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B Cell signaling and Immunosuppression in Geriatrics: A Review

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Summary

The human immune system undergoes significant changes with age, leading to a phenomenon termed immunosenescence- A decline in immune functionality. This decline in immune function is characterized by a diminished ability to respond to novel antigens and increased susceptibility to infections. B cells, responsible for antibody production and humoral immunity, are particularly affected by immunosenescence. This review explores the intricate interplay between B cell signaling pathways and the development of immunosuppression in the elderly. It also discusses the alterations in B cell receptor (BCR) signaling, co-stimulatory molecules, and the influence of the inflammatory environment on B cell function. Additionally, the impact of chronic co-morbidities prevalent in geriatrics on B cell signaling was examined. Finally, the potential therapeutic strategies to rejuvenate B cell responses secondary to an enhanced vaccine efficacy in older adults was examined.

Keywords: B cells, B cell signaling, Immunosenescence, Geriatrics, Immunosuppression, Vaccines

Introduction

The human immune system displays a remarkable ability to protect us from a diverse range of pathogens throughout life. However, this complex network of cells and molecules experiences a gradual decline in function with advancing age. This phenomenon, termed immunosenescence, is characterized by a weakened ability to mount effective immune responses against novel antigens and increased susceptibility to infections, including influenza, pneumonia, and shingles (Goronzy & Weyand, 2020).

B cells, unlike the other two classes of lymphocytes, T cells and natural killer cells, express B cell receptors (BCRs) on their cell membrane (Murphy, 2012). BCRs allow the B cell to bind to a foreign antigen, against which it will initiate an antibody response (Jespersen *et al.,* 2019).

B cells, a critical component of the adaptive immune system; responsible for the production of highly specific antibodies that neutralize pathogens. Upon encountering a foreign antigen, B cells are activated via a complex signaling cascade initiated by the B cell receptor (BCR). This activation leads to B cell proliferation, differentiation into antibody-secreting plasma cells, and the generation of a tailored antibody response. B cell receptors are extremely specific, with all BCRs on a B cell; recognizing the same epitope (Jespersen *et al.,* 2019). However, in the context of immunosenescence, B cell function is significantly compromised (Harrington *et al*., 2018).

This review delves into the intricate mechanisms underlying B cell signaling and explores how these pathways are disrupted in the elderly, contributing to immunosuppression. Thus, the review focuses on discussing B cell development, its activation, understanding of the Geriatric immunity, B Cell receptor and it's signaling, the alterations observed in BCR signaling, co-stimulatory molecules, and the influence of chronic inflammation on B cell function. Additionally, this review examines the impact of prevalent co-morbidities in geriatrics

on B cell signaling and explore potential therapeutic avenues to enhance B cell responses and improve vaccine efficacy in older adults.

B Cell Development

B cells develop from haematopoietic stem cells (HSCs) that originate from bone marrow (Fischer *et al.,* 2020). HSCs first differentiate into multipotent progenitor (MPP) cells, then common lymphoid progenitor (CLP) cells. From here, their development into B cells occurs in several stages, each marked by various gene expression patterns and immunoglobulin H chain and L chain gene loci arrangements, the latter due to B cells undergoing V(D)J recombination as they develop (Pelanda & Torres, 2012). B cells undergo two types of selection while developing in the bone marrow to ensure proper development, both involving B cell receptors (BCR) on the surface of the cell. Positive selection occurs through antigen-independent signaling involving both the pre-BCR and the BCR. If these receptors do not bind to their ligand, B cells do not receive the proper signals and cease to develop (Martenson *et al.*, 2010). Negative selection occurs through the binding of self-antigen with the BCR; if the BCR can bind strongly to self-antigen, then the B cell undergoes one of four fates: clonal deletion, receptor editing, anergy, or ignorance (B cell ignores signal and continues development). This negative selection process leads to a state of central tolerance, in which the mature B cells do not bind self-antigens present in the bone marrow. To complete development, immature B cells migrate from the bone marrow into the spleen as transitional B cells, passing through two transitional stages: T1 and T2. Throughout their migration to the spleen and after spleen entry, they are considered T1 B cells. Within the spleen, T1 B cells transition to T2 B cells. T2 B cells differentiate into either follicular (FO) B cells or marginal zone (MZ) B cells depending on signals received through the BCR and other receptors. Once differentiated, they are now considered mature B cells, or naive B cells (Cerutti *et al.,* 2013).

