Cellular Immunotherapy: Up & Coming Applications to Major Neurodegenerative Diseases

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Introduction

Inflammation is often a sign of a healthy immune system— contrary to the unregulated propagation and damage caused by irregular, chronic inflammation present in neurodegenerative diseases. Regular inflammation is a means by which the body creates an environment inhospitable by microbes, such as bacteria or viral particles. The most apparent physical representation of inflammation in the body is a fever— the body's method of increasing the blood pressure to allow the delivery of immune cells to the site of infection more rapidly and efficiently.

A fever, however, is a response that is largely the first resort, meaning that it is a natural defense considered to be part of the innate immune system's response to foreign invaders/bodies. The entire immune system is split into two divisions: the innate and the adaptive. These two divisions are still largely intertwined, and immunologists today still don't have a complete explanation for all the ways that the two parts of the immune system work together. Fever is only one example of inflammation that occurs in the body, but it is inflammatory responses related to fever that— when not properly regulated by the body's homeostatic mechanisms—can lead to neurodegenerative diseases, such as Parkinson's disease (PD) or Alzheimer's disease (AD).

Immunotherapy is a fairly new field of science and is rapidly taking over the field of alternative medicine in areas of research such as cancer and allergies. This poster focuses on the recent applications of immunotherapy to prevalent neurodegenerative diseases such as PD and AD. Other neurodegenerative diseases that are not discussed in this poster but are notable include Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's disease), Motor Neuron disease (MND), and Huntington's disease (HD).

Current Research

The most common immunotherapeutic approaches to neurodegenerative diseases involve the use of antibodies (most commonly, the IgG antibody subtype) in both passive (antibodies made prior to injection) and active (immune system given the parameters/antigens to make own antibodies) immunization of the patient. Both of these methods utilize the innate and adaptive branches of the immune system to achieve a reduced propagation of symptoms associated with neurodegenerative diseases, such as plaque aggresomes or oxidative stress.

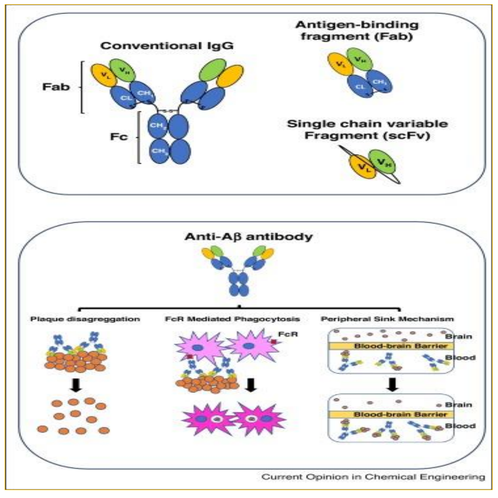

Figure #1: Routes of Passive Immunization in Neurodegenerative Disease Models (Anti-amyloid beta). *Plaque disaggregation, FcR mediated phagocytosis, and the Peripheral Sink Mechanism are all methods that involve the injection of antibodies to the protein amyloid-beta (anti-Aβ IgGs). Plaque disaggregation involves Fab-fragment binding of Anti-Aβ to Aβ protein and subsequent proteasomal degradation of these marked antigens. FcR Mediated Phagocytosis involves the recruitment of microglial cells to Aβ aggresomes plaques and degradation via activation of the FcR microglia receptor sites by IgGs. Peripheral sink mechanism involves flushing/off-loading of CSF (cerebral spinal fluid) Aβ populations through the blood-brain barrier, where antibodies on the other side can mark the proteins for immune response.* ***Image Source***: Montoliu-Gaya, L., & Villegas, S. (2018). Immunotherapy for neurodegenerative diseases: The Alzheimers disease paradigm. *Current Opinion in Chemical Engineering,19*, 59-67.

Other methods include using molecules of a plant-based derivative as a treatment to reduce the chronic inflammation that the overabundance of cytokines such as the interleukins (IL-6 or IL-8), interferon-γ (IFN-γ), and tumor necrosis factor-β (TNF-β) cause due to microglial overactivation.

