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INSIGHTS

Glial tauopathy: Neurons optional?

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In some neurodegenerative disorders, tau protein accumulates in astrocytes and/or oligodendrocytes, even though these glial cells produce much less of the protein than do neurons. Testing the hypothesis that the aggregated tau in glia derives from neurons, Narasimhan et al. (https://doi.org/10.1084/jem.20190783) make the unexpected discovery that neuronal tau expression is not required for the formation of glial tau inclusions. The circumstances governing the variable cell-specificity of tauopathy thus remain to be fully defined.

Glial cells have long been second-class citizens in the nervous system, the "glue" that supports and protects the real functionaries, the neurons. While there is some truth to this disproportionate relationship, research over the past few decades has revealed a surprisingly complex and much more nuanced view of glia and their interactions with neurons in both health and disease. Indeed, their essential role in maintaining brain homeostasis implicates glial cells in the pathophysiology of most, if not all, neuropathologic conditions.

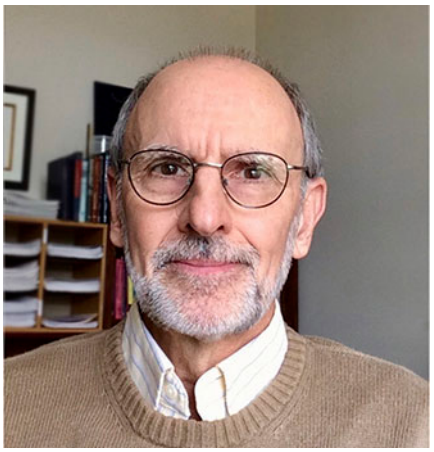
The tauopathies comprise one class of such conditions; these are clinically and pathologically diverse neurodegenerative disorders in which a normally produced cellular protein called tau takes on excess phosphate groups, misfolds, and abnormally polymerizes within cells (Spillantini and Goedert, 2013). The tauopathies are best known for the distinctive formation of aggregates called neurofibrillary tangles within neurons. At least 25 different diseases involve tauopathy as a primary or secondary lesion (Spillantini and Goedert, 2013), making it one of the most prevalent degenerative processes to afflict the nervous system.

In the 1960s, two uncommon neurodegenerative disorders called progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) were linked to the presence of neurofibrillary changes in neurons. Owing to limitations of the available histopathologic methods, the researchers did not report the pathology that today is considered to be characteristic of the two diseases—the abnormal accumulation of tau in glial cells (Ikeda, 2018). The affected glia are astrocytes, which normally perform a variety of homeostatic and protective functions, and oligodendrocytes, which primarily form the myelin sheaths that insulate axons in the central nervous system.

In PSP, tau forms various inclusions within glial cells, notably "tufted astrocytes" and oligodendrocytic "coiled bodies"; in CBD, coiled bodies and astrocytic inclusions also are present, along with "astrocytic plaques" consisting of clusters of tau-immunoreactive cellular processes (Irwin, 2016; Ikeda, 2018). The pathological features of PSP and CBD show considerable overlap; in both disorders, tau inclusions are widespread in the brain, and subcortical regions are heavily affected (Irwin, 2016). Glial tauopathy is increasingly recognized in a wide variety of diseases (Ferrer, 2018), and studies in which glial tauopathy is selectively induced in animal models indicate that it is deleterious to both glia and neurons (reviewed in Kahlson and Colodner, 2016).

What is remarkable about glial tauopathy is that oligodendrocytes and astrocytes express much less tau than do neurons; relatively low levels of tau mRNA (Zhang et al., 2014) and protein (LoPresti et al., 1995; Seiberlich et al., 2015) have been demonstrated in oligodendrocytes, but mRNA expression is even lower in astrocytes (Zhang et al., 2014), and tau protein is minimal, at best, in astrocytes under normal conditions (Kahlson and Colodner, 2016).

Where, then, does the copious tau in the glial inclusions come from? In this issue of *JEM*, Narasimhan et al. describe their test of the hypothesis that the tau in glial inclusions derives from neurons. Unexpectedly, they found that neuronal tau is not required for the development of tauopathy in oligodendrocytes or astrocytes, although it may facilitate the spread of astrocytic tauopathy from one brain region to another.



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In cultured cells, the researchers showed that oligodendrocytes express tau (although much less so than neurons) and that the protein can be induced to aggregate by a crystallization-like process in which the cells are exposed to seeds of aggregated tau from PSP or CBD brains. Normal astrocytes in culture, however, expressed no detectable tau, and inclusions could not be stimulated to form in the cells by exogenous tau seeds.

To determine whether neurons influence the initiation and spread of glial tauopathy in the living brain, the researchers) then turned to a new mouse model in which the production of tau protein is reduced or eliminated in neurons (neuronal tau "knockdown" mice). In the mouse brain, they confirmed that tau protein expression is detectable in oligodendrocytes but not astrocytes. When tau seeds derived from

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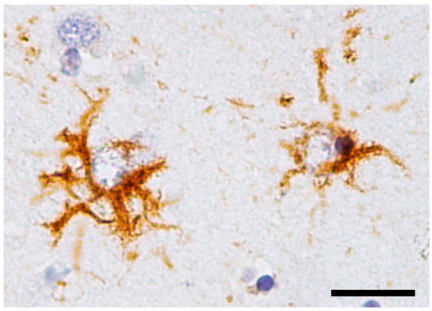

Tauopathy in astrocytes from a case of PSP. Immunohistochemical stain for tau (brown) and a Nissl counterstain (blue). Bar, 20 µm.

