Babol university of Medical Sciences
Current Research in Medical Sciences
ISSN: 2538-6212
Student Research Committee
Current Research in Medical Sciences

An overview of the influence of germinal centers on antibody production

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Article Info

Article type:
Review Article

Received: 20 September 2021
Revised: 15 November 2021
Accepted: 15 December

ABSTRACT

Abstract: Secretory antibodies produced by B lymphocytes mediate humoral immunity. B-cells develop after maturation in bone marrow from stem cells to obtain the necessary properties to identify and combat against pathogens. B lymphocytes settle in peripheral lymphoid tissues to interact with foreign antigens. The activation of B cells in the peripheral lymphoid tissues lead to the proliferation, differentiation, and production of memory B cells and antibody-secreting plasma cells. The production of memory B cells requires the formation of germinal centers that act as a site for affinity maturation and B cells acquire the necessary changes to detect antigens and produce long-lived plasma cells. In this review, we will focus on related mechanisms of germinal center formation and production of antibodies.

Keywords: B cell; Germinal center; Antibody; plasmacells

Cite this article: Rahmani, et al. An overview of the formation of the germinal centers and the production of antibodies. *Current Research in Medical Sciences*. 2021; 5(2):12-22.

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Publisher: Babol University of Medical Sciences

Introduction

Expanding the B and T lymphocyte lineage is an essential principle of the immune system in all vertebrates. The discovery of the structure and type of antibodies was the first step in understanding the relationship between antigen and antibody that was carried out by Thylusus in the 1930s using serum protein electrophoresis, and it was found that antibodies were detected in the serum protein electrophoresis in the gamma gobulin region (1-3). Later, Gerald Edelman and Rodney Pereter, in the late 1950s, recognized the structural nature of antibodies and stated that the structure of the antibody consists of two heavy chains and two light chains (4-7). Each light and heavy chain of antibodies consists of constant and variable regions that bind to the antigen from the variable region. After that, Frank McFarlane-Brent also proposed the clonal selection hypothesis, and according to this hypothesis, each B cell produces one type of antibody when exposed to a specific antigen, and in the subsequent exposure with the same antigen,

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[DOI: 10.22088/crms.5.2.10]

produces more antibodies. (8). In 1890, Emile Van Behring and Shibassaburro Kitasato introduced the importance of cells now known as B cells in humoral immunity (9). Earlier it was thought that antibodies were produced by B cells, but in 1948 it became clear that antibodies were produced by plasma cells (10, 11).

Development of B lymphocyte

Lymphocytes represent a wide variety of antigen receptors to identify an extensive range of antigens. This diversity occurs during the development of B-lymphocytes from precursor cells. The hematopoietic stem cells generate distinct precursors for various blood cells, one of which is the common lymphoid progenitor that generates B and T cells. The induction of the transcription factor plays a vital role in B and T cell linages. The Notch1 and GATA3 transcription factor cause the developing of T cell lines (12, 13). In contrast, the EBF, E2A, and Pax-5 transcription factors cause express the genes required for B cell development and leads to the B cell commitment. Pro-B cells are the first differentiate from of lymphoid progenitor cells and became a B cell by transcription factors EBF, E2A, and Pax-5. Then, due to the activation of RAG and TDT enzymes, the cell transforms from pro-B cell to pre-B cell. In the pre-B cell stage, B cell receptor was synthesised and, in the next step the pre-B cellconverted to the immature B cell, in which IgM antibody is produced and placed on the cell surface. The immature B cell then enters the selection step and leaves the bone marrow and then they are delivered to the spleen and maturation process is continued. In the last step of maturation phase, the immature B cells convert to mature B cells, and exposed IgD along with IgM on their surface. The mature B cell acquires the ability to interact with the antigen, and after being exposed to the antigen, it becomes an activated B cell. This cell then becomes a centroblast and initiate germinal center formation. (14, 15).

Generally, B lymphocytes include two lymphocyte groups of the B-1 and B-2 cells, are different in their functions. B-2 cells contain a more significant percentage of B-cell lymphocytes in adults, while B-1 cells make up fewer B-lymphocytes. B-1 cells develop predominantly in the embryonic and prenatal, but B-2 cells are produced after birth. B-1 cells respond rapidly to non-protein antigens and spontaneously produce IgM antibodies. In other words, B-1 cells are liable for responding to T cell-independent antigens and are the primary source of natural antibody production. B-2 lymphocytes activate by T cells in response to protein antigens, and by forming the germinal center, they produce long-lived plasma cells, memory B cells, and a variety of antibodies. (16, 17).

