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NEW APPROACHES ON TAUOPATHIE'S STUDIES: A QUICK REVIEW

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ABSTRACT

Review tau protein's role at tauopathies, by comparing and converging classic and new data. Describe new therapeutic approaches on tauophatie's field. The study is a systematic review of the scientific literature, based on preliminary research and interpretation of material, book report summaries, material analysis and interpretation, bibliography, review and final report. The following databases were used to support the bibliographic research: PORTAL CAPES, SCIELO, SCIENCEDIRECT, PubMed and MEDLINE. The descriptors used were: "tauopathies", "tau protein", "Alzheimer's Disease", "Parkinson's Disease" and "therapy". Among the analysed papers, 13 guided tau protein's biochemical analysis, 9 referenced the study about pathologic tau, 14 conducted the research about Alzheimer's and Parkinson's Disease and 18 based the review about new therapeutic approaches.

Keywords: tau protein's, Alzheimer's disease, cytoskeletal elements, Parkinson's disease.

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INTRODUCTION

Tau is a protein which main function is promoting aggregation and microtubule (MT) stabilization, primarily found on nervous system cells. Studies point that it can be reversible fosforilated in many conditions, like through fetal development. However, on pathologic conditions generates an inequity in this process, succeeding an irreversible hyperphosphorylation. Due to this, occurs a neurofibrillary aggregation and tangles formation, causing cellular death and stress. The process characterizes pathologies like Alzheimer's disease (AD), Frontotemporal dementia and Parkinsonism linked to chromosome 17 (FTDP-17), progressive supranuclear palsy and corticobasal degeneration, named tauopathies[1].

As multifactorial pathologies, actual treatments seek different approaches, conversely with no cure. Existing treatments restricts to a partial life progress for the patients as it only enhances the symptoms. Therefore, the developments of new therapeutic techniques placed on the newest insights in the area are extremely necessary.

This literature review briefly discusses the pathophysiology and treatments of the main tauopathies. Including basic concepts linked to *tau* protein and its pathological malfunctions pursuing interest on the topic and prompt new discoveries.

METHOD

The author and three co-authors performed the study in a systematic literature review. This approach promotes an extensive understanding of the subject, confronting and converging the present data. PORTAL CAPES, SCIELO, SCIENCE-DIRECT, PubMed amd MEDLINE were used to underpin the bibliographic research. "tauopathies", "tau protein", "Alzheimer's Disease", "Parkinson's Disease" and "therapy" were used as descriptors. The steps applied to this study were: preliminary identification and bibliographic search, a summary report, analysis and material interpretation, bibliography, review and final report. At last, 54 papers were selected, from 79 compiled, for the final report resting on the following criteria: relevance and publication time.

RESULTS AND DISCUSSION

1. TAU

Member of mitogen-activated protein (MAP), which are MTs association proteins, *tau* protein is found in the central nervous system, despite non-neuronal cells may have trace amounts which it is possible to identify *tau* mRNA in assorted peripheral tissues such lung, heart, pancreas, kidney and fibroblasts[2,3]. Tau's main function is to connect, stabilize and promote MTs association, restricting its flexibility and conceding interaction with other cytoskeletal elements and plasma membrane[2]. Mice studies demonstrated that this protein is essential for neuron full development. *Tau*-knockout rodents showed a slower neuronal maturation, therefore more likely to acquire neurodegenerative diseases[4].

1.1 STRUCTURE

In the adult brain, tau protein is found in six different isoforms, each having a specific number of amino acids. Each isoform plays a certain role in the body, as gene expression during development is different.

1.1.2 PROJECTION DOMAIN

The protein interaction through its N terminus with cytoskeletal elements is responsible for signal transduction pathways and promotes the termed "projection domains". Those domains delimit the space between MTs and axons and may result in a larger neuron site diameter[5]. Consequently peripheral neuronal projections are longer and thicker, containing additional N terminus.

1.1.3 BINDING DOMAIN

The C-terminal, protein acid part, possess the "binding domains" where occurs the association with microtubules on repeat region (R1, R2, R3, R4)[2,6]. Exon 10 isoforms are called 3R and those having a strong interaction with MTs [9] and more efficient[8] are 4R, without the exon 10.

1.2 PHOSPORYLATION CONTROL

The bond formed in the C terminal partially depends of the *tau* phosphorylation state. Studies point out that phosphorylated proteins showing an elongation growth are less efficient than dephosphorylated, damaging the protein and MTs cluster[11].

In neurons development, *tau* phosphorylation can be regulated by cellular enzymes compound mechanisms. Kinases are responsible for protein phosphate addition, examples are glycogen synthase kinase-3 (GSK-3), cyclin dependent protein kinase-5 (cdk-5), PDPK, cdc2 *tau*-tubulin, kinase protein kinase A (PKA), calcium and calmodulin-dependent protein kinase-II (CaMKII), casein kinase-1 (CK-1), MAP, ERK1/2 kinase and stress-activated protein kinases (SAPKs)[2,12,13]. The phosphatases dephosphorylate and contribute for the whole process control and balance.

2. TAUOPATHIES

An unusual *tau* metabolism is observed in certain pathologies leading to intracellular accumulation in glial cells and neurons. This particularity characterizes the tauopathies, which cover a broad range of neurodegenerative diseases. Actually it is known the key role of this protein in understanding such diseases, as neurofibrillary tangles are formed of hyperphosphorylated *tau*[14,1].

2.1 PATHOLOGIC TAU

In a normal adult brain, *tau* can be found in the axons of nerve cells. However, in a tauopathy this protein is distributed among dendrites and cell body due to MTs association loss, facilitating its aggregation and accumulation[15, 16]. It becomes phosphorylated and less soluble assembling intracellular abnormal filaments. In parallel with occurs a progressive destabilization and MTs loss, synapses also dendrites and axons disintegration of the affected neuron, resulting in cell death[15,17,18].

Neurotoxicity, due to extracellular signals, is the consequence of this process. It is noted that *tau* repeat regions phosphorylation is abnormally elevated[15], making it dormant and disturbing its functions regulated by the phosphorylation extent[15,19].

The hyperphosphorylation is attached to kinase protein activity and phosphatases proteins inequality. Is known that this balance determinates the phosphorylation state of a protein, if there is an abnormal activity the phosphorylation levels can increase or decrease[19].

Series of kinase proteins, in general super expressed in cells, are involved on normal *tau* phosphorylation, resulting in available *tau* hyperphosphorylation[19]. In addition, it is remarkable the PP-2A, the main brain phosphatase, irreversible activity decrease[20] and PP-1. This non-reversible characteristic occurs in thauopathies, leading to neurodegeneration and dementia[19].

PP-2A is not only able to regulate *tau* phosphorylation, but also regulates several brain *tau* kinases in the brain. Additionally, two endogenous inhibitors, super expressed on tauopathies, regulates PP-2A, contributing to a minor phosphatase activity[19, 21].

2.1.2 FILAMENT STRUCTURE

Hyperphosphorylated *tau* loses its microtubules binding capacity and promotes intracellular aggregation, forming filaments and neurofibrillary tangles. Those filaments have no morphology (paired helical or straight filaments), composition (specific *tau* isoform) or fixed location among tauopathies[14,15]. Adversely, the filaments aspects vary depending on the disease, and present with different widths. Nevertheless, a diffused layer is formed around the filament repeat region by amino and carboxyl terminal regions[16]. This layer, opposite of the nucleus, is protease sensible then frequently proteolysed along the disease. Although initially made and assembled by its full size protein, the filament only composes the *tau* repeat region[16,22].

2.2 TAUOPATHY IN ALZHEIMER

Alzheimer's Disease (AD) is the main cause of worldwide dementia and the major degenerative disease on elderly population. The β-amyloid plaques deposition is the main difference between AD and other tauopathies. In the 80's, studies report *tau* identification as a component of neurofibrillary tangles (NFT)[23,24]. Nonetheless, few information is found regarding to protein phosphorylation levels and its functional state, pointed as an attainable cause of agglomeration and synthesis abnormality or injuries to pyramidal neurons. Nowadays, there is an extensive literature with high level of understanding on molecular mechanism related in *tau* dysfunction. As a multifactorial disease, a high disagreement concerning the actual role of tauophaty on disease's development persists, may presenting it as a cause or possible adaptation to oxidative

stress[25].

Similarly to other tauophties, AD presents a *tau* hyperphosphorylation, heading to formation and subsequent neurofibrillary tangles deposition[26]. In this pathology, the tangles deposition is through paired helical filaments, differing from other format[27,28] present on distinct pathologies, as will be discussed below.

