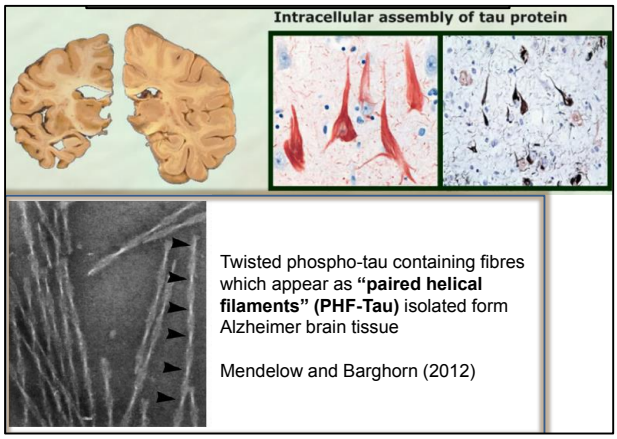
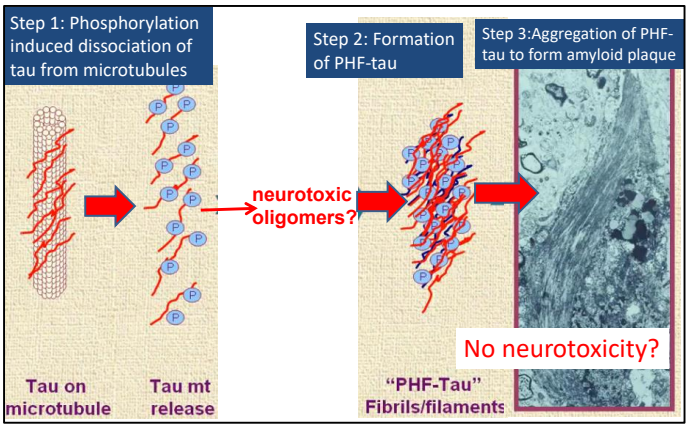
Phospho-Tau forms paired helical filament in AD brain



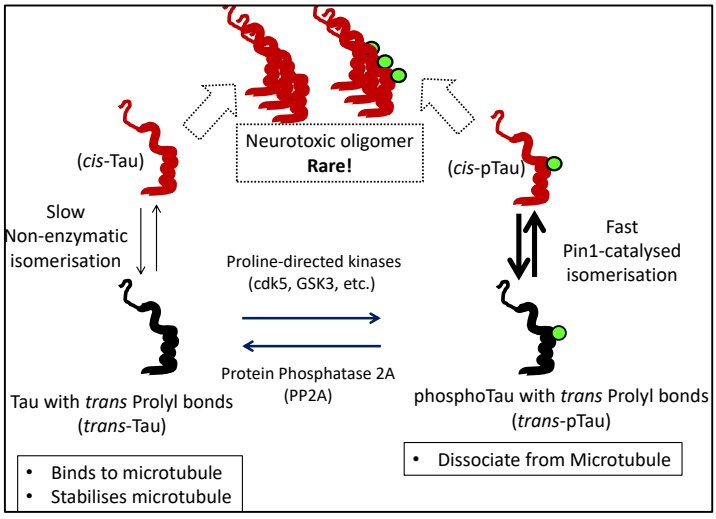
- The diagram shows the structure of an Alzheimer's brain
- The amyloid plaques have a lot of intracellular assemblies of tau proteins (these assemblies are inclusion bodies)
- There are twisted phosphorylated tau as seen in the electron-micrograph. These twisted phosphorylated tau forms fibre like structures called paired helical filaments (PHF-Tau).
- They are misfolded but are arranged in beta sheet structures and they are very resistant to proteolysis.
- PHF-Tau are mainly made of Tau oligomers and most of the tau protein here are hyperphosphorylated and the enzymes mainly responsible for this phosphorylation are cdk5 and GSK3

Steps in formation of amyloid plaques (this is a prediction)



- In the unphopshorylated state, tau binds to microtubules
- But when tau is phosphorylated, it dissociates from the microtubules and forms monomeric tau. These then move around freely as monomers.
- However, we know that phosphorylated tau can go through prolyl cis/trans isomerisation (in the absence of PIN1 this process is slow)
- This causes the formation of PHF-tau fibrils/filaments
- The PHF-tau structures will then bundle together and form aggregates to form amyloid plaques.
- But what is the step between the formation of the monomeric phosphorylated tau to the formation of PHF-tau. In this case, in this step they form a neurotoxic oligomer first which will in turn form the PHF leading to the formation of the amyloid plaque.
- The idea is that the formation of the amyloid plaques is actually a neuroprotective mechanism. That is that this is a way that the cell is trying to collect all these 'rubbish' which are the phosphorylated tau and contain them into a well contained environment so that the cells can gradually eliminate the neurotoxic oligomers.
    - So the amyloid plaques actually have no neurotoxicity which is why we think this is a neuroprotective mechanism
    - Note: we don't know the exact structure of these neurotoxic oligomers
- When we get more and more of the neurotoxic oligomers, then it comes to a point of no return which causes cell death.
- **Formation of amyloid plaques as a mechanism to remove hyper-phospho-tau, which are the precursors of neurotoxic oligomers**

Structural features of these neurotoxic tau oligomers?

