TAUOPATHIES: Role of Tau in neurodegenerative diseases

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MATERIALS AND METHODS

Search in PubMed and Medline for articles published between January 1, 2005 and December 31, 2012. No language restriction. Search terms "Tau protein", "tau neurodegeneration", "tauopathies", "tau gene" and "tau pathology" in addition to disease-specific terms.

NEURODEGENERATIVE DISEASES

- Group of chronic and progressive diseases characterized by symmetric and selective loss of the neurons in motor, sensory or cognitive systems
- They cause abnormalities in the transport, degradation and aggregation of proteins that lead to cell-specific changes
- Common in all the neurodegenerative diseases is the cell loss and intraneuronal accumulations of fibrillary materials

TAU PROTEIN

- Tau are low molecular weight proteins whose function is the assembly and stabilization of microtubules, and they play a key role in the anterograde transport by kinesin and retrograde transport by dyneins.
- Abundant in the central nervous system, expressed mainly in the axons, although they can be also found on the axons of the peripheral nervous system.

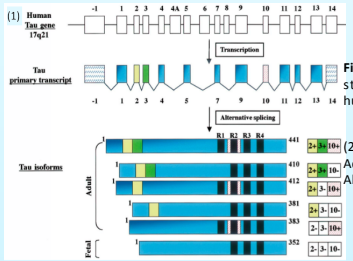
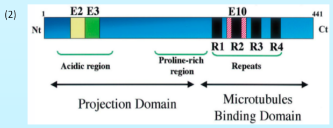


Figure 1: (1) Tau gene structure and adult human isoforms.



(2) Parts of tau protein. Adapted from Buée et Al. 2000

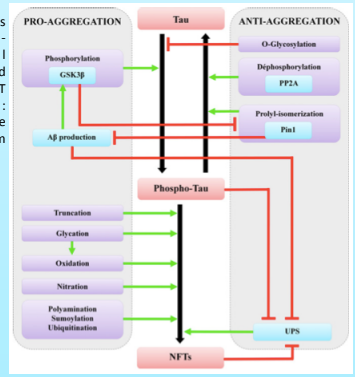


Figure 2: Connections between tau post-translational modifications and regulation of NFT formation. UPS: ubiquitin–proteasome system. Adapted from Martin et Al. 2011

ALZHEIMER'S DISEASE

- It is characterized by the presence of amyloid plaques, intracellular neurofibrillary tangles (NFT) and oxidative stress
  - The amyloid plaques (or senile plaques) are extracellular deposits of aggregated β-amyloid peptides (Aβ) typically surrounded by neurons with dystrophic neurites
  - Neurofibrillary tangles (NFTs) are generally intraneuronal cytoplasmatic bundles of paired helical filaments (PHFs), whose subunit protein is Tau (3R and 4R isoforms)
- No treatment to stop AD neurodegeneration, just to slow its progression
- Three transgenic mice models have been developed:
  1. Aβ-pathology model
  2. Tau-pathology model
  3. Triple – transgenic model: mutations in APP, PSEN1 and MAPT

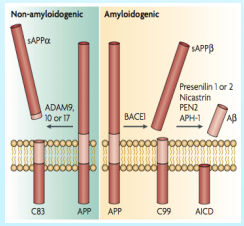


Figure 3: APP proteolysis. LaFerla et Al. 2012

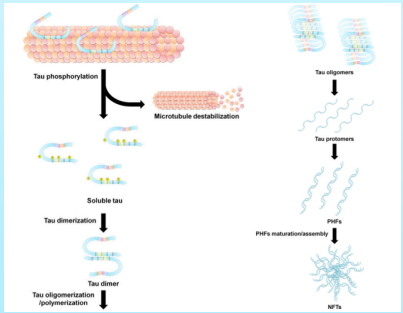


Figure 4: Process of Tau aggregation. Adapted from Martin et Al. 2011.

TAU BASED THERAPIES

- Three therapies are in clinical phases of development (Gotz et Al.2012) :
  - Methylene blue: Inhibits tau aggregation by introducing into the structure of paired-helical filaments and destabilizes them.
  - Lithium chloride: Inhibidor of GSK3, one of the kinases that phosphorylates tau. Therefore, it inhibits tau aggregation.
  - Neuroprotective octapeptide NAP: Microtubule – stabilizing compound

PICK'S DISEASE

- 3R – Tauopathy first described by Arnold Pick. Onset age < 65 years old.
- Characterized by behavioural changes such as desinibition, language problems, extrapyramidal signs and aphasia. Executive functions, such as planning and organization, may become impaired, while memory, orientation and visual-spatial function are preserved.
- Asymmetric frontotemporal atrophy that affects more the left hemisphere than the right, atrophy of the bilateral caudate nuclei and evident reduction in perfusion of frontal and temporal lobes

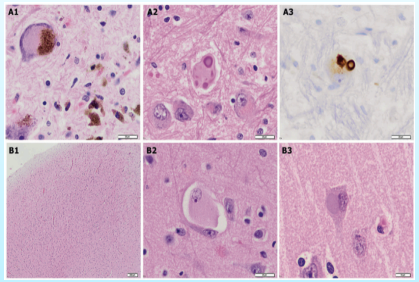


Figure 5: Neuropathological changes in Pick disease. **(A1)** Loss of neurons of pigmented brain stem nuclei. **(A2)** Lewy bodies with bizarre morphology in dorsal nucleus of vagal nerve. **(A3)** Lewy bodies are immunoreactive of a-synuclein. **(B1)** Neuronal loss and gliosis. Hematoxilin and Eosin Stain. **(B2)** Ballooned neurons or Pick Cells **(B3)** Neurons containing basophilic inclusions or Pick-Bodies. Adapted from *Vilas et Al 2012*.

PICK'S DISEASE CLASSIFICATION	Alternative names	Microscopic features	Gross Brain Features
Type A	Classic Pick's Disease	Presence of both Pick bodies and Pick cells	Prominent frontotemporal and limbic degeneration
Type B	Frontotemporal dementia with Parkinsonism linked to chromosome 17	Absence of Pick bodies and numerous Pick cells	Superior frontal and parietal lobes degeneration
Type C	Dementia lacking distinctive histopathology	Neither Pick bodies nor Pick cells	General cortical degeneration

Table 2: Tissot, Constantinidis and Richard's classification of Pick's disease based in their gross and microscopic features.

CORTICOBASAL DEGENERATION

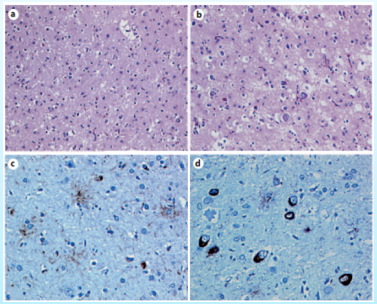


Figure 6: Histological features of Corticobasal degeneration. **(a)**Marked neuronal loss, astrogliosis and spongiosis in H-E stained sections of the parietal cortex **(b)** together with some ballooned cells. **(c)**Cortical AT8 stained astrocytic plaques. **(d)** Neuronal tau pathology. Adapted from Jung et Al. 2012.

- Rare progressive neurodegenerative 4R-tauopathy associated with a wide variety of motor, sensory, behavioral and cognitive symptoms.
- Complicated clinical diagnosis due to the variability of presentation of true corticobasal degeneration and the syndromes that look like it but are caused by other neurodegenerative diseases (CBD mimickers)
- Gradual progression: From unilateral to affect both hemispheres

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