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Disease-Modifying Drugs and Stem Cell Therapies for the Treatment of Myelin Degeneration due to Multiple Sclerosis

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ABSTRACT

Myelin, a modified plasma membrane wrapped around axons, is an essential part of signal propagation in the nervous system. Formed by oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system (PNS), myelin lowers the amount of energy needed to send or receive signals. Multiple Sclerosis (MS) is an autoimmune, hyperinflammatory disease that attacks the nervous system, specifically myelin. MS is characterized by three types of lesions in the brain and along the blood brain barrier, making it very difficult to diagnose through conventional magnetic resonance imaging (MRI) and even more difficult to treat. It has an unpredictable pathophysiology that cannot be cured by current drug therapies. Stem cell therapies have been heavily researched in recent years to try to combat the autoimmune disease by stopping demyelination and recovering lost function through the regeneration of differentiated cells.

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Abbreviations

CNS: Central Nervous System

DMD: Disease-Modifying Drugs

EAE: Experimental Autoimmune Encephalomyelitis

GA: Glatiramer Acetate

HSC: Hematopoietic Stem Cells

MS: Multiple Sclerosis

MRI: Magnetic Resonance Imaging

MSC: Mesenchymal Stem Cells

PNS: Peripheral Nervous System

PPMS: Primary-Progressive Multiple Sclerosis

RRMS: Relapsing-Remitting Multiple Sclerosis

SPMS: Secondary-Progressive Multiple Sclerosis

Introduction

Standard Central Nervous System (CNS) Development and Function

The CNS is the baseline of function in the human body, consisting of the brain and spinal cord. In order to have any motor function, the brain must transmit impulses down the spinal cord and through efferent neurons in the peripheral nervous system. In order to receive sensory information, sensory receptors must transmit impulses through afferent neurons, up to the spinal cord, which then carries the impulse to the brain. The key to efficient neurological impulse propagation is myelin, a modified plasma membrane that wraps around nerve axons to help with speed

of signal transmission [1]. In the CNS, myelin is formed by oligodendrocytes, and in the PNS myelin is formed by Schwann cells [1]. Myelin functions to increase axon conduction speed, which allows for rapid transmission of impulses over longer distances than unmyelinated axons causing an increase in cognitive function [2]. It also allows for less energy expense and space occupied by axon fibers during impulse propagation because of increased transmission efficiency with myelinated axons [1]. Along myelinated axons are spaces of unmyelinated fiber, called nodes of Ranvier. These unmyelinated fibers are the location of saltatorial conduction; active excitation of the axon membrane causing impulse propagation by the “jumping” of signals between nodes [1]. Once the membrane becomes excited, the impulse cannot continue propagating through the highly-resistant myelin sheath and instead depolarizes the membrane at the next node [1]. There are two main regions of the node where impulse propagation occurs: the paranode and juxtaparanode regions (Figure 1) [2]. These regions are where axons and myelinating glial cells, or immune cells, interact with one another. There are four interactions that need to take place between an axon and glial cell for proper node function. The node itself must be a place free of glial myelin for there to be no immune system interference [2]. There must be localization of voltage-gated sodium channels (Nav1.1, Nav1.6, and KCNQ2/3) in the axon membrane at the node of Ranvier and localized potassium channels (Kv1) in the juxtaparanode (Figure 1) [2]. The final interaction needed between the two involves myelin attachment to the axon itself [2]. This is regulated by cell adhesion and scaffolding proteins in the paranode and juxtaparanode, which are also demonstrated in Figure 1 [2].

