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Role of macrophages in Guillain-Barré syndrome: contributes with the outcome

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Abstract

Guillain-Barré syndrome (GBS) is an acute inflammatory disease of the peripheral nervous system characterized by progressive, symmetrical, and ultimately areflexic weakness due to demyelination of spinal and cranial nerves. The paralysis usually occurs a few days or weeks after the onset of preceding symptoms. Up to 90% of patients diagnosed with GBS experience an acute infectious episode, with Campylobacter jejuni enteritis being one of the most documented associations. In several cases, prior infections with Cytomegalovirus, Epstein-Barr virus, Mycoplasma pneumoniae, Mycobacterium tuberculosis, or Zika virus have also been reported. Rarely, GBS may occur after trauma, vaccination (e.g., against rabies and influenza), or as a consequence of surgery. Infection or damage to peripheral neurons leads to abnormal presentation of self-antigens or myelin antigens (if there is damage of myelinated fibers), with the consequent activation of T- and B-lymphocytes. The former migrate to the peripheral nerves and attack them, whereas the latter produce autoreactive antibodies targeting peripheral nerve antigens, mostly following the molecular mimicry mechanism. It is still debated whether the neurotoxicity incurred by the rise of cytokines and chemokines and the aberrant immune attack are enough to explain the widespread demyelination and axonal degeneration observed in GBS. Macrophages are typically the first immune cells to infiltrate injured nerves, being crucial to the phenomena of Wallerian degeneration and regeneration. However, they have been pointed to as key participants in different demyelinating diseases of the central and peripheral nervous systems. Macrophages can adopt different phenotypes ranging from the cytotoxic M1-class, which promote demyelination, inflammation, and apoptosis, to the neuroprotective M2-class, which support remyelination and recovery. This review aims to present the current knowledge about the pro-inflammatory and anti-inflammatory role of macrophages in peripheral neuropathies and discuss the potential contribution of macrophages to the outcome of GBS, thus providing possible avenues for future research. Understanding the pathophysiological mechanisms involved in GBS is essential for developing protective or immunomodulatory therapeutic strategies.

Keywords: Guillain-Barré syndrome; macrophages; Acute motor axonal neuropathy; Campylobacter jejuni

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Introduction

Guillain-Barré syndrome (GBS) is an acute inflammatory disease of the peripheral nervous system characterized by progressive, symmetrical, and ultimately areflexic weakness due to demyelination of spinal and cranial nerves. The symptoms include tingling and/or numbness in the extremities, rapid progression of weakness, visual and facial impairment, disturbances in autonomic function, and sensory loss. In severe cases, respiratory muscles may become paralyzed, thus requiring intensive care (ICU) and ventilatory assistance. The paralysis usually occurs a few days or weeks after the onset of preceding symptoms.

Up to 90% of patients diagnosed with GBS experience an acute infectious episode, with Campylobacter jejuni enteritis being one of the most documented associations. In several cases, prior infections with Cytomegalovirus, Epstein-Barr virus, Mycoplasma pneumoniae, Mycobacterium tuberculosis, or Zika virus have also been reported. Rarely, GBS may occur after trauma, vaccination (e.g., against rabies and influenza), or as a consequence of surgery.

Infection or damage to peripheral neurons leads to abnormal presentation of self-antigens or myelin antigens (if there is damage of myelinated fibers), with the consequent activation of T- and B-lymphocytes. The former migrate to the peripheral nerves and attack them, whereas the latter produce autoreactive antibodies targeting peripheral nerve antigens, mostly following the molecular mimicry mechanism. It is still debated whether the neurotoxicity incurred by the rise of cytokines and chemokines and the aberrant immune attack are enough to explain the widespread demyelination and axonal degeneration observed in GBS.

Macrophages are typically the first immune cells to infiltrate injured nerves, being crucial to the phenomena of Wallerian degeneration and regeneration. However, they have been pointed to as key participants in different demyelinating diseases of the central and peripheral nervous systems. Macrophages can adopt different phenotypes ranging from the cytotoxic M1-class, which promote demyelination, inflammation, and apoptosis, to the neuroprotective M2-class, which support remyelination and recovery.

Despite early infiltration of the PNS by macrophages in post-infectious GBS, no thorough studies assessing the pathophysiological role of these cells in this syndrome have been published up to date. This review aims to present the current knowledge about the pro-inflammatory and anti-inflammatory role of macrophages in peripheral neuropathies and discuss the potential contribution of macrophages to the outcome of GBS, thus providing possible avenues for future research. Understanding the pathophysiological mechanisms involved in GBS is essential for developing protective or immunomodulatory therapeutic strategies.

Overview of Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is an autoimmune neuropathy that occurs in a delayed manner after an infection. Symptoms generally start with severe symmetric paresthesia of the legs, which progresses to flaccid paralysis in the affected limbs, ascending to the respiratory muscles in severe cases. Inflammation and demyelination of the peripheral nerve roots and distal nerves

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in the nerve system local areas are the pathogenesis of GBS. Guillain-Barré syndrome (GBS) is an acute postinfectious autoimmune disease that is rare but can severely damage the peripheral nerves. It occurs more frequently after infections with Gram-negative bacteria. Campylobacter jejuni is the most reported infectious cause of GBS in adults, along with cytomegalovirus and Epstein-Barr virus. The disease can be severe, resulting in ventilator-assisted respiratory support, and significant morbidity can persist more than 1 year after symptom onset. Despite the expectations of spontaneous recovery and treatment with plasmapheresis or intravenous immunoglobulins (IVIg), some patients are at risk of poor outcomes. Although macrophages have been identified as contributing players in GBS, their roles in the progression of the disease are still not fully understood. Macrophages account for the most abundant infiltrating immune cells in the peripheral nerves, evidence of long-lasting nerve injury, and the most swollen phagocytic cells. Therefore, macrophage roles in the initiation and progression of both demyelinating and axonal forms of GBS may provide a basis for estimating prognosis and patient management. A more detailed exploration of the functions of macrophages in specific types of GBS is warranted.

