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**Sirtuins in B lymphocytes metabolism and function**

Ghirotto B *et al.* Sirtuins and B lymphocytes

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**Abstract**

Sirtuins (SIRTs) are NAD+-dependent histone deacetylases and play a role in virtually all cell biological processes. As SIRTs 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 SIRTs 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 SIRTs 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 SIRTs and B lymphocytes are potential targets to treat several immunomediated disorders, including cancer. Here, we provide an outlook of recent studies regarding the role of SIRTs 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 directions.

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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 this 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-alpha (HIF-1α), c-Myc protein, peroxisome proliferator-activated receptors (PPARs) and sterol regulatory element-binding proteins (SREBPs)[3]. Recently, another protein family has been pointed out as an important metabolic sensor, the sirtuins (SIRTs). 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[8]. The wide range of SIRTs 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 SIRTs 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 SIRTs 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 life span[14]. Thus, the SIRs (or SIRTs in humans/mice) were first classified as class III histone deacetylases.

The SIRTs activity is controlled by the intracellular NAD+/NADH ratio, being activated when NAD+ levels are increased[15,16]. SIRTs 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 SIRTs were originally identified as histone lysine deacetylases, several other biological processes over numerous non-histone substrates have also been described. Hence, some SIRTs subtypes may play roles as deacetylase, desuccinylase, demaloynylase, deglutarylase, long-chain deacylase, lipoamidase or ADP-ribosyl transferase enzymes[19,20]. It has also been showed that SIRT isotypes display different specificities for ε-N-acyllysine post-translational modifications (PTM), an essential epigenetical modification process. Moreover, SIRTs affinities for various substrates still need to be investigated[21,22]. It is also important to emphasize that all enzymatic activity performed by SIRTs are dependent on the NAD+ availability, thus reflecting the cellular metabolic status. Consequently, SIRTs have also been classified as metabolic sensors.

SIRTs 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 Rossman-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]. SIRTs 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 can be observed 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, SIRTs 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 SIRTs for all cellular biological activities. The dependency of SIRTs on NAD+ make them as critical metabolic sensors that control several metabolic processes that will be described below.

**SIRTUINS AND METABOLISM**

As important metabolic sensors, studies have demonstrated that SIRTs 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 destinated 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 fuel the tricarboxylic acid (TCA) cycle or converted into lactate. Since lactate production usually occurs upon oxygen deprivation, this metabolic pathway is referred to "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, SIRTs 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-1α (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 stabilize HIF-1α 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 SIRTs 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 SIRTs during inflammatory responses[39]. We speculate that SIRTs, 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 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].

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 described above, SIRT6 was described as an important regulator of c-Myc activity. c-Myc has been associated with glutamine metabolism by activating the enzyme glutaminase (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 by activating both PPAR-α and PGC1α, 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 superoxide dismutase 2 (SOD2) enzyme. 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, SIRTs 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 promote 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 SIRTs[48,49]. Studies show that SIRT1 forms a positive feedback loop with AMPK: AMPK increases NAD+ levels in cells, which in turn enhances SIRT1 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 PGC1α 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[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-1α and therefore inhibit transcription of glycolytic genes in many cell lineages such as Hep3B, HeLa, HEK293T and MDA-MB-231[55] (Figure 1).

Briefly, SIRTs may either activate or inhibit metabolic pathways depending on their isotypes, localization and cellular activation status. Moreover, SIRT1 is the most well-described isotype 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 referred to 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 assembly the pre-BCR and termed as 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 (Igα and Igβ); 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 pre-BCR promotes intracellular changes that block second allele recombinations, 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.

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 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 IgM and IgA polyspecific natural antibodies, which recognize several carbohydrate residues and rapidly respond to mucosal pathogens[57,73].

Another emerging B lymphocytes population are the B regulatory (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 cells 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, 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, the B lymphocyte undergoes 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 GLUT1showsignificantly 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 in the generation of 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 SIRTs 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 SIRTs 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 SIRTs 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-κB transcription factor subunit p65 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 this protein 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-1α 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-1α is pro-glycolytic (Figure 2).

Recent researches indicate that mTORC1 activity is essential for the germinal center (GC) reaction, 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 (Figure 2). Nevertheless, underlying mechanisms describing how this putative metabolic shift occurs during the process is unknown. Also, future studies should investigate whether SIRTs have distinct roles in differentiating plasma cells and memory B lymphocytes in GC reaction.

Importantly, B lymphocytes plays substantial role in the pathogenesis of metabolic (*e.g.*, obesity, cancer, diabetes, periodontal disease) and non-metabolic (SLE, reumathoid arthritis, graft-verus-host diseases, HIV infection) conditions[93-103]. Therefore, future investigations on the impact of SIRTs 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 SIRTs in B lymphocytes remains under investigation, and the association with metabolic aspects is at the beginning of understanding. Further studies focusing on comprehension of SIRTs functions in the development and metabolism of B lymphocytes under homeostasis conditions must also be encouraged.