B Cell Activation

B cell activation occurs in the secondary lymphoid organs (SLOs), such as the spleen and lymph nodes (Murphy, 2012). After B cells mature in the bone marrow, they migrate through the blood to SLOs, which receive a constant supply of antigen through circulating lymph. At the SLO, B cell activation begins when the B cell binds to an antigen via its BCR (Yuseff *et al.,* 2013). Although the events taking place immediately after activation have yet to be completely determined, it is believed that B cells are activated in accordance with the kinetic segregation model, initially determined in T lymphocytes. This model denotes that before antigen stimulation, receptors diffuse through the membrane coming into contact with Lck and CD45 in equal frequency, rendering a net equilibrium of phosphorylation and non-phosphorylation. It is only when the cell comes in contact with an antigen presenting cell that the larger CD45 is displaced due to the close distance between the two membranes. This allows for net phosphorylation of the BCR and the initiation of the signal transduction pathway. Of the three B cell subsets, FO B cells preferentially undergo T cell-dependent activation while MZ B cells and B1 B cells preferentially undergo T cell-independent activation (Nutt *et al.,* 2015).

B cell activation is enhanced through the activity of CD21, a surface receptor in complex with surface proteins CD19 and CD81 (all three are collectively known as the B cell co-receptor complex). When a BCR binds an antigen tagged with a fragment of the C3 complement protein, CD21 binds the C3 fragment, co-ligates with the bound BCR, and signals are transduced through CD19 and CD81 to lower the activation threshold of the cell (Asokan *et al.,* 2013).

B Cell signaling Pathways: A Primer

B cell activation is orchestrated by a well-defined signaling cascade initiated upon BCR engagement with a specific antigen. The BCR complex comprises an antigen-binding moiety (immunoglobulin molecule) and signaling modules that transduce signals into the cell (Kilic & Trebak, 2020). BCR engagement leads to the phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs) in the

cytoplasmic tails of Igα/β heterodimers. This triggers the recruitment and activation of tyrosine kinases like Syk, leading to the activation of downstream signaling pathways such as Bruton's tyrosine kinase (BTK), phospholipase Cγ (PLCγ), and mitogen-activated protein kinase (MAPK) pathways. These pathways culminate in B cell proliferation, differentiation, and antibody production (Goodwin *et al.,* 2016).

However, BCR signaling alone is insufficient for robust B cell activation. Co-stimulatory signals delivered through molecules like CD40 and CD80/CD86 on antigen-presenting cells (APCs) are essential for optimal B cell activation, survival, and antibody class switching (Paludan *et al.,* 2022). These co-stimulatory signals activate pathways like NF-κB, which cooperate with BCR signaling to induce B cell proliferation and differentiation into plasma cells. Additionally, cytokines produced by T cells and APCs, such as IL-21 and BAFF, further enhance B cell survival, antibody production, and memory B cell formation (Goodwin *et al.,* 2016).

Immunosuppression

The immune system contains a vast array of cell types and effector molecules specialized to detect and destroy pathogenic microorganisms and the cells and tissues that harbor them. With this highly toxic protective function comes the need for tight regulation so that once the danger of infection has passed, the system can return to relative calm and further damage can be avoided. This regulation is mediated by subsets of cells and immunosuppressive molecules that are specialized to actively suppress the immune response.

Ideally, immune suppression balances the destructive forces of inflammation while allowing clearance of pathogenic infectious agents. Failures of immune suppression may manifest themselves clinically in the form of severe acute inflammation and cytokine storms that, if improperly controlled, ultimately result in death. In other cases, poor immune regulation may contribute to chronic or aberrant inflammation including allergies, asthma and autoimmune diseases Reciprocally, over-suppression of the immune system may lead to poor clearance of pathogens, leading to persistent infections or ineffective tumor surveillance leading to cancer.

