Tau links developmental to neurodegenerative diseases

Thomas W. Rösler[a,b], Günter U. Höglinger[a,b,c,*]

[a]Department of Translational Neurodegeneration, German Center for Neurodegenerative Diseases (DZNE), 81377 Munich, Germany; [b]Technical University of Munich, School of Medicine, Department of Neurology, 81675 Munich, Germany; [q]Munich Cluster for Systems Neurology (SyNergy), 81377 Munich, Germany.

*Corresponding author: Prof. Dr. Günter U. Höglinger, German Center for Neurodegenerative Diseases (DZNE), Department for Translational Neurodegeneration, Feodor-Lynen-Str. 17, 81377 Munich, Germany, Phone: +49-89-4400-46465, guenter.hoeglinger@dzne.de

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The microtubule-associated protein tau can be found in aggregated form in cytoplasmic inclusions of neurons, characterizing a group of neurodegenerative diseases, termed tauopathies. With the exception of some cases where the diseases can clearly be assigned to a genetic cause, tauopathies develop sporadically and present disease symptoms predominantly in aged people. Whether the tau inclusions found in patients are responsible for the degeneration of neurons or a consequence of impaired physiological mechanisms, e.g., post-translational modification or cellular degradation mechanisms of tau, is the object of intensive research of the last four decades. It is well known that tau binds to tubulin and stabilizes the cytoskeleton of neurons, however, research of recent years has shown that this is not its only role. Tau may also be involved in axonal transport, interneuronal signaling, maintenance of structural integrity and neurogenesis (Guo et al., 2017), fundamentally important for brain development.

The latter concept is seized by Rankovic and Zweckstetter in their recent review, in which they summarize the current knowledge of tau function under neurodevelopmental aspects (Rankovic and Zweckstetter, 2019). Tau can be alternatively spliced into six isoforms, three containing three microtubule-binding domains (3R) and three containing four domains (4R). The appearance of different ratios of 3R/4R tau in the brain dependent on the developmental state of the brain, corroborates a possible role of tau in brain development. Additionally, distinct isoforms of tau can be found intracellularly in the nucleus and nucleolus (Bukar Maina et al., 2016), suggesting a probable interaction of tau with DNA, which might also be of relevance in brain development. As mentioned by Rankovic and Zweckstetter, tau can interact with several proteins, e.g., α-synuclein, presenilin 1 or heparin (Rankovic and Zweckstetter, 2019), emphasizing the many faces that tau might have in neuronal function. Furthermore, tau can be released into the extracellular space, which was formerly believed to be a pure consequence of neuronal death. It becomes more and

more clear that extracellular tau may have several physiological functions as well. However, the exact function still remains elusive. Tau is also subject to several post-translational modifications, e.g., phosphorylation or acetylation, which are known to foster aggregation of tau and to contribute to the pathology of tauopathies. Although it is conceivable that post-translational tau modifications, as essential component of cell signaling, are important determinants for brain development, in-depth knowledge is still missing. Rankovic and Zweckstetter reveal important parallels, but also distinct differences, of tau pathologies found in developmental diseases and neurodegenerative tauopathies (Rankovic and Zweckstetter, 2019). In their review they mention hemimegalencephaly, tuberous sclerosis complex, focal cortical dysplasia type 2b, ganglioglioma, and Wolcott-Rallison syndrome. All these developmental diseases are caused by genetic defects, having severe implications on brain development. Affected individuals show already in early stages of life (infant or child) distinct types of tau pathology, e.g., increased levels of phosphorylated tau or cellular inclusions of tau. Although these tau pathologies can be similarly visualized as in neurodegenerative tauopathies, e.g. by tau antibodies or tau tracers, they seem to differ in their neuropathological character. Rankovic and Zweckstetter stated that changes of tau in developmental diseases rather affect morphogenesis and brain development (e.g., cellular differentiation, growth or migration) while in neurodegenerative diseases they clinically manisfest through e.g., dementia (Rankovic and Zweckstetter, 2019).

With the exception of Wolcott-Rallison syndrome, all developmental disorders reviewed by Rankovic and Zweckstetter, are caused by defects in genes of the mTOR (mammalian target of rapamycin) signaling pathway. This pathway is highly complex and essential for many different processes in cells, in particular for autophagy, mitochondrial function and glucose metabolism in the brain (Perluigi et al., 2015). Impairment of these processes are also believed to be involved in

the pathogenesis and progression of neurodegenerative tauopathies. Autophagy as a major degradation pathway, might be of high relevance for removing abnormal or aggregated tau. Defects in this pathway may be one possible reason why cellular tau inclusions are formed.

The developmental disease Wolcott-Rallison syndrome is caused by a genetic mutation in the *EIF2AK3* gene encoding PERK (pancreatic endoplasmic reticulum kinase). PERK is a key player of the unfolded protein response, a complex mechanism to restore proteostasis. It is conceivable that defects in this mechanism might contribute to the formation of cellular inclusion of tau. Unlike the other developmental diseases, defects of PERK seen in Wolcott-Rallison syndrome can be directly linked to a neurodegenerative tauopathy, as a single nucleotide polymorphism in *EIF2AK3* was shown to be a risk factor for the neurodegenerative tauopathy progressive supranuclear palsy (Höglinger et al., 2011). When comparing the occurrence of phosphorylated tau species and tau inclusions in developmental and neurodegenerative diseases, it seems that Wolcott-Rallison syndrome resembles most closely the features found in a neurodegenerative disease.

In conclusion, Rankovic and Zweckstetter provide a comprehensive overview on how developmental diseases with tau pathology may be connected to adult-onset neurodegenerative tauopathies (Rankovic and Zweckstetter, 2019). These diseases seem to have several tau features in common but also show distinct differences. Connecting the two groups of diseases may offer tremendous chances for research. As developmental diseases progress rapidly, but neurodegenerative diseases over a longer period of time, genetic mutations causative for developmental diseases could serve as a tool to create *in vitro* and *in vivo* disease models to test, in a short time, novel therapeutic strategies, that may be helpful for both, developmental but also neurodegenerative diseases. Useful models that closely resemble the disease pathology are still missing for neurodegenerative tauopathies. Developmental diseases are rare diseases that affect a

small number of patients. Unfortunately, only minor research efforts are made to develop effective therapies. Putting these developmental diseases and neurodegenerative tauopathies under one umbrella in research can therefore be of great help, for the development of diagnostic tools but also for novel effective therapies, and of fundamental help for patients.

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