DDN

TRAVELING TO NEW

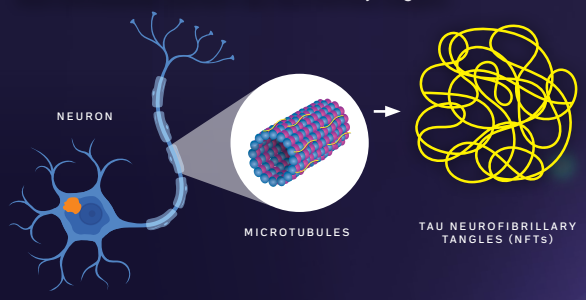
FRONTIERS

ANTIBODY THERAPY FOR NEURODEGENERATIVE DISEASE

Scientists once believed that the central nervous system and brain were inaccessible to antibody therapeutics. The blood-brain barrier, a highly selective border that guards entry into the brain, seemed impenetrable. Now, scientists are developing innovative blood-brain-barrier crossing antibodies to treat neurological diseases, such as Alzheimer's disease.

PROBLEMATIC PROTEINS

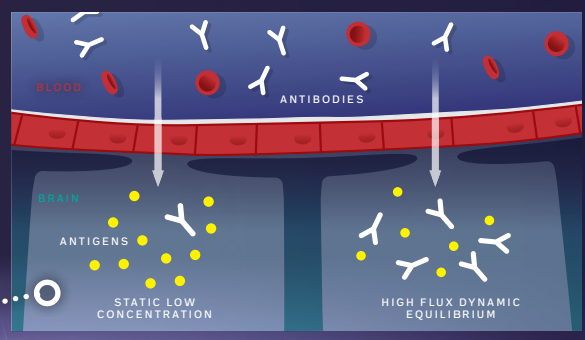
Aggregated assemblies of abnormal proteins in the brain lead to neurodegeneration. Tau proteins stabilize neuronal microtubules in healthy neurons. In Alzheimer's disease (AD), tau proteins dissociate from microtubules and form tau neurofibrillary tangles.[1]



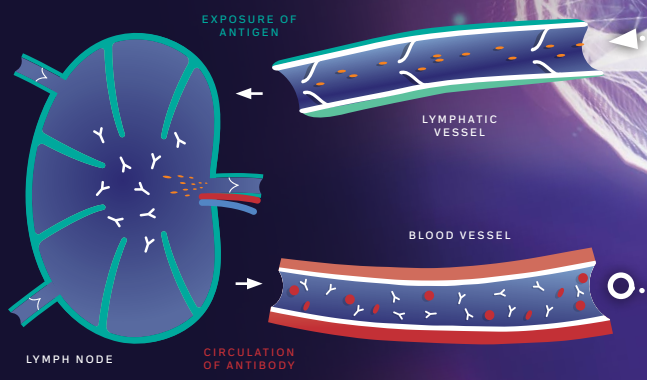
Alpha-synuclein (αS) regulates synaptic vesicle trafficking and neurotransmitter release in healthy neurons, but abnormal αS protein aggregates contribute to the formation of Lewy bodies and Parkinson's Disease (PD).[1]

CROSSING THE BARRIER

Blood vessels in the brain are comprised of endothelial cells with tight junctions that limit the movement of solutes into the central nervous system. Antibody cycling at low concentrations into the brain results in low antigen binding. Scientists believe that rapid cycling of antibodies in and out of the brain allows for the increased antibody binding needed to produce a beneficial effect.[1]



AUTO-ANTIBODIES



Brain conditions during AD or PD development result in the outflow of neo-antigens through lymphatic vessels to lymph nodes. This causes the body to generate auto-antibodies that selectively target AD or PD-associated proteins. These antibodies penetrate the blood-brain barrier.[1,2] Individuals in their 70s and 80s with the mental and physical capacity of decades younger individuals have higher levels of naturally occurring auto-antibodies.[3]

ANTIBODY THERAPEUTICS

Most antibody therapies in clinical trial for neurodegeneration target Aβ aggregates, a peptide implicated in familial AD. These therapies fall into two categories: therapies that induce protective immunity through active vaccination and therapies that induce passive immunotherapy through monoclonal antibody infusion.

ACTIVE ANTIBODIES

AN1792 is an active antibody vaccine that targets full-length Aβ. Clinical trials on AN1792 halted when 6% of patients developed meningoencephalitis, likely due to a T cell-mediated response. Scientists are developing second-generation active vaccines that target just the N terminus of the Aβ peptide. This avoids activation of a T cell epitope on the full-length protein.[1]

PASSIVE ANTIBODIES

Passive antibody therapies have seen more success against Aβ than active vaccines. Gantenerumab, aducanumab, and bapineuzumab each stimulate reductions in Aβ biomarkers. Passive immunotherapies induce more amyloid-related imaging abnormalities, especially in patients that carry the APOE4 allele. Scientists suspect that this is due to excess antibody binding to Aβ plaques and monomers instead of fibrils.[1]

LOOKING FORWARD

Variable or incomplete protection and long-term side effects are possible with active vaccination. Passive immunotherapy avoids long-term damage to T cell responses and allows scientists to precisely control dosing and epitope targeting. Thus far, there has been no clinical benefit from antibody therapies in Phase III clinical trials for patients with advanced AD. Earlier interventions with antibody therapies may be more beneficial for mitigating neurodegeneration.[1]

Reference

1. Katsinelos, T. *et al*. The role of antibodies and their receptors in protection against ordered protein assembly in neurodegeneration. *Frontiers in Immunology* (2019).
2. Sim, K-Y. *et al*. The functional roles and applications of immunoglobulins in neurodegenerative disease. *International Journal of Molecular Sciences* 21(5295), (2020).
3. Moir, R.D. *et al*. Autoantibodies to redox-modified oligomeric Abeta are attenuated in the plasma of Alzheimer's disease patients. *Journal of Biological Chemistry* 280(17), P17458-17463 (2005).

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