Molecular Signal Transduction in Immune-Mediated Neuropathy: Therapeutic Relevance of Signaling Pathways in Guillain–Barré Syndrome

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Abstract

Guillain–Barré syndrome (GBS) is an acute immune-mediated peripheral neuropathy characterized by rapidly progressive muscle weakness, sensory disturbances, and autonomic dysfunction. Despite advances in supportive care and immunomodulatory therapies such as intravenous immunoglobulin and plasmapheresis, disease-specific targeted treatments remain limited. Increasing evidence indicates that dysregulated intracellular and intercellular signaling pathways play a central role in GBS pathogenesis by orchestrating immune activation, inflammatory cascades, Schwann cell injury, and axonal degeneration. This review critically examines the major signaling pathways implicated in the development and treatment of Guillain–Barré syndrome, including Toll-like receptor, NF-κB, MAPK, JAK–STAT, PI3K–Akt, complement, and cytokine-mediated pathways. Therapeutic modulation of these pathways offers promising avenues for targeted intervention beyond nonspecific immunosuppression. By integrating molecular immunology, neurobiology, and pharmacological insights, this review highlights signaling-based strategies as a conceptual framework for future GBS therapeutics and precision medicine approaches.

Keywords: Guillain–Barré syndrome; immune signaling pathways; neuroinflammation; peripheral neuropathy; cytokine signaling; targeted therapy

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1. Introduction

Guillain–Barré syndrome (GBS) represents a spectrum of acute immune-mediated neuropathies affecting the peripheral nervous system. It is clinically characterized by ascending muscle weakness, areflexia, sensory abnormalities, and, in severe cases, respiratory failure and autonomic instability. GBS remains the leading cause of acute flaccid paralysis worldwide, with an incidence of approximately 1–2 cases per 100,000 population annually.

Although the clinical presentation of GBS is well recognized, its underlying molecular mechanisms are complex and multifactorial. The disease is often preceded by infectious triggers, most notably Campylobacter jejuni, cytomegalovirus, Epstein–Barr virus, and Zika virus. These infections initiate aberrant immune responses through molecular mimicry, resulting in the generation of autoantibodies and immune cells that target peripheral nerve components.

Current therapeutic strategies—primarily intravenous immunoglobulin (IVIg) and plasma exchange—aim to broadly suppress or remove pathogenic immune factors. While effective in reducing disease severity and duration, these treatments do not specifically target the molecular signaling events driving nerve injury. Moreover, a significant proportion of patients experience incomplete recovery or long-term disability, highlighting the need for more precise therapeutic interventions.

Recent advances in neuroimmunology have revealed that intracellular and intercellular signaling pathways play pivotal roles in immune activation, inflammatory amplification, Schwann cell dysfunction, and axonal degeneration in GBS. Understanding these signaling networks provides critical insights into disease mechanisms and opens avenues for targeted therapeutic modulation. This review systematically examines key signaling pathways implicated in GBS pathogenesis and evaluates their relevance as therapeutic targets.

2. Overview of Guillain–Barré Syndrome Pathophysiology

GBS encompasses several clinical and pathological subtypes, including acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor-sensory axonal neuropathy (AMSAN), and Miller Fisher syndrome. Despite phenotypic heterogeneity, immune-mediated mechanisms underlie all forms.

2.1 Immune Activation and Molecular Mimicry
2.2

The initiating event in GBS is often an aberrant immune response to microbial antigens that share structural similarity with peripheral nerve components. This molecular mimicry leads to the activation of autoreactive T cells and the production of antiganglioside antibodies, which target myelin or axonal membranes.

2.3 Neuroinflammation and Nerve Injury
2.4

Activated immune cells infiltrate peripheral nerves and dorsal root ganglia, releasing cytokines, chemokines, and complement proteins. These mediators disrupt the blood–nerve barrier, damage Schwann cells, and initiate demyelination or axonal degeneration.

At the molecular level, these processes are regulated by tightly interconnected signaling pathways that control immune cell activation, survival, and effector functions.

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3. Toll-Like Receptor Signaling Pathway

Toll-like receptors (TLRs) are pattern recognition receptors that play a crucial role in innate immune activation. In GBS, TLRs serve as the initial sensors of microbial components and endogenous danger signals.

3.1 TLR Activation in GBS
3.2

TLR2 and TLR4 are particularly implicated in GBS, recognizing lipooligosaccharides from Campylobacter jejuni. Activation of TLRs on macrophages, dendritic cells, and Schwann cells initiates downstream inflammatory signaling cascades.

3.3 Therapeutic Implications
3.4

TLR signaling leads to activation of transcription factors such as NF-κB and AP-1, promoting pro-inflammatory cytokine production. Targeting TLR signaling represents an upstream strategy to prevent excessive immune activation in GBS.

