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Review

Regulation of B cell fate, survival, and function by mitochondria and autophagy

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ABSTRACT

B cells are responsible for protective antibody production after differentiation into antibody-secreting cells during humoral immune responses. From early B cell development in the bone marrow, to their maturation in the periphery, activation in the germinal center, and differentiation into plasma cells or memory B cells, B cells display ever-changing functions and properties. Autophagy and mitochondria play important roles in B cell development, activation, and differentiation to accommodate the phenotypic and environmental changes encountered over the lifetime of the cell. Among their many functions, mitochondria and autophagy generate energy, mediate cell survival, and produce/eliminate reactive oxygen species that can serve as signal molecules to regulate differentiation. As B cells mature and differentiate into plasma or memory cells, both autophagic and mitochondrial functions undergo significant changes. In this review, we aim to provide an overview of the role of the autophagosome and mitochondria in regulating B cell fate, survival, and function. Moreover, we will discuss the interplay between these two highly metabolic organelles during B cell development, maturation, and differentiation.

1. Introduction

Vertebrates have developed various strategies to counter the constant and myriad barrage of pathogens they face throughout their lifespans. The adaptive arm of the immune system is capable of discriminating between different pathogens by recognizing the unique molecular markers, or antigens, that distinguish the various pathogens (Litman et al., 2010; Parra et al., 2013). This allows immune responses to tailor their response to specific pathogens, to remember previous pathogen encounters, and to mount a rapid and potent response upon subsequent exposure to the same pathogen (Litman et al., 2010; Parra et al., 2013). Lymphocyte activation, proliferation, and effector functions, as well as the formation of memory cells, are linked to dynamic changes in cellular metabolism (Buck et al., 2017). The metabolic functions of lymphocytes rely heavily on the mitochondria, the cellular metabolic hub that regulates energy production through coordination of the electron transport chain (ETC) and the tricarboxylic acid (TCA) cycle. Moreover, mitochondria catabolize nutrients, including glucose, amino acids, and fatty acids, to produce building blocks for cell activation and expansion (Ahn and Metallo, 2015). In order for the cell to meet its metabolic demands, they have to change their mitochondrial volume, membrane potential ($\Delta\Psi m$), and location in response to nutrient availability and growth stimuli. The engagement of various metabolic pathways is controlled by growth factors and nutrient availability dictated by competition between other interacting cells, as well as the balance of internal metabolites, reactive oxygen species (ROS), and reducing and oxidizing substrates (Buck et al., 2017).

Mitochondria couple metabolite oxidation to aerobic respiration, making them a major energy producer within a cell. Glucose and fatty acids, after being catabolized through glycolysis and β-oxidation, form acetyl-CoA, which fuels the TCA cycle. Acetyl-CoA is further oxidized into carbon dioxide to generate NADH and FADH2, the main sources of electrons for the electron transport chain (ETC). The ETC transfers electrons provided by NADH and FADH2 to oxygen, while generating $\Delta\Psi m$ with proton gradient across the mitochondrial inner membrane. This proton gradient is further utilized to produce ATP (Weinberg et al., 2015). Mitochondria also contribute to lipid and amino acid synthesis to build macromolecules. Glutamine uptake provides another source of carbons that can be used either for oxidative metabolism or anabolism after conversion into nucleic acid precursors and other amino acids (Boothby and Rickert, 2017). At present, the balances among these varied processes have not yet been fully elucidated in specific B lineages. Mitochondria bridge nutrient metabolism to fulfill the bioenergetic demands of the cell through the coordination of the TCA cycle and ETC (Boothby and Rickert, 2017; Chao et al., 2017). It will be important to determine the functions of mitochondria in the regulation

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of B cells at different stages of differentiation.