**CONCLUSION**

Altogether, these results show that SIRTs 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 SIRTs 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 SIRTs are important to each B lymphocyte subtype in both healthy and pathological states. The better comprehension of how metabolic sensors, especially SIRTs, 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.

**REFERENCES**

1 **Kelly B**, O'Neill LA. Metabolic reprogramming in macrophages and dendritic cells in innate immunity. *Cell Res* 2015; **25**: 771-784 [PMID: 26045163 DOI: 10.1038/cr.2015.68]

2 **Buck MD**, O'Sullivan D, Pearce EL. T cell metabolism drives immunity. *J Exp Med* 2015; **212**: 1345-1360 [PMID: 26261266 DOI: 10.1084/jem.20151159]

3 **Yuan HX**, Xiong Y, Guan KL. Nutrient sensing, metabolism, and cell growth control. *Mol Cell* 2013; **49**: 379-387 [PMID: 23395268 DOI: 10.1016/j.molcel.2013.01.019]

4 **Pearce EL**, Pearce EJ. Metabolic pathways in immune cell activation and quiescence. *Immunity* 2013; **38**: 633-643 [PMID: 23601682 DOI: 10.1016/j.immuni.2013.04.005]

5 **Pieper K**, Grimbacher B, Eibel H. B-cell biology and development. *J Allergy Clin Immunol* 2013; **131**: 959-971 [PMID: 23465663 DOI: 10.1016/j.jaci.2013.01.046]

6 **León B**, Ballesteros-Tato A, Misra RS, Wojciechowski W, Lund FE. Unraveling effector functions of B cells during infection: the hidden world beyond antibody production. *Infect Disord Drug Targets* 2012; **12**: 213-221 [PMID: 22394173]

7 **Capasso M**, Rashed Alyahyawi A, Spear S. Metabolic control of B cells: more questions than answers. *Front Immunol* 2015; **6**: 80 [PMID: 25762999 DOI: 10.3389/fimmu.2015.00080]

8 **Jing H**, Lin H. Sirtuins in epigenetic regulation. *Chem Rev* 2015; **115**: 2350-2375 [PMID: 25804908 DOI: 10.1021/cr500457h]

9 **Guarente L**. Diverse and dynamic functions of the Sir silencing complex. *Nat Genet* 1999; **23**: 281-285 [PMID: 10545947 DOI: 10.1038/15458]

10 **Brachmann CB**, Sherman JM, Devine SE, Cameron EE, Pillus L, Boeke JD. The SIR2 gene family, conserved from bacteria to humans, functions in silencing, cell cycle progression, and chromosome stability. *Genes Dev* 1995; **9**: 2888-2902 [PMID: 7498786]

11 **Finkel T**, Deng CX, Mostoslavsky R. Recent progress in the biology and physiology of sirtuins. *Nature* 2009; **460**: 587-591 [PMID: 19641587 DOI: 10.1038/nature08197]

12 **Klar AJ**, Fogel S, Macleod K. MAR1-a Regulator of the HMa and HMalpha Loci in Saccharomyces Cerevisiae. *Genetics* 1979; **93**: 37-50 [PMID: 17248968]

13 **Aparicio OM**, Billington BL, Gottschling DE. Modifiers of position effect are shared between telomeric and silent mating-type loci in S. cerevisiae. *Cell* 1991; **66**: 1279-1287 [PMID: 1913809]

14 **Kaeberlein M**, McVey M, Guarente L. The SIR2/3/4 complex and SIR2 alone promote longevity in Saccharomyces cerevisiae by two different mechanisms. *Genes Dev* 1999; **13**: 2570-2580 [PMID: 10521401]

15 **Lin SJ**, Defossez PA, Guarente L. Requirement of NAD and SIR2 for life-span extension by calorie restriction in Saccharomyces cerevisiae. *Science* 2000; **289**: 2126-2128 [PMID: 11000115]

16 **Revollo JR**, Grimm AA, Imai S. The NAD biosynthesis pathway mediated by nicotinamide phosphoribosyltransferase regulates Sir2 activity in mammalian cells. *J Biol Chem* 2004; **279**: 50754-50763 [PMID: 15381699 DOI: 10.1074/jbc.M408388200]

17 **Tanner KG**, Landry J, Sternglanz R, Denu JM. Silent information regulator 2 family of NAD- dependent histone/protein deacetylases generates a unique product, 1-O-acetyl-ADP-ribose. *Proc Natl Acad Sci USA* 2000; **97**: 14178-14182 [PMID: 11106374 DOI: 10.1073/pnas.250422697]

