Complementing tau: new data shows the complement system is involved in degeneration in tauopathies

Neuron Preview

Complementing tau: new data shows the complement system is involved in degeneration in tauopathies

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Abstract

Innate immunity is increasingly recognised to contribute to the pathogenesis of neurodegenerative disorders. Here, Dejanovic et al. (2018) and Litvinchuk et al. (2018) describe mechanisms by which the complement system influences tau-mediated degeneration in mouse models of tauopathy.

Main text

Alzheimer's disease (AD), the most common cause of dementia, affects more than 30 million people worldwide and costs the world's economies over $500 billion per year. An incomplete understanding of AD pathogenesis has thus far prevented the development of disease-modifying treatments. A potential pathway to synapse and neuron degeneration involves increased activation of the complement cascade, part of the brain's innate immune system. Originally thought to be a secondary outcome to degenerative processes, a growing body of genetic and epidemiological evidence now strongly implicates cells and proteins involved in the innate immune system in modulating the risk of developing AD (De Strooper and Karran 2016, Henstridge et al. 2018).

During normal brain development, microglia- and astrocyte-mediated synapse pruning is crucial in forming precise synaptic circuits (Stevens et al. 2007; Schafer et al. 2012). This process involves activation of the classical complement system, initiated by deposition of C1q on material to be eliminated. The cascade converges on the central complement component C3, whose fragments interact with their receptors, C3aR and CR3, to enact downstream immune effects such as phagocytosis.

In disease, these developmental mechanisms might be reactivated, with glial engulfment of synapses contributing to synapse loss and disease progression. In AD patient brains, the pathological proteins amyloid-β (Aβ) and tau are thought to contribute to the synapse and neurons loss that causes dementia symptoms (Spires-Jones and Hyman 2014). There are several papers now linking Aβ-mediated synapse loss to the complement system in mouse models of AD. In plaque-bearing mouse models, C1q decorates post-synaptic densities that are then thought to be cleared by microglia through activation of CR3 (Hong et al. 2016). Although the complement pathway has been suggested to play an active role in tau pathology and tau-mediated synapse loss (Britschgi et al. 2012), the mechanisms remain unknown.

In this issue of *Neuron*, Dejanovic et al. (2018) and Litvinchuk et al. (2018) provide mechanistic data linking tau pathology and the complement system. Both studies examined human brain tissue from AD and tauopathy patients as well as the PS19 mouse model of tauopathy, where animals express human tau containing the P301S frontotemporal dementia associated mutation.

In the human AD brain, Dejanovic et al. found C1q and pathological tau proteins to be increased and enriched at post-synapses. Consistent with these proteins associating with one another, C1q levels positively correlated with the levels of pathological tau. Using RNAseq data from human AD patients, Litvinchuk et al. show that increased expression of the downstream complement components *C3* and *C3aR1* are associated with worsened cognitive function and with the degree of tau pathology. Additionally, in the brains of patients with other tauopathies which lack Aβ pathology, *C3* and *C3aR1* expression was also increased, supporting a role for complement components in human tauopathy.

To probe how the complement system might influence tau-mediated synapse loss, Dejanovic et al. utilised the PS19 tauopathy mouse model at an age when they are in the early stages of disease progression, before they exhibit overt neuronal loss in their hands. Proteomics of post-synapses in these mice revealed C1q to be one of the most highly upregulated proteins. The amount of C1q present was positively correlated with the amount of pathological tau, like in the human AD brain. Temporally, the increase in synaptic C1q lagged slightly behind increases in pathological tau, consistent with tau inducing C1q accumulation at the synapse. Interestingly, C1q and human tau preferentially associated with one another at excitatory synapses, while inhibitory post-synapses were largely spared. C1q accumulation at post-synapses was also higher in the tauopathy mice than in a model of Aβ pathology, suggesting that pathological tau is particularly potent in activating the complement system.

C1q-tagged synapses are thought to be engulfed by microglia, potentially contributing to synapse loss. In line with this, tau transgenic mice had reduced synapse density and microglia in these animals had increased levels of synaptic markers within lysosomes. Thus, pathological tau likely induces C1q accumulation at synapses, tagging them for removal by microglial phagocytosis. Notably, neutralisation of C1q in tau transgenic mice, via intracerebral injection of an anti-C1q antibody, reduced microglial engulfment of synaptic components and led to a small but significant rescue of synapse density 5 days after injection, highlighting the translational potential of these results.

