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Commentary

Is loss of perineuronal nets a critical pathological event in Alzheimer's disease?

Amy C. Reichelt*,[a]

[a] Department of Physiology and Pharmacology, Schulich School of Medicine and Dentistry, Western University, 1151 Richmond St, London, Ontario, Canada

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With the pathogenesis of Alzheimer's disease (AD) continuing to elude researchers, new approaches that look beyond amyloid β plaques (Aβ) deposition and tauopathy are needed to broaden the understanding of neurodegenerative mechanisms that propagate dementia.

An innovative approach to understanding cognitive impairment in neurodegenerative disorders is to look *beyond neurons* to examine extracellular structures called perineuronal nets (PNNs). PNNs are condensed extracellular matrix (ECM) structures that surround neurons, forming a key element of the tetrapartite synapse. PNNs have multiple roles, but two of the most critical are the regulation of plasticity by stabilising synapses, and the protection of neurons and synaptic connections against damaging environmental stressors [1].

Within the cortex, PNNs form protective 'scaffolds' that envelop parvalbumin-expressing (PV^+) GABAergic inhibitory interneurons that are vital for cognition [2]. The fast spiking nature of PV+ interneurons means that they have high energy demands, enhancing their susceptibility to disruption, leading to excitatory / inhibitory imbalance in the cortex and cognitive dysfunction [3].

When PNNs are degraded the protective shield surrounding neurons is removed, and exposure to neurotoxic insults can result in cell death [4]. Degradation of PNN structures is seen in a number of neurodegenerative diseases, including AD, and poses a critical pathogenic feature underpinning cognitive decline.

A hallmark of AD is neuroinflammatory changes within the cortex, thought to be both a result and cause of cell death. One of the main drivers of the neuroinflammatory process are microglia – the brain's resident immune cells [5]. Activation of microglia in AD occurs as a response to cell damage, as microglia dispose of neuronal debris by phagocytosis. However, it remains controversial whether prolonged activation of microglia is beneficial or detrimental in the pathogenesis of neurodegenerative diseases. When chronically activated, microglia can exacerbate neuronal damage through the release of proinflammatory cytokines (eg, TNF-α, IL-1β), reactive oxygen species and proteinases. Critically, these proteinases include ECM-cleaving enzymes known as matrix metalloproteinases (MMPs) – which have the capacity to cleave components of PNNs. Increased concentrations of MMPs, particularly MMP9, has been associated with the degradation of PNNs [6].

In the case of AD neuropathology, activated microglia not only secrete these PNN remodelling enzymes, but interact with injured neurons to strip away synapses [7]. Although studies using neuronal cultures show that PNNs act as a protective barrier against Aβ evoked toxicity [8], the additional activation of microglia in pathological disease states is likely to be a critical mediator of neurodegeneration.

In a study recently published by *EBioMedicine*, the link between PNN loss and microglial activation was directly examined by Crapser et al (in press [9]), using postmortem brain tissue from transgenic mouse models of Alzheimer's disease pathology and AD patients. Using detailed histological stains and fluorescent microscopy, Crapser et al., observed the loss of PNNs from the subiculum – a brain region involved in memory that becomes damaged early in the course of AD pathogenesis. Within this tissue, fragmented components of PNNs were evident within microglia in both the 5xFAD mouse model of AD and human tissue, indicating that microglial cells had engulfed PNNs, or consumed the debris from their degradation. Either way, activated microglia appear critically implicated in PNN degradation – either indirectly through the secretion of ECM-cleaving enzymes and then engulfing the resulting PNN fragments, or by directly interacting with neurons to strip away PNNs.

The suppression of microglia has been considered a therapeutic strategy in neurodegenerative states, as it may halt pathological neuroinflammation and allow regeneration. Crapser et al., show that inhibiting microglia by the administration of colony-stimulating factor 1 receptor inhibitor (CSF1R) PLX562 prevented the loss of PNNs in 5xFAD and aged 3xTg-AD mice, and also in mice systemically treated with pro-inflammatory LPS.

Increased Aβ plaque-load is associated with the progression of AD pathology. Interestