^[4]. Hence, immune cells are metabolically active populations which quickly respond to external signals (cytokines, chemokines, hormones, growth factors) to meet their bioenergetic demand.

However, the role of the metabolic sensors has been evaluated in only a few immune cell types, such as T cells, macrophages and dendritic cells^[1,2]. The B lymphocytes are the main components of humoral responses, responding to both specific and non-specific antigens, producing antibodies after differentiation into plasmablasts/plasma cells [antibody-secreting cells (ASCs)], and generating immunological memory after antigen re-exposure^[5]. The functional diversity of B lymphocytes (protection, regulation, effector function, memory) makes these cells essential during immune responses^[6]. Thus, any changes in B cell development or function is sufficient to develop several diseases (immunodeficiency, autoimmunity, cancer). Despite their great importance in immune responses, the means by which the metabolic sensors act on the development and function of B lymphocytes has been sparsely evaluated^[7].

The molecular sensors have evolutionarily developed within the cells. They converge a plethora of environmental signals that induce abrupt metabolic changes, leading the cells to achieve different fates (*e.g.*, differentiation, activation, anergy, autophagy or cell death)^[3]. The most studied metabolic sensors include the mammalian (or mechanistic) target of rapamycin complex 1 (mTORC1), AMP-activated protein kinase (AMPK), hypoxia-inducible factor 1- α (HIF-1 α), c-Myc protein, peroxisome proliferator-activated receptors (PPARs) and sterol regulatory element-binding proteins (SREBPs)^[8]. Recently, another protein family has been pointed out as an important metabolic sensor, the sirtuins (SIRT). These nicotinamide adenine dinucleotide (NAD⁺)-dependent deacetylases or adenosine diphosphate-ribosyltransferases are not only related to cell metabolism, but also to cell proliferation, survival, senescence, stress, gene stability, ribosomal DNA recombination and epigenetic regulations^[9]. The wide range of SIRT functions is due to their variable distribution within cells (cytoplasm, nucleus, and mitochondria) and highlights the importance of these proteins in cell biology. Here we briefly describe the SIRT structure, distribution and functions, outline their role on general metabolism aspects, characterize the origin and development of B lymphocyte subtypes, and provide an outlook of recent studies regarding the role of SIRTs on metabolism, growth and function of B lymphocytes, pointing out the gaps that need to be filled in the next few years.

SIRTUINS

Initially identified in *Saccharomyces cerevisiae* as lifespan yeast proteins^[9], it is now known that SIRT constitute a highly conserved protein family among bacteria, plants and mammals^[10,11]. The founding member of this family was discovered through a spontaneous mutation that caused sterility in yeast. The mutation reduced the transcription of the silent mating-type loci HML and HMR, later called as Mating-type Regulator 1 (MAR1) and currently named as Silencing Information Regulator 2 (SIR2)^[12]. Twelve years later, it was identified that the SIR2-induced silencing of the mating-type loci in yeasts was associated with low levels of histone acetylation at the

N-terminal lysine residues of H4 histones^[13]. Consistent with this finding, the overexpression of SIR2 promoted significant histone hypoacetylation and consequently extended yeast lifespan^[14]. Thus, the SIRs (or SIRT in humans/mice) were first classified as class III histone deacetylases.

The SIRT activity is controlled by the intracellular NAD⁺/NADH ratio, being activated when NAD⁺ levels are increased^[15,16]. SIRT catalyze the acetyl groups removal of acetylated lysine-containing proteins to generate a deacetylated protein, free nicotinamide and a unique acetyl-ADP-ribose (O-ADP-ribose) metabolite, which is formed by the transfer of the acetyl group into the ADP-ribose fraction of NAD⁺^[17,18].

Although SIRT were originally identified as histone lysine deacetylases, several other biological processes over numerous non-histone substrates have also been described. Hence, some SIRT subtypes may play roles as deacetylase, desuccinylase, demalonylase, deglutarylase, long-chain deacylase, lipoamidase or ADP-ribosyl transferase enzymes^[19,20]. It has also been shown that SIRT isotypes display different specificities for ϵ -N-acyllysine post-translational modifications (PTM), an essential epigenetical modification process. Moreover, SIRT affinities for various substrates still need to be investigated^[21,22]. It is also important to emphasize that all enzymatic activity performed by SIRT are dependent on the NAD⁺ availability, thus reflecting the cellular metabolic status. Consequently, SIRT have also been classified as metabolic sensors.