In addition to the C1q effects, proteomics in tau transgenic mice also revealed the downregulation of a group proteins that are involved in the regulation of Rho GTPases, which control actin dynamics and have previously been implicated as critical components in AD pathogenesis (Bolognin et al. 2014). Experimental depletion of these proteins *in vitro* resulted in reduced spine density that could be rescued by pharmacological stabilisation of actin. Thus, tau pathology may downregulate these proteins and lead to altered actin dynamics and subsequent spine loss, highlighting a molecular mechanism by which tau pathology may directly mediate synapse loss without the need for microglial engulfment.

The paper by Litvinchuk et al. in this issue further supports a role for the complement system in the development of tau pathology, tau-mediated synapse degeneration and neuron loss. Following on from their finding that central complement components are increased in human tauopathies, Litvinchuk et al. examine how signalling by C3-C3aR modulates tau pathology by crossing PS19 mice with mice deficient in *C3aR1*, the gene for C3aR. Tau transgenic mice developed tau pathology, neuroinflammation, synapse and neuronal loss, and impairments of neuronal plasticity and cognition by 9 months of age in this study. Quite remarkably, upon knock out of *C3aR1*, somatodendritic accumulation of tau was almost completely ameliorated. This was accompanied by a curtailing of neuroinflammation, rescue of synapse and neuronal loss and improvements in neuronal function. Transcriptomics of bulk tissue and specific cell types (microglia and astrocytes) revealed a host of genes related to immune pathways to be upregulated in tau transgenic mice. Strikingly, deletion of *C3aR1* normalised transcription of these immune-related genes and also reversed gene signatures typical of disease-associated microglia and neurotoxic astrocytes, which have been implicated in neurodegeneration, indicative of C3-C3aR signalling regulating these changes and mediating immune homeostasis in the context of tau pathology.

Considering that deletion of *C3aR1* had such widespread effects on many genes, Litvinchuk et al. postulated that C3aR may regulate transcription factors, particularly within microglia. Indeed, they identify the transcription factor STAT3 as a novel direct target and downstream effector of C3aR. Upon activation, the STAT family of transcription factors become phosphorylated and translocate to the nucleus where they mediate target gene transcription. Inhibition of STAT3 phosphorylation with a pharmacological compound was able to reduce tau pathology and neuroinflammation, although to a slightly lesser degree than *C3aR1* knockout, providing novel insights into this pathway that may be amenable to therapeutic intervention.

Both of these studies highlight a role for the complement system in modulating tau pathology and tau-mediated synapse loss. Taking these two studies together, it might be possible to hypothesise that, in regard to tau pathology, the complement system contributes to a ‘double-hit’ mechanism, perpetuating a cycle of exacerbated tau pathology and tau-mediated synapse loss (Fig.1). In such a cycle, enhanced activation of C3-C3aR signalling, potentially acting through STAT3, exacerbates tau pathology and neuroinflammation. Exacerbated tau pathology results in increased C1q tagging of synapses and subsequent synapse loss by microglial engulfment. Activation of the classical complement pathway via C1q leads to increased activation of C3 and increased signalling through C3aR, thereby perpetuating the cycle and exacerbating tau pathology and synapse loss, eventually leading to the gross neuronal loss and atrophy seen in AD.

Although outstanding in many ways, the current studies do have limitations. These include using a single mutant tau overexpressing transgenic model for mechanistic studies. One example of a limitation of this model is apparent in the differing phenotypes observed at the same age between these two studies. Neuron loss was not observed by one group and was observed and modulated by knockout of *C3aR1* by the other. Additionally, the human tau mutation in these transgenic models is associated with frontotemporal dementia and so may not be entirely representative of other tauopathies, such as AD. It will be valuable in

future to repeat these studies in other tau mouse models including knock-in lines and to further test whether modulating the complement system can prevent or reverse synapse dysfunction, synapse loss and neuronal loss. Nonetheless, it is encouraging that in both papers, the authors include human tissue and/or data sets and report complementary findings to those in their mouse models, suggesting these data might be translationally relevant.