18 **Borra MT**, Langer MR, Slama JT, Denu JM. Substrate specificity and kinetic mechanism of the Sir2 family of NAD+-dependent histone/protein deacetylases. *Biochemistry* 2004; **43**: 9877-9887 [PMID: 15274642 DOI: 10.1021/bi049592e]

19 **Choudhary C**, Weinert BT, Nishida Y, Verdin E, Mann M. The growing landscape of lysine acetylation links metabolism and cell signalling. *Nat Rev Mol Cell Biol* 2014; **15**: 536-550 [PMID: 25053359 DOI: 10.1038/nrm3841]

20 **Wagner GR**, Hirschey MD. Nonenzymatic protein acylation as a carbon stress regulated by sirtuin deacylases. *Mol Cell* 2014; **54**: 5-16 [PMID: 24725594 DOI: 10.1016/j.molcel.2014.03.027]

21 **Imai S**, Guarente L. Ten years of NAD-dependent SIR2 family deacetylases: implications for metabolic diseases. *Trends Pharmacol Sci* 2010; **31**: 212-220 [PMID: 20226541 DOI: 10.1016/j.tips.2010.02.003]

22 **Garske AL**, Denu JM. SIRT1 top 40 hits: use of one-bead, one-compound acetyl-peptide libraries and quantum dots to probe deacetylase specificity. *Biochemistry* 2006; **45**: 94-101 [PMID: 16388584 DOI: 10.1021/bi052015l]

23 **Finnin MS**, Donigian JR, Pavletich NP. Structure of the histone deacetylase SIRT2. *Nat Struct Biol* 2001; **8**: 621-625 [PMID: 11427894 DOI: 10.1038/89668]

24 **Prasad GS**, Sridhar V, Yamaguchi M, Hatefi Y, Stout CD. Crystal structure of transhydrogenase domain III at 1.2 A resolution. *Nat Struct Biol* 1999; **6**: 1126-1131 [PMID: 10581554 DOI: 10.1038/70067]

25 **Chakrabarty SP**, Balaram H. Reversible binding of zinc in Plasmodium falciparum Sir2: structure and activity of the apoenzyme. *Biochim Biophys Acta* 2010; **1804**: 1743-1750 [PMID: 20601220 DOI: 10.1016/j.bbapap.2010.06.010]

26 **Sanders BD**, Jackson B, Marmorstein R. Structural basis for sirtuin function: what we know and what we don't. *Biochim Biophys Acta* 2010; **1804**: 1604-1616 [PMID: 19766737 DOI: 10.1016/j.bbapap.2009.09.009]

27 **Frye RA**. Characterization of five human cDNAs with homology to the yeast SIR2 gene: Sir2-like proteins (sirtuins) metabolize NAD and may have protein ADP-ribosyltransferase activity. *Biochem Biophys Res Commun* 1999; **260**: 273-279 [PMID: 10381378 DOI: 10.1006/bbrc.1999.0897]

28 **Frye RA**. Phylogenetic classification of prokaryotic and eukaryotic Sir2-like proteins. *Biochem Biophys Res Commun* 2000; **273**: 793-798 [PMID: 10873683 DOI: 10.1006/bbrc.2000.3000]

29 **Michishita E**, Park JY, Burneskis JM, Barrett JC, Horikawa I. Evolutionarily conserved and nonconserved cellular localizations and functions of human SIRT proteins. *Mol Biol Cell* 2005; **16**: 4623-4635 [PMID: 16079181 DOI: 10.1091/mbc.E05-01-0033]

30 **Chang HC**, Guarente L. SIRT1 and other sirtuins in metabolism. *Trends Endocrinol Metab* 2014; **25**: 138-145 [PMID: 24388149 DOI: 10.1016/j.tem.2013.12.001]

31 **Houtkooper RH**, Pirinen E, Auwerx J. Sirtuins as regulators of metabolism and healthspan. *Nat Rev Mol Cell Biol* 2012; **13**: 225-238 [PMID: 22395773 DOI: 10.1038/nrm3293]

32 **Caro-Maldonado A**, Wang R, Nichols AG, Kuraoka M, Milasta S, Sun LD, Gavin AL, Abel ED, Kelsoe G, Green DR, Rathmell JC. Metabolic reprogramming is required for antibody production that is suppressed in anergic but exaggerated in chronically BAFF-exposed B cells. *J Immunol* 2014; **192**: 3626-3636 [PMID: 24616478 DOI: 10.4049/jimmunol.1302062]

33 **Maciver NJ**, Jacobs SR, Wieman HL, Wofford JA, Coloff JL, Rathmell JC. Glucose metabolism in lymphocytes is a regulated process with significant effects on immune cell function and survival. *J Leukoc Biol* 2008; **84**: 949-957 [PMID: 18577716 DOI: 10.1189/jlb.0108024]

34 **Navale AM**, Paranjape AN. Glucose transporters: physiological and pathological roles. *Biophys Rev* 2016; **8**: 5-9 [PMID: 28510148 DOI: 10.1007/s12551-015-0186-2]

35 **Vander Heiden MG**, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* 2009; **324**: 1029-1033 [PMID: 19460998 DOI: 10.1126/science.1160809]

36 **Lunt SY**, Vander Heiden MG. Aerobic glycolysis: meeting the metabolic requirements of cell proliferation. *Annu Rev Cell Dev Biol* 2011; **27**: 441-464 [PMID: 21985671 DOI: 10.1146/annurev-cellbio-092910-154237]

37 **Guarente L**. The many faces of sirtuins: Sirtuins and the Warburg effect. *Nat Med* 2014; **20**: 24-25 [PMID: 24398961 DOI: 10.1038/nm.3438]

38 **Nishida Y**, Rardin MJ, Carrico C, He W, Sahu AK, Gut P, Najjar R, Fitch M, Hellerstein M, Gibson BW, Verdin E. SIRT5 Regulates both Cytosolic and Mitochondrial Protein Malonylation with Glycolysis as a Major Target. *Mol Cell* 2015; **59**: 321-332 [PMID: 26073543 DOI: 10.1016/j.molcel.2015.05.022]

39 **Liu TF**, Vachharajani VT, Yoza BK, McCall CE. NAD+-dependent sirtuin 1 and 6 proteins coordinate a switch from glucose to fatty acid oxidation during the acute inflammatory response. *J Biol Chem* 2012; **287**: 25758-25769 [PMID: 22700961 DOI: 10.1074/jbc.M112.362343]

40 **Parihar P**, Solanki I, Mansuri ML, Parihar MS. Mitochondrial sirtuins: emerging roles in metabolic regulations, energy homeostasis and diseases. *Exp Gerontol* 2015; **61**: 130-141 [PMID: 25482473 DOI: 10.1016/j.exger.2014.12.004]

41 **Fernie AR**, Carrari F, Sweetlove LJ. Respiratory metabolism: glycolysis, the TCA cycle and mitochondrial electron transport. *Curr Opin Plant Biol* 2004; **7**: 254-261 [PMID: 15134745 DOI: 10.1016/j.pbi.2004.03.007]

42 **Loftus RM**, Finlay DK. Immunometabolism: Cellular Metabolism Turns Immune Regulator. *J Biol Chem* 2016; **291**: 1-10 [PMID: 26534957 DOI: 10.1074/jbc.R115.693903]

43 **Hallows WC**, Lee S, Denu JM. Sirtuins deacetylate and activate mammalian acetyl-CoA synthetases. *Proc Natl Acad Sci USA* 2006; **103**: 10230-10235 [PMID: 16790548 DOI: 10.1073/pnas.0604392103]

44 **Wallace DC**. Mitochondria and cancer. *Nat Rev Cancer* 2012; **12**: 685-698 [PMID: 23001348 DOI: 10.1038/nrc3365]

45 **Ye X**, Li M, Hou T, Gao T, Zhu WG, Yang Y. Sirtuins in glucose and lipid metabolism. *Oncotarget* 2017; **8**: 1845-1859 [PMID: 27659520 DOI: 10.18632/oncotarget.12157]

46 **Mei Z**, Zhang X, Yi J, Huang J, He J, Tao Y. Sirtuins in metabolism, DNA repair and cancer. *J Exp Clin Cancer Res* 2016; **35**: 182 [PMID: 27916001 DOI: 10.1186/s13046-016-0461-5]

47 **Delgoffe GM**, Pollizzi KN, Waickman AT, Heikamp E, Meyers DJ, Horton MR, Xiao B, Worley PF, Powell JD. The kinase mTOR regulates the differentiation of helper T cells through the selective activation of signaling by mTORC1 and mTORC2. *Nat Immunol* 2011; **12**: 295-303 [PMID: 21358638 DOI: 10.1038/ni.2005]

48 **Sarbassov DD**, Ali SM, Sengupta S, Sheen JH, Hsu PP, Bagley AF, Markhard AL, Sabatini DM. Prolonged rapamycin treatment inhibits mTORC2 assembly and Akt/PKB. *Mol Cell* 2006; **22**: 159-168 [PMID: 16603397 DOI: 10.1016/j.molcel.2006.03.029]

49 **Shimizu I**, Yoshida Y, Suda M, Minamino T. DNA damage response and metabolic disease. *Cell Metab* 2014; **20**: 967-977 [PMID: 25456739 DOI: 10.1016/j.cmet.2014.10.008]

50 **Price NL**, Gomes AP, Ling AJ, Duarte FV, Martin-Montalvo A, North BJ, Agarwal B, Ye L, Ramadori G, Teodoro JS, Hubbard BP, Varela AT, Davis JG, Varamini B, Hafner A, Moaddel R, Rolo AP, Coppari R, Palmeira CM, de Cabo R, Baur JA, Sinclair DA. SIRT1 is required for AMPK activation and the beneficial effects of resveratrol on mitochondrial function. *Cell Metab* 2012; **15**: 675-690 [PMID: 22560220 DOI: 10.1016/j.cmet.2012.04.003]

51 **Zhang M**, Pan Y, Dorfman RG, Yin Y, Zhou Q, Huang S, Liu J, Zhao S. Sirtinol promotes PEPCK1 degradation and inhibits gluconeogenesis by inhibiting deacetylase SIRT2. *Sci Rep* 2017; **7**: 7 [PMID: 28127057 DOI: 10.1038/s41598-017-00035-9]

52 **Jing E**, Gesta S, Kahn CR. SIRT2 regulates adipocyte differentiation through FoxO1 acetylation/deacetylation. *Cell Metab* 2007; **6**: 105-114 [PMID: 17681146 DOI: 10.1016/j.cmet.2007.07.003]

53 **Lu H**, Huang H. FOXO1: a potential target for human diseases. *Curr Drug Targets* 2011; **12**: 1235-1244 [PMID: 21443466]

54 **Ma R**, Ji T, Zhang H, Dong W, Chen X, Xu P, Chen D, Liang X, Yin X, Liu Y, Ma J, Tang K, Zhang Y, Peng Y, Lu J, Zhang Y, Qin X, Cao X, Wan Y, Huang B. A Pck1-directed glycogen metabolic program regulates formation and maintenance of memory CD8+ T cells. *Nat Cell Biol* 2018; **20**: 21-27 [PMID: 29230018 DOI: 10.1038/s41556-017-0002-2]

55 **Kiran S**, Anwar T, Kiran M, Ramakrishna G. Sirtuin 7 in cell proliferation, stress and disease: Rise of the Seventh Sirtuin! *Cell Signal* 2015; **27**: 673-682 [PMID: 25435428 DOI: 10.1016/j.cellsig.2014.11.026]

56 **Shen P**, Fillatreau S. Antibody-independent functions of B cells: a focus on cytokines. *Nat Rev Immunol* 2015; **15**: 441-451 [PMID: 26065586 DOI: 10.1038/nri3857]

57 **Cerutti A**, Puga I, Cols M. Innate control of B cell responses. *Trends Immunol* 2011; **32**: 202-211 [PMID: 21419699 DOI: 10.1016/j.it.2011.02.004]

58 **Chen X**, Jensen PE. The role of B lymphocytes as antigen-presenting cells. *Arch Immunol Ther Exp* (Warsz) 2008; **56**: 77-83 [PMID: 18373241 DOI: 10.1007/s00005-008-0014-5]

59 **Wesemann DR**, Portuguese AJ, Meyers RM, Gallagher MP, Cluff-Jones K, Magee JM, Panchakshari RA, Rodig SJ, Kepler TB, Alt FW. Microbial colonization influences early B-lineage development in the gut lamina propria. *Nature* 2013; **501**: 112-115 [PMID: 23965619 DOI: 10.1038/nature12496]

60 **Allman D**, Li J, Hardy RR. Commitment to the B lymphoid lineage occurs before DH-JH recombination. *J Exp Med* 1999; **189**: 735-740 [PMID: 9989989]

61 **Meffre E**, Casellas R, Nussenzweig MC. Antibody regulation of B cell development. *Nat Immunol* 2000; **1**: 379-385 [PMID: 11062496 DOI: 10.1038/80816]

62 **Nutt SL**, Heavey B, Rolink AG, Busslinger M. Commitment to the B-lymphoid lineage depends on the transcription factor Pax5. *Nature* 1999; **401**: 556-562 [PMID: 10524622 DOI: 10.1038/44076]

63 **Nagasawa T**. Microenvironmental niches in the bone marrow required for B-cell development. *Nat Rev Immunol* 2006; **6**: 107-116 [PMID: 16491135 DOI: 10.1038/nri1780]

64 **Herzog S**, Reth M, Jumaa H. Regulation of B-cell proliferation and differentiation by pre-B-cell receptor signalling. *Nat Rev Immunol* 2009; **9**: 195-205 [PMID: 19240758 DOI: 10.1038/nri2491]

65 **Melchers F**. Checkpoints that control B cell development. *J Clin Invest* 2015; **125**: 2203-2210 [PMID: 25938781 DOI: 10.1172/JCI78083]

66 **Shimizu T**, Mundt C, Licence S, Melchers F, Mårtensson IL. VpreB1/VpreB2/lambda 5 triple-deficient mice show impaired B cell development but functional allelic exclusion of the IgH locus. *J Immunol* 2002; **168**: 6286-6293 [PMID: 12055243]

67 **Pillai S**, Cariappa A. The follicular versus marginal zone B lymphocyte cell fate decision. *Nat Rev Immunol* 2009; **9**: 767-777 [PMID: 19855403 DOI: 10.1038/nri2656]

68 **Vossenkämper A**, Spencer J. Transitional B cells: how well are the checkpoints for specificity understood? *Arch Immunol Ther Exp* (Warsz) 2011; **59**: 379-384 [PMID: 21789626 DOI: 10.1007/s00005-011-0135-0]

69 **Teague BN**, Pan Y, Mudd PA, Nakken B, Zhang Q, Szodoray P, Kim-Howard X, Wilson PC, Farris AD. Cutting edge: Transitional T3 B cells do not give rise to mature B cells, have undergone selection, and are reduced in murine lupus. *J Immunol* 2007; **178**: 7511-7515 [PMID: 17548583]

70 **Song H**, Cerny J. Functional heterogeneity of marginal zone B cells revealed by their ability to generate both early antibody-forming cells and germinal centers with hypermutation and memory in response to a T-dependent antigen. *J Exp Med* 2003; **198**: 1923-1935 [PMID: 14662910 DOI: 10.1084/jem.20031498]

71 **Cariappa A**, Mazo IB, Chase C, Shi HN, Liu H, Li Q, Rose H, Leung H, Cherayil BJ, Russell P, von Andrian U, Pillai S. Perisinusoidal B cells in the bone marrow participate in T-independent responses to blood-borne microbes. *Immunity* 2005; **23**: 397-407 [PMID: 16226505 DOI: 10.1016/j.immuni.2005.09.004]

72 **Suzuki K**, Maruya M, Kawamoto S, Fagarasan S. Roles of B-1 and B-2 cells in innate and acquired IgA-mediated immunity. *Immunol Rev* 2010; **237**: 180-190 [PMID: 20727036 DOI: 10.1111/j.1600-065X.2010.00941.x]

73 **Baumgarth N**. The double life of a B-1 cell: self-reactivity selects for protective effector functions. *Nat Rev Immunol* 2011; **11**: 34-46 [PMID: 21151033 DOI: 10.1038/nri2901]

74 **Mauri C**, Bosma A. Immune regulatory function of B cells. *Annu Rev Immunol* 2012; **30**: 221-241 [PMID: 22224776 DOI: 10.1146/annurev-immunol-020711-074934]

75 **Shen P**, Roch T, Lampropoulou V, O'Connor RA, Stervbo U, Hilgenberg E, Ries S, Dang VD, Jaimes Y, Daridon C, Li R, Jouneau L, Boudinot P, Wilantri S, Sakwa I, Miyazaki Y, Leech MD, McPherson RC, Wirtz S, Neurath M, Hoehlig K, Meinl E, Grützkau A, Grün JR, Horn K, Kühl AA, Dörner T, Bar-Or A, Kaufmann SHE, Anderton SM, Fillatreau S. IL-35-producing B cells are critical regulators of immunity during autoimmune and infectious diseases. *Nature* 2014; **507**: 366-370 [PMID: 24572363 DOI: 10.1038/nature12979]

76 **Baba Y**, Matsumoto M, Kurosaki T. Signals controlling the development and activity of regulatory B-lineage cells. *Int Immunol* 2015; **27**: 487-493 [PMID: 25957265 DOI: 10.1093/intimm/dxv027]

77 **Nashi E**, Wang Y, Diamond B. The role of B cells in lupus pathogenesis. *Int J Biochem Cell Biol* 2010; **42**: 543-550 [PMID: 19850148 DOI: 10.1016/j.biocel.2009.10.011]

78 **Bhalla S**, Gordon LI. Functional characterization of NAD dependent de-acetylases SIRT1 and SIRT2 in B-Cell Chronic Lymphocytic Leukemia (CLL). *Cancer Biol Ther* 2016; **17**: 300-309 [PMID: 26794150 DOI: 10.1080/15384047.2016.1139246]

79 **Milasta S**, Dillon CP, Sturm OE, Verbist KC, Brewer TL, Quarato G, Brown SA, Frase S, Janke LJ, Perry SS, Thomas PG, Green DR. Apoptosis-Inducing-Factor-Dependent Mitochondrial Function Is Required for T Cell but Not B Cell Function. *Immunity* 2016; **44**: 88-102 [PMID: 26795252 DOI: 10.1016/j.immuni.2015.12.002]

80 **Dufort FJ**, Gumina MR, Ta NL, Tao Y, Heyse SA, Scott DA, Richardson AD, Seyfried TN, Chiles TC. Glucose-dependent de novo lipogenesis in B lymphocytes: a requirement for atp-citrate lyase in lipopolysaccharide-induced differentiation. *J Biol Chem* 2014; **289**: 7011-7024 [PMID: 24469453 DOI: 10.1074/jbc.M114.551051]

81 **van Anken E**, Romijn EP, Maggioni C, Mezghrani A, Sitia R, Braakman I, Heck AJ. Sequential waves of functionally related proteins are expressed when B cells prepare for antibody secretion. *Immunity* 2003; **18**: 243-253 [PMID: 12594951]

82 **Sequeira J**, Boily G, Bazinet S, Saliba S, He X, Jardine K, Kennedy C, Staines W, Rousseaux C, Mueller R, McBurney MW. sirt1-null mice develop an autoimmune-like condition. *Exp Cell Res* 2008; **314**: 3069-3074 [PMID: 18687325 DOI: 10.1016/j.yexcr.2008.07.011]

83 **Yu W**, Denu RA, Krautkramer KA, Grindle KM, Yang DT, Asimakopoulos F, Hematti P, Denu JM. Loss of SIRT3 Provides Growth Advantage for B Cell Malignancies. *J Biol Chem* 2016; **291**: 3268-3279 [PMID: 26631723 DOI: 10.1074/jbc.M115.702076]

84 **Waibel M**, Christiansen AJ, Hibbs ML, Shortt J, Jones SA, Simpson I, Light A, O'Donnell K, Morand EF, Tarlinton DM, Johnstone RW, Hawkins ED. Manipulation of B-cell responses with histone deacetylase inhibitors. *Nat Commun* 2015; **6**: 6838 [PMID: 25913720 DOI: 10.1038/ncomms7838]

85 **Mohan M**, Kumar V, Lackner AA, Alvarez X. Dysregulated miR-34a-SIRT1-acetyl p65 axis is a potential mediator of immune activation in the colon during chronic simian immunodeficiency virus infection of rhesus macaques. *J Immunol* 2015; **194**: 291-306 [PMID: 25452565 DOI: 10.4049/jimmunol.1401447]

86 **Le A**, Lane AN, Hamaker M, Bose S, Gouw A, Barbi J, Tsukamoto T, Rojas CJ, Slusher BS, Zhang H, Zimmerman LJ, Liebler DC, Slebos RJ, Lorkiewicz PK, Higashi RM, Fan TW, Dang CV. Glucose-independent glutamine metabolism via TCA cycling for proliferation and survival in B cells. *Cell Metab* 2012; **15**: 110-121 [PMID: 22225880 DOI: 10.1016/j.cmet.2011.12.009]

87 **Jeong SM**, Lee A, Lee J, Haigis MC. SIRT4 protein suppresses tumor formation in genetic models of Myc-induced B cell lymphoma. *J Biol Chem* 2014; **289**: 4135-4144 [PMID: 24368766 DOI: 10.1074/jbc.M113.525949]

88 **Meng X**, Grötsch B, Luo Y, Knaup KX, Wiesener MS, Chen XX, Jantsch J, Fillatreau S, Schett G, Bozec A. Hypoxia-inducible factor-1α is a critical transcription factor for IL-10-producing B cells in autoimmune disease. *Nat Commun* 2018; **9**: 251 [PMID: 29343683 DOI: 10.1038/s41467-017-02683-x]

89 **Beier UH**, Wang L, Bhatti TR, Liu Y, Han R, Ge G, Hancock WW. Sirtuin-1 targeting promotes Foxp3+ T-regulatory cell function and prolongs allograft survival. *Mol Cell Biol* 2011; **31**: 1022-1029 [PMID: 21199917 DOI: 10.1128/MCB.01206-10]

90 **Michalek RD**, Gerriets VA, Jacobs SR, Macintyre AN, MacIver NJ, Mason EF, Sullivan SA, Nichols AG, Rathmell JC. Cutting edge: distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4+ T cell subsets. *J Immunol* 2011; **186**: 3299-3303 [PMID: 21317389 DOI: 10.4049/jimmunol.1003613]

91 **Raybuck AL**, Cho SH, Li J, Rogers MC, Lee K, Williams CL, Shlomchik M, Thomas JW, Chen J, Williams JV, Boothby MR. B Cell-Intrinsic mTORC1 Promotes Germinal Center-Defining Transcription Factor Gene Expression, Somatic Hypermutation, and Memory B Cell Generation in Humoral Immunity. *J Immunol* 2018; **200**: 2627-2639 [PMID: 29531165 DOI: 10.4049/jimmunol.1701321]

92 **McLetchie S**, Raybuck A, Cho SH, Lin J, Boothby MR. mTORC1 in B cells regulates antibody responses and promotes mitochondrial and metabolic fitness. *Immunology* 2017; **198**: 195

93 **Pillai S**, Mattoo H, Cariappa A. B cells and autoimmunity. *Curr Opin Immunol* 2011; **23**: 721-731 [PMID: 22119110 DOI: 10.1016/j.coi.2011.10.007]