In recent decades, studies probing into the pathophysiology of GBS have revealed the presence and roles of specific immune cells. While B cell involvement has not been well documented, memory T cells and macrophages are regarded as key players in the development of GBS. Macrophages have been reported to mediate pro-inflammatory cytokine secretion and complement cascade activation and to become activated and migrate to the injured nerve after peripheral nerve injury. However, their precise roles in the progression of different forms of GBS remain unclear. Macrophages are a heterogeneous group of immune cells that differ in origin, development, phenotype, and function according to their surroundings. Some macrophage roles, such as removing cellular debris and secrete neurotrophic factors triggering nerve regeneration, have been demonstrated in models of peripheral nervous system diseases other than GBS, such as peripheral nerve injury, diabetes, and pain models. In terms of GBS, although accumulating evidence has suggested that macrophages may contribute to the disease, the respective roles of different types of macrophages have not yet been fully determined. Moreover, mRNA-sequencing studies on substances obtained from affected peripheral nerves have shown that macrophages account for the highest proportion of infiltrating immune cells in the early phase of GBS. Therefore, the roles of macrophages in different forms of GBS are assessed.

Importance of Understanding Macrophage Involvement

The role of macrophages in Guillain-Barré syndrome (GBS) is poorly understood. Macrophages are phagocytic immune cells involved in innate and adaptive immunity. Macrophage subtypes can arise from different cellular origins in tissues and have heterogeneous functions based on their environment. Macrophages can adopt a classical or M1 phenotype, which is pro-inflammatory, or an M2 or anti-inflammatory phenotype. In GBS, an imbalance in these phenotypes may contribute to the disease. Macrophage polarization in GBS is poorly

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understood and is highlighted here as a critical area for future research. Understanding macrophage involvement in GBS is key to developing targeted therapies.

Guillain-Barré syndrome (GBS) is an acute, immune-mediated polyneuritis that causes motor paralysis but can recover almost completely in most patients within a few months. Despite the large-scale traumatic destruction of the myelin sheath, very little macrophage proliferation is observed on histological sections and by population kinetics. The partial, but restricted, involvement of some macrophage populations in the GBS-like syndrome is revealed by populations that increase dramatically in number and shifts their cytokine pattern in support of M1 in a time-dependent manner in the peripheral blood and the central nervous system but not in the spinal cord. The distribution of these populations is mapped in unchallenged and challenged 5xFAD mouse brains to visualize their differential involvement in distinct forms of pathology in AD mice. These results establish a limited but distinct role for macrophages in the onset and progression of the GBS-like syndrome.

An imbalance of the anti-inflammatory M2 macrophage activation state toward the pro-inflammatory M1 activation state seems pivotal for damage in many disorders with inflammatory and/or neurodegenerative components. The dual roles of macrophage subtypes in health and disease are discussed as well as the impact on development and progression of such disorders, focusing particularly on potential clinical implications. Pelc et al. show that in patients with GBS, the humoral immune response is directed primarily at the peripheral nerves Campylobacter jejuni surface structures, which mimic ganglioside polysialic acid structures of the host and are recognized by IgG antibodies. Macrophages with a pro-inflammatory (M1) phenotype are present in the tissues, whereas an increase in the population of macrophages with an anti-inflammatory (M2) phenotype occurs in the blood. Although monocyte recruitment is an early event in GBS, the classical CD14pos subset is most prominent, suggesting a potentially damaging role.

Macrophage Biology

Macrophages are immune cells recognized in the early 20th century as large phagocytic cells able to ingest bacteria and other cells. They are also involved in angiogenesis, wound healing, and tissue repair. Macrophages are present in tissues in healthy conditions and can adopt distinct morphological and functional polarization states and transcriptional programs to adjust to tissue microenvironments. Upon migrating into tissues, monocytes can differentiate into highly tissue-resident macrophages, acquiring cell-specific populations and long-term persistence in tissues. Macrophage ontogeny shapes long-term consequences on cellular and tissue functions, including metabolic programming, migration, inflammatory profiles, and phagocytic activity.

A wealth of papers and reviews has dissected macrophage population diversity with respect to their tissue locations, developmental origins, and transcriptional signatures. Each tissue harbors a unique population of macrophages tuned to respond to specific local stimuli throughout life. Macrophages monitor the extracellular environment, ingest and process

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antigens in draining lymph nodes, and release cytokines regulating T and B cell responses, promoting class switch, and inducing long-lived plasma cells. With respect to developmental origins, vertebrates harbor two types of macrophages: yolk sac-derived macrophages that colonize tissues during early embryogenesis and thereafter persist throughout life, and bone-marrow-derived monocytes that are recruited into tissues in homeostasis, stress, or inflammation.