Some key questions for future work remain. It is still not clear whether microglia phagocytose 'live' synapses or simply clear debris left by injured neurons. Although Dejanovic et al. suggest that, at least *in vitro*, microglia remove intact synapses, this requires further investigation. It will also be imperative to determine whether this occurs in human brain. It is interesting that Dejanovic et al. find inhibitory synapses to be largely protected from C1q-tagging and subsequent microglial engulfment. Imbalance of excitatory and inhibitory connections in the brain have repeatedly been implicated in many neurodegenerative diseases, and hopefully future work will determine why there appears to be preference for complement-mediated removal of excitatory synapses and how this impacts upon network function. It will also be important to identify synaptic receptors for C1q, which may help shed light on how synapses are selected for elimination, while also revealing targets more amenable to therapeutic intervention. In regard to Litvinchuk et al., an investigation into how C3-C3aR signalling influences the neuronal transcriptome might also reveal more mechanistic insight into how this pathway modulates tau pathology.

In conclusion, both studies support a role of the complement system in tauopathy and tau-mediated synapse degeneration, and highlight avenues for potential therapeutic intervention that warrant further investigation. This adds to a growing, dare we say "inflamed", excitement in the field surrounding the cross-talk between multiple cell types in neurodegeneration.

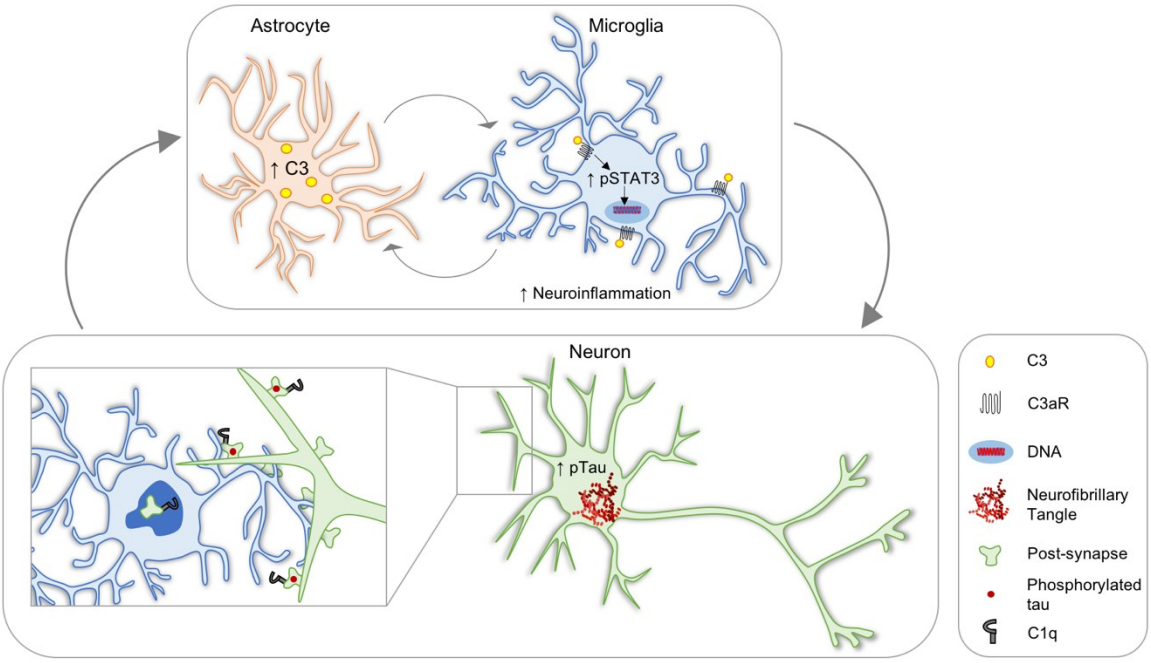

Figure 1. Role of complement in the development of tau pathology and tau-mediated synapse loss. Litvinchuk et al. show C3-C3aR signalling is augmented in human tauopathies. C3aR can act directly through the transcription factor STAT3, which becomes phosphorylated (pSTAT3) and translocates to the nucleus to mediate immune-related gene expression, increasing neuroinflammation. This is likely heightened by cross-talk between microglia and astrocytes. Increased C3-C3aR signalling also exacerbates tau pathology in neurons. Exacerbated tau pathology likely increases synaptic tau levels, resulting in the tagging of synapses with C1q and subsequent microglial engulfment, as shown by Dejanovic et al., thus contributing to tau-mediated synapse loss. Microglia may also phagocytose tau-containing synapses and contribute to the spread of tau pathology through the release of tau-containing exosomes that act as seeds. Activation of C1q leads to the initiation of the classical complement cascade, increasing C3-C3aR signalling and perpetuating the cycle of exacerbated tau pathology and synapse loss.

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Declaration of Interests
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