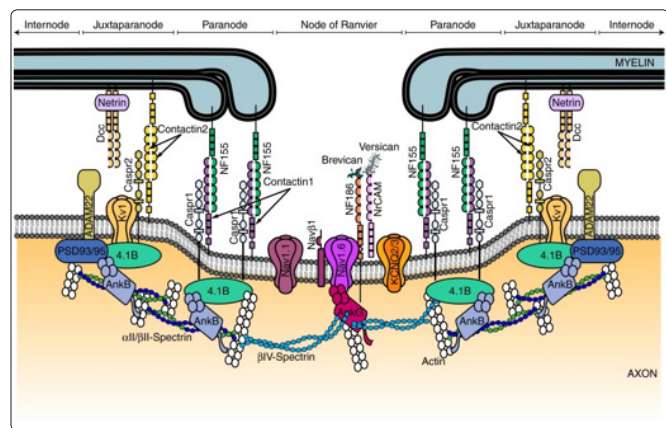


Figure 1: Diagram of proteins found at the node of Ranvier, paranode, juxtaparanode, and internode [2].

In order for myelin to reduce the axonal membrane capacitance, and therefore decrease the energy needed to propagate signals across the node, there needs to be little current flow under the myelin sheath. One way there is reduced current flow is through adhesive junction formation between glial cells and axons [2]. To help with reducing current flow in the myelin-axon gap, potassium channels in the juxtaparanode are placed under the myelin to reduce potential voltage drops, which then reduces activation in normal environmental circumstance [2]. Disruption of paranode structure can loosen extracellular space at the node, leading to increased current beneath the myelin and more activation of juxtaparanode potassium channels. Increased potassium channel activation in the juxtaparanode can prevent impulse propagation across the membrane, which leads to lowered effective neurological function [2]. Compared to normal physiology (Figures 2a and 2b) [2], increased current flow, paranode elongation, and myelin retraction (Figures 2c, 2d, 2e, respectively) [2] are all ways in which the node can negatively impacted. Without correct CNS development and function, the body cannot properly transmit impulses which leads to defective function, as seen in multiple sclerosis pathology.

Multiple Sclerosis Pathology and Diagnosis

Multiple Sclerosis is considered an autoimmune, inflammatory disease that is located in the central nervous system, with symptoms spreading throughout the whole body [3]. It has an extremely unpredictable pathological progression, starting with small, recurring episodes of neurological deficit and ends with irreversible myelin degeneration and dysfunction. The average disease pathology lowers human lifespan by seven years, yet the majority of the developmental period of MS is not expressive [4]. There are four classifications of MS: Relapsing-Remitting Multiple Sclerosis (RRMS), Secondary-Progressive Multiple Sclerosis (SPMS), Primary-Progressive Multiple Sclerosis (PPMS), and Progressive-Relapsing Multiple Sclerosis [3]. RRMS, the most prevalent classification, affects around 85% of patients diagnosed with MS [3]. RRMS consists of symptom flare-up followed by periods of remission, where no symptoms are present. It is two times as likely that females will present with RRMS as males [4]. RRMS is diagnosed by evidence of inflammation in areas with demyelination and destroyed oligodendrocytes. The inflamed lesion area consists of lymphocytes and monocytes (white blood cells) that have the potential to bypass the blood brain barrier, becoming an imminent threat to the brain. After penetrating the barrier, the lesions caused by white blood cells are detected as MS progression, leaving plaque-like, demyelinated compartments in the parenchyma [4, 5]. There are three classifications of lesions