94 **Moir S**, Fauci AS. B-cell responses to HIV infection. *Immunol Rev* 2017; **275**: 33-48 [PMID: 28133792 DOI: 10.1111/imr.12502]

95 **Zouali M**. The emerging roles of B cells as partners and targets in periodontitis. *Autoimmunity* 2017; **50**: 61-70 [PMID: 28013554 DOI: 10.1080/08916934.2016.1261841]

96 **Yuen GJ**, Demissie E, Pillai S. B lymphocytes and cancer: a love-hate relationship. *Trends Cancer* 2016; **2**: 747-757 [PMID: 28626801 DOI: 10.1016/j.trecan.2016.10.010]

97 **Head PE**, Zhang H, Bastien AJ, Koyen AE, Withers AE, Daddacha WB, Cheng X, Yu DS. Sirtuin 2 mutations in human cancers impair its function in genome maintenance. *J Biol Chem* 2017; **292**: 9919-9931 [PMID: 28461331 DOI: 10.1074/jbc.M116.772566]

98 **Pirinen E**, Lo Sasso G, Auwerx J. Mitochondrial sirtuins and metabolic homeostasis. *Best Pract Res Clin Endocrinol Metab* 2012; **26**: 759-770 [PMID: 23168278 DOI: 10.1016/j.beem.2012.05.001]

99 **Bao X**, Wang Y, Li X, Li XM, Liu Z, Yang T, Wong CF, Zhang J, Hao Q, Li XD. Identification of 'erasers' for lysine crotonylated histone marks using a chemical proteomics approach. *Elife* 2014; **3** [PMID: 25369635 DOI: 10.7554/eLife.02999]

100 **Mathias RA**, Greco TM, Oberstein A, Budayeva HG, Chakrabarti R, Rowland EA, Kang Y, Shenk T, Cristea IM. Sirtuin 4 is a lipoamidase regulating pyruvate dehydrogenase complex activity. *Cell* 2014; **159**: 1615-1625 [PMID: 25525879 DOI: 10.1016/j.cell.2014.11.046]

101 **Kumar S**, Lombard DB. Functions of the sirtuin deacylase SIRT5 in normal physiology and pathobiology. *Crit Rev Biochem Mol Biol* 2018; **53**: 311-334 [PMID: 29637793 DOI: 10.1080/10409238.2018.1458071]

102 **Rahnasto-Rilla M**, Tyni J, Huovinen M, Jarho E, Kulikowicz T, Ravichandran S, A Bohr V, Ferrucci L, Lahtela-Kakkonen M, Moaddel R. Natural polyphenols as sirtuin 6 modulators. *Sci Rep* 2018; **8**: 4163 [PMID: 29515203 DOI: 10.1038/s41598-018-22388-5]

103 **Paredes S**, Villanova L, Chua KF. Molecular pathways: emerging roles of mammalian Sirtuin SIRT7 in cancer. *Clin Cancer Res* 2014; **20**: 1741-1746 [PMID: 24536059 DOI: 10.1158/1078-0432.CCR-13-1547]

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**Table 1 Sirtuins localization and function**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Sirtuin** | **Localization** | **Enzymatic activity** | **General functions** | **References** |
| SIRT1 | NucleusCytoplasm | DeacetylaseDeacylase | MetabolismMitochondrial biogenesisCellular stressChromatin regulationCell differentiation | [30] |
| SIRT2 | CytoplasmNucleus | DeacetylaseDemyristoylaseADP-ribosylaseDeacylase | Cell cycleCell differentiationMetabolismTumor suppression | [97] |
| SIRT3 | Mitochondria | DeacetylaseDecrotonylaseDeacylase | MetabolismMitochondrial biogenesisAntioxidant activity | [98,99] |
| SIRT4 | Mitochondria | ADP-ribosylaseLipoamidaseDeacetylaseDeacylase | Tumor suppressionMetabolismTumor suppression | [100] |
| SIRT5 | Mitochondria | DesuccinylaseDeacylaseDemalonylaseDeglutarylaseDeacetylase | Metabolism | [101] |
| SIRT6 | Nucleus | DeacylaseDeacetylaseADP-ribosylase | DNA repairMetabolismInflammation | [102] |
| SIRT7 | Nucleus | DeacetylaseDeacylase | Ribosome biogenesisTumor promotionMetabolism | [103] |

ADP: Adenine diphosphate; SIRT: Sirtuin.

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**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-1α 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 upregulate 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-1α 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-1α: 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-1α; PPAR-α: Peroxisome proliferator-activated receptor alpha; ROS: Reactive oxygen species; SIRTs: Sirtuins; TCA: Tricarboxylic acid.

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**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 SIRTs in healthy B lymphocytes have not been adequately investigated, some studies 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-1α 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-1α: 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.