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A Study of Multiple Sclerosis

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Autoimmune diseases are diseases in which the immune system starts attacking itself. The immune system defends the body from pathogens such as bacteria and viruses by recognizing antigens on these pathogens. Usually, the immune system can recognize itself and develop tolerance to prevent it from attacking itself. However, there are instances where the immune system loses tolerance and starts attacking itself, leading to autoimmune disease. Multiple Sclerosis is an autoimmune disease in which the immune system attacks the central nervous system.

The immune system comprises two system types: the innate immune system and the adaptive immune system. The innate immune system is the first line of defense when a pathogen enters the body and can generate the same response regardless of the type of pathogen. On the other hand, the adaptive immune system is more specialized, taking a few days to weeks to be activated. Once activated, adaptive immune cells can target that specific pathogen and result in a faster response if encountered again. T and B cells are part of the adaptive immune system and have unique development and activation. Both the T and B cells originate from the bone marrow; however, the T cells go to the thymus to finish development, while B cells finish their development in the bone marrow.

The activation of T cells differs from B cells in that they need be presented with an antigen via antigen-presenting cells (APCs). APCs such as macrophages and dendritic cells can recognize pathogens via pathogen-associated molecule patterns (PAMPs) or damaged cells via damage-associated molecule patterns (DAMPs). The APCs would bind to PAMPs or DAMPs via pattern recognition receptors such as toll-like receptors and C-type lectin receptors. These receptors are located either on the outside or inside a cell and can bind to specific pathogens depending on PAMPs and the location of the PAMPs. Once activated, the APCs would phagocytose these molecules and present them on the major histocompatibility complex (MHC).

There are two types of MHC, MHC Class I and MHC Class II. The type of MHC produced depends on the pathway. The endogenous pathway produces MHC class I and can only bind to CD8+ cytotoxic T cells, while the exogenous pathway produces MHC class II and can only bind to CD4+ helper T cells. Costimulatory molecules are also required for T cells to become activated when binding to MHC. These costimulatory molecules are CD28 on T cells and CD80/86 on APCs. There are also coinhibitory molecules that prevent T cells from becoming activated. With both MHC and costimulatory molecules, T cells can become activated and go through positive and negative selection in the thymus.

During the development of T and B cells, they go through positive and negative selection. Positive selection is where the T and B cells are tested to see if they can engage with self-antigen. If they do not engage with self-antigen, they will die due to a lack of stimulation from other cells, such as antigen-presenting cells. Negative selection is where the T and B cells are tested to see if they bind too strongly to the self-antigen. If they do, then they die via apoptosis. In the thymus, the T cells are presented with antigens from the body to test for negative selection. The antigens presented from all over the body are from medullary thymic epithelial cells (mTECs). mTECs have a protein, AIRE, that allows mTECs to express, process, and present proteins found in specific organs. They bind to epigenetic marks on histones and recruit transcription factors to allow RNA polymerase to access the area. This process can prevent self-reactive T cells from leaving the thymus and circulating in the body. B cells do not have this mechanism because B cells require helper T cells to become activated. If there is a self-reactive B cell, it will need a helper T cell that is also self-reactive, but due to negative selection in the thymus, T cells would have died from apoptosis.

Negative selection results in central tolerance, where our T and B cells can recognize themselves but react against it. Without negative selection, T and B cells will react too strongly to themselves, leading to autoimmunity. Peripheral tolerance occurs when some of the self-reactive T or B cells manage to escape selection and enter the periphery. Peripheral tolerance induces T and B cell anergy. Cell anergy is when the cells become unresponsive to stimulus and can occur when binding to cells without the costimulatory molecules or binding to cells but a coinhibitory molecule bind to the cell instead of a costimulatory molecule. Some self-reactive T cells that escape to the periphery become regulatory T cells (Treg) which down-regulates inflammation by inhibiting APCs and T cells.

Multiple Sclerosis (MS) is an autoimmune disease that attacks the central nervous system (CNS) – brain, and the spinal cord. It causes chronic inflammation in the CNS that leads to demyelination and neurodegeneration (Correale et al., 2017). This disease primarily affects young adults, mainly women, and over two million are

affected worldwide. (Garg & Smith, 2015) The cause of MS is unknown; however, it is believed to be triggered by genetic and environmental factors. Some genetic factors that have been identified are the interleukin-2 receptor alpha gene and the interleukin-7 receptor alpha genes. Environmental factors that have been linked to MS are the Epstein-Barr virus (EBV) and vitamin D deficiency (Garg & Smith, 2015). Studies have shown that MS is prevalent in populations living further away from the equator, correlating with the increasing vitamin D deficiency. Immigrants from countries near the equator that moved further away from the equator, such as Europe, have a lower risk of developing MS; however, children from those immigrants living in Europe have a higher chance of developing MS (Dobson & Giovannoni, 2018).

Multiple Sclerosis is caused by the loss of self-tolerance, where our immune system would not recognize myelin antigen and attack it. This loss of self-tolerance could be triggered by an environmental factor such as EBV infection. When EBV infects the body, it can trigger a release of autoantigens due to damage to the cell. The autoantigen can lead to the molecular mimicry or bystander activation of T cells. Molecular mimicry is when a foreign antigen, in this a virus antigen, shares similarities with the myelin antigen. In terms of MS, the immune system can secrete antibodies that attacks the EBV nuclear antigen EBNA1. However, this can cross-react with glial cell adhesion proteins on the CNS, creating T and B cells that are specific for those antigens. Studies have shown in where patients with MS anti-glial cell adhesion proteins antibodies have, supporting the idea that molecular mimicry between the EBNA1 antigen and host glia cell adhesion protein contributes to the development of MS (Dempsey, 2022).