brought on by multiple sclerosis. Type I contains cortical areas of demyelination and leukocyte contamination of subcortical white matter; Type II has small areas of demyelination to the cortical lesion area surrounding blood vessels; and Type III has areas of demyelination that extend from the pia surface above the cortex into cortical layers 3 and 4 of the brain [6]. All of these lesions, further diagramed in Figure 3, develop without significant leukocyte invasion making MS extremely difficult to diagnose early on in pathology development [6]. Highlighted in orange are the areas of the cortical membrane impacted by autoimmune attack consistent with each type of lesion (Figure 3) [6]. Another difficulty for clinical diagnosis is presented here: cortical lesions with an intact blood brain barrier cannot be detected with a conventional MRI [6]. As the disease progresses from RRMS into SPMS, there is a clinically significant axonal-density decrease with, or without, periods of symptom remission [4]. Due to the seamless transition between RRMS and SPMS, only the loss of symptom remission can differentiate between the two [7] leading to further diagnostic and drug treatment difficulties. Aside from loss of symptom remission, characteristic of SPMS is the irreversible neurological decline with observable, functional deficits to the patient [4,7]. Two separate classifications of MS, PPMS and progressive-relapsing, consist of nearly constant neurological decline [3]. PPMS is defined by an increase in T-cell presence within the meninges of the brain, suggesting that PPMS should, instead of the lack of T-cell activation, be characterized by the lack of T-cell presence in brain and spinal cord parenchyma yet extreme presence in the meninges [5]. There are no remission stages in PPMS like there are in RRMS and SPMS, and PPMS is even more resistant to drug therapies [3]. Progressive-relapsing MS, like PPMS, is progressive from its onset and has no remission periods. There is also a reduced time until irreversible damage is done to the brain, a greater degree of inflammation, and a younger onset of progressive-relapsing MS [8]. PPMS and progressive-relapsing MS affect between 5-10% of patients each [3]. According to Goldenberg in his 2012 review on multiple sclerosis, the diagnostic criteria is as follows: at least two different lesions are found in white matter of the central nervous system, and at least two different neurological episodes over the course of at least one month apart [3]. Another diagnostic tool used by clinicians is a spinal tap to examine oligoclonal bands for inflammation, determined by cerebral spinal fluid analysis [3]. Depending on the diagnosis, there are many different current disease-modifying drug (DMD) therapies that vary in usefulness per classification of MS.

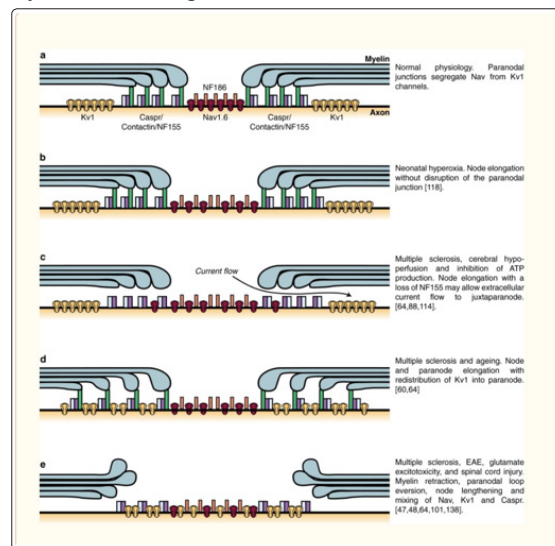


Figure 2: Diagram of myelin interaction under normal and pathological influence [2].

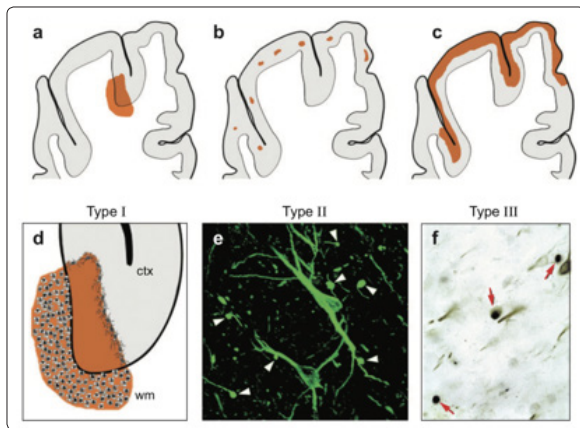


Figure 3: Diagrams of the Lesions I-III that develop during MS pathology [6].

Current Therapeutic Techniques: Disease-modifying Drugs (DMD)

