The Role of Human Leukocyte Antigens in Multiple Sclerosis and Brain Atrophy

Written by Tanisha Mandal

Abstract

Human Leukocyte Antigens (HLA) are significant components of the human immune system responsible for autoimmunity. These genes are located on chromosome 6 and encode for proteins that assist the body in fighting against foreign invaders. However, HLA may have the potential to induce varying degrees of brain atrophy (BA) and multiple sclerosis (MS), both of which are neurodegenerative disorders. Examining the protective and aggravating effects of HLA on these neurological disorders, as well as potential preventive measures that could be implemented through HLA, may prove to have significant effects on the approach to BA and MS.

Introduction

Brain Atrophy (BA) is a progressive neurodegenerative disorder that leads to neuronal loss and connectivity. As a result, brain volume decreases and symptoms such as memory loss, seizures, and aphasia occur. While it is not uncommon to lose neurons as one gets older, BA refers to when an individual has more abnormal brain changes than what is expected for their age. In its most severe forms, BA can become fatal (Harris TC, de Rooij R, Kuhl E., 2019). There are two types of BA, focal and generalized. Focal refers to atrophy in a specific part of the brain, and generalized refers to atrophy spread throughout the brain.

Another chronic neurological disorder is Multiple Sclerosis (MS) which is caused by the autoimmune system, inducing the body to attack the central nervous system (CNS). Common symptoms include muscle weakness, coordination issues, cognitive difficulties such as memory problems, and slowed processing speed. The exact causes of MS remain unclear, but several factors contribute, particularly genetic predisposition. In an individual with MS, the autoimmune system attacks the myelin sheath surrounding the body's neurons, which disrupts communication between neurons (National Institute of Neurological Disorders and Stroke, 2024). The loss of neuronal connections caused by the presence of MS, is also an aforementioned key symptom of BA. Thus, MS can significantly worsen the damage done by atrophy. In addition, MS can also be the primary cause of BA, when the loss of connection is so great that it can be considered abnormal.

Due to the fact that MS is an autoimmune disorder, it can be linked to Human Leukocyte Antigens. Human leukocyte antigens, or HLA for short, are found on chromosome 6 and encode for proteins that present as antigenic peptides on T cells. This means that MS is a T-cell-mediated autoimmune disorder. HLA -DR antigens specifically are membrane heterodimeric glycoproteins, which means that they consist of proteins that are found in cell membranes, and often play a role in communication and signaling (Scholz, E. M, Marcilla, M, Daura, X, et al., 2017). In the case of HLA specifically, they play an important role in the autoimmune response system of the human body. As a result, many autoimmune disorders are caused by defects in the HLA gene. After extensive research, the allele responsible for this development has been narrowed down to Class II HLA-DRB1*1501 (Lorefice L, Fenu G, Sardu C, et al., 2019).

More research has uncovered that HLA can also provide protective effects against the demyelination caused by BA and MS. This is due to another class II allele, specifically DRB1*1302, which works in the CNS and has been shown to prevent the rapid degeneration of neurons associated with BA. Class II HLA has complex effects on the CNS, thus contributing to the development of brain atrophy and multiple sclerosis, with different alleles of the same gene providing vastly different outcomes.

Description of HLA Class II Alleles - Structure and Function

As seen in Figure 1, the primary structural difference between two types of human Leukocyte antigens is that Class 1 HLA molecules have 1 polypeptide chain, combined with a beta-2 microglobulin subunit while class II molecules contain 2 polypeptide chains. This results in the distinct roles that the molecules play in the human body.

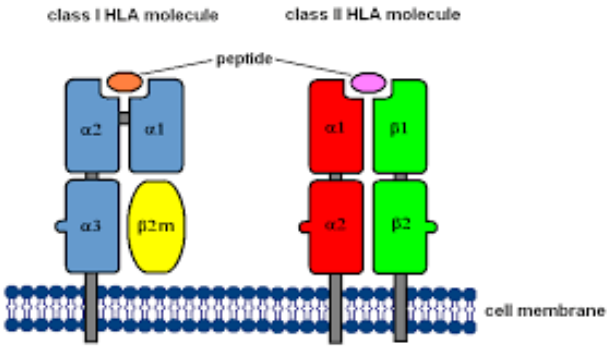

Figure 1: Structure of Class I and Class II HLA Molecules (Grubic, 2017).

Class I molecules are responsible for facilitating cell destruction, whereas class II molecules are responsible for recognizing invaders and producing the appropriate antibodies (James, L. M., & Georgopoulos, A. P., 2019). However, since class II HLA binds to antigen-presenting cells (APC) and is ultimately responsible for determining what the body considers a harmful microorganism, a miscoding in certain alleles can cause the body to attack itself, known as an autoimmune disorder. As previously stated, MS is classified as an autoimmune disorder, meaning that the introduction of MS in the body is almost entirely due to class II HLA molecules. This is why class II HLA molecules are the primary focus concerning BA and MS.