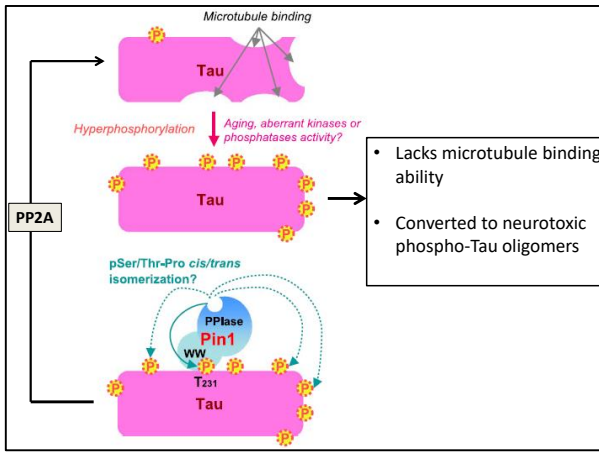


- PIN1 and PP2A interplay to prevent formation of neurotoxic cis-tau and cis-ptau oligomers
- In the unphopshorylated state, PIN1 doesn't work so the isomerisation process here is very slow
- We have Proline-directed protein kinases phosphorylating tau at specific Ser-prolyl/Thr-prolyl motifs. And we also have protein phosphatase 2A that dephosphorylates phosphorylated tau in the trans configuration
- When tau is phosphorylated, it is free to form oligomers but tau needs to be in the cis conformation to do so
- Cis form of tau can easily undergo misfolding which can cause it form oligomers. When the cis tau is not phosphorylated, it can still form oligomers – BUT THIS IS VERY RARE normally!

- Even if these oligomers do form, as they are in low quantities there are methods used by our cells to scavenge and remove them
- The reason why this is rare is because:
  - The unphopshorylated tau tends to accumulate more in the trans form than the cis form. And the conversion of trans to cis-tau in the unphopshorylated state is very slow.
  - When tau is in the unphopshorylated trans conformation, it has a high propensity to bind to microtubules which thereby prevents the conversion of trans to cis-tau.
  - PP2A can readily dephosphorylate trans-p-tau.
  - Also, although cis-p-tau can't be dephosphorylated by PP2A, cis-p-tau can be readily converted to trans-p-tau through the actions of PIN1 which will then be dephosphorylated by PP2A etc.

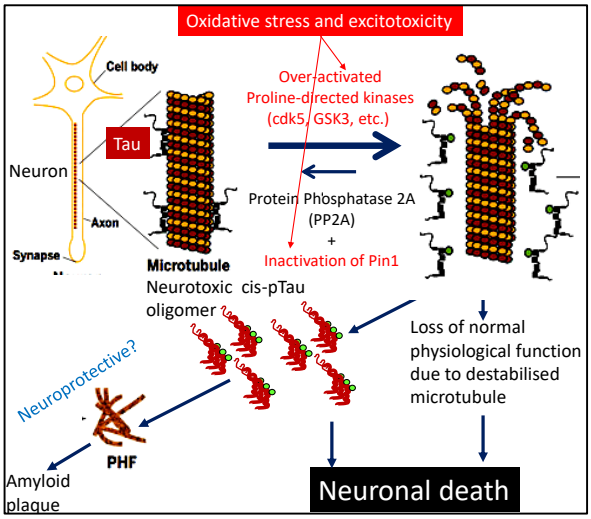
- Under normal conditions, we can say that the isomerisation of trans-tau to cis-tau doesn't happen because it is very very rare (only happens to a very insignificant amount)
- Some of the Proline-directed kinases are regulatory subunits such as cdk5 which are processed under excitotoxic conditions or in AD patients. In pathological conditions, cdk5 is misdirected to the area where tau is localised (this is normally not the case)

PIN1 and Protein Phosphatase 2A (PP2A) prevent hyperphosphorylated tau from forming neurotoxic oligomers



- When microtubules are phosphorylated, the p-tau will dissociate from the microtubules. They can now convert to neurotoxic p-Tau oligomers
- However, in the presence of PIN1, PIN1 will be able to modulate the multiple cis-phosphorylated sites and can turn them into trans-p-tau
- Perturbations to any of the steps in the pathway (i.e. overactivation of the PP2A, inactivation of PIN1 etc.) can cause the accumulation of oligomers
- Oxidative stress can activate cdk5 and gsk3 – so there is an increase in the activity of the neurotoxic Proline directed kinases causing the hyperphosphorylation of tau.
- PP2A can get inactivated under oxidative stress conditions, this will decrease the chance of the dephosphorylation of trans p-tau
- Hyperphosphorylated tau can't bind microtubules because the microtubule binding sites are phosphorylated which prevents binding to the microtubules
- Once hyperphosphorylated, this p-tau has a number of fates:
  - This can be converted to neurotoxic p-tau oligomers (cis-tau has a high propensity to turn into neurotoxic oligomers)
  - This can also form PHF-Tau which is a major component of the neurofibrillary tangles in Alzheimer's disease. The PHF-tau filaments can form larger plaques and eventually form amyloid plaques
- PIN1 and protein phosphatase 2A tries to prevent the hyperphosphorylated form of tau
  - PIN1 will turn the cis form of p-tau to trans form of p-tau and now PP2A can act on trans p-tau to dephosphorylate it

What happens in pathological conditions?



- Along the axons, we have microtubule bundles
- Mitochondria and synaptic vesicles travel along microtubules bundles
- Microtubule bundles are decorated with unphopshorylated tau
- Under oxidative stress, Proline dependent kinases are overactivated which will phosphorylate the tau. This will cause their disassociation from the microtubules leading to disassembly of the microtubules.
- PP2A activity can be decreased in 2 ways:
  - By a decrease in intrinsic phosphatase activity due to oxidative stress
  - Due to inactivation of PIN1