More than 30 *tau* abnormal phosphorylation sites are already investigated, which may vary depending on mutations presence or absence [29]. However, exists a controversy in regard of kinases role in this pathophysiology. Currently ERK suffered some questioning, since under physiological conditions appears to do not phosphorylate *tau*, as demonstrated by previous studies. Hence, more studies about its pathologic function are necessary[30].

Recent studies display that *tau* could be associated to AD pathophysiology through its interaction with PMCA - important calcium extrusion via. This situation caused calcium ions uncontrolled influx to the neuron, already known it is linked to neuronal aging. Further are fundamental to elucidate the true correlation between proteins, but current literature proposes that *tau* operates in homeostatic and age-dependent conditions as a calcium extrusion pumps inhibitor, resulting in a hypercalcemic intracellular environment. This framework is aggravated by GSK3β, *tau* key kinase, calcium dependence; intracellular calcium increasing could indirectly operate the disease progress, predisposing cellular environment to *tau* hyperphosphorylation[31].

2.3 TAUOPATHY IN PARKISON

Parkinson's disease is the most common neurodegenerative disease with motor impairment, culminating in akinesia, tremor and other clinical signals. The literature is still controversial around Parkinson's disease and tau dysfunction connection. Various studies attempted to explore the possibility of protein concentration in the cerebrospinal fluid be seen as a biomarker for several parkinsonism types, however the differences among the used methodologies lead to difficulties in meta-analysis preparation[32].

There is additional evidence on MAPT mutations, tau encoder, are associated with familiar Parkinsonism, pathology known as FTPD-17. The possibility aroused after studies associated tau microdeletions *in locus* 17q21.3 with intellectual development delays[33]. In chromosome 17 mutated mice, defects in axonal transport, hyperphosphorylated tau accumulation in presynaptic terminals and an evident synaptic loss was seen[34,35]. These mutations, predispose protein hyperphorsphorylation and filament aggregation[22] therefore, accelerate tauopathy effects.

However, in recent literature the most common connection of *tau* dysfunction with Parkinson's disease pathophysiology is by its interaction with alpha synuclein protein. This protein mediates transport routes through the cell, for neurons, which are extremely important presynaptic vesicles extrusion[27]. *Tau* and alpha-synclein protein aggregation occurs *in vitro,* producing fibrillation, which leads to protein deposition coupled with axonal transport impediment, two typical brain findings in Parkinson's disease[33]. In these cases, alpha synclein is pathologically oxidized, phosphorylated and nitrated, predisposing it to aggregation[36].

3. NEW THERAPEUTIC APPROACHES IN TAUOPATHIES

The first tauopathies treatment arrived in the market at the beginning of the century, neurotransmitters moderators such N-methyl D-aspartate moderators (NMDA) and acetylcholinesterase inhibitors. These treatments still are the basis of AD mitigation and frontotemporal dementia, relieving memory deficits. Over recent years, research around the world has focused on tauophaties regression using immunotherapies and drugs.

3.1 ACTIVE IMMUNOTHERAPIES IN TESTS

AC Immune AG, KU Leuven, Fred van Leuven, and Jansen Pharmaceuticals

ACI-35 is an active vaccine developed by AC Immune AG (Lausanne, Switzerland) in collaboration with Fred van Leuven from Leuven Catholic University (KU Leuven), in partnership with Jansen Pharmaceuticals. This vaccine is tau 393-408 (pS 396, 404 pS) in *di-myristoylphosphatidylcholine* liposomes (DMPC), *di-myristoylphosphatidylglycerol* (DMPG), cholesterol, and

the adjuvant *monophosphoryl lipid A* (MPLA). It generates a rapid immune response in P301L transgenic mice, producing a smooth reduction of pathologic hyperphosphorylated *tau* (64 kDa) and pathologic *tau* characterized by immunohistochemistry[37]. Furthermore, these beneficial effects were not associated with inflammatory responses, suggesting security for a human study. Clinical trials have been initiated, but results were not released yet.

