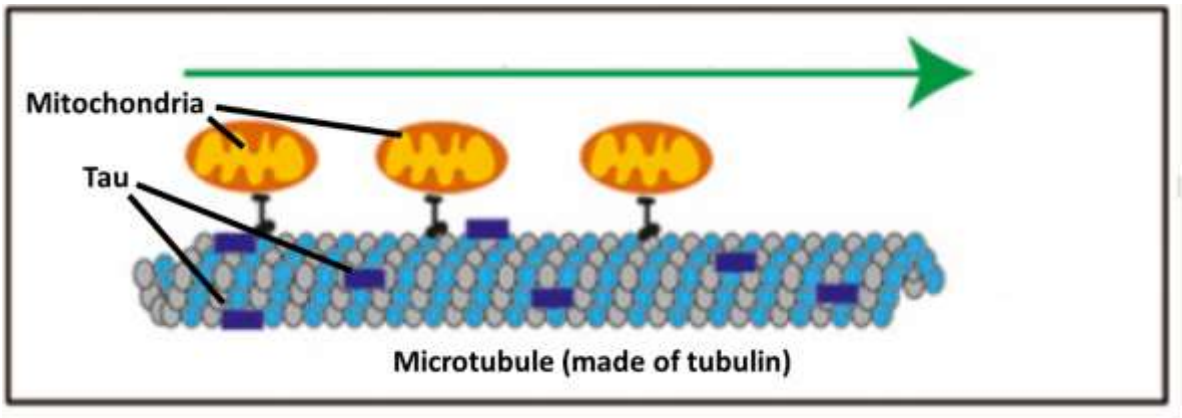
Adjourning Alzheimer's

Microtubule Disassembly (Day 22)

We have now discussed several pathological events that occur in Alzheimer's. The facts suggest that both tau accumulation and mitochondria dysfunction are both more tightly linked to the Alzheimer's pathological process than amyloid beta (Aβ) plaques. Thus, to discover the origins of Alzheimer's, we will focus on linking **tau accumulation** with **mitochondria dysfunction**. There must be something that links them, and indeed there is - microtubules.

Microtubules are hollow tubes made of a protein called **tubulin** that provide shape and structure for all cells, most especially neurons; the brain contains the highest concentrations of microtubules in the body. Essentially, microtubules form the "skeleton" of neurons. Tau **binds** the microtubules, whereas mitochondria **utilize** the microtubules to transport themselves within the neuron. In Alzheimer's, microtubules are the missing link that connects tau with mitochondria.

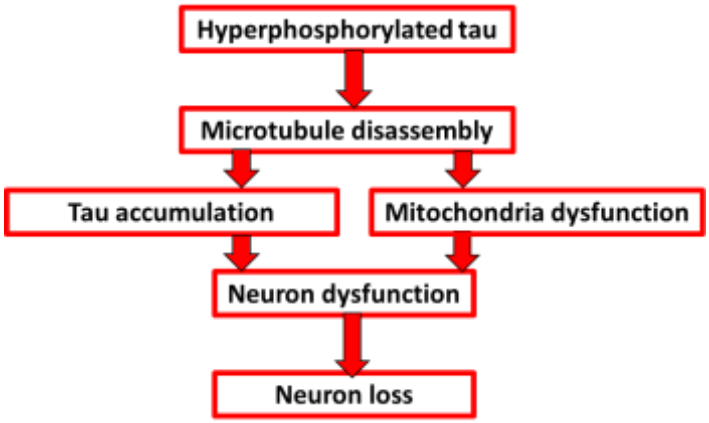


Microtubules - bound and stabilized by tau, utilized by mitochondria.

Tau binds microtubules and regulates their **assembly and disassembly** in the neuron axons. Tau does this by flipping between two states - **dephosphorylated tau** (removal of a phosphate group) promotes assembly, whereas **phosphorylated tau** (addition of a phosphate group) promotes disassembly. If the balance of dephosphorylated to phosphorylated tau is compromised, microtubule structural integrity is compromised.

While tau regulates microtubule structure, microtubules are utilized by mitochondria as a **means of transport** within the neuron. The mitochondria run along the microtubules, using them as "tracks" to get their energy to where it is needed. Intact microtubules are imperative for mitochondrial transport; if the microtubules are compromised, mitochondrial population dynamics, structure, and function are all compromised.

Due to the intimate relationship between microtubules, tau, and mitochondria, some researchers have proposed the **microtubule hypothesis**, postulating that an initial build-up of abnormal, "hyperphosphorylated" tau leads to excessive microtubule disassembly within the neuron. This breakdown in microtubule structure releases large amounts of tau from the microtubules themselves, leading to early tau accumulation. Their tracks destroyed, the mitochondria cannot undergo proper fusion and fission, so any damaged mitochondria cannot be repaired or removed; mitochondria dysfunction ensues.



The microtubule hypothesis posits that hyperphosphorylated tau triggers excessive microtubule disassembly, leading to tau accumulation, mitochondria dysfunction, and neuron loss.

The concept of **microtubule disassembly** is appealing, for it links tau accumulation with mitochondria dysfunction, both of which are strongly linked with Alzheimer's. Yet is it supported by the facts?

(1) If hyperphosphorylated tau is a key event in microtubule disassembly, **hyperphosphorylated tau ought to be highly concentrated in the Alzheimer's brain** - Indeed, hyperphosphorylated tau is 3-4 times as concentrated in Alzheimer's compared to cognitively normal elderly brains.

(2) If microtubule disassembly drives Alzheimer's, **evidence of disassembly ought to begin in the region of the neuron with the most mitochondrial traffic, the axon** - Indeed, Heiko Braak noted that pretangles first appear in the proximal axon. Moreover, mitochondria in early Alzheimer's move abnormally slowly within the axon well before the other hallmarks of Alzheimer's appear.

(3) If microtubule disassembly drives Alzheimer's, **neurons in Alzheimer's ought to show evidence of severe microtubule disassembly** - This does appear to be the case; in fact, microtubule assembly appears to be inhibited so much in Alzheimer's that microtubules do not assemble at all. Interestingly, the neurons with the most extensive tau accumulation - neurofibrillary tangles - lack any microtubules whatsoever.

Thus, reasonable evidence supports the microtubule hypothesis; however, **some questions** are raised:

(1) If hyperphosphorylated tau ultimately triggers microtubule disassembly, **what process produces hyperphosphorylated tau** in the first place?

(2) Microtubules are highly concentrated throughout all brain structures, so **why does neuron loss selectively afflict the hippocampus and cerebral cortex**, sparing many other brain structures (such as the basal nuclei and cerebellum)?

These are **good questions**, and they certainly warrant an explanation. We will return to them soon!

To sum up, several facts support the idea that **an initial build-up of abnormal, hyperphosphorylated tau promotes microtubule disassembly, resulting in further tau accumulation as well as contributing to mitochondria dysfunction**. Importantly, the microtubule hypothesis links tau accumulation with mitochondria dysfunction. However, we still have not explained where the initial build-up of hyperphosphorylated tau comes from, or why the hippocampus and cerebral cortex are selectively targeted in Alzheimer's. We are close to the origin now.

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References

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