B cell activation

Mature B-lymphocytes are produced from precursors in the bone marrow and accumulate in peripheral lymphoid tissues, where they are interacted with antigens. The detection of antigens by specific B lymphocytes characterizes humoral immunity. B cell activation leads to the proliferation, differentiation, and production of memory B cells and antibody-producing plasma cells. During B cells development, lymphocytes express the receptor for proliferation and maturation are selected for survival, and cells that do not show a functional receptor are cleared by apoptosis. In order to produce a long-lived antibody, it is necessary to form a structure called the germ center. Probably effective antibodies are produced through germinal centers.

The lymph node is a structure composed of follicles and mainly consists of B cells. In addition, there is a T cell-rich area at the margin of these follicles. B cell activation occurs in the lymph node in two areas,

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The first, outside the follicle and the second is inside the follicle. In the extra-follicular region, B cells produce short-lived plasma cells after exposure to the antigen. The follicular dendritic cells (FDCs) in the follicles secrete a cytokine that dirved one of the B cells to the center of the follicle and forms the germinal center. The first step in forming of germinal center is activating naive B cells, which are carried out by foreign antigens. Once the antigen is detected, B cells migrate to the inter-follicular region, outside the area of B and T cells and proliferate, interacting with T cell-specific antigens for more activation. However, not all antigen-activated B cells enter the germinal centers. Following interaction with T cells, a subset of B cells differentiates into short-lived plasmablasts that have low-affinity antibodies to the antigen. Moreover, those that have a high affinity for antigens often differentiate into long-lived plasmablasts. Only those B cells delivered to the germinal center have a high affinity for binding to the specific antigen.

Gerenation of germinal centers with light and dark zones

Germinal centers are temporary structures in peripheral lymphatic organs formed in response to T cell-dependent antigens. In the germinal centers, B cells are proliferated and through somatic mutation, B cell with high affinity for binding to antigens would be selected, In germinal centers, these B cells proliferate and differentiate into antibody-secreting plasma cells and memory B cells. (18, 19).

In response to T cell-dependent (TD) antigens, long-lived plasma cells are produced. After being detected by B cell, these antigens will be processed, and presented to to T_{CD4+} cells, and the B cells will be activated. (20). In response to T cell-independent (TI) antigens, short-lived plasma cells will be produced. The antibody response to TI antigens mediates by using repetitive epitope such as polysaccharides, lipids, and nucleic acids without T cell interactions. Once activated, these B cells differentiate into short-lived plasma cells and produce mainly IgM antibodies.

The initial response of B cells to TD antigens causes the formation of germinal centers. Antigen-activated B cells, along with T follicular helper (T_{FH}) cells, migrate from the extra-follicular centers into the inside of follicles, forming the germinal centers. (21). After encountering the antigen, the B cell forms the secondary follicle. The secondary follicles include the mantle zone and the germinal center. The germinal center itself has the following parts: apical light zone, basal light zone, and dark zone. The formation of the germinal center and a humoral immune response is mediated by identifying the same TD antigens by B cells and T cells.

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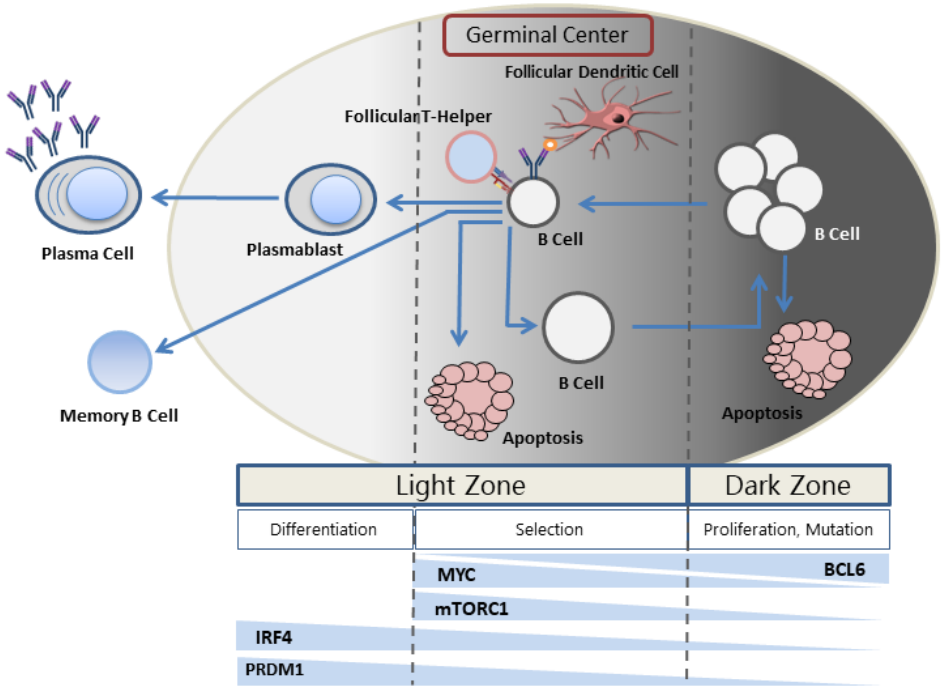