During differentiation into effector and memory cells, deleterious products, such as oxidized proteins and lipids, can accumulate in the cells (Bhattacharya and Eissa, 2015; Bullon et al., 2016; Puleston and Simon, 2013; Rathmell, 2012). Autophagy is an intracellular homeostatic mechanism important for the degradation of waste components from the cytoplasm in acidic lysosomal compartments (Yang and Klionsky, 2010). Originally, surplus parts of the cytoplasm that acted as targets for autophagy were thought to comprise only cellular organelles and proteins, but this has now been extended to include a range of pathogens (Kuballa et al., 2012). Autophagy is involved in the regulation of cell survival and homeostasis in B and T cells (Bhattacharya and Eissa, 2015; Puleston and Simon, 2013; Rathmell, 2012). In the thymus, autophagy can modulate the selection of certain $CD4^+$ T cell clones, while in the bone marrow autophagy is needed for B cell differentiation and survival at specific stages (Arnold et al., 2016; Bhattacharya and Eissa, 2015; Puleston and Simon, 2013).

T and B cells are the major lymphocyte lineages for adaptive immunity (Litman et al., 2010; Parra et al., 2013). B cells have a semi-nomadic life cycle due to their role in patrolling the body for foreign antigens. However, cell activation and differentiation can lead to the retention of B cells in distinct microenvironments that differ in nutrient availability, oxygen, and redox species (Boothby and Rickert, 2017). B cells are specifically responsible for mediating the humoral arm of the adaptive immune system (Hoffman et al., 2016). Humoral immunity involves the production of antibodies that recognize antigens *via* a unique antigen-binding pocket (Schroeder and Cavacini, 2010; Sela-Culang et al., 2013). Antibodies, also known as immunoglobulins, exist as in a membrane-bound form before secretion, where they serve as the B cell antigen receptor (BCR) (Hoehn et al., 2016; Hoffman et al., 2016). The immunoglobulins expressed by a given B cell have the same antigenic specificity to recognize a particular antigen (Hoehn et al., 2016). In this section, we will summarize how mitochondria and autophagy control B cell fate and long-term maintenance.

2. Mitochondria in early B cell development and maturation

In mammals, conventional B cells are generated from the common lymphoid progenitor and undergo early development in the bone marrow (Hoffman et al., 2016). One of the essential tasks of a developing B cell is to assemble a complete immunoglobulin gene from a diverse pool of gene segments in order to express a functional pre-B cell receptor (BCR) (Melchers, 2015). Early B cell development is characterized by alternating states of quiescence and activation in response to BCR and IL-7 receptor (IL-7R) signaling (Heizmann et al., 2013; Herzog et al., 2009; Stein et al., 2017). Pro-B cells represent the earliest stage of B cell development, and transition to the pre-B cell stage following the successful rearrangement of their immunoglobulin heavy chain gene loci to form the pre-BCR (Fig. 1), one of the first major checkpoints in B cell development (Herzog et al., 2009). Pre-B cells can be further subdivided into the immature, actively dividing large pre-B cell stage and the more mature, quiescent small pre-B cell stage (Herzog et al., 2009; Stein et al., 2017). Pro-B cells develop in IL-7-rich regions in the bone marrow, with IL-7 serving to induce cell division and survival (Clark et al., 2014; Hamel et al., 2014; Heizmann et al., 2013). As pro-B cells transition to large pre-B cells, they undergo a burst of proliferation (Clark et al., 2014; Hamel et al., 2014). However, pre-BCR signaling antagonizes IL-7R signaling, constraining the clonal expansion of large pre-B cells to several divisions (Clark et al., 2014; Hamel et al., 2014; Smart and Venkitaraman, 2000). Large pre-B cells start to lose IL-7 responsiveness and migrate towards IL-7-poor regions, causing them to exit the cell cycle and develop into small pre-B cells (Clark et al., 2014; Hamel et al., 2014; Smart and Venkitaraman, 2000).