SIRT have a conserved catalytic core formed by two domains which are responsible for catalyzing the transference of an acetyl group from a protein to a NAD⁺ molecule. One domain is a large and well-conserved Rossmann-fold domain, characteristic of NAD⁺/NADH binding proteins, which accommodates NAD⁺^[23,24]. The other domain is smaller, less conserved and contains a zinc binding site. Although zinc does not actively participate in the deacetylation process, it plays a role in the structural integrity required for the reaction, since the SIRT deacetylase function is abolished when the zinc binding site is mutated^[25]. There are also four polypeptide chains linking both larger and smaller domains, forming a cleft in which the substrates, NAD⁺ and acetyl-lysine-containing protein bind on opposite sides. These four connecting polypeptide chains vary in size and sequence according to different SIRT isotypes, and such diversity may interfere with enzymatic activity, protein location and substrate specificity^[10,26].

In yeasts, four SIRs have been identified (SIR1-4), whereas in humans and mice seven homologs (SIRT1-7) have been described^[27]. SIRT can be divided according to a specific terminology based on their structural sequence: SIRT1, 2 and 3 (class I), SIRT4 (class II), SIRT5 (class III) and SIRT6 and 7 (class IV)^[28]. Despite the high structural similarity among the SIRTs, each one presents unique features regarding their enzymatic activities, cellular sublocations, and molecular targets as shown in **Table 1**. Therefore, the classification based on cellular sublocation has been most widely used, being SIRT1, 3, 6 and 7 classified as nuclear (SIRT1 may also be found in cytoplasm), SIRT2 as cytoplasmic (but it can also be found in nucleus) and SIRT3, 4 and 5 as mitochondrial proteins^[29].

In summary, SIRT were formerly described as histone deacetylases, but their enzymatic capacity has now been extended to several other non-acetylated substrates. Moreover, their ubiquitous distribution within cells and different tissues virtually expands the function of SIRT for all cellular biological activities. The dependency of SIRT on NAD⁺ make them critical metabolic sensors that control several metabolic processes which will be described below.

SIRTUINS AND METABOLISM

As important metabolic sensors, studies have demonstrated that SIRT modulate the gene expression, PTMs, and activity of key metabolic enzymes associated to glycolysis, oxidative phosphorylation (OXPHOS), glutamine metabolism, β -oxidation and fatty acid synthesis (**Figure 1**)^[30,31].

Glucose is the primary cell metabolic fuel and provides several intermediates to other biosynthetic reactions in all mammalian cells, plants and many microorganisms. Glucose is transported into cells *via* the high-affinity glucose transporters (GLUT)^[32]. While adipose tissue, liver, and muscle depend on the GLUT4 isoform, both T and B lymphocytes rely on GLUT1^[33]. Moreover, other non-immune cells may express sodium-glucose linked transporters (SGLT), which import both glucose and sodium ions into the cell^[34]. The glucose may be addressed to several metabolic pathways within a cell but is primarily destined for glycolysis.

Glycolysis is a cytosolic metabolic pathway in which glucose is converted into two pyruvate molecules. The pyruvate can be either used to synthesize acetyl-CoA and

Table 1 Sirtuins localization and function

Sirtuin	Localization	Enzymatic activity	General functions	References
SIRT1	Nucleus Cytoplasm	Deacetylase Deacylase	Metabolism Mitochondrial biogenesis Cellular stress Chromatin regulation Cell differentiation	[30]
SIRT2	Cytoplasm Nucleus	Deacetylase Demyristoylase ADP-ribosylase Deacylase	Cell cycle Cell differentiation Metabolism Tumor suppression	[97]
SIRT3	Mitochondria	Deacetylase Decrotonylase Deacylase	Metabolism Mitochondrial biogenesis Antioxidant activity	[98,99]
SIRT4	Mitochondria	ADP-ribosylase Lipoamidase Deacetylase Deacylase	Tumor suppression Metabolism Tumor suppression	[100]
SIRT5	Mitochondria	Desuccinylase Deacylase Demalonylase Deglutarylase Deacetylase	Metabolism	[101]
SIRT6	Nucleus	Deacylase Deacetylase ADP-ribosylase	DNA repair Metabolism Inflammation	[102]
SIRT7	Nucleus	Deacetylase Deacylase	Ribosome biogenesis Tumor promotion Metabolism	[103]

ADP: Adenine diphosphate; SIRT: Sirtuin.