MS is currently classified as a lifelong disease due to no cure presented to date. For decades there has been an attempt to treat symptom-presentation through DMD, with much of the focus on RRMS symptom treatment [9]. The goals of DMD are to shorten episode frequency and duration while relieving any chronic symptoms that affect daily patient life [3], as well as immediate episode relief was observed when using corticosteroids, along with few adverse side effects in most patients [3]. Corticosteroids are not long-term or helpful after multiple doses, though, which is why they are not as effective in treating MS after diagnosis when other DMD are available. Beta-interferon drugs were early DMD, affecting naturally occurring cytokines that are secreted by immune cells [3]. Cytokines, proteins released by cells that have a specific effect on tissue they interact with, are be pro-inflammatory or anti-inflammatory, which can be effective in MS symptom treatment [10]. MS affects pro-inflammatory cytokines, causing the extreme inflammation seen in MRI scans. The anti-inflammatory effects of beta-interferons reduce pain (nerve desensitization) caused by episode flare-ups [3]. While they are effective in reducing pain during an episode, beta-interferons also put patients at risk for liver dysfunction, thyroid disease, depression, and leukopenia [3, 4]. Leukopenia is a severe, abnormal decrease in white blood cell circulation that puts patients at risk of infection [3]. While studying the effects of beta-interferons on MS pathology, Rice et al. found that, while overall quality of life improved in patients, 37 out of the 117 patients in the study stopped treatment at one point [11]. Of the 37 who stopped treatment, 17 patients stopped due to adverse side effects and 10 had continued disease progression [11]. Beta interferon treatment is only somewhat effective in reducing symptoms for patients and, for some, can be harmful.

Glatiramer Acetate (GA), more commonly known as Copaxone or Glatopa [3], is a DMD used primarily for patients with RRMS who responded with adverse effects to beta interferons. GA was synthesized to be a competitive inhibitor of myelin protein to reduce the rate of relapsing episodes [3] but it also reduces antigen presentation and can stimulate the secretion of anti-inflammatory cytokines [4]. These two sets of effects, together, make GA a more successful deterrent of the debilitation set on by MS. Issues can arise by the frequent intramuscular and subcutaneous injections that are required to deliver GA, with common side effects such as flu symptoms and skin reactions [4].

Another DMD that is used for interference of DNA repair is Mitoxantrone [3] (commonly known as Novantrone) which is also

used as a chemotherapeutic agent. Mitoxantrone interferes with topoisomerase II, a DNA repair enzyme, although the mechanism of immunomodulation is yet to be fully explained [12]. During in vitro studies, the drug was well-tolerated by patients while also showing an improvement of RRMS and SPMS symptoms over a two-year period [12]. There were reduces in relapse rate, along with a slowing of disease progression [12] that gave medical professionals reason to use Mitoxantrone for MS treatment as well as a chemotherapeutic agent. Although it has shown great capabilities to reduce repair enzyme activity in cytokines, there weren't any effects by Mitoxantrone on the phagocytic activity of macrophages during the in vitro study [12].

A much more recent DMD developed to suppress leukocyte binding is Natalizumab, commonly known as Tysabri [2, 3]. Natalizumab binds to alpha integrins expressed on leukocytes to inhibit the alpha-4 mediated adhesion of the leukocyte to receptors, making the DMD its own immunoglobulin antibody [3]. This can effectively reduce the attack rate brought on by MS. It was recently found that pairing Natalizumab with T-cell therapy has the potential to normalize inflammation levels [5] which will also reduce pain during episodes. T-cell therapy is still in clinical trials, and during a 2018 phase III study there was a large incidence of adverse side effects with no significant reduction of SPMS progression [13]. Taking Natalizumab risks the patient of developing Progressive Multifocal Leukoencephalopathy, a viral infection of the brain that can lead to death or severe disability the more the patient takes the DMD [3].

A second more recent DMD is Teriflunomide, commonly known as Aubagio. Teriflunomide can reversibly inhibit dihydroorotate dehydrogenase, a mitochondrial enzyme in the pyrimidine synthesis pathway [14]. In turn, inhibition reduces activation of T and B cells without cell death as well as S-phase cell cycle interruption, limiting T and B cell inflammation [14]. During animal experiments, Teriflunomide was able to reduce CNS lymphocyte invasion, axonal loss, and preserve moderate neurological functioning [14]. There has yet to be effects on cell viability, as there are with Mitoxantrone [3] and immunosuppressants, but during clinical trials there was mean decrease in leukocyte count of about 15% from baseline measurements over the course of 3 months [14], after which there was no improvement. Each of the DMD discussed have shown slight improvement compared to placebos during trials, yet none have significantly improved quality of life of RRMS or PPMS patients. Stem cell therapy has been a more recent development that can contribute to slowing the progression of MS.