PSP or CBD brains were injected into the brains of neuronal tau knockdown mice and normal control mice, the resulting pathology resembled that in the human diseases, i.e., CBD-tau induced astrocytic tau plaques, PSP-tau induced tufted astrocytes, and both tau seeds induced coiled bodies. Thus, the characteristics of tau seeds differ in different tauopathies, and these features are transmissible to mouse models, supporting the concept that tau misfolds into functionally distinct variants known as strains. Importantly, glial inclusions were seeded even in neuronal tau-knockdown mice, indicating that neuronal tau is not essential for the induction of glial tauopathy. Once tauopathy was initiated in neuronal tau-knockdown mice by exogenous seeds, oligodendrocytic tauopathy spread systematically to other brain regions, whereas astrocytic inclusions remained confined to the injection site. The findings also indicate that tauopathy in oligodendrocytes is harmful to the cells, even in the absence of significant neuronal tau expression.

To shed light on the means whereby oligodendrocytic tau spreads, the scientists used immuno-electron microscopy to visualize tau polymers in mice seeded intracerebrally with CBD-tau. They showed that fibrillar tau assemblies were localized almost entirely within the processes of oligodendrocytes but not within axons, suggesting that the seeds pass from oligodendrocyte to oligodendrocyte rather than traveling via, e.g., intraneuronal transport mechanisms.

Unlike oligodendrocytic tauopathy, the spread of astrocytic tauopathy from one site to another appears to require the presence of neuronal tau. In an earlier study of tau seeding in nontransgenic mice (which naturally express neuronal tau), the researchers found that both neuronal tau and astrocytic tau propagated in parallel through the brain from an initial seeding site (Narasimhan et al., 2017). In this scenario, aberrant tau presumably is transported and released by neurons, whence it is taken up by astrocytes situated in proximity to the chain of affected neurons.

These studies highlight the variety of ways in which astrocytes and oligodendrocytes are involved in neurodegenerative tauopathies. The seeding and systematic propagation of tauopathy in oligodendrocytes can be explained by the demonstrable constitutive expression of tau in these cells (LoPresti et al., 1995; Seiberlich et al., 2015), possibly in conjunction with inter-oligodendrocytic communication via gap junctions (Nualart-Marti et al., 2013). Even though the expression of tau protein in astrocytes is very low under normal conditions (Kahlson and Colodner, 2016), the accumulation of hyperphosphorylated tau in astrocytes can be quite remarkable in human tauopathies. Given evidence that astrocytes and oligodendrocytes also communicate with one another via gap junctions (Nualart-Marti et al., 2013), it is conceivable that different types of glial cell could exchange abnormal tau with one another.

Perhaps more likely, given that astrocytic tau fails to propagate in the absence of neuronal tau even when oligodendrocytic tau does (as described above), is that astrocytic tau expression is induced or augmented in vivo by various stressors (such as exposure to exogenous tau seeds in the present paradigm). The observation that experimental tau overexpression in astrocytes induces human-like astrocytic tauopathy in tau-transgenic mice (Forman et al., 2005) indirectly supports this possibility. Interestingly, there is a similar disconnect between the paucity of constitutive α-synuclein expression in oligodendrocytes and the rampant accumulation of the protein in these cells in an aggressive neurodegenerative proteopathy called multiple system atrophy (Peng et al., 2018).

A central question remains: how does the same protein assume different molecular states in different cells to cause different diseases? The clinicopathologic and molecular diversity of tauopathies (Spillantini and Goedert, 2013) presents a salient challenge for the development of therapies. Tau in humans has six different isoforms, and tauopathies often are classified based on the predominant presence of three or four microtubule-binding domains in the proteins (3R tau and 4R tau). The tauopathy of PSP and CBD consists mainly of 4R tau, whereas in Pick's disease, the protein that accumulates is predominantly 3R tau. In Alzheimer's disease—in which tauopathy accompanies the buildup of misfolded Aβ protein in plaques—both tau isoforms are present in neurons (Spillantini and Goedert, 2013), but tau in astrocytes is mainly the 4R type (Okamoto, 2019). There also is evidence for a role of microglia in the evolution of tauopathy (Kahlson and Colodner, 2016), but the involvement of these resident immune cells needs clarification.

In the analysis of neurodegenerative proteopathies, we neuropathologists understandably tend to focus on the clumps of protein that are obvious under the microscope, but very small, cryptic assemblies known as oligomers may contribute importantly to the dysfunction and demise of cells in the tauopathies (Shafiei et al., 2017). In addition, an exploration of possible atypical roles of tau in cell function, i.e., those other than microtubule stabilization, could help to inform the involvement of the protein in glial tauopathies. As Narasimhan et al. (2019) point out, the most informative animal models should include glial tauopathy, as glia could facilitate disease by mechanisms other than those that prevail in neurons. Finally, advancing age is a risk factor for neurodegenerative proteopathies, and it might be instructive to determine whether senescence differentially influences the susceptibility of diverse cell types to tauopathy.

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