fuel the tricarboxylic acid (TCA) cycle or converted into lactate. Since lactate production usually occurs upon oxygen deprivation, this metabolic pathway is referred to as "lactic fermentation." Nevertheless, in B lymphocytes and other cells, the lactate production can occur even in the presence of oxygen, and it is termed "aerobic glycolysis" or Warburg effect^[35]. For each molecule of glucose produced during glycolysis, there is a net sum of two units of adenosine triphosphate (ATP), an energy storing molecule^[36]. As stated earlier, SIRT's play several roles in regulating glycolysis. SIRT1, 3 and 6 have been shown to suppress glycolysis while enhancing β -oxidation. SIRT1 activates the peroxisome proliferator-activated receptor γ coactivator-1 α (PGC1- α) and inhibits HIF1- α , essential inducers of OXPHOS/ β -oxidation and glycolysis, respectively. Mice lacking SIRT3 increase the reactive oxygen species (ROS) production, which in turn stabilizes HIF-1 α inside the cell nucleus, enhancing glycolysis^[37]. SIRT3, in turn, inhibits superoxide dismutase 2 (SOD2) enzyme to suppress the ROS-mediated stabilization of HIF1- α . SIRT6 acts as a co-repressor of HIF1- α and also inhibits c-Myc, another crucial glycolytic regulator which is also associated with glutamine metabolism^[37]. On the other hand, SIRT5 can increase glycolysis by activating the glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH) through demalonylation reactions^[38]. Altogether, these results show that several SIRT's control positive and negatively the glycolysis. However, further studies are needed to understand why similar proteins have opposite or overlapped functions in regulating the glucose within cells.

One study showed that during the late acute inflammatory response, there is a metabolic shift from glycolysis towards OXPHOS in several immune cells types, characterized by lower expression levels of GLUT1, which was shown to be dependent on SIRT1 and SIRT6^[39]. Furthermore, knockdown of these proteins results in a decreased GLUT1 expression in human monocytic cell lines activated with LPS, indicating an essential metabolic role of SIRT's during inflammatory responses^[39]. We speculate that SIRT's, as regulators of glycolysis, might affect the GLUT1 expression among immune cell subpopulations. However, this information is still understudied and requires further investigation.

If the pyruvate is not converted into lactate, it can be oxidized into acetyl-CoA by the pyruvate dehydrogenase (PDH) complex in the mitochondria, entering the TCA cycle. Acetyl-CoA combines with oxaloacetate to originate citrate and a series of following reactions take place to give rise to important products: NADH and FADH₂. Most non-proliferating and terminally differentiated T cells (*e.g.*, naïve and memory T cells), as well as resting B lymphocytes, use the TCA cycle to generate NADH and FADH₂ coenzymes, which transfer electrons to fuel OXPHOS^[40]. The OXPHOS produces thirty six molecules of ATP per mol of glucose^[41], and it is the most efficient method for generating energy from different metabolic intermediates, such as glucose, fatty acids or amino acids, although the slowest one^[42].