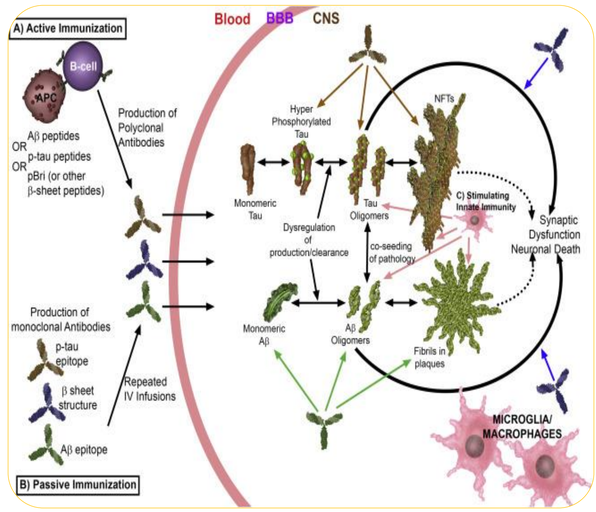

Figure #2: Passive vs. Active Immunization in an AD Model

Image Source: Wisniewski, T., & Goñi, F. (2015). Immunotherapeutic Approaches for Alzheimer's Disease. *Neuron,85*(6), 1162-1176.

Research done with *immunomodulation,* or the modification of the immune response (in this case, through the use of plant-based derivatives that alter cytokine production) is largely cellular-based currently and usually involves cocultures of immortalized mouse microglial cells (such as BV-2 or IMG) and mouse hippocampal neuronal cell lines (such as HT22); using human monocytes with this research model is on the rise.

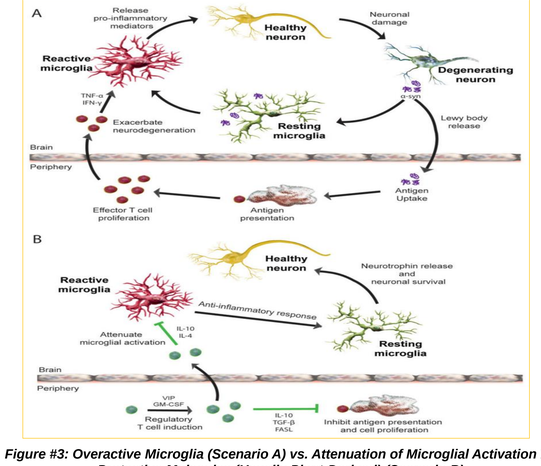

Figure #3: Overactive Microglia (Scenario A) vs. Attenuation of Microglial Activation by Protective Molecules (Usually Plant-Derived) (Scenario B)

Image Source: Olson, K. E., & Gendelman, H. E. (2016). Immunomodulation as a neuroprotective and therapeutic strategy for Parkinsons disease. *Current Opinion in Pharmacology,26*, 87-95.

Conclusions

Immunotherapy targets– whether indirectly or directly– the internal environmental of the CSF. Microglial cells are macrophage derivatives and act as the 'clean-up crew' for the brain, sweeping debris from the surrounding area after a successful defense. Plaque formation triggers microglial activation, which triggers the release of inflammatory cytokines such as IL-6, TNF-β, etc. In normal amounts, these cytokines simply act as ways of communication between neuronal cells. However, when the microglial population surrounding an area is consistently activated due to the accumulation of aggresomes, the cytokines can cause chronic inflammation of the surrounding area, inflaming neural bodies and causing physical damage to both neuroglia and neuron cells alike. It is this mechanism that often causes or helps worsen many neurodegenerative diseases such as AD or PD. It is also this area that is of intense focus in the field of immunotherapy when researching the many factors causing neurodegenerative diseases.

Immunotherapy is currently on the rise because research in this field is not only applicable to neurodegenerative diseases but also cancer, allergies, organ transfers (through antibody treatment and MHCI/MHCII) and so on.

Acknowledgements

1. Burrows, M., Assundani, D., Celis, E., Tufaro, F., Tanaka, A., & Bradley, W. G. (2009). Oral administration of PPC enhances antigen-specific CD8 T cell responses while reducing IgE levels in sensitized mice. *BMC Complementary and Alternative Medicine,9*(1).
2. Gelinas, D., DaSilva, K., Fenili, D., St. George-Hyslop, P., & McLaurin, J. (2004). Immunotherapy for Alzheimer's Disease. Proceedings of the National Academy of Sciences of the United States of America, 101, 14657-14662.
3. Johnston, J., Ward, C., & Kopito, R. (1998). Aggresomes: A Cellular Response to Misfolded Proteins. The Journal of Cell Biology, 143(7), 1883-1898.
4. Panza, F., Solfrizzi, V., Imbimbo, B. P., Tortelli, R., Santamato, A., & Logroscino, G. (2014). Amyloid-based immunotherapy for alzheimer's disease in the time of prevention trials: The way forward. Expert Review of Clinical Immunology, 10(3), 405-19.
5. Schilling, S., Rahfeld, J.-U., Lues, I., & Lemere, C. (2018). Passive Aβ Immunotherapy: Current Achievements and Future Perspectives. Molecules, 23(5), 1068.