Fig. 1 - The initial response of B cells to TD antigens causes the formation of a germinal center. B-cells activated with the antigen, along with T_{FH} cells, cause the germinal center formation. B cells proliferate and differentiate into plasmablasts. The dark zone is characterized by many dense blast cells, and the light zone is characterized by the presence of several types of cells, such as T_{FH}, follicular dendritic cells, and macrophages. The plasma cells continue to produce antibodies after the antigen's removal. Memory B cell is capable of responding promptly to the next entry of the antigen. Some memory B cells remain inside the mantle zone. IFR4: Interferon Regulatory Factor 4; BCL6: B-Cell Lymphoma 6; PRDM1: PR domain zinc finger protein 1; MTORC1: Mechanistic Target Of Rapamycin Kinase 1.

After antigen arrival to the lymph node, the dendritic cells present the antigen to the naïve T $CD4^+$ cells that are located in the T cell zone (paracortex) of the lymph node, and the naïve T cells become actived and differentiated into T helper cells. Also, B cells in the outer of follicles area are activated after exposure to the antigen. Activated B and T lymphocytes move towards and will intracted together by expressing chemokines, which results in the proliferation and initial production of antibodies and the differentiation of B cells into short-lived plasma cells (22, 23). The primary antibodies produced by B cells are mainly IgM, which enters the bloodstream and attaches to the antigen and can activate the complement, leading to the formation of an antigen-antibody complex, and picked up by CD21 on the follicular dendritic cell surface (FDC) to be presented to B cell. Activated T cells move toward activated B cells by increasing the expression of CXCR5 chemokine, and also the B cells migrate to the T cell zone by increasing the expression of the CCR7 chemokine. After B and T cell interaction, B cells again expresses CXCR5 and enter to the lymphoid follicle, and followed by proliferation that result in generation of the secondary follicle, or in other words, a germinal center (24, 25). Histologically, follicles are recognizable on the fourth day after immunization in the primary germinal center. During this time, B cells proliferate and differentiate into centroblast cells. Approximately, 6-5 days after immunization, the size of the germinal center will increase with the proliferation of B cells and light and dark zones will appeared. The dark zone is characterized with dense blast cells, and in the light zone, the B cells are less than the dark

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zone and are characterized by several cells such as follicular T cells, follicular dendritic cells, and macrophages. With the proliferation of centroblasts, the somatic mutation occurs in these cells, in which the cells are divided into two groups, the high-affinity centroblasts and the low-affinity centrocytes, and move toward the light zone. Centrocytes will be competed in the light zone to obtain the antigen-antibody complex located on the surface of the follicular dendritic cells. Those high-affinity centrocytes can detect antigens presented by follicular dendritic cells, receive the survival signal, enter the next selection stage, and will be survived. Those low-affinity centrocytes cannot detect antigens presented by follicular dendritic cells and they have targeted to apoptosis. The affinity maturation process causes affinity increase of the immune response. After selecting of B cells with high-affinity binding to antigens, these cells deliver the immune complex in the apical light zone to the T follicular helper cells (T_{FH}). According to signals received from the T_{FH} cells, B cells differentiate into antibody-producing plasma cells or memory B cells. The T_{FH} cell plays a vital role in developing the germinal center and the production of plasma cells by producing IL-21(18, 26). B cells that differentiate into plasma cells migrate to the bone marrow and are the major source of antibody production. These long-lived plasma cells continue to produce antibodies for months, even years after the antigen clearance. The memory B cells will be transfered into the mantle zone, then exit of the lymph node and enters the bloodstream, which can respond promptly to the next entry of the antigen. Of course, some memory B cells remain inside the mantle zone (27).