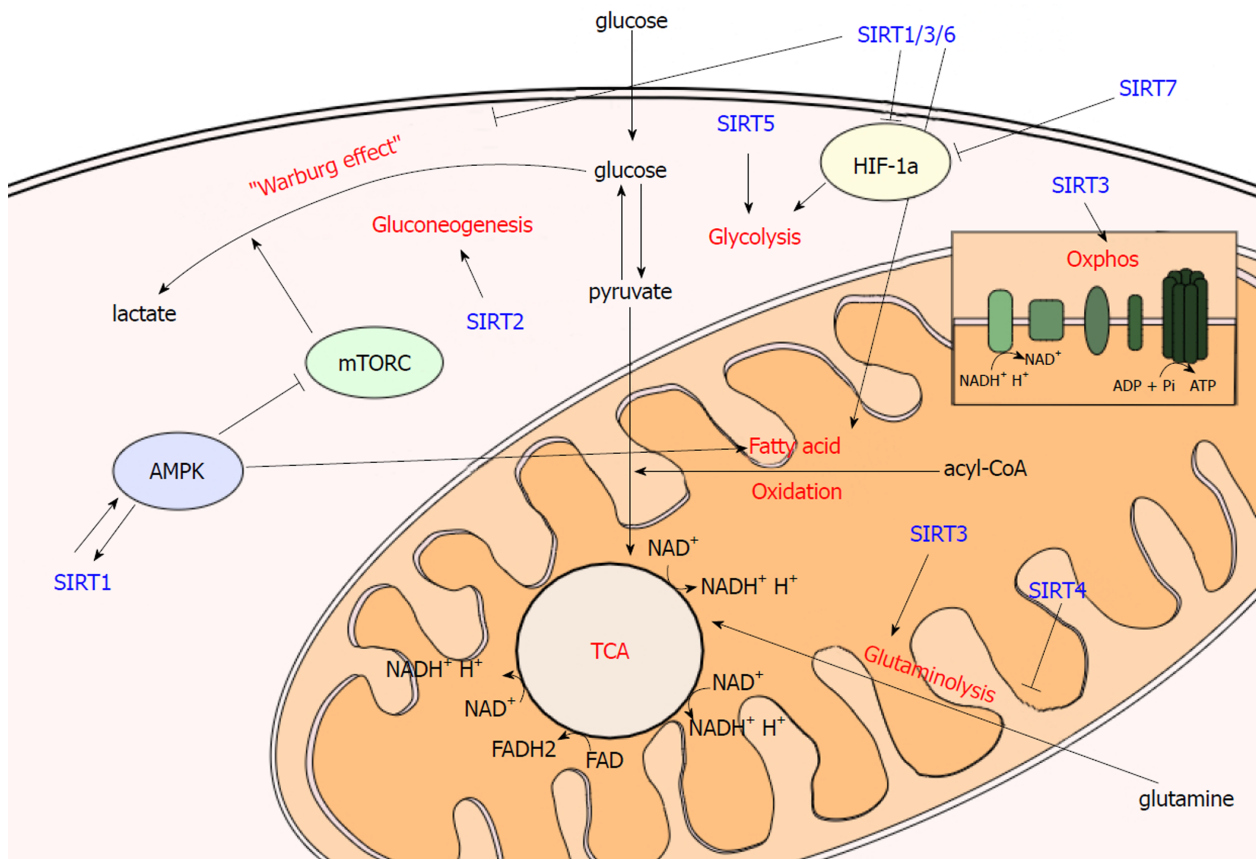


Figure 1 Sirtuins and metabolism. SIRTs are metabolic sensors that modulate a variety of metabolic pathways, including glycolysis (Warburg effect), gluconeogenesis, fatty acid oxidation, glutaminolysis, TCA cycle and OXPHOS. SIRTs 1, 3 and 6 restrain the glycolytic pathway through HIF-1 α inhibition or direct effects. SIRT3 upregulates OXPHOS pathway by enhancing the activity of the mitochondrial complexes I, II and III and dampening ROS production. SIRT1 is also able to increase the fatty acid oxidation by activating PPAR- α and PGC1- α , while SIRT3 upregulates the fatty acid oxidation upon caloric restriction conditions. SIRT2 induces gluconeogenesis. SIRT3 and 4 activates and inhibits, respectively, the glutaminolysis by regulating the GDH activity. SIRT5 increases glycolysis by increasing the activity of the GAPDH enzyme. SIRT7 can also repress HIF-1 α and therefore inhibit transcription of glycolytic genes. At last, SIRT1 performs a positive feedback loop with AMPK, since AMPK rises NAD⁺ levels in cells, which in turn enhances SIRT1 activity and lastly leads to AMPK activation. AMPK suppresses glycolysis via mTORC1 inhibition and promotes fatty acid oxidation. In the Figure, SIRTs are represented based on their functions only and not by localization. AMPK: AMP-activated protein kinase; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase; GDH: Glutamate dehydrogenase enzyme; HIF-1 α : Hypoxia-inducible factor 1-alpha; mTORC1: Target of rapamycin complex 1; NAD⁺: Nicotinamide adenine dinucleotide; OXPHOS: Oxidative phosphorylation; PGC1- α : Proliferator-activated receptor γ coactivator-1 α ; PPAR- α : Peroxisome proliferator-activated receptor alpha; ROS: Reactive oxygen species; SIRTs: Sirtuins; TCA: Tricarboxylic acid.

It is described that SIRT3 deacetylates several enzymes related to the TCA cycle, enhancing their activities. SIRT3 targets isocitrate dehydrogenase 2 (IDH), which catalyzes the oxidative decarboxylation of isocitrate to 2-oxoglutarate, and acetyl-coenzyme synthetase 2 that provides acetyl-CoA to the TCA in a PDH-independent manner^[40]. SIRT1 has shown to be an activator of acetyl-CoA synthetase 1, restoring acetyl-CoA levels^[43].

Fatty acids and glutamine also supply the TCA cycle and OXPHOS by additional metabolic reactions such as β -oxidation and glutaminolysis, respectively^[44]. As stated above, SIRT6 was described as an important regulator of c-Myc activity. c-Myc has been associated with glutamine metabolism by activating the glutaminase 1 (GLS1), which converts glutamine to glutamate. SIRT3, in turn, increases the activity of glutamate dehydrogenase (GDH), responsible for converting glutamate into α -ketoglutarate, while SIRT4 inhibits GDH activity^[31]. SIRT4 acts as a tumor suppressor protein, being able to inhibit mitochondrial glutamine metabolism by repressing GDH activity (Figure 1).

Regarding β -oxidation, SIRT1 has been shown to increase this pathway activity by activating both PPAR- α and PGC1 α , thus promoting the expression of downstream targeted genes which are related to increased use of lipids. At the same time, SIRT1 inhibits lipid synthesis through deacetylation of SREBP-1c or *via* suppression of PPAR- γ ^[45]. Upon caloric restriction, SIRT3 activates long-chain Acyl-CoA dehydrogenase (LCAD) and 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2), promoting β -oxidation and ketogenesis, respectively. Also, SIRT3 also enhances cellular respiration by enabling mitochondrial complexes I, II and III and decreasing ROS production, given it stimulates the activity of the SOD2. SIRT4 dampens the

transcription of genes underlying β -oxidation, such as PPAR- α , whereas SIRT6 is thought to repress the transcription of fatty-acid synthesis-related genes^[45].