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4. Nuclear Factor-κB (NF-κB) Signaling Pathway

NF-κB is a central regulator of immune and inflammatory responses. It integrates signals from TLRs, cytokine receptors, and complement pathways.

4.1 Role in Neuroinflammation
4.2

In GBS, NF-κB activation promotes transcription of inflammatory mediators including TNF-α, IL-1β, IL-6, and chemokines that recruit immune cells to peripheral nerves. Persistent NF-κB activation exacerbates demyelination and axonal injury.

4.3 Therapeutic Targeting
4.4

Pharmacological inhibition of NF-κB signaling has demonstrated neuroprotective effects in experimental autoimmune neuritis, the animal model of GBS. Modulating this pathway may attenuate inflammation while preserving host defense mechanisms.

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5. Mitogen-Activated Protein Kinase (MAPK) Pathways

MAPK signaling pathways—including ERK, JNK, and p38—regulate cell proliferation, differentiation, and stress responses.

5.1 MAPK Activation in Peripheral Nerve Injury
5.2

In GBS, MAPK pathways are activated in immune cells and Schwann cells, contributing to cytokine production, apoptosis, and myelin breakdown. P38 MAPK, in particular, is strongly associated with inflammatory demyelination.

5.3 Therapeutic Potential
5.4

Selective MAPK inhibitors have shown promise in reducing neuroinflammation and improving functional recovery in experimental models, suggesting potential translational relevance.

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6. JAK–STAT Signaling Pathway

The Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway mediates cytokine signaling critical for immune cell differentiation and function.

6.1 Cytokine-Driven Immune Dysregulation

6.2

Pro-inflammatory cytokines such as IFN-γ and IL-6 activate JAK–STAT signaling, promoting Th1 and Th17 immune responses implicated in GBS pathogenesis.

6.3 Therapeutic Relevance

6.4

JAK inhibitors, already approved for autoimmune diseases, represent attractive candidates for targeted immunomodulation in GBS. Their ability to selectively suppress pathogenic cytokine signaling may offer advantages over broad immunosuppression.

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7. PI3K–Akt Signaling Pathway

The PI3K–Akt pathway plays a dual role in immune regulation and neuronal survival.

7.1 Neuroprotective Functions

7.2

Activation of PI3K–Akt signaling promotes Schwann cell survival, axonal regeneration, and remyelination. Dysregulation of this pathway contributes to nerve degeneration in GBS.

7.3 Therapeutic Implications

7.4

Enhancing PI3K–Akt signaling may support nerve repair and functional recovery, complementing immunosuppressive strategies.

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8. Complement Signaling Pathway

Complement activation is a hallmark of antibody-mediated nerve injury in GBS, particularly in axonal variants.

8.1 Mechanisms of Complement-Mediated Damage
8.2

Antiganglioside antibodies activate the complement cascade, leading to membrane attack complex formation and axonal degeneration.

8.3 Targeted Complement Inhibition
8.4

Therapeutic inhibition of complement components, such as C5 inhibitors, has emerged as a promising strategy to prevent antibody-mediated nerve injury.

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9. Cytokine and Chemokine Signaling Networks

Cytokines and chemokines orchestrate immune cell recruitment, activation, and persistence in peripheral nerves.

9.1 Pro-Inflammatory Cytokines
9.2

Elevated levels of TNF-α, IL-1β, and IL-6 correlate with disease severity in GBS. These cytokines amplify inflammatory signaling through NF-κB and JAK–STAT pathways.

9.3 Anti-Inflammatory Signaling
9.4

Regulatory cytokines such as IL-10 play protective roles by limiting immune-mediated damage. Enhancing anti-inflammatory signaling may promote resolution of inflammation.

10. Integration of Signaling Pathways in GBS Pathogenesis

GBS pathophysiology results from the convergence of multiple signaling pathways rather than isolated molecular events. Crosstalk among TLR, NF-κB, MAPK, and cytokine pathways creates a self-amplifying inflammatory network that drives nerve injury.

Understanding this signaling integration is essential for designing combination therapies that target multiple nodes within the inflammatory cascade.

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11. Therapeutic Implications and Future Directions

Targeting signaling pathways offers a paradigm shift from nonspecific immunotherapy to precision medicine in GBS. Future therapeutic strategies may include:

Pathway-specific inhibitors

Combination therapies integrating immune suppression and neuroprotection

Biomarker-guided patient stratification

Timing-based interventions targeting early signaling events

Advances in molecular profiling and systems biology will be instrumental in translating signaling pathway insights into clinical practice.

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12. Conclusion

Signaling pathways play a central role in the initiation, amplification, and resolution of immune-mediated nerve injury in Guillain–Barré syndrome. Therapeutic modulation of these pathways represents a promising frontier for improving disease outcomes beyond current immunomodulatory approaches. By integrating molecular immunology with clinical neurology, signaling-based therapies hold the potential to redefine the treatment landscape of Guillain–Barré syndrome and advance precision neuroimmunology.

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