Bystander activation of T cells are T cells activated in a T cell receptor-independent and cytokine-dependent manner (Kim & Shin, 2019). So, when there is a viral infection such as EBV, it can cause the body to release series of cytokines to attack the virus. In doing so, these cytokines can activate myelin antigen specific T cells, in this case, MS. These cells do not have specificity for the pathogens, but they can still participate in the immune response by secreting cytokines or exerting cytotoxicity. Some studies have shown that activation of NK, NKT and dendritic cells in response to virus such as murine cytomegalovirus can cause the release of IL12 and IFN-γ. These cytokines can result in the bystander activation of antigen specific T and B cells in MS and other autoimmune diseases (McCoy et al, 2006).

Once these CNS reactive T cells are activated in the body, they can enter the CNS through the blood-brain barrier. This migration involves the interaction between very late antigen-4 (VLA-4) on the T cells and the vascular cell adhesion molecule-1 (VCAM-1) on capillary endothelial cells (Garg & Smith, 2015). Once these T cells enter the CNS, they will react with the antigens in the brain.

CD8+ T cells play a significant role in this response by binding to antigen presented by MHC class I receptor on the antigen-presenting cells. (APC) The CD4+ T cells also play a role, binding to APC presenting the myelin antigen on MHC class II receptors (Garg & Smith, 2015). This binding can trigger an inflammatory cascade, releasing cytokines and chemokines, recruiting more inflammatory cells, and increasing inflammation. This constant inflammation results in demyelination of the myelin sheath on axons. The pro-inflammatory cytokines are released by CD4+ TH1 cells, such as interferon-gamma, IL-2, and TNF-alpha. Another subset of CD4+ T cells like TH17 plays a role in inflammation by secreting IL-17. Due to high levels of TH1 T cells, it downregulates TH2, which secretes interleukin 4, 5, and 10, limiting the effects of TH1 cell response (Garg & Smith, 2015). This downregulation of TH2 can increase pro-inflammatory responses.

While T cells play a huge in MS, there has been evidence that B cells play a role in MS. There has been recent evidence of clonal B cell proliferation in both the CNS and the rest of the body (Alroughani & Yamout, 2018). Follicle structures have been found in the meninges, containing proliferating B cells, helper T cells, and follicular dendritic cells. The follicular dendritic cells in these follicles are shown to secrete CXCL13 which recruits B cells into the area (Correale et al., 2017). Due to B cell proliferation, it can maintain meningeal inflammation by producing the antibody, secreting cytokine, presenting antigen, and forming follicle structures.

Both T and B cell activity leads to demyelination and early axonal injuries by directly attacking myelin and oligodendrocytes and secretion of antibodies. CD8+ T cells can bind to MHC I on APC which can induce axonal injuries, but the exact mechanism is not clear (Garg & Smith, 2015). Myelin and oligodendrocytes can also indirectly be affected by the pro-inflammatory cytokines such as IL6, IL22 and TNF-alpha. IL6 can encourage the differentiation of effector T cell and down regulate Treg. Some studies have shown that IL22 can trigger oligodendrocytes to express Fas expression, increasing apoptosis. (Vani & Chitra, 2022) So, treatments have been designed to target T and B cells and limit the pro-inflammatory cytokines; however, the exact mechanism of these treatments is yet to be understood.

The main form of treatment is the immunomodulatory therapies (IMT) which include a variety of medications to suppress the immune response caused by autoreactive lymphocytes. One treatment of IMT is using beta interferon (Garg & Smith, 2015). Beta-interferons can stabilize the blood-brain barrier, thus limiting T cells from entering the CNS, modulating T and B cell functions, and altering the expression of cytokines (Garg & Smith, 2015). Once beta-interferon binds to cell receptors, it can increase the expression of anti-inflammatory cytokines such as IL-10 and IL-4. It can also shift from TH1/Th17 towards TH2 anti-inflammatory response (Filipi & Jack, 2019).

There are a variety of interferon-beta therapies that the FDA has approved, and their efficacy can vary depending on the dosage and frequency of injection of the drug.

The other form of treatment is using glatiramer acetate (GA), a synthetic complex of four amino acids similar to myelin basic protein (Garg & Smith, 2015). Studies have shown that GA upregulates differentiation of CD4+ T cells into TH2 cells, downregulates TH17 differentiation, and increases the frequency of regulatory T cells (Häusler et al., 2022). The increase in regulatory T cells allows for an increase in anti-inflammatory cytokines. It also played a huge role in decreasing B cell activation and differentiation while increasing IL-10 secretion and MHC class II expression. Increasing IL-10 secretion decreases the production of a pro-inflammatory cytokine such as TNF-alpha (Häusler et al., 2022).

Multiple Sclerosis is an autoimmune disease that affects people between the ages of 20 and 40 years. While its exact cause is unknown, several genetic and environmental factors have been identified that can increase susceptibility to the disease, including Vitamin D deficiency and EBV. Multiple Sclerosis affects the CNS, resulting in T cells attacking myelin and oligodendrocytes. Combined with constant inflammation by pro-inflammatory cytokines and B cells, these attacks damage neurons in the CNS, resulting in loss of brain function and leading to cognitive and emotional deficits. Treatments have been created to lessen the T and B cells' effect and upregulate the production of anti-inflammatory cytokines. More research is needed to understand the exact mechanism and role of B and T cells in MS, and through that, better treatment can become more available.

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