Stem Cell Therapy

Over the course of the last decade, three types of stem cells have been heavily studied in the attempt to have a bigger impact on the debilitation of MS: exosomes, hematopoietic stem cells (HSC), and mesenchymal stem cells (MSC). Exosomes are small, membrane-wrapped vesicles secreted by most cells to play a role in immune-system signaling and inflammation [15]. Different cell-originated exosomes evoke different responses in the recipient cell. By engineering specific, clearly-defined surface markers on a target recipient, there can be a high therapeutic success rate using exosomes [15]. Exosomes derived from MS patients could selectively target cells that are specific to the MS pathway, acting as an immunosuppressant [15]. While using experimental autoimmune encephalomyelitis (EAE) rat models, Li et al. showed that exosome treatment decreased negative neural behavior scores, reduced inflammatory cell infiltration, and decreased the rate of demyelination [16]. They also measured significantly

increased protein and mRNA expression levels [16] which implies new neural growth in areas previously demyelinated. One study provided a possible mechanism of delivering exosomes encapsulating curcumin intranasally, which successfully protected mice from brain inflammation brought upon by MS degeneration [17]. Because of their low immunogenicity, low toxicity, and their ability to encapsulate bioactive molecules while crossing the blood brain barrier, exosomes show promise in treating degenerative disorders. Further animal studies and clinical trials using standard exosomes are needed to understand the immunosuppressing ability. A second type of exosome study, using MSC-derived exosomes, reduced the mean clinical score of EAE mice compared to control [18]. It showed an increase in motor function, reduction of inflammation, and a reduction in demyelination [18]. Spinal cord sections from the exosome-induced mice, pictured in Figure 4 [18], show reduced macrophage size and complexity. Treatment transformed macrophage morphology from swollen, activated forms, to small cell bodies as if the cells were healthy (Figure 4) [18]. This study published last year shows that exosomes can serve as a therapy solution in response to autoimmune and CNS disorders, such as MS.

Another recent development is the use of HSC when treating neurodegenerative disorders. HSC are cells isolated from bone or bone marrow that can differentiate into various, specialized cells [1]. HSC can renew themselves with hyperactivity of telomerase [1], an enzyme used to protect the telomeres from destruction, which allows HSC to retain stem cell properties and not specialize each generation of new cells [19]. A primary application of HSC since its research origins has been autoimmune disorders. When targeting MS degeneration, HSC therapy is meant to eliminate lymphocytes that are autoreactive and create a new immune system that is not in an inflamed environment [20]. As described in Burt et al.'s study, after 1 year of treatment using HSC disease progression was 1.92% and at 4 years 9.71%, compared to DMD

(24.5% and 75.3%, respectively) [20]. HSC therapy requires transplantation of stem cells into the bloodstream, which can cause a variety of adverse events. Transplantation can result in mucositis, inflammation of mucous membranes; sinusoidal obstruction syndrome, enlargement of the liver and extreme fluid retention; failing to ovulate post-transplantation; and stunted growth in adolescents [19].

The third focus area of stem cell therapy for MS is MSC therapy. MSC are a subclass of adult stem cell that support hematopoiesis, the formation of new blood cells [9]. An early stem cell study found that MSC inhibit T-cell proliferation [21]. This suggested that MSC can induce an autoimmune tolerance, making it a candidate for neurodegenerative, autoimmune disorders like MS. Such findings were found by researchers when MSC improved clinical scores in EAE mice models induced with progressive MS pathophysiology [5]. Amniotic MSC have been recently discovered to also have immunomodulatory and immunosuppressive effects. They have the capability to reduce the activity of inflammatory cells, the migration of microglia, and can inhibit immune cell migration towards injury sites [22]. Abbasi-Kangevari et al. also found a multitude of other effects amniotic MSC have on MS: MSC can enhance neurogenesis in brain injuries by inhibiting inflammation at the injury site, can increase neurotrophic factor expression levels to prevent neurons from initiating apoptosis, and can induce differentiation of neural stem cells to neurons [22]. Sparking regrowth in lesion areas will help MS patients combat the deterioration, as well as continue to repair the lesions themselves. It was also found that MSC can be directed where to go in their migration through the blood brain barrier, so lesion areas can be targeted directly [23]. Mansoor et al. discovered that MSC can arrest the B-cell cycle, effectively inhibiting the production and distribution of antibodies as well as stopping activation of dendritic and natural killer cells [23].

