A Tale of Tangles We Weave, Chapter 2

What's Behind Alzheimer's Disease?

In Chapter 1 in our Tale of Tangles, theories about the underlying dysfunction of Alzheimer's disease (AD), such as the cholinergic hypothesis, guided development of the first successful medicines that addressed symptoms. Science has expanded our comprehension of the brain and continued to refine our understanding of how the disease drives the degenerative process, yielding further hypotheses in an attempt to understand AD pathology. While there are many proposed causes for AD, three stand out as being most important to finding a cure: amyloid-β, tau and inflammation. We'll provide a run-down of the perspectives guiding the most promising work being done in AD and share some of the companies leading the narrative.

The Amyloid Hypothesis

The amyloid-β peptide was discovered by George Glenner and Caine Wong at the University of California San Diego in 1984.[1] In the years following this discovery, the amyloid hypothesis was proposed which attributes the accumulation of amyloid-β protein as the cause of AD resulting in plaque formation, cell loss, vascular damage and dementia. The amyloid-β hypothesis has substantial support in the laboratory; however, many amyloid-β targeting antibodies have failed to generate an improvement in AD patients. Most of the programs in development have relied on the amyloid hypothesis and it was the underpinning of Aduhelm, the only approved therapy with disease-modifying potential.

The Tau Hypothesis

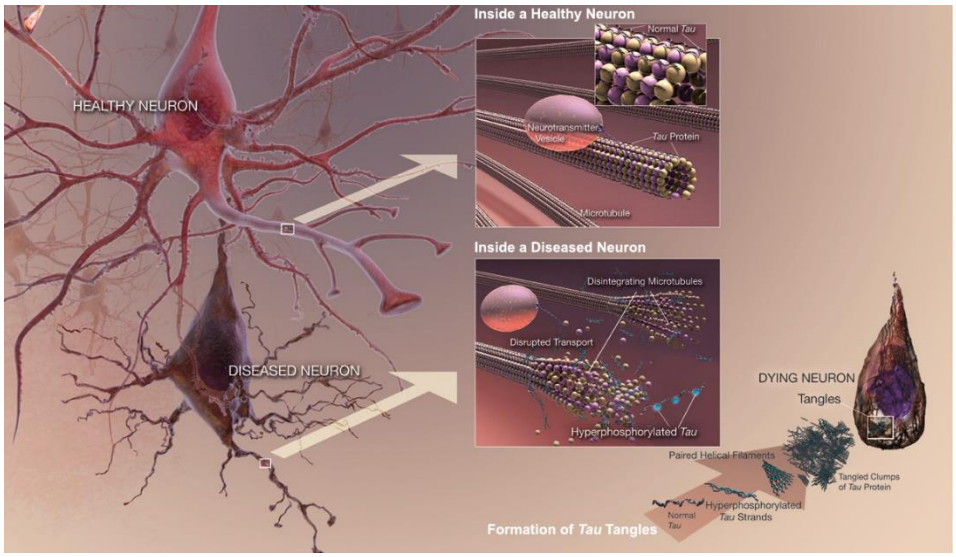
In the mid-1980s, several laboratories discovered that the main protein composing neurofibrillary tangles was tau. Tau is a microtubule-associated protein that regulates the stability of tubulin assemblies inside neurons. The tau hypothesis arose decades after these discoveries and attributes the primary cause of AD to excessive or abnormal phosphorylation and aggregation of tau. When the tau becomes hyperphosphorylated,[2] it dissociates from the microtubules and aggregates to create neurofibrillary tangles. The neurofibrillary tangles are a strong predictor of AD and other tauopathies. While the tau hypothesis has support in its high degree of correlation with neurodegenerative disease, none of the candidates targeting the protein have yet demonstrated material efficacy.

Tau Tangles[3]

[1] Glenner, G.; Wong, C. Alzheimer's Disease: Initial Report on the Purification and Characterization of a Novel Cerebrovascular Amyloid Protein. Biochemical and Biophysical Research Communications, Vol. 120, No.3 1984.

[2] Hyperphosphorylation occurs when a biochemical with multiple phosphorylation sites is fully saturated. Abnormal hyperphosphorylation of tau in the brain plays a vital role in the molecular pathogenesis of AD and in neurodegeneration.

[3] Source: Tau Tangle Formation, National Institute on Aging.



Inflammation

After the scientific community's embrace of the Amyloid and Tau Hypotheses, inflammation emerged as another characteristic hallmark of AD. Studies have demonstrated a direct link between brain inflammation and neuronal death in animal models. As the disease manifests and the brain's immune system mounts a response to clear unwanted proteins, the brain suffers a prolonged state of inflammation. Microglia, which respond to the presence of amyloid-β aggregates by triggering an inflammatory immune response, have many interactions with amyloid-β and are implicated in the early stages of AD. Inflammation is a defense against infection, toxins and injury; however, when it persists, pro-inflammatory and toxic products such as reactive oxygen species, nitric oxide and cytokines are released. Brain inflammation is thought to initially occur as a protective response against dementia. However, over the long term, sufferers show a steep rate of cognitive decline.[4] Many interrelated mechanisms conspire to instigate AD as amyloid buildup creates an environment of chronic inflammation which can induce tau hyperphosphorylation leading to the separation of tau from microtubules and formation of neurofibrillary tangles.

Who is Doing the Work?

Researchers from Eli Lilly (LLY), Acumen Pharmaceuticals (ABOS) and ProMIS Neurosciences (PMN.TO) have embraced the amyloid hypothesis and are working on products that bind and clear harmful amyloid-β from the brain. These products recognize the evolved version of the amyloid hypothesis that identifies toxic oligomers of amyloid-β as the source of neurodegeneration in AD.

In tau, AC Immune (ACIU) and Genentech, a subsidiary of Roche (RHHBY), are developing semorinemab, an anti-tau antibody that recently provided topline data for its Lauriet Phase II trial. Semorinemab achieved its cognition endpoint but missed its activities of daily living target. An open label extension of the study is ongoing. One of the leading candidates addressing inflammation is NE3107, an anti-inflammatory insulin-sensitizing therapy being advanced by BioVie (BIVI). The Phase 3 trial enrolled its first patient last August and is expected to be complete by the end of 2022.

[4] Walker, K. *et al.* Understanding the Role of Systemic Inflammation in Alzheimer's Disease. ACS Chem. Neurosci. 2019, 10, 8, 3340–3342

Stay tuned for the next chapter of our series where we review the decades long dry spell between the last drug approved for treating symptoms and the first approved as a disease modifying therapy and how it sets the foundation for the next generation of AD therapies.

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