Interestingly, SIRT6 can play their role along with another critical metabolic sensor, the AMPK. AMPK is usually activated by increasing intracellular calcium influxes or AMP/ATP ratio in the cells. This kinase inhibits the activity of mTOR, a member of the PI3Ks protein kinase family which plays a central role in upregulating glycolysis as well as protein synthesis, energy balance, cell proliferation and survival^[3]. Therefore, AMPK inhibits glycolysis and promotes both β -oxidation and OXPHOS in several cell types^[3,46,47]. AMPK can also act on metabolic reprogramming through transcriptional and PTM as observed in SIRT6^[48,49]. Studies show that SIRT6 forms a positive feedback loop with AMPK: AMPK increases NAD⁺ levels in cells, which in turn enhances SIRT6 activity and lastly leads to AMPK activation^[50].

Although the role of SIRT2 in metabolism has not been appropriately investigated, it induces gluconeogenesis in the adipose tissue *via* PGC1 α and FOXO1 activation^[51,52]. FOXO1 is a vital coordinator of longevity, tumor suppression, metabolism and cell growth^[53]. Gluconeogenesis is a metabolic pathway in which glucose is synthesized from non-carbohydrate precursors (*e.g.*, lactate, glycerol and some amino acids) being activated in some specialized tissues under glucose deprivation states. Gluconeogenesis has not been described in immune cells, but a recent study showed that memory T cells upregulate the gluconeogenesis-related enzyme Pck-1 to increase gluconeogenesis activity^[54]. SIRT7 expression and function in immune cells have not been well characterized. However, SIRT7 regulates low glucose-induced cellular stress by uncoupling rRNA synthesis and enabling energy storage in HEK293T cells^[55]. Also, SIRT7 can also repress HIF-1 α (Figure 1) and therefore inhibit the transcription of glycolytic genes in many cell lineages such as Hep3B, HeLa, HEK293T and MDA-MB-231^[55].

Briefly, SIRT6 may either activate or inhibit metabolic pathways depending on their isoforms, localization and cellular activation status. Moreover, SIRT6 is the most well-described isoform and regulates several metabolic pathways, whereas SIRT2 and 7 lack metabolic descriptions in immune cells.

B LYMPHOCYTES

B lymphocytes have a pivotal role in adaptive immune responses through cytokine secretion, antigen presentation to T cells, as well as by their unique ability to produce antibodies after differentiating into ASCs^[56-58].

Early in life, B lymphocytes are produced in the fetal liver, and after birth, they are generated in the bone marrow (BM) throughout life^[5] (Figure 2). In addition, current studies have found that B lymphocytes can also develop from the gut shortly after birth and the resident microbiota plays a crucial role in increasing the antigen receptor repertoire of these cells^[59].

The first B-cell lineage-committed progenitors are derived from hematopoietic stem cells and known as pre-pro B lymphocytes. These cells express B lymphocyte-specific surface proteins such as B220 (or CD45R)^[60]. Subsequently, these cells undergo μ heavy chain somatic recombination through rearrangement of V(D)J gene segments to assemble the pre-BCR, becoming pro-B lymphocytes^[61]. In this stage, cells start to express the CD19 coreceptor under the control of the transcription factor Pax5^[62]. The pre-BCR is a transitory complex consisting of a successful V(D)J recombination, a surrogate light chain and two intracellular signaling proteins (Ig α and Ig β); pre-BCR is expressed in the surface of pre-B lymphocytes^[63,64]. If the pre-BCR results from a nonproductive V(D)J recombination process, then the pre-B lymphocyte development stops and the cell undergoes apoptosis^[65]. The correct signaling through the pre-BCR promotes intracellular changes that block second allele recombination, in a process termed as allelic exclusion^[66]. Furthermore, the proper BCR signaling induces somatic recombination of κ or λ light chains through the rearrangement of VJ segments, allowing the BCR assembly^[64,65]. Upon reaching the immature stage, B lymphocytes express a functional BCR as a surface IgM protein. Finally, the immature B lymphocytes leave the BM towards the spleen where further developmental steps occur, by the time they are ultimately differentiating into follicular (FO) or marginal zone (MZ) B lymphocytes.

Before B lymphocytes differentiate into FO or MZ B cells they go through three transitional stages (T1, T2 and T3)^[67], which are quite different between human and mouse^[68]. T1 and T2 B lymphocytes give rise to mature B lymphocytes, whereas the development and function of T3 cells remains unclear^[69]. The role of these transitional B lymphocytes is to allow the second round of regulatory checkpoint aiming to decrease potential cell autoreactivity.