The dark and light zone of the germinal center is characterized by the expression of the CXCR4 and CXCR5 chemokine receptors, respectively. The difference between the dark and light zones is characterized by the expression of CXCR4 and the activation of CD83 and CD86 markers (28). In the dark zone, centroblasts are detected by $CXCR4^{hi}$,$CD83^{lo}$, and $CD86^{lo}$ expression, whereas centrocytes are recognized by $CXCR4^{lo}$, $CD83^{hi}$, and $CD86^{hi}$.

Germinal center controlling molecules

The germinal center controlling molecules include BCL-6, MEF2B, MCL1, MYC, and IRF4 (29). BCL-6 is a transcription factor that able to control transcriptional processes for the formation of germinal centers and is required for the migration of the precursor B cell to the center of the follicle and the movement of the B cells to the germinal center. It seems that increased expression of BCL-6 by B cells will increase interaction of B cells and Tcells that are integrin-dependent. Increased expression of the BCL-6 molecule is essential for the formation of the germinal center, so that the defect in BCL-6 results in the absence of the construction of the B cell growth site. MEF2B is expressed in a small quantity by antigen-activated B-cells before increasing the expression of the BCL-6 molecule to activate transcription of BCL6 at the germinal center. The IRF4 molecule plays an essential role in the early development of the germinal center. On the first day after the activation by the antigen, the expression of IRF4 is increased and causing the expansion of the B cell germinal center when the B cell is still outside the follicle. In other words, IRF4 induces and suppresses the expression of BCL6 by binding to a specific region of the transcriptional binding site (30, 31). MCL1 is a myelogenous anti-apoptotic protein and a particular type of cyclin D that regulates the proliferation of B cells in dark zones. In addition, MYC is also necessary for the formation of germinal centers and the re-entry of cells from light to dark zone. However, it is not expressed in most cells in this center (32,33). The PAX5 is expressed in all stages of the life of the mature B cell except for the stage of commitment to plasma cell differentiation, while the expression of BCL-6 is only specific to

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the stage of germinal centers. The IRF4 factor would be expressed when the germinal center formed, but it is not expressed in the dark zone and again will be expressed in the light zone (29, 34).

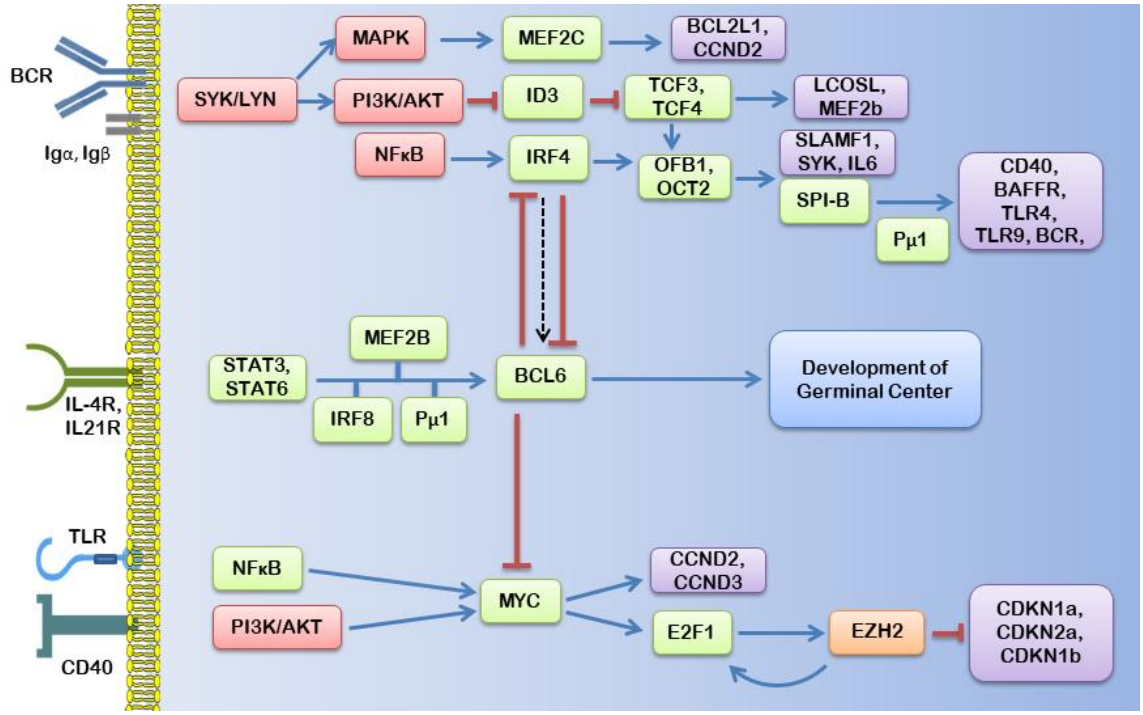

Fig. 2 - The germinal center controlling molecules include BCL-6, MEF2B, MCL1, MYC, and IRF4. Most of these molecules are applied in pathways that lead to BCL-6 expression. Increased expression of BCL-6 by B cells will increase interaction of B cells and integrin-dependent T-cells. So BCL-6 is essential for the formation of the germinal center and defects in the pathway shown, could result in the absence of the B cell proliferation site.