Suppression of the immune system after the resolution of infection or inflammation is an important process that limits immune-mediated pathogenesis and autoimmunity. Several mechanisms of immune suppression have received a great deal of attention in the past three decades. These include mechanisms related to suppressive cytokines, interleukin (IL)-10 and transforming growth factor (TGF)-β, produced by regulatory cells, and mechanisms related to apoptosis mediated by death ligands, Fas ligand (FasL) and tumor necrosis factor–related apoptosis-inducing ligand (TRAIL), expressed by killer or cytotoxic cells.

Geriatric Immunosuppression

Ageing in general has broad consequences for immune responses, organ function, repair mechanisms and metabolic function. Immunosenescence is linked to higher rates of diabetes, bacterial infections and malignancies. Immunosenescence may predispose elderly patients to the risks of over-immunosuppression. As we grow older, the immune system functionality reduces as well, where the following immune system changes may occur:

- The immune system becomes slower to respond. This increases the risk of getting sick. Flu shots or other vaccines may not work or protect the body for as long as expected.
- An autoimmune disorder may develop: This is a disease in which the immune system mistakenly attacks and damages or destroys self-healthy body tissues.
- Healing may become slower: There are fewer immune cells in the body to bring about healing.

The immune system's ability to detect and correct cell defects may also decline: This can result in an increased risk of ailment (Franceschi *et al*., 2018).

Role of B-cell Receptor signaling in Immunosuppression

Regulatory B cells (Bregs) is a term that encompasses all B cells that act to suppress immune responses. Bregs contribute to the maintenance of tolerance, limiting ongoing immune responses and reestablishing immune homeostasis.

The role of regulatory B cells (Bregs) in immunosuppressive responses has been documented in different contexts and diseases. It has been shown, for instance, that Bregs can suppress animal models of autoimmunity, such as experimental autoimmune encephalomyelitis (EAE), collagen-induced arthritis (CIA), and spontaneous colitis. Bregs have also been proved to modulate allergy (Palomares *et al.*, 2017), transplantation (Alhabbab *et al.,* 2019), cancer (Sarvaria *et al.*, 2017), infections (Fillatreau, 2016), and chronic metabolic diseases (Strom *et al.*, 2015). Initial studies in the early 2000s attributed this immunomodulation to IL-10, which became the hallmark of Breg suppression (Carter *et al.,* 2015). More recent studies have suggested a role for this population in other immune-related conditions, such as infections, allergy, cancer, and chronic metabolic diseases (Carter *et al.,* 2015).

B Cell signaling in Immunosenescence

With advancing age, several alterations disrupt the delicate balance of B cell signaling pathways, leading to a blunted immune response, increased susceptibility to infections, decreased response to vaccinations, and higher incidence of autoimmune diseases and cancer. B cells, a type of lymphocyte responsible for antibody production, play a crucial role in the immune response and are affected by immunosenescence. Here, we explore some key aspects of this decline:

Impaired BCR signaling: Studies have shown reduced expression and function of key signaling molecules like Syk and BTK in B cells from older individuals (Pereira *et al*., 2020). This translates to a diminished response to BCR engagement, leading to weaker activation and antibody production.

Defective Co-stimulation: The expression and function of co-stimulatory molecules like CD40 and CD80/CD86 are also downregulated in APCs from elderly individuals (Beek *et al.,* 2019). This impairs the ability of APCs to provide the necessary co-stimulatory signals for optimal B cell activation.

Chronic Inflammation and B Cell Dysfunction: The ageing immune system exhibits a chronic low-grade inflammatory state termed "inflammageing". This persistent inflammation is characterized by elevated levels of pro-inflammatory cytokines like IL-6 and TNF-α (Franceschi *et al*., 2018). Main while, acute inflammation is essential for immune responses, but chronic inflammation can have detrimental effects on B cell function.

Negative Regulation by Inhibitory Receptors: B cells express various inhibitory receptors, such as programmed cell death protein 1 (PD-1) and Tim-3, that dampen B cell activation upon binding to their ligands. Chronic inflammation leads to increased expression of these inhibitory receptors on B cells, further suppressing their responses (Nimmerjahn & Ravetch, 2008).