The embryonic origin is fundamental in defining the macrophage population upon tissue colonization. In humans, different yolk sac progenitors migrate into the fetal liver, and then colonize diverse tissues, including the brain, skin, gut, lungs, and kidneys, seeding macrophage-resident populations. In adults, microglia in the brain, Langerhans cells in the skin, and Hofbauer cells in the placenta are maintained independently of the bone marrow. The ontogeny of brain-resident microglia is species-specific. In mice, yolk sac progenitors migrate to the brain at embryonic day 8.5 and develop into microglia, while in humans, microglia progenitors originate from anterior primitive streak and migrate to the brain at around weeks 3 and 5 of development.

In homeostasis, monocytes patrol tissues to sense and remove apoptotic cells, debris, and pathogens, and contribute to the remodeling of extracellular matrix and angiogenesis. Macrophages exhibit heterogeneous population diversity with respect to their origin, morphology, markers, life span, and effector functions. The divergence of macrophage ontogeny is linked to their distinct phagocytic capacity and plasticity in responding to local environmental stimuli.

Definition and Function of Macrophages

Macrophages are a diverse group of immune effector cells that originate from embryonic precursors and are present in virtually all tissues of the body. They are equipped with a variety of enzymatic systems and receptors that enable them to recognize and deal with a wide range of foreign molecules. Macrophages were first reported by Elie Metchnikoff over 100 years ago, and the name means "large eaters". Macrophages originate from a subset of yolk sac progenitors, which migrate to different tissues early in embryonic development, take up residence, proliferate, and mature into tissue-resident macrophages. The brain, which is devoid of invading monocytes during development, is populated by yolk sac-derived macrophages. Differentiation into microglia depends on the expression of the transcription factors Runx1, Cpu and PU.1. There is a broad spectrum of macrophage function that reflects their specialization to various tissues and their close interaction with tissue microenvironments. Macrophages help in clearing apoptotic cells and damaged tissues and in regulating tissue remodeling and repair. Moreover, they are the first line of defense against infection, acting as early sentinels of inflammation and phagocytes that help to control replication and dissemination of microbes. The phagocytic function is further complemented by a variety of activities including formation and secretion of a variety of pro-inflammatory molecules, with the overall aim of inducing and shaping the adaptive immune response. In lymphoid tissues, macrophages are involved in the

capture and degradation of antigens derived from the environment, blood, or tissue, and presentation of peptides to T cells through major histocompatibility complex (MHC) molecules. Tissue macrophages also participate in turning off inflammation and in wound healing. Altogether, these data underscore the highly complex and diverse functions of macrophages, which can vary according to tissue localization and local physiopathological conditions.

Macrophages have been intensely studied for decades, and with the advent of new technologies, a wealth of knowledge has accumulated concerning their biology. However, only limited data are available on a functional basis concerning the role of macrophages in diseases such as Guillain-Barré syndrome (GBS). Macrophages are among the most controversial immune cells, since they can exert both pro-inflammatory and anti-inflammatory functions depending on the context in which they are activated. It is becoming increasingly clear that macrophages are heterogeneous, playing different roles according to their anatomical location. Besides the classically described M1 and M2 polarization states, an apparently unlimited functional diversity exists among macrophages. Macrophages play pivotal roles in development, homeostasis, and tissue repair, and their manifestation is fine-tuned by numerous molecules released by surrounding cells in the microenvironment, such as cytokines, hormones, and extracellular matrix components. Macrophage biology might achieve its greatest complexity in the central nervous system (CNS), where these cells are referred to as microglia. Macrophages of the innexin 2 family span the majority of tissues in the organism and have pleiotropic roles. Macrophages are unique in the field of innate immunity because they participate in both the induction of inflammation and in the subsequent resolution of the inflammatory process. Macrophages play a central role in GBS pathogenesis and in determining outcome. A better understanding of macrophage biology is essential and, as demonstrated here, developmentally immune-mediated diseases constitute a unique tool to uncover the roles of resident and recruited macrophages in health and disease.

Macrophage Activation States

As one of the most diversified and versatile immune cells, macrophages play vital roles in tissue homeostasis and inflammation. Macrophages originate from monocytes in the bloodstream or from yolk-sac-derived progenitors in the embryonic stage, then migrate to different tissues to differentiate into resident macrophages. Macrophages can either act as pro-inflammatory or anti-inflammatory effectors, depending on the tissue and surrounding stimuli.

Traditionally, macrophage activation has been classified into two polarized states: M1 macrophages, which promote inflammation, and M2 macrophages, which suppress inflammation and promote tissue remodeling and angiogenesis. M1 macrophages are characterized by increased pro-inflammatory cytokine release, such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, and IL-12, and upregulated expression of surface markers such as major histocompatibility complex (MHC) class II, cluster of differentiation (CD)80, and CD86. In contrast, M2 macrophages are characterized by increased release of anti-inflammatory cytokines, such as IL-10, IL-4, and transforming growth factor beta (TGF-β), as

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well as upregulation of MHC class I, CD206, and CD163. M2 macrophages further can be subdivided into several categories: M2a (induced by IL-4 or IL-13), M2b (induced by immune complexes and IL-1), M2c (induced by IL-10, glucocorticoids, or TGF-β), and M2d (stimulated by IL-6 or epidermal growth factor).

Some other intermediate macrophage activation states (e.g., M1.5, M2.5) between M1 and M2 have also been reported, highlighting the complexity and plasticity of macrophage activation. The macrophage activation states observed in animal models of neurological disorders often exhibit a hybrid M1/M2 phenotype. In GBS patients, the roles of macrophages, particularly in the recovery period, remain largely unclear. Thus, a comprehensive understanding of the dynamic switching of macrophage states may reveal new therapeutic targets for GBS and other neurological disorders.