The Protective Effects of DRB1*1302 on Demyelination and Atrophy

Studies have discovered that the frequency of Class II HLA-DRB1*1302 has an inverse association with dementia, which is caused by the loss of synaptic connections, in 14 Western European countries (James, L. M., & Georgopoulos, A. P., 2019). As displayed in Figure 2, this is suspected to be due to the fact that the HLA DRB1*1302 allele helps encode for antibodies that specifically protect against pathogens that cause neurodegeneration. Dementia is linked to BA through the most prominent symptoms of neurodegeneration, loss of memory. Since the frequency of the DRB1*1302 allele has an inverse association with the loss of synaptic connections, it is suspected that the allele protects against pathogens that cause this neurological degeneration, which in turn causes BA. Therefore, it is reasonable to assert that the presence of the DRB1*1302 allele has an inverse effect on the onset of dementia, and thus the onset of BA.

For populations that express a high frequency of DRB1*1302, neurodegeneration can be slowed by around 45.2%. Scientists hypothesize that its protective effect could be due to the removal of antigens that persist in causing gradual brain atrophy. These beneficial effects have also been attributed to DRB1*13:02's binding to cathepsin S, a known harmful substance in brain aging (James, L. M., & Georgopoulos, A. P., 2019). This is best demonstrated in the research done on DRB1*1302's effect on dementia and Gulf War Illness, which are both caused by some levels of neurodegeneration. Thus, it is reasonable to assume that DRB1*1302 demonstrates preventative effects against general atrophy of the brain.

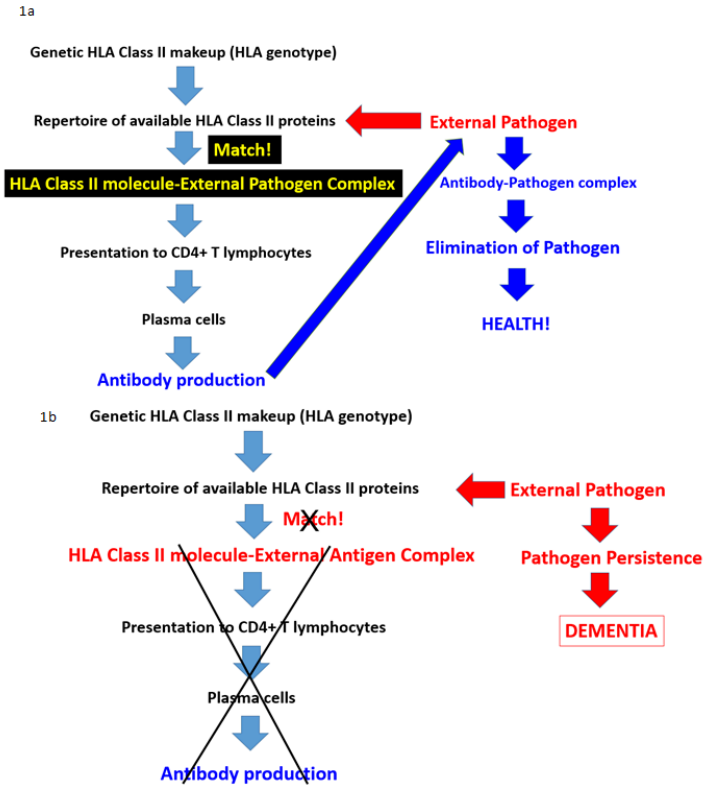

Figure 2: Flowchart Demonstrating Link Between Decreased HLA and Dementia (James, L. M., & Georgopoulos, A. P., 2019)

The Harmful Effects of DRB1*1501 on MS and Brain Atrophy

HLA-DRB1*1501 is an HLA haplotype, a group of closely linked alleles that are frequently inherited together and has been linked to a significantly higher risk of MS, and consequently, also to BA (Scholz, E. M, Marcilla, M, Daura, X, et al., 2017). In fact, DRB1*1501 is the single strongest genetic factor in the development of MS. While T-cells aren't typically considered APC, they do express major histocompatibility complex (MHC is known as HLA in humans) class II antigens, which are precisely what class II HLA control (Pichler, W. J & Wyss-Coray, T, 1994).

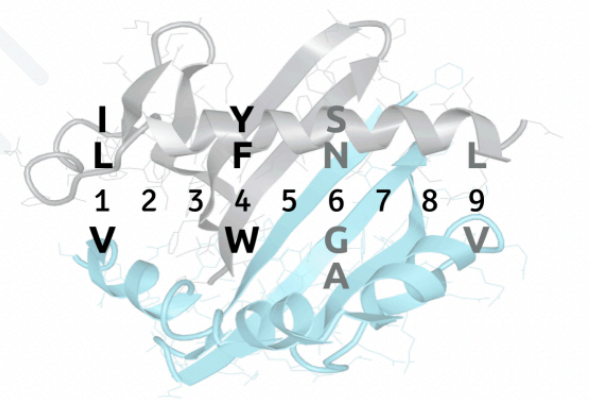

Figure 3: Binding Motif of HLA DRB1*1501 (HLA Protein, 2024).