AADvac1 vaccine is the first which already started clinical trials, is being developed by Axon Neuroscience (Bratislava, Slovakia Republic). It consists of a *tau* peptide fragment, Tau294-305 (294KDNIKHVPGGGS305), linked to a KLH (*keyhole linked hemocyanin*) by N-terminal cysteine and administered with an aluminium hydroxide adjuvant. The vaccine reduced pathologic tau and associated behavioural deficits in transgenic mice [38]. The safety, tolerance and efficacy are being evaluated in a Phase I clinical study conducted in Austria laboratories[39]. Mild-moderate AD patients will receive 3-6 vaccine doses.

3.2 PASSIVE IMMUNOTHERAPIES IN TEST

Biogen Idec, Panima Neurosciences, and Roger Nitsch

Roger´s Nitsch group at Zurich University (Switzerland) has used an unconventional route towards *tau* therapeutic antibodies discovery, by isolation of *tau* autoantibodies from healthy elderly subjects without neurodegenerative tauopathies. The advantage is on directly obtaining humans antibodies, rather than the traditional mice antibodies cloning. Human *tau* recombinant (2N4R) was used as a bait to obtain tau-specific antibodies and isolate several antibodies. These were screened for discriminate isolated *tau* from healthy and sick subjects ability. Three antibody, 4E4, 4A3 and 24B2 were described in their research[40,41], with the ability to recognize amino acids in the C-terminal and MT connection region. These antibodies exhibit no phosphor-specificity.

C2N Diagnostics, David Holtzman and Marc Diamond

C2N Diagnostics Inc., founded by David Holtzman and Randall Bateman at School of Medicine, Washington University, focused mostly on developing diagnostic tools for early detection of neurodegenerative diseases. In cooperation with Marc Diamond, using human and rat tau generated antibodies. Eight and five antibodies recognized human and rat *tau*, respectively[6]. Three antibodies were used for *in vivo* tests (*HJ9.3, HJ9.4 e HJ8.5)*, only the HJ8.5 specifc to human *tau.* The selection was based on its ability to prevent the transcellular pathologic tau spread mechanism[42,43,44].

The evaluation by intracerebroventricular injection on P301S transgenic mice studies demonstrated its ability to decrease hyperphosphorylated tau levels. No information about the antibodies therapeutic development has been reported, but HJ8.5 was the most effective during experiments and should be a promising antibody.

Lundbeck, NYU, and Einar Sigurdsson

This program was the first to demonstrate the effectiveness of *tau*-based immunotherapy. JNPL3 (P301L) mice were immunized with the active vaccine containing a *tau* peptide fragment 379-408 (pS396, pS404) along Adju-Phos adjuvant. A prominent reduction of pathologic tau was observed in vaccine treated mice compared to the control group, attenuation in motor deficit was also detected. Other mouse model (hTau / PS1), not driven by mutant *tau,* also tested the vaccine [45]. Similar effects were obtained around the same time with the PHF1 antibody, which recognizes the pS396 / pS404 segment as well as other antibodies against this fragment developed by Sigurdsson laboratory at the School of Medicine of New York University[34,35].

3.3 *TAU* BASED THERAPIES

As previously mentioned in this review article, microtubule destabilization is related to AD. In this manner, several compounds aim to reverse this situation through in development microtubule stabilization. Among these, can be remarked:

-Paclitaxel: Improves axonal transport speed, density and microtubule function[46]

-Epothilone: Improves Tauopathies[10].

-Neuropeptides NAP (NAPV-SIQ) and D-SAL (SALLRISPA): Promotes microtubule stabilizing effects[47, 48].

-Astemizole and Lansoprazole: Prevents *taus* in-

teraction and oligomerization[35].

-Blue Methylene: Inhibits amyloid aggregation, reduces oxidative stress, improves electric transport and prevent mitochondrial damage[49,50,51].

-Hsp90 Inhibitor: Promotes *tau* degradation[52].

-EC102Hsp90 Inhibitor: Reduces *tau* aggregation[53].

FINAL CONSIDERATIONS

The tau protein knowledge application, given the particularities of each tauopathy, enables better analysis of different pathophysiologies. Thus, need of more studies in this topic in order to complete the remaining gaps and expand the therapeutic options. Studies on the protein dysfunction front of a genetic, epigenetic and biochemical bias are also necessary.

Recent studies demonstrate that *tau* homeostasis and/or dysfunction and other cellular components are associated. On this issue, the expanding literature demand additional investigations.

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