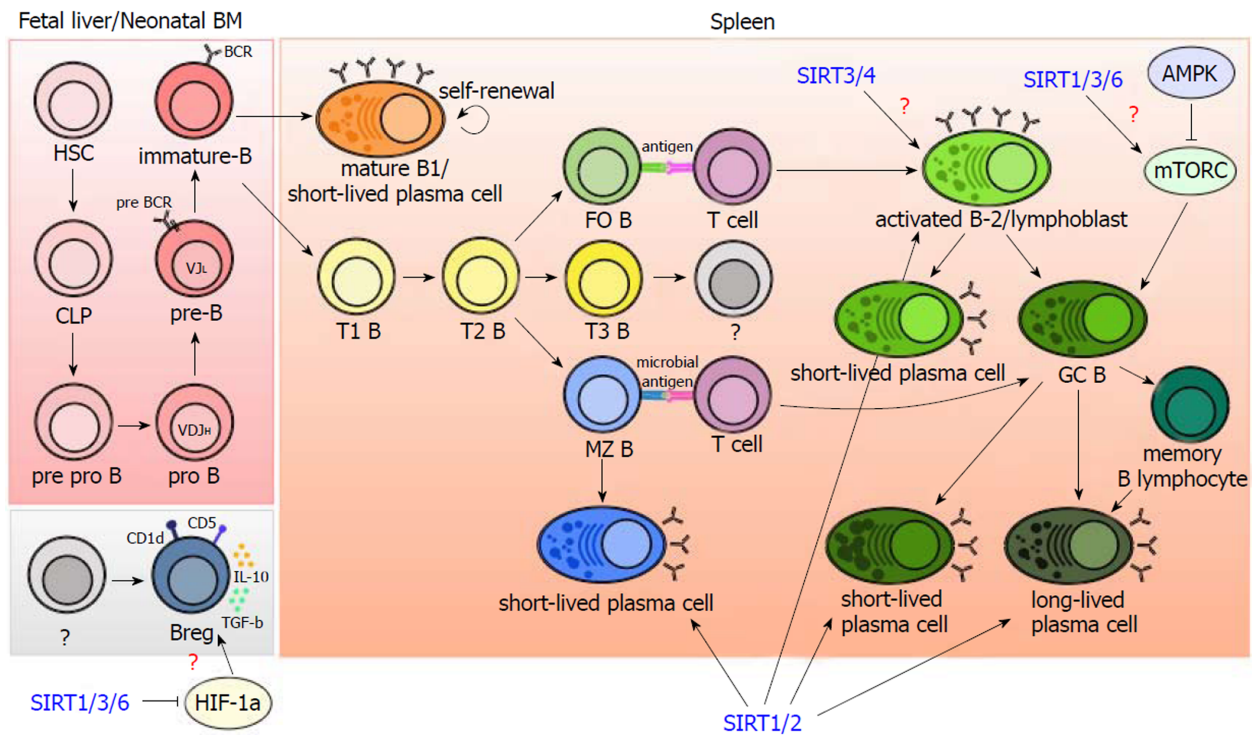


Figure 2 Sirtuins and B lymphocytes. B lymphocyte development begins in the fetal liver or bone marrow and continues in the periphery. B-1 and B-2 B lymphocytes differentiate into ASCs by distinct pathways. The origin of Breg cells is still not precise. Despite the role of SIRT in healthy B lymphocytes have not been adequately investigated, some studies have described some functions in a disease context. SIRT1 and 2 inhibition are essential to treat CLL, although other studies show that SIRT1 is important at some point of ASCs differentiation. Moreover, since AMPK-mTORC1 axis regulates GC reactions and antibody production, it suggests that SIRT1 (or SIRT3/4) also coordinate this process. Glutaminolysis was shown to be an essential metabolic pathway to enhance proliferation of Burkitt lymphoma-derived B lymphocytes. Thus, SIRT3 and 4 might play roles in the pathogenesis by activating or inhibiting, respectively, the GDH activity. Additionally, HIF-1 α was shown to be essential to IL-10-producing Bregs development, suggesting that SIRT1/3/6 are downregulated in these populations. The question marks indicate speculative roles of SIRTs. AMPK: AMP-activated protein kinase; ASCs: Antibody-secreting cells; B: B lymphocytes; BCR: B cell receptor; Breg: B regulatory lymphocytes; CLL: Chronic lymphocytic leukemia; CLP: Common lymphoid progenitor; FO B: Follicular B lymphocytes; GC: Germinal center; GDH: Glutamate dehydrogenase enzyme; HIF-1 α : Hypoxia-inducible factor 1-alpha; HSC: Hematopoietic stem-cell; mTORC1: Target of rapamycin complex 1; MZ: Marginal zone; SIRTs: Sirtuins; T1/T2/T3: Transitional stages 1, 2 and 3, respectively, of B lymphocytes.

Although MZ B lymphocytes are usually associated to T-independent B lymphocyte responses, one study showed that they could respond to T lymphocytes, differentiate into germinal center (GC) cells and subsequently in ASCs and memory B lymphocytes^[70]. However other studies are needed to confirm this observation.