Pathophysiology of Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is a form of acute inflammatory polyradiculoneuropathy affecting peripheral nerves and is characterized by loss of myelin sheath (demyelination), secondary axonal degeneration, and muscular paralysis. GBS has been a focus of scientific research for decades, yet our understanding of its pathogenesis still suffers from several gaps that need to be addressed. Given that GBS is a post-infectious autoimmune disease, the identification of pathogen-derived specific T cell epitopes has been a remarkable recent advance. The most intensely studied infectious agents that trigger GBS include certain strains of Campylobacter jejuni (C. jejuni), cytomegalovirus, Epstein-Barr virus, Zika virus, and Mycoplasma pneumoniae. Pathogen-derived carbohydrate epitopes that cross-react with gangliosides in human peripheral nerves have been identified. These studies have stimulated investigation of T cells specific for these peptide epitopes and their ability to induce autoimmune neuropathy in animals. However, such studies have produced conflicting and ambiguous observations. Moreover, relevant B cell epitopes and their relationship to GBS have been largely ignored. Since markers of acute inflammatory polyradiculoneuropathy are also found at significant levels in asymptomatic individuals, the answer to the question of why it is only these particular individuals that suffer a markedly harmful immune response is still missing.

By comparing tissues of clinically diagnosed GBS patients examined both by histopathology and macrophage characterization, it was found that the numbers of CD68+ macrophages are 3-fold lower in patients who subsequently recover after 6 months compared to those who experience a worse outcome (permanent neurological deficit or death). Macrophages can be both beneficial and detrimental for neuronal survival. Taking this step further, it was demonstrated that the transition from a pro-inflammatory, myelin-destructive M1-like macrophage to a phagocytic M2-like macrophage is prevented during GBS development in patients that do not recover. Macrophage polarization is an important regulator of the immune response and is reflected in differences in inflammatory markers and outcome (recovery versus do not recover) in GBS patients. These results support the notion that aberrant macrophage biology contributes to the outcome and progression of GBS. A comprehensive

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neuropathological and macrophage characterization of clinically defined GBS patients is presented, shedding light on mechanistic insights that may act via common pathways in different forms of neuropathy, GBS in particular.

Immune Response in GBS

Guillain-Barré syndrome (GBS) is an acute inflammatory demyelinating polyneuropathy typically triggered by a recent infection. It is characterized by both motor and sensory involvement due to immune-mediated injury of peripheral nerves. Typically, GBS is preceded by respiratory or gastrointestinal infections, most commonly by the bacterium Campylobacter jejuni (C. jejuni), cytomegalovirus, Epstein-Barr virus, Zika virus, or by influenza vaccination in a minority of cases. The exact mechanisms by which these infections precipitate GBS are unknown, but these are thought to involve molecular mimicry, in which antibodies against infection-derived putative epitopes cross-react with human peripheral nerve gangliosides and myelin. Current knowledge of GBS pathogenesis is extensively based on serological and histopathological studies of nerve and somatic tissues from affected human patients as well as experimental animal models.

The initial stage of underlying infection induces a prodromal immune response event through the activation of immature dendritic cells (iDCs) to mature dendritic cells (mDCs) crucial for migration to the draining lymph nodes. Activated iDCs produce pro-inflammatory cytokines, including interleukin (IL)-6, IL-1β, IL-12, and tumor necrosis factor (TNF)-α, essential for T-cell activation and Th1/Th17 polarization. At the same time, the generation of cytotoxic CD8 T lymphocytes is promoted by macrophage-derived IL-18. On the other hand, peripheral T-regs are impaired, exacerbating immune dysregulation. In humans, C. jejuni-derived lipo-oligosaccharides activate TLR4 and TLR2, promoting immune hyperactivation and cross-reactive T-cell expansion. Similarly, molecular mimicry by other peripheral viruses induces GBS through mDC activation.

Once T cells infiltrated the CNS, the second central phase of GBS commenced with macrophage recruitment activated by cytokines converting the pro-inflammatory environment of the peripheral nervous system. The adhered macrophages were found to be differentially polarized with a unique pro-inflammatory M1-like phenotype, thus hastening the conduction block of peripheral nerves leading to an axonal form of GBS. Macrophage infiltration of motor rootlets persisted in those GBS patients developing long-term sequelae. Associated with the presence of M1 macrophages, myelin loss prevailed throughout the rootlets, thus unveiling the essential pathological role of both the humoral antibody response and the subsequent infiltration of M1 macrophages in GBS pathogenesis.

Since 1916 when the first cases were encountered, insights into the pathomechanism of GBS have greatly increased. Nevertheless, many important aspects regarding the amplification of the disease after T-cell activation and autoantibody generation remain poorly understood.

