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Strategies to Prevent Graft Rejection of iPSC-derived Inhibitory Interneurons in Drug-resistant Epilepsy

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Introduction

Epilepsy, a chronic neurological disorder characterized by recurrent seizures, affects millions of individuals globally, with a significant subset approximately 30% developing resistance to conventional Antiepileptic Drugs (AEDs). This Drug-Resistant Epilepsy (DRE) poses a considerable therapeutic challenge, leading to diminished quality of life, cognitive impairment, and elevated morbidity. Among the most promising experimental therapies for DRE is the transplantation of inhibitory interneurons derived from Induced Pluripotent Stem Cells (iPSCs). These interneurons have the potential to restore the excitatory-inhibitory balance disrupted in epileptic brains by enhancing GABAergic inhibition. iPSC-derived neural transplants offer a patient-specific, renewable, and ethically viable source of cells for therapy. However, despite the remarkable potential of this approach, one of the greatest obstacles remains the host immune response and subsequent graft rejection, which can compromise therapeutic efficacy [1].

Description

The transplantation of iPSC-derived inhibitory interneurons into epileptic brain regions holds significant therapeutic promise, particularly due to the ability of these cells to integrate into existing neural circuits and suppress hyperexcitable activity. However, the immune response remains a key barrier to long-term graft survival and function. Unlike in traditional solid organ transplantation, immune rejection in neural grafts is influenced by both systemic immune cells and the local CNS immune environment, including resident microglia and astrocytes. Strategies to mitigate graft rejection can be broadly categorized into three domains: immune suppression, cell engineering, and immune-evasive scaffold development. Traditional immunosuppressive drugs, such as cyclosporine A and tacrolimus, have been used to prevent T-cell mediated rejection, but chronic administration carries significant systemic risks, including infection and organ toxicity, especially concerning in pediatric or vulnerable populations. As a result, research has turned to more refined approaches, such as transient immunosuppression during the critical engraftment window or the use of biologics [2].

These "universal donor" cells have shown reduced immune activation in preclinical models without compromising differentiation or functionality. Unlike autologous transplants, allogeneic or gene-edited iPSC-derived cells may still trigger immune activation due to minor antigenic mismatches, epigenetic differences, or even unintended mutations during reprogramming and differentiation. The complexity of immune recognition in the central nervous system once thought to be immunoprivileged has become increasingly evident, particularly in the context of transplantation, where microglial activation, MHC expression, and local cytokine signaling can influence graft survival. This paper aims to explore the emerging strategies aimed at overcoming graft rejection in iPSC-derived inhibitory interneuron transplantation for DRE, including immune modulation, cell engineering, and advances in immunosuppressive protocols, offering a comprehensive review of the multidisciplinary efforts required to bring cell-based therapies into clinical practice [3].

Another emerging strategy is the co-transplantation of regulatory T cells (Tregs) or mesenchymal stem cells, which can create a locally immunosuppressive microenvironment, reducing the likelihood of rejection without systemic immunosuppression. Additionally, encapsulation of transplanted neurons in biocompatible hydrogels or polymeric matrices has been explored to provide physical immune shielding while permitting nutrient and neurotransmitter exchange. Beyond biological strategies, optimizing the site and timing of transplantation is crucial; transplantation into regions with naturally lower immune activity or post-status epilepticus recovery phases may improve integration and reduce immune activation. Importantly, the source of iPSCs whether autologous, allogeneic, or from universal donor lines also influences immunogenicity. Autologous iPSCs, while theoretically ideal, are time-intensive and costly, and their immunogenicity is not negligible due to reprogramming-associated mutations or epigenetic memory.. Collectively, these multifaceted strategies represent a synergistic approach to overcoming the immunological barriers that currently limit the success of iPSC-derived neural therapies for drug-resistant epilepsy [4].

The success of these strategies could extend well beyond epilepsy, setting the stage for a new era of neurological treatment where customized cellular therapies address diseases at their root cause rather than merely suppressing symptoms. As research progresses from preclinical studies to human trials, interdisciplinary collaboration between neuroscientists, immunologists, and bioengineers will be essential to translating these innovations into durable, safe, and effective treatments. Ultimately, by addressing the challenge of graft rejection with scientific precision and innovation, we bring the field one step closer to a future where intractable neurological disorders like DRE can be managed through biologically intelligent, restorative solutions. like monoclonal antibodies that target specific immune pathways (e.g., CTLA-4, PD-1). Meanwhile, advances in genetic engineering have enabled the creation of hypoimmunogenic iPSCs via targeted deletion of MHC class I and II molecules and insertion of immunomodulatory genes, making grafts less visible to host immune surveillance [5].

Conclusion

The integration of iPSC-derived inhibitory interneurons into the clinical management of drug-resistant epilepsy represents a revolutionary step forward in personalized neuromodulator and regenerative medicine. However, graft rejection remains a formidable barrier, threatening to undermine the potential of this otherwise promising therapy. As our understanding of neuroimmunology deepens, it becomes increasingly clear that overcoming immune rejection requires a nuanced, multi-pronged strategy balancing immune suppression with safety, enhancing cellular invisibility without compromising function, and fostering tolerance without systemic compromise. Advances in immunogenetic engineering, selective immunomodulation, and immune-privileged biomaterials offer new avenues for enhancing graft survival.

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Conflict of Interest

There are no conflicts of interest by author.

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