Research suggests that pathogens involved with demyelination may appear to be similar to the actual myelin itself. As a result, DRB1*1501 could be especially susceptible to being "tricked" by this mimicry and produce agents that begin attacking myelin instead of the pathogens (Sospedra, M., & Martin, R., 2005). In addition, research shows that DRB1*1501 is suspected to interact with specific cytokines that are responsible for signaling immune responses in the brain, causing inflammation and degeneration of cells in the CNS. They essentially secrete proinflammatory cytokines that predispose the body to autoimmune diseases such as MS. When reviewing patients who expressed a high frequency of DRB1*1501, scientists found that "carriage of HLA-DRB1*15 was associated with increases in the development of brain grey and white matter pathology, as reflected by reduced [magnetization transfer ratio] (MTR), a trend toward increased T2 lesion load over 5 years, and greater T2 lesion volumes at each time point over the follow-up" (Tur, C., Ramagopalan, S., Altmann, D. R., et al., 2014). Thus, it was concluded that individuals showed a significant amount of brain atrophy when contrasted with the healthy control group. This shows a strong positive correlation between the presence of the DRB1*1501 allele and abnormal amounts of atrophy in the brain.

Effects of HLA on the Pathways of MS and BA

In nearly every case of MS, the early stages of pathology result from abnormal amounts of inflammation in the brain (Kiss, M. & McAlpine, C.S., 2023). Neuroinflammation is caused by the increased presence of T-cells in response to supposed invaders, which in cases of MS are the body's own cells, and the regulation of these T-cells is linked back to HLA. Individuals carrying the DRB1*1501 allele, have an increased susceptibility to MS and more severe disease progression, which can lead to greater demyelination. This is due to the role of these alleles in promoting an autoimmune response against myelin proteins. Similarly, the onset of BA is caused by abnormal amounts of demyelination in the brain. One of the most common causes of demyelination is inflammation, linking the root cause of BA to the root cause of MS. Thus, BA is similarly influenced by the HLA alleles.

Proposed Preventative Gene Therapy:

Brain Atrophy and Multiple Sclerosis have long been thought to be incurable, with treatment mainly consisting of just improving the quality of life of people afflicted with these diseases. Since different alleles of HLA can produce different effects on BA and MS, a potential goal for gene therapy could be to activate DRB1*1302 more often and suppress the expression of DRB1*1501 in HLA. As a result, preventative effects would be much higher, and the rate of BA and MS in individuals would likely decrease significantly. One form of gene therapy could focus on monoallelic expression, as demonstrated in Figure 4, which is when one allele of a gene is expressed, and another allele of that same gene is silenced.

Techniques such as CRISPR have been used to selectively silence one allele while leaving the other intact, which seems to be exactly what individuals at risk for atrophy need (Hsu, P. D., Lander, E. S., & Zhang, F., 2014). Overall, a preventative cure for atrophy may be just around the corner, providing a means to protect against one of the most complicated and unstoppable neurodegenerative effects.

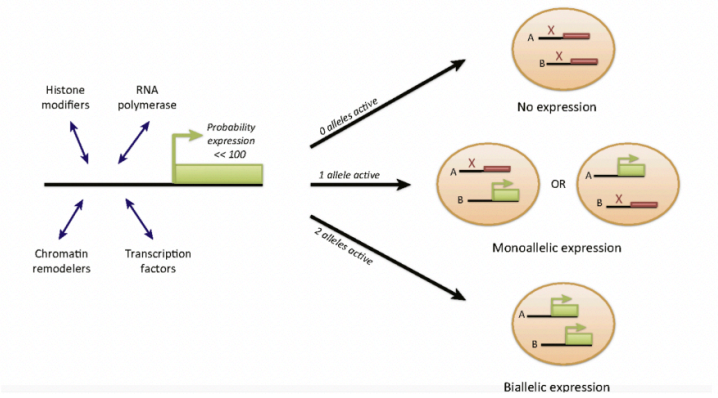

Figure 4: Diagram of Monoallelic Gene Therapy (Eckersley-Maslin, M. A.,& Spector, D. L., 2014)

Conclusion

Although the significance of HLA on the pathways of BA and MS has not been widely explored, the link between the two is most certainly present. Due to both neurodegenerative diseases being directly linked to the loss of synapses onset by autoimmune responses in the brain, and HLA being responsible for the immune system, HLA is a clear factor in the development of BA and MS. The two alleles most closely related to the onset of the diseases, DRB1*1501 and DRB1*1302, are haploids of HLA, so genomic editing and therapy may provide the first preventative cure for BA and MS.

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