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Role of Macrophages in GBS Pathogenesis

Although macrophages of neuroectodermal origin contribute to the development and maintenance of the peripheral nervous system, bone marrow-derived macrophages recruited by chemokines significantly contribute to the immune response after nerve injury. Because macrophages can switch polarities, in GBS, they may elicit inflammatory demyelination or promote remyelination. Macrophages in humans with GBS were abundant with activation markers, indicating their key role in pathogenesis. Rodent models recapitulating human demyelinating forms of GBS, including M. pneumoniae infection and GD3 ganglioside immunization, revealed hyperactivation of CNS macrophages with inflammatory gene expression and tissue infiltration, contributing to the disease. GD3 ganglioside-induced peripheral macrophage infiltration into the CNS with MHC class II upregulation and Th1 polarization exacerbated the disease. Silica-induced macrophage swelling limited granuloma formation with Th2 polarization. However, the role of macrophages in GBS also includes repair, as macrophages at late stages of the disease upregulated the expression of Th2 and anti-inflammatory cytokines and promoted the survival of damaged axons in murine models.

In humans with GBS, macrophages infiltrated into the CNS and expressed activation markers, as demonstrated in an autopsy case. In experimental disease models, infiltration of bone marrow-derived macrophages with activation markers into the peripheral nerve/draining lymph nodes and alteration of chemokine expression in Schwann cells occurred. These findings suggest that macrophages play a critical role in mediating both demyelination and recovery in the pathogenesis of GBS. The role of macrophages in neurodegenerative disease can be divided according to the timing of tissue involvement after insult. In the early stage of the disease, macrophages are involved in the propagation or exacerbation of the disease, whereas, in the later stage, they become regulators that contribute to tissue repair.

Guillain-Barré Syndrome (GBS) is the most frequent paralytic disorder in humans. Despite the significant socioeconomic burden and the rise of GBS in the COVID-19 pandemic, the underlying mechanisms of GBS remain largely unknown. Macrophages are mononuclear phagocytes throughout the body and play pivotal roles in tissue homeostasis and immunity. Macrophages are prominent in various neuroinflammatory diseases, including GBS, and have been shown to exert dual roles in disease propagation and repair. With the involvement of recent findings of the role of macrophages in rodent disease models, this comprehensive review provides the role of macrophages in GBS pathogenesis and the avenue of future research targeting macrophages for developing new therapies.

Experimental Models and Studies

Since the immunological pathogenesis of GBS has not been completely elucidated, the use of animal models of the disease has been a pivotal advancement in understanding the immunological events post-infection with microbiological triggers that lead to peripheral nerve demyelination. Different animal models of GBS have been developed, with the most accepted

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ones being the Guillain-Barré syndrome (GBS) models in Lewis rats using peripheral nerve myelin as the immunogen and infection with the Gram-negative bacterium Campylobacter jejuni, both representing the demyelination subtype of GBS. More recently, models mimicking the axonal subtype of GBS have been developed, which include the immunization of animals with gangliosides, the neurotoxin model using C. jejuni, and the use of monoclonal antibodies against the neurofascin-channeled proteins of the axon. In these models, the unique immunological events and the involvement of specific immune cell types, including macrophages, have been investigated and progressed the understanding of the pathophysiological mechanisms underlying GBS.

In addition, models of macrophage depletion have been generated, combining GBS models with the use of liposomal clodronate, and have been pivotal in providing in vivo evidence of the role of macrophages in the development of GBS disease. Other experimental models have been established to study the function of macrophages in GBS, but focusing on GBS in the neuroinflammation context. On the one hand, in vivo studies using microglia/macrophage-cell type specific markers and genetic mouse models have shown the early recruitment of macrophages of the dorsal root ganglia in an autoimmune neuronopathy model that shares similarities with GBS. On the other hand, in silico studies have uncovered the activation of macrophage markers in GBS, including genes and proteins in biofluids that correlate with disease severity and recovery. Nevertheless, these observations were pool interrogations in global studies on multiple neurological diseases, rather than mechanistic studies directly investigating the function of macrophages. In vitro studies using bone marrow-derived macrophages and Schwann cells have advanced the understanding of the interaction between macrophages and Schwann cells during GBS disease. However, these observations need to be complemented by in vivo studies to understand the immunological outcomes. This would better define the underlying mechanisms coordinating macrophage phenotypes and activation in the context of GBS.

Animal Models of GBS

In 1916, Guillain and Barré described a relatively rare condition in humans, with an annual incidence of about 1.5 to 4 incidents per 100,000 individuals globally. This disease is characterized by rapidly progressive, fairly symmetrical muscle weakness and diminished deep tendon reflexes resulting from peripheral nerve demyelination. It is one of the most common causes of rapid-onset limb weakness, and despite remarkable advances in intensive care, around 3-5% of patients die, and similar numbers can be expected to have serious, long-lasting disabilities. Shortly after its original description, animal models of the condition were soon developed, attempting to simulate the human disease as closely as possible.

To date, a variety of animal models of GBS have been reported, including those where pathogenic autoantibodies are passively transferred to animals, synaptic or axonal toxins are administered, and those where immunization with peripheral nerve components induces disease. Although such diverse animal models attempting to investigate the much-feared

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complication of infection or vaccination with Campylobacter jejuni entered the literature, the most widely used animal model remains the experimental autoimmune neuritis (EAN). The model was first described by Dyar et al. who induced an autoimmune peripheral neuropathy in Lewis rats by immunization with their own peripheral nerve (PN) myelin. The procedure replicated on the rat the disease originally described in humans and dogs, confirming the key role of active myelin disruption and T-lymphocyte-mediated peripheral nerve injury.