FO B lymphocytes can recirculate and migrate to follicles within secondary lymphoid organs. They are located nearby follicular CD4⁺ T cells, allowing bidirectional cooperation during T-dependent B lymphocytes responses. However, FO B lymphocytes are also found within the BM in small clusters, where they respond to bloodborne pathogens in a T-independent manner^[71]. FO B lymphocytes are the primary source of memory B lymphocytes and plasmablasts that can terminally differentiate in long-lived plasma cells and synthesize large amounts of antibodies.

Another possible fate of immature B lymphocytes is to become B-1 cells, which are able to self-renew in the periphery, populating the fluids from the pleural, peritoneal and intestinal cavities^[72,73]. These cells produce antibodies independently of T cell assistance and are often referred to as innate mediators. An important role of B-1 cells is to synthesize polyspecific natural antibodies (IgM and IgA), which recognize several carbohydrate residues and rapidly respond to mucosal pathogens^[57,73].

Another emerging B lymphocyte population are the regulatory B cells (Bregs). Similarly to the well-described regulatory T lymphocytes (Tregs), Bregs inherently produce IL-10 to control inflammatory responses, but also TGF- β and IL-35^[74,75]. In addition, Bregs can induce apoptosis or anergy of T cells, suppress the differentiation of monocytes and dendritic cells and cooperate with Treg differentiation^[74]. The origin of these cells is not well established, although it is known that conventional B lymphocytes can differentiate into Breg cells at all stages of development^[76].

B lymphocytes are associated with several pathological conditions, such as autoimmunity, non-autoimmune inflammatory diseases, and cancer. In Systemic lupus erythematosus (SLE), for instance, larger amounts of autoantibodies able to recognize nuclear proteins are produced and may accumulate as immune complexes

in the joints, skin, kidney and serosal membranes, leading to a severe inflammatory status^[77]. Moreover, chronic lymphocytic leukemia (CLL), the most common form of leukemia in western countries, is a type of cancer that arises from uncontrolled proliferation of B lymphocytes in lymphoid and non-lymphoid organs^[78]. CLL is characterized by a poor outcome and reduced survival rates among the affected patients.

In summary, B lymphocytes are the powerhouses of humoral immune responses given their ability to secrete antibodies capable of neutralizing and opsonizing pathogens. Besides, B lymphocytes undergo multiple developmental steps to generate different subsets. Thus, given the complexity of B lymphocytes, it is reasonable to assume that these cells cooperate in maintaining homeostasis and that any putative changes in their function or maturation steps might contribute to the development of several pathologies.

SIRTUINS, B LYMPHOCYTES, AND METABOLISM

Few studies have focused on understanding B lymphocyte metabolism compared to other immune and non-immune cell types. It is described that in a resting state, B lymphocytes present higher rates of glycolysis when compared to T cells; upon activation, they increase both glycolysis and OXPHOS at similar rates^[32]. However, only glycolysis but not OXPHOS was shown to be essential for LPS-activated B lymphocyte development, proliferation, and function^[79]. When glycolysis is impaired *in vitro* at distinct steps, the proliferation of stimulated B lymphocytes and antibody secretion are strongly suppressed^[32]. B lymphocytes lacking GLUT1 show significantly IgM and IgG production impairment in immunization models^[32]. In addition to glycolysis, fatty acids are also produced *de novo* to support synthesis and expansion of membranes in plasma cells^[80]. Concomitantly, fatty acids are essential to generate energy *via* β -oxidation. Since antibodies are glycoproteins, the metabolism of amino acids and glucose-derived intermediates are necessary during all antibody generation process^[81].

The role of SIRT1 in B lymphocytes has been described under pathological conditions and lacks information on healthy B lymphocytes. Recent studies indicate that SIRT1 regulates the immune response by delaying the onset of autoimmunity since nuclear-reactive autoantibodies were found in the sera of SIRT1-null mice. Moreover, these animals had deposits of immune complexes within the liver and the kidneys, indicating an autoimmune-like condition due to the lack of SIRT1^[82]. Since a rapid and increased glycolytic activity is found under chronic B lymphocyte Activating Factor (BAFF)-exposure in B lymphocytes^[32] to induce experimental autoimmunity, it is plausible to consider that SIRT1 counter-regulates the glucose pathway in healthy B lymphocytes. However, it is still not a matter of investigation.

Another study showed that both SIRT1 and 2 contribute to CLL pathogenicity. SIRT1 mRNA expression and protein levels were increased in B lymphocyte-derived cell lines from human patients with CLL compared to control healthy group^[78]. Additionally, pharmacological inhibition of both SIRT1 and 2 using EX-527 and sirtinol, respectively, in PBMC cells from patients with CLL resulted in dose-dependent cytotoxicity, increased apoptosis rates and elevated mitochondrial ROS production^[78]. These results indicate SIRT1 as potential targets for clinical trials in patients affected by CLL and for other B lymphocyte-related conditions.