Antibody-producing cells

The production of antibody-secreting cells in response to T-cell dependent antigens occurs in several steps. These events are triggered by the activation of three transcription factors including IRF4, BLIMP1, and XBP1. BLIMP1, with transcription suppression and IRF4 through genes activation are required for the commitment of B cells to plasma cells. XBP1 protects plasma cells from damages caused by unfolded proteins that are produced during protein synthesis augmentation. IRF4 increases the expression of XBP1 and maintains B cells. On the other hand, by increasing the expression of IRF4 in B cells, the activated B cells will be differentiated to plasma cell, while decreased expression of IRF4 will change activated B cells into memory B cell (35, 36).

Transition of plasmablast to plasma cell

A great deal of research has been done to describe the factors that control the initial commitment in the fate of the ASC. However, less is known about the conversion of short-lived, cycling plasmablasts and prolonged lived and postmitotic plasma cells. It has been shown that by measuring the level of BLIMP1 expression, we can differentiate between plasmablasts and plasma cells. Plasmablasts express a much lower amount of BLIMP1 than plasma cells. There is a similar distinction between human plasmablast and

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plasma cells, whether the expression of BLIMP1 increased is relevant to this transition or not. Nevertheless, it is important to notice that plasma cells neutralize the cell cycle program, including the MYC transcription factor, which aims to suppress the interference of BLIMP1. It is remained an un-answered question whether plasma cells are a direct product of germinal center B cells or pass through a plasmablast-like stage. The analysis of antigen-specific cells in mice's blood shortly after initial vaccination indicates that the ASCs that are likely to be progressive for long-lived bone marrow plasma cells exhibit moderate levels of BLIMP1, and they are similar to plasmablasts. Also, ASCs express the proliferation marker Ki67 following recall challenge, which is consistent with being plasmablasts. Analysis of homing molecule and chemokine of plasmablasts showed that only a subset of cells responds to bone marrow tropic factors.

Establishment and survival of plasma cells

During the embedding process in the bone marrow, antibody-producing cells from the secondary lymphoid organs enter the bloodstream, also activation of the sphingosine-1-phosphate receptor (S1PR1), the chemokine 12 ligand (CXCL12), and its receptor CXC-chemokine receptor 4 (CXCR4) are essential for **antibody-secreting cells** (ASCs) migration to bone marrow and keep them in this place (37). Several factors, including IL-6, tumor necrosis factor (TNF-α), and APRIL (a proliferation-inducing ligand), have been shown to survive plasma cells in bone marrow as well as APRIL signaling that expresses the anti-apoptotic protein of myeloid cell leukemia (MCL1) that is essential for survive of ASCs. In other words, survival of plasma cells in the long term depends on their location. To induce plasma cell survival factors (APRIL and IL-6) require the induction of nitric oxide synthase, which indicates the importance of nitric oxide in inducing the ASC survival signal. Also, the binding of the BAFF factor to the BCMA membrane receptor on the surface of plasma cell plays a critical role in preserving the plasma cell survival signal (38, 39).

Conclusion

Significant improvements have been made in understanding of the immune responses in the germinal center. Following the initial antigenic interaction, the formation of the germinal center and its maturity are obtained to select the high-affinity antibody. However, it was difficult to detect the complexity of the germinal center response (40). B cells are rapidly changed between different cellular states in the germinal center. The dynamics of this system are controlled by complex mechanisms, which are likely to be achieved through the coordination of transcriptional, post-translational, and epigenetic programs (41). Therefore, understanding the differentiation of plasma cells is important, especially as they are related to the selection of high-affinity clones and the life span of the plasma cells. However, main are uncleared that including how plasma cells with high-affinity binding are selected and occupied in the bone marrow (42, 43).

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[DOI: 10.22088/crms.5.2.10]

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[DOI: 10.22088/crms.5.2.10]

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