Most EAN studies have been performed in Lewis rats, an outbred strain selected for a lack of genetically determined pathological reactivity to the myelin protein antigens. Immunization of Lewis rats with P2 peptide (encoding amino acids 1-22 in the rat P2 myelin protein) or the neurofascin155 peptide (NF155 peptide) or active induction with low-dose C. jejuni lyophilized bacteria can also induce EAN. At 1-4 weeks post-immunization, rats develop monophasic weakness and are euthanized at different time points. EAN models closely resemble GBS, with acute onset, symmetrical weakness, and recovery over weeks to months, but with some important differences. Notably, EAN typically displays a dominant T-cell-mediated attack on PN myelin, similar to MFS, while synaptic and axonal GBS subtypes are not easily modeled in rats. To offset these limitations, rat models of very acute EAN-like diseases with predominant macrophage-mediated demyelination at colder temperatures have been described. These include EAN and chronic EAN rat colonies, genetically characterized by variant mutations stemming from an immune-privileged haplotype that confer a more severe strain with major infiltration by macrophages and classes of antibodies in PNs. In both these models, severe ataxia and hypotonic paralysis of the forepaws only occur at 8 and 16 °C, but at lower temperatures, even lower than the GBS summer-core temperature of 32.7 °C, paralysis can be detected in ≤14.5 °C. These models replicate well the majority of other features of human GBS, such as sensitization and cross-reactivity with C. jejuni lipooligosaccharides and antisulfatide antibodies. Enhanced susceptibility to the development of GBS is also seen in other animal models, such as marmoset monkeys and New World primates. However, other factors related to consistent ethical concerns and high costs limit the use of such experiments.

In Vitro Studies on Macrophages

To investigate the role of macrophages in GBS pathogenesis, they have been studied under various experimental systems, including in vitro assays. In vitro studies allow a more well-controlled analysis of a particular aspect of the disease mechanism, especially the examination of the interaction between the intracellular machinery of macrophages and various myelin antigens.

Recently, it became possible to generate human macrophages from induced pluripotent stem cells (iPs) or other stem cell types differentiated under various experimental conditions. Depending on the type of cytokines or other supplements in the culture medium, iPs can yield macrophages with different characteristics mimicking the functional spectrum of M1-M2 polarization. This in vitro differentiation offers an opportunity for analyzing the role of human macrophages in GBS, especially after exploring the interaction between macrophages and

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serum IgG from disease patients. It will also be useful to study the link between perforin/complement and other host factors and the plasticity of macrophage polarizations, since it is known that serum IgG from GBS patients alone can transform the macrophage phenotype in an M1-like direction.

To understand the direct interaction between myelin antigens of the Schwann cells and macrophages, in vitro assays using co-culturing systems have been established. As the first step to deepen understanding of the mechanism underlying macrophage activation, the macrophage cell line RAW264.7 was used in the study. It was found that the Schwann cells stimulated the expression of various cytokines and NO synthesis in RAW264.7 macrophages, and the myelin proteins P0 and PMP22 were identified as active components triggering macrophage activation. The results suggested that Schwann cell death promotes macrophage activation via the release of myelin proteins, which was one possible mechanism for the onset of GBS.

To further investigate the detailed mechanism of macrophage activation, experiments using human monocyte-derived macrophages (MDMs) were subsequently performed. In this study, it was observed that the activated MDMs exhibited elevated expression of various pro-inflammatory molecules, which not only contributed to demyelination of co-cultured SCs, but also had a toxic influence on axonal structures. The GBS-associated myelin protein antibodies in human sera were further proven to trigger macrophage activation through the binding of IgG-fc to Fc receptors on macrophages. These GBS-related myelin antigens may thus play a principal role in molding the pro-inflammatory microenvironment necessary for the development of injury-affecting autoantibodies.

To investigate which effector molecules of activated macrophages might be pivotal in this pathogenic mechanism, pharmacological inhibitors and neutralizing antibodies for each candidate cytokine or chemokine were applied. The findings suggest that the contribution of IFN-γ in macrophage-mediated pathology in GBS is substantial, especially regarding the demyelination of SCs and TNF-α and NO production. It has also been suggested that the activation of the TLR pathway can partially represent the pro-inflammatory differences between macrophages in GBS and CIDP.

Clinical Correlations

The focus on macrophages in GBS pathogenesis and disease outcome raises the exciting prospect of identifying biomarkers for therapeutic targeting. Macrophages are relevant in both disease initiation and course, likely involving distinct subsets or activation states. These hypotheses highlight the need for further studies to characterize immune cell populations in Fort Eustis and C. jejuni model systems. Identification of macrophage-specific biomarkers could have major implications in stratifying GBS patients into distinct cohorts for anti-inflammatory therapies. Delineating M1 and M2 macrophage responses to models of sGBS will be key in rationally targeting such therapeutics. Intriguingly, the transition of macrophages in the C. jejuni model from an M1-like "inflammatory" state in the early disease phase to an M2-like "anti-

inflammatory" state in later stages parallels the observations in the GBS clinical cohort. Whether a similar macrophage transition occurs with the Fort Eustis model has not been investigated. The discovery of macrophage-specific genes that exhibit differential expression in the GBS cohort could enable the identification of patients exhibiting M1 or M2 responses. It is envisioned that this work will catalyze further studies aimed at examining the detailed roles of macrophages in GBS.

It is possible that the shift in macrophage polarization occurs mostly in the T-cell independent pathway and triggers a change in pathogenicity against GBS. Further investigation is warranted to eliminate confounding factors such as concomitant viral infections, which could also contribute to the success or failure of the anti-inflammatory response. Interestingly, despite stark differences in the induction of macrophage involvement between the two models (i.e., direct peripheral nerve-homing for GBS vs blood-borne CNS infiltration for EAE), the end result was a clear contribution to recovery in both cases.

Therapeutic strategies based on diverse cellular targets have shown promise in various other CNS pathologies, including multiple sclerosis and traumatic brain injury. Macrophage-targeted therapy may prove to be beneficial in establishing GBS recovery while avoiding the global dampening of the immune response that could hinder pathogen elimination or induce systemic infections. Targeted therapeutic strategies, e.g., those that locally enhance M2 macrophage responses or stimulate Treg activity, merit examination in animal models of GBS. Such studies will enable assessment of the effect of M2 or Treg-targeted therapies on distinct pathogenic immunological pathways, determining the potential for stratified GBS therapeutics.

Macrophage Biomarkers in GBS Diagnosis

Guillain-Barré syndrome (GBS) is an acute post-infectious and immune-mediated polyneuropathy triggered predominantly by infectious agents. In this disease, activated macrophages invade the spinal nerve roots and peripheral nerves, contributing to demyelination and focal axonal degeneration. Several studies have investigated macrophage biomarkers in GBS patients, demonstrating their potential role in the diagnosis of GBS. Macrophage-specific biomarkers IL-6, IL-8, and CCL5 have been identified in the serum of GBS patients. Macrophage-specific chemokine CCL2 has been associated with clinical severity. Monocyte-specific markers CD11b and IL-1RA have been detected in CSF of GBS patients. Biomarker levels are elevated in the early stages of GBS. For sensitivity, the ideal profile includes serum cytokines IL-6, IL-8, and CCL5, with a cutoff of 50 pg/mL for IL-6, 60 pg/mL for IL-8, and 450 pg/mL for CCL5. This profile identifies 91% of GBS patients and predicts the clinical outcome after 2 months with a sensitivity of 87%. For specificity, the most powerful is the CSF-endothelial profile CD11b (detection of human monocytes) combined with IL-1RA (detection of human macrophages), identifying over 93% of GBS patients. Overall, these studies suggest that macrophage biomarkers are useful in the clinical diagnosis of GBS. Macrophages currently serve as a therapeutic target of GBS. Macrophages were found to regulate the inflammatory milieu and fate in demyelinated nerves, obsessed by the infiltration

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of macrophages, through the release of neurotrophic factors (NGF and BDNF) and mediators with neuroprotective properties (IL-10/TGF-β/miR-21). Due to their role in regulating injury-triggered signals, these macrophage phenotypes are referred to as "neuroprotective macrophages." Several studies have attempted to manipulate macrophage phenotypes in experimental models of neuropathy and neuropathic pain, some with promising results and potential therapeutic use in GBS.

Macrophage-Targeted Therapies

Macrophages are critical mediators of peripheral nerve damage in Guillain-Barré syndrome (GBS), and recent research has revealed important macrophage subsets in the nodal and internodal segments of the recovery process. This correlates with functional recovery in model systems of GBS and provides a possible therapeutic target for enhancing Schwann cell repair. Potential therapeutics have been identified and evaluated in model systems, including depleting macrophages to inhibit demyelination, as well as recruitment or local activation of macrophages to promote a recovery response and repair. Small molecule drugs such as simvastatin, laquinimod, and lovastatin target macrophages and reduce pathologic damage from both autoimmune and traumatic nerve injury. In an ongoing clinical study addressing safety and efficacy of simvastatin treatment in GBS patients, the influence of these agents on specific macrophage subsets in peripheral nerve during recovery is evaluated. Modeling the macrophage response in preclinical studies alongside these clinical trials may provide important insight into the therapeutic potential of macrophage-mediated strategies for nervous system injury and disease.

All aspects of the macrophage response to injury are potentially amendable to therapeutic targeting. Macrophage recruitment is mediated by a number of potent chemotactic signals, including the lipoxin A4 family of eicosanoids, ATP, CCL2, and the proandrostenedione-mediated signals. Recruitment signals can be potentiated by blocking macrophage SWAP-70, facilitating the recruitment of additional macrophage subsets. Recruitment and transendothelial migration is impaired under conditions of aberrant substrate-induced mechanosensing/integrin activity. Macrophage-mediated proteolytic and endocytic clearance of myelin debris is dramatically potent, specifically in the absence of upregulation of pro-inflammatory pathways or cytokine production, and this is a macrophage-specific capacity. Macrophage surface TIM-4 and proteinase processing of found factor may provide therapeutic strategies to enhance the clearance function of macrophages in either inflammatory or demyelination-induced injury in peripheral nerve or central nervous system.

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Conclusions

The comprehensive review presented herein highlights the specific contributions of macrophages to the complex and multifaceted outcome of GBS in man, with the emphasis placed on those matters supported by detailed studies in the widely used animal model of the disease, EAN. A thorough review of the literature concerning the origins, localization, and functional roles of macrophages in EAN is made in order to clearly delineate the argument for their specific involvement in determining the clinical phenotype of the disease. Macrophages appear to target and demyelinate specific subtypes of peripheral nervous system sensory and motor axons with particular characteristics. The outcome of this demyelination depends on the specific functional properties of individual macrophage subsets, with some providing protection and being referred to as M2 macrophages, while others contribute to disease progression and are designated M1 macrophages. This conclusion on the diverse outcomes offers an interesting parallel with the well-known dichotomy of the roles assigned to macrophages in brain pathology. Finally, the excellent three- and six-week recovery observed in selected subsets of the original animal GBS model, whilst preserving fully normal nerve roots, suggests that macrophage recruitment and deactivation or repopulation is a crucial step in recovery from pathogenic demyelination. It is expected that this new knowledge of macrophage biology in GBS will provide the basis for the eventual design of targeted therapeutic interventions.

The implications of this knowledge provide many avenues for future studies, particularly further understanding of the specific roles played during the cellular contribution to the clinical outcomes of the EAN model. The extent to which the roles of the different macrophage functions noted here translate to similar actions in human disease would be a very valuable area for future research. Furthermore, would selective therapeutic targeting of the macrophage subtypes noted here provide the basis for ameliorating human disease? This latter question links with the types of studies undertaken in many countries, where banks of human biological samples have either recently been, or are planned to be, established.

The worldwide research on Guillain-Barré syndrome focuses to date on the role of macrophages in experimental models of autoimmune peripheral neuropathy. In this comprehensive review, the contribution of macrophages to the outcome of Guillain-Barré syndrome is summarized from distinct aspects like changes in their number and morphology as well as cytokine and chemokine expression. Macrophages are observed at early time points after Guillain-Barré syndrome induction both in cerebrospinal fluid, blood, and biofluids and in the peripheral nervous system, anterior roots, and ganglia in experimental animal models of autoimmune peripheral neuropathy as well as in biofluids, nerve biopsies, and post-mortem patient tissue in Guillain-Barré syndrome.

The relative number of macrophages is commonly increased at later time points as compared to controls, but changes depend on the individual trial focus and have to be interpreted with care. Activated macrophages are mostly foamy, resorb myelin, and upregulate various

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cytokines and chemokines important for Guillain-Barré syndrome pathophysiology, whereby different experimental autoimmune neuritis models point towards distinct macrophage populations. Macrophages contribute both to myelin/axon recovery and to demyelination processes in Guillain-Barré syndrome. However, attempts to understand the unique role of macrophages in the outcome of Guillain-Barré syndrome underlying their pro-inflammatory role or driving macrophage polarization towards an anti-inflammatory phenotype are lacking. Macrophages provide a disease-specific system of immune cells in the periphery and in the central nervous system that share common properties while displaying a specific cell surface marker profile and contributions to the outcome of distinct diseases. The accumulation of macrophages is studied in various diseases including stroke, multiple sclerosis, Alzheimer's disease, amyotrophic lateral sclerosis, and GBS. Macrophage injection studies in rodent disease models have substantiated their key role in the outcome of these disease processes.

Potential for Macrophage-Based Therapeutic Interventions

The understanding of the immune system's role in diseases has greatly improved recently. Within this progress, macrophages have emerged as a significant player in central nervous system (CNS) diseases, as the proven orchestrators of immune processes. Young, apparently naive macrophages are now recognized as functional cells, constituting the majority of the brain's microglial population. Once believed to become homogeneous under homeostasis, affluent studies unveil their remarkable adaptability when challenged by progressive risks or conditions. In other diseases of the CNS, such as multiple sclerosis (MS) and Alzheimer's disease (AD), a plethora of secreted mediators by microglia/macrophages have been identified, but their contribution to these diseases still remains largely enigmatic.

A sequence of studies has substantiated that macrophages are key players in the development and clinical course of the disease as well as in its long-term outcome. Recently, clinical data on the role of macrophages in GBS is provided, along with experimental data teaching important lessons in the interpretation of mouse models of disease. A more sophisticated understanding of the neuro-immune mechanisms shaping disease severity and long-term outcome will undeniably raise hopes for the development of macrophage-based therapeutic interventions in GBS and other CNS diseases. Macrophages are potent immune suppressors that could be harvested for adoptive transfer, engineered for more specific targeting, or pharmacologically regulated in their activity at the time of onset of disease or after disease occurrence. Rather than universally targeting macrophages' inflammatory actions, a better understanding of macrophage heterogeneity and plasticity may lead to modulation of only specific subsets. Engineering of other immune mechanisms (e.g., regulatory T cells) may work in concert with macrophage approaches.

The outcome of GBS is strikingly heterogeneous: from spontaneous full recovery (75% of cases) to severe disability and even death. Accumulating findings indicate that within further understanding of the mechanisms shaping GBS severity at the individual level, hopes for the development of better prognostic tools arise. Even with encouraging data showing a protective

action of M2 macrophages in animal models, CNS diseases with a macrophage-driven inflammatory component should be approached with caution, antedating potentially devastating outcomes. With the broader understanding of the neuro-immune mechanisms shaping the severity and long-term outcome of GBS, broader hopes for the development of macrophage-based therapeutic interventions in other diseases arise as well. By potentially tuning the neuro-immune interactions in a way that confines the pathogenic actions of immunity, this may open up exciting possibilities for the treatment of a plethora of neuro-immu

Competing interests

The authors declare no conflict of interest.

Ethics Statement

This study has been approved by the Ethical Review Committee of the Chinese Academy of Medical Sciences and Peking Union Medical College. The publication of any potentially identifiable images or data contained in the article requires personal written informed consent. The research team will provide consultations for all subjects and their families to answer any research questions. Before signing the informed consent form, after the patients and their families fully understand the research process, our team members will organize the patients to sign the informed consent form or withdraw from the research. All subjects or their guardians will sign informed consent. Authors tend to submit research results to peer-reviewed journals or academic conferences for publication.

Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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