The development of pro-B cells into small pre-B cells is driven by pre-BCR and IL-7R-induced metabolic changes involving the mitochondria (Heizmann et al., 2013; Stein et al., 2017). Withdrawal of IL-7 in pre-B cell line cultures results in down-regulation of genes related to mitochondrial function (Heizmann et al., 2013). Compared to small pre-B cells, large pre-B cells have increased mitochondrial membrane potential, glucose uptake, and reactive oxygen species (ROS) levels, consistent with their proliferative state (Stein et al., 2017). Swiprosin-2, a calcium-binding inner mitochondrial membrane protein, regulates a metabolic program triggered as pro-B cells develop into small pre-B cells (Stein et al., 2017). Swiprosin-2 is expressed in pro-B cells but is repressed in pre-B cells due to the expression of the pre-BCR (Stein et al., 2017). Knockout of swiprosin-2 in a pro-B cell line results in decreased oxidative phosphorylation, but increased glycolysis, relative to wild-type controls (Stein et al., 2017). A metabolic switch regulated by swiprosin-2 is triggered as dividing pro-B cells develop into quiescent small pre-B cells.

After the initial development stages in the bone marrow, B cells migrate to the spleen and undergo maturation (Hoffman et al., 2016). Maturing B cells can develop into follicular B cells or marginal zone B cells (Hoffman et al., 2016; Pillai and Cariappa, 2009). Follicular B cells are circulating cells that represent the majority of mature B cells, whereas marginal zone B cells are non-circulating cells that reside in the marginal zone of the spleen (Hoffman et al., 2016; Pillai and Cariappa, 2009). The choice of becoming a follicular B cell or a marginal zone B cell depends upon the strength of BCR signaling, with strong signaling favoring a follicular B cell fate, while weak signaling favoring a marginal zone B cell fate (Hoffman et al., 2016; Pillai and Cariappa, 2009). Additionally, signaling through the Notch2 receptor is crucial to drive marginal zone B cell development (Hoffman et al., 2016; Pillai and Cariappa, 2009). Compared to follicular B cells, marginal zone B cells have increased size and a lower threshold for activation (Jellusova et al., 2017; Pillai and Cariappa, 2009). Moreover, marginal zone B cells are also long-lived and can undergo self-renew (Pillai and Cariappa, 2009). Activated B cells increase glucose uptake and mitochondrial mass, resulting in increased glycolysis and oxidative phosphorylation (Table 1) (Caro-Maldonado et al., 2014). Marginal zone B cells seem to exhibit increased glucose uptake compared to follicular B cells (Jellusova et al., 2017). The metabolic demands are high in the proliferative early B cell stages and decrease in the pre-B, immature, and transitional stages. Glucose uptake, which increases substantially after B cell activation (Caro-Maldonado et al., 2014; Cho et al., 2011; Dufort et al., 2007), provides the substrate for glycolysis (Table 1). Whether marginal zone B cells also increase their mitochondrial mass and oxidative phosphorylation remains to be investigated.

3. Mitochondria in activated B cells

Upon encountering cognate antigen and receiving costimulation from T cells, antigen-specific naïve B cells become activated and migrate to secondary lymphoid tissues, where they undergo rapid growth and proliferation in regions called germinal centers (GC) (Litman et al., 2010; Parra et al., 2013; Wykes, 2003). In the GC, B cells undergo class switch recombination (CSR) to different classes of immunoglobulins, as well as editing their immunoglobulin genes through somatic hypermutation (SHM) to generate high affinity BCRs, a process known as affinity maturation (Litman et al., 2010; Parra et al., 2013). GC B cells that have successfully completed affinity maturation undergo differentiation into either antibody-secreting plasma cells or long-lived memory B cells (Bhattacharya et al., 2007). Additionally, in response to certain types of antigens, naïve B cells can become activated without T cell help and differentiate directly into short-lived antibody-secreting plasma cells (Tangye et al., 2003).

B cells can be activated by a variety of signals, including ligation of the BCR, Toll-like receptors (TLRs), CD40, and cytokine receptors. The type and extent of activation depends upon the specific signal(s) involved, with some of these signals capable of synergizing to produce a more potent or different activation than they would individually.