It has also been described that SIRT3 expression is reduced in CLL, leading to accumulation of ROS and induction of a Warburg-like metabolic pathway that supports the uncontrolled proliferation of B lymphocytes^[83]. However, the underlying metabolic changes in these pathogenic B lymphocytes require further investigations.

Pan-histone-deacetylase inhibitors (HDACi) such as panobinostat have shown to be capable of reducing autoreactive plasma cell counts and autoantibodies in a mouse model for SLE^[84]. However, immunological memory was not compromised after the treatment, given that the level of circulating memory B lymphocytes remained unaltered. Meanwhile, it is not possible to state whether SIRT1 mediate these changes or if other histone deacetylases are more relevant in this context.

Another study suggests that the microRNA 34a(miR34a)-SIRT1-p65 axis is crucial for activating intestinal immune responses during chronic simian immunodeficiency virus (SIV) infection in rhesus macaques. It was described that miR-34a upregulation coupled with a downregulation of SIRT1 enhance the NF- κ B activity in both IgA⁺ and IgG⁺ intestinal plasma cells, contributing to B lymphocyte hyperresponsiveness in chronic SIV-infected macaques^[85].

The glutamine metabolism has been shown as an essential regulator of B lymphocyte proliferation and survival under glucose deprivation and hypoxia

conditions in P493 cells, a B lymphocyte-derived cell line to study Burkitt lymphoma^[86]. Hypoxia is an essential feature found in tumor microenvironments. Since SIRT3 and SIRT4 activates and inhibits, respectively, the glutaminolysis pathway, these proteins are potential targets for future studies focusing on glutamine metabolism in normal or cancerous B lymphocytes. Interestingly, SIRT4 deletion in a mouse model for Burkitt-lymphoma resulted in increased tumor proliferation and mortality rates, indicating that SIRT4 might act as a tumor suppressor as described in other cell types^[87]. However, the association among B lymphocytes, metabolism and SIRT3/4 remains to be clarified in the Burkitt-lymphoma context (Figure 2).

Breg metabolism characterization has not been described so far, although HIF-1 α is essential to IL-10-producing B lymphocytes development^[88]. Nevertheless, it is well established that Treg metabolism rely on mitochondrial OXPHOS^[4]. SIRT1 has already been associated with the induction of FoxP3⁺ Treg cells, although it is still under investigation^[89]. Moreover, AMPK has also been described as an important molecular sensor to induce Treg differentiation^[90]. Altogether, these results suggest that Breg and Treg have different regulators since HIF-1 α is pro-glycolytic (Figure 2).

Recent researches indicate that mTORC1 activity is essential for the GC reactions, increasing the rate of somatic hypermutation and affinity maturation of isotype-switched B lymphocytes^[91]. However, AMPK has also shown to induce terminally differentiated plasma cells and enhance antibody production^[92], suggesting that SIRT1 might be downregulated in GC B lymphocytes and upregulated in plasma cells. Nevertheless, underlying mechanisms describing how this putative metabolic shift occurs during the process is unknown. Also, future studies should investigate whether SIRT1s have distinct roles in differentiating plasma cells and memory B lymphocytes during GC reactions.

Importantly, B lymphocytes play substantial roles in the pathogenesis of metabolic (e.g., obesity, cancer, diabetes, periodontal disease) and non-metabolic (SLE, rheumatoid arthritis, graft-versus-host diseases, HIV infection) conditions^[93-103]. Therefore, future investigations on the impact of SIRT1s in B lymphocytes metabolism and function will provide potential alternatives on treating or dampening the progression of a wide range of illnesses.

In summary, the role of SIRT1s in B lymphocytes remains under investigation, and the association with metabolic aspects is at the beginning of understanding. Further studies focusing on comprehension of SIRT1s functions in the development and metabolism of B lymphocytes under homeostasis conditions must also be encouraged.

CONCLUSION

Altogether, these results show that SIRT1s play roles in virtually all biological processes in cells but should be further evaluated in B lymphocytes since they are related to several homeostatic and pathologic responses. Moreover, several SIRT1s isotypes have not been sufficiently investigated, and future studies are necessary to achieve a broader and more complete understanding of their functions in the cell metabolism. It is important to state that B lymphocytes have several cell subsets and the assessments regarding the role of metabolic sensors should be performed in specific B lymphocyte subpopulations. Thus, future investigations must answer whether or which SIRT1s are important to each B lymphocyte subtype in both healthy and pathological states. The better comprehension of how metabolic sensors, especially SIRT1s, control the development, metabolism, function, and lifespan of immune cells is therefore essential and suggests they may be valuable and potential pharmacological targets to treat several metabolic-related diseases.

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