Skewed B Cell Differentiation: Chronic inflammation can skew B cell differentiation towards the generation of plasma cells that produce low-affinity, short-lived antibodies. This reduces the efficacy of the humoral immune response and limits the ability to effectively combat infections (Ferrero *et al*., 2019).

Impact of Co-morbidities on B Cell Signaling

Several age-related co-morbidities prevalent in geriatrics can further exacerbate B cell dysfunction by disrupting signaling pathways. Here are some notable examples:

Autoimmunity: In autoimmune diseases like rheumatoid arthritis, chronic inflammation can lead to B cell hyperactivation and the production of autoantibodies that attack healthy tissues (Rahman & Newell, 2019). This persistent activation can eventually lead to B cell exhaustion and impaired responses to new antigens.

Diabetes: Chronic hyperglycemia in diabetes can impair B cell signaling pathways and antibody production through mechanisms like increased oxidative stress (Wu *et al.*, 2018).

Chronic Viral Infections: Persistent viral infections, such as cytomegalovirus (CMV), can contribute to B cell exhaustion and limit their ability to respond to new pathogens (Nikolich-Zugich *et al.*, 2018).

B Cell Receptor (BCR) Signaling: B cells recognize antigens through their BCRs. With age, alterations in BCR signaling can occur, leading to decreased B cell activation and impaired response to pathogens. This diminished responsiveness contributes to reduced antibody production and impaired adaptive immune responses in older individuals.

Co-stimulatory Signaling: Co-stimulatory molecules, such as CD40, CD80, and CD86, provide additional signals necessary for B cell activation and differentiation. Dysregulation of co-stimulatory signaling pathways can occur during immunosenescence, resulting in impaired B cell function and reduced antibody production.

Cytokine Signaling: Cytokines play a crucial role in regulating B cell responses. Alterations in cytokine signaling pathways, such as decreased interleukin-6 (IL-6) or interleukin-10 (IL-10) production, can impact B cell function during immunosenescence. Moreover, chronic low-grade inflammation, known as inflammageing, characteristic of aging can influence cytokine production and signaling, further affecting B cell responses.

Toll-like Receptor (TLR) Signaling: TLRs are involved in recognizing pathogen-associated molecular patterns (PAMPs) and activating B cells. Changes in TLR signaling pathways with age can impair B cell responses to infections and vaccinations.

B Cell Signaling Crosstalk: B cell signaling is intricately linked with other components of the immune system, including T cells, dendritic cells, and innate immune cells. Alterations in the crosstalk between B cells and these other immune cells can contribute to immunosenescence.

Epigenetic Regulation: Epigenetic changes, such as DNA methylation and histone modifications, can impact B cell signaling pathways during immunosenescence, leading to altered gene expression profiles and functional changes in B cells.

Therapeutic Strategies for Enhancing B Cell Responses in Geriatrics

Given the critical role of B cells in protective immunity, several strategies such as those outlined below, are being explored to rejuvenate B cell function and enhance vaccine efficacy in older adults:

Toll-like receptor (TLR) Agonists: Toll-like receptor (TLR) agonists are molecules that mimic pathogen-associated molecular patterns (PAMPs) and activate Antigen Presenting Cells (APCs). TLR agonists have shown promise in stimulating B cell activation and antibody production in older adults (Ropert, 2019; Lende *et al.,* 2022).

B Cell Receptor Targeting Therapies: Drugs that target specific B cell signaling molecules, such as BTK inhibitors, are being investigated to enhance B cell responses or suppress autoantibody production in autoimmune diseases (Trebak *et al.*, 2019).

Checkpoint Blockade: Antibodies targeting inhibitory receptors like PD-1 have revolutionized cancer therapy. Similar approaches are being explored to reinvigorate B cell function in older adults by blocking inhibitory pathways (Gupta *et al.,* 2019).

Vaccination: Vaccination remains one of the most effective strategies for enhancing B cell responses in older adults. However, due to immunosenescence, the response to vaccines may be diminished in the elderly. To address this, specific vaccines tailored for older adults, such as:

High-dose vaccines: Administration of high-dose influenza vaccines has been shown to enhance antibody responses in older adults compared to standard-dose vaccines (DiazGranados et al., 2014).

