Neurofibrillary tangle

A neurofibrillary tangle is a pathological hallmark commonly associated with Alzheimer's disease and other neurodegenerative disorders. These tangles represent abnormal aggregations of proteins within nerve cells (neurons) in the brain. The primary protein component of neurofibrillary tangles is a protein called tau.

Here are some key points about neurofibrillary tangles:

Tau Protein: Tau is a microtubule-associated protein that plays a crucial role in stabilizing microtubules, which are structures important for maintaining the structure and function of nerve cells. In neurofibrillary tangles, tau proteins become abnormally modified, causing them to form twisted filamentous structures within neurons.

Aggregation: In healthy neurons, tau proteins bind to and stabilize microtubules, helping them maintain their shape and function. However, in neurofibrillary tangles, tau proteins accumulate in an abnormal, hyperphosphorylated state. This causes them to detach from microtubules and aggregate into paired helical filaments and other abnormal structures within the neuron.

Cellular Disruption: The accumulation of tau in neurofibrillary tangles disrupts the normal functioning of neurons. It can interfere with intracellular transport processes, impair synaptic function, and ultimately lead to cell death.

Association with Alzheimer's Disease: Neurofibrillary tangles, along with another hallmark pathology called amyloid plaques (composed of beta-amyloid protein), are key features of Alzheimer's disease. The presence of these tangles in the brain is associated with cognitive decline and the progressive loss of memory and cognitive abilities.

Spread in the Brain: Neurofibrillary tangles typically start in specific regions of the brain, such as the entorhinal cortex and hippocampus, and then spread to other regions as the disease progresses. This spatial spread corresponds to the progression of cognitive decline in Alzheimer's disease.

Diagnosis: The presence of neurofibrillary tangles is often confirmed through post-mortem examination of brain tissue, typically in individuals who have had Alzheimer's disease or other tau-related neurodegenerative disorders.

It's important to note that while neurofibrillary tangles are strongly associated with Alzheimer's disease, other neurodegenerative disorders, such as frontotemporal dementia and some forms of Parkinson's disease, can also involve abnormal tau protein aggregation and the formation of similar tangles, though the specific characteristics and distribution of these tangles may vary among different diseases. Researchers are actively studying the mechanisms behind tau-related pathologies and their potential as therapeutic targets in neurodegenerative diseases.

Control of breast-to-brain metastases remains an urgent unmet clinical need. While chemotherapy is essential in reducing systemic tumor burden, they have been shown to promote non-brain metastatic invasiveness and drug-driven neurocognitive deficits through the formation of neurofibrillary tangles (NFT), independently.

Saatian et al. investigated the effect of chemotherapy on brain metastatic progression and promoting

tumor-mediated NFT. Results show chemotherapies increase brain-barrier permeability and facilitate enhanced tumor infiltration, particularly through the blood-cerebrospinal fluid barrier (BCSFB). This is attributed to increased expression of matrix metalloproteinase 9 (MMP9) which, in turn, mediates loss of Claudin-6 within the choroid plexus cells of the BCSFB. Importantly, increased MMP9 activity in the choroid epithelium following chemotherapy results in cleavage and release of Tau from breast cancer cells. This cleaved Tau forms tumor-derived NFT that further destabilize the BCSFB. The results underline for the first time the importance of the BCSFB as a vulnerable point of entry for brain-seeking tumor cells post-chemotherapy and indicate that tumor cells themselves contribute to Alzheimer's-like tauopathy [1].

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Saatian B, Deshpande K, Herrera R, Sedighi S, Eisenbarth R, Iyer M, Das D, Julian A, Martirosian V, Lowman A, LaViolette P, Remsik J, Boire A, Sankey E, Fecci PE, Shiroishi MS, Chow F, Hurth K, Neman J. Breast-to-brain metastasis is exacerbated with chemotherapy through blood-cerebrospinal fluid barrier and induces Alzheimer's-like pathology. J Neurosci Res. 2023 Oct 3. doi: 10.1002/jnr.25249. Epub ahead of print. PMID: 37787045.