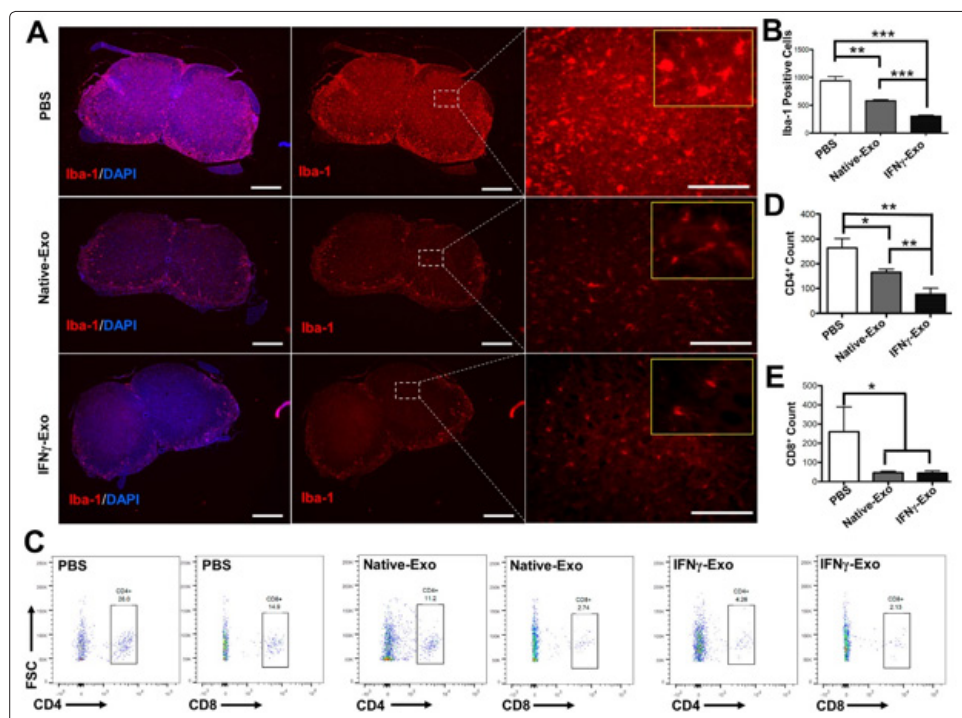


Figure 4: MSC-derived exosome treatment of macrophages and T cells in EAE mice spinal cords. Shows reduction in size and simplification of morphology of macrophages [18].

Conclusions

Stem cell therapy trials have shown success in slowing down demyelination caused by MS [16, 18, 21, 22, 23]. There have also been challenges presented during these trials. During Mansoor et al.'s trial using MSC to suppress demyelination it was found that the immunosuppressive capabilities of MSC allow room for opportunistic diseases to take control of the body [23]. The next step for MSC research is to develop a method of delivery for MSC-secreted exosome cells to the body. Exosomes are smaller in size, allowing them to travel more freely through capillaries and have improved delivery to the lesion site [18]. Figuring out the correct route of administration for the other stem cell therapies is also an important development to investigate in future studies. For decades there have been attempts to slow MS progression with DMD, and for the past decade there has been lot of developing research on stem cell therapies. Neither have completely stopped the debilitating disease from progressing, but it is possible that together they can. Many DMD used in today's battle against MS are effective in reducing the disease's ability to progress at the rate it would without intervention, while stem cell therapies can regenerate properly differentiated cells. DMD therapy can potentially slow down MS progression enough so that stem cell therapies, like MSC-derived exosomes or HSC, can start reversing the damage done to the brain by lesions.

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