Adjuvanted vaccines: Adjuvants such as MF59 or AS01 have been incorporated into vaccines to enhance immune responses in older adults by stimulating B cell activation and antibody production (Leroux-Roels *et al*., 2017).

Nutritional interventions: Proper nutrition is essential for maintaining immune function, including B cell responses, in older adults. Certain nutrients, such as vitamins C and D, zinc, and antioxidants, omega 3, 6 & 9 play critical roles in supporting B cell function and antibody production. Dietary supplementation or dietary modifications to ensure adequate intake of these nutrients can help enhance B cell responses in geriatrics (Calder *et al.,* 2020).

Exercise: Regular physical activity has been shown to have immunomodulatory effects, including enhancing B cell function. Exercise can improve immune function by reducing inflammation, promoting better circulation of immune cells, and enhancing the production of antibodies by B cells. Incorporating regular exercise into the lifestyle of older adults can help enhance B cell responses and mitigate immunosenescence (Simpson *et al.*, 2020).

Immunomodulatory therapies: Various immunomodulatory therapies have been explored to enhance B cell responses in older adults. These includes:

- **Cytokine therapy**: such as interleukin-7 (IL-7) or interleukin-15 (IL-15), which can stimulate B cell proliferation and function. Additionally, monoclonal antibody therapy targeting specific immune checkpoints, such as programmed cell death protein 1 (PD-1) or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), can help restore B cell function by relieving immune suppression (Moro-García *et al*., 2014).
- **Senolytics**: Senolytic drugs, which selectively eliminate senescent cells, have shown promise in rejuvenating immune function, including B cell responses, in preclinical studies (Yousefzadeh *et al.*, 2018).

Stem cell therapy: Stem cell therapy, particularly hematopoietic stem cell transplantation (HSCT), holds promise for rejuvenating the immune system in older adults. HSCT can replenish the aging immune system with new, functional immune cells, including B cells, thereby enhancing B cell responses and reversing immunosenescence. However, stem cell therapy comes with risks and is typically reserved for specific conditions or situations where other therapies have failed.

Lifestyle modifications: Certain lifestyle factors, such as smoking, excessive alcohol consumption, and chronic stress, can negatively impact immune function, including B cell responses. Encouraging older adults to adopt healthy lifestyle habits, such as smoking cessation, moderate alcohol consumption, stress management techniques, and adequate sleep, can help support B cell function and overall immune health.

Targeted immunotherapies: Advancements in immunotherapy, such as B cell-targeted therapies, offer novel approaches to enhance B cell responses in older adults. These therapies may involve the use of monoclonal antibodies targeting specific B cell markers or signaling pathways to modulate B cell function and promote a more robust immune response.

Personalized Medicine Approaches: Given the heterogeneity of aging and immunosenescence among individuals, personalized medicine approaches may be beneficial in tailoring therapeutic interventions to specific needs:

- Biomarker-guided therapy: Biomarkers of immunosenescence, such as immune cell phenotypes or inflammatory markers, could be used to identify individuals who are most likely to benefit from targeted interventions (Fulop *et al*., 2016).
- Genetic and epigenetic profiling: Understanding the genetic and epigenetic factors underlying immunosenescence could facilitate the development of targeted

therapies aimed at restoring B cell function in aging individuals (Marttila *et al*., 2019).

Conclusion

Immunosenescence poses a significant challenge to public health as the elderly population grows. Understanding the molecular mechanisms underlying the alterations in B cell signaling pathways and the factors that contribute to B cell dysfunction in geriatrics is crucial for developing effective interventions to mitigate age-related immune dysfunction. Therapeutic interventions targeting B cell signaling pathways may hold promise for improving immune responses and overall health in the elderly, as ongoing research on TLR agonists, BCR-targeting therapies, and checkpoint blockade offers exciting possibilities for improving vaccine efficacy in older individuals and potentially reversing the decline in B cell function associated with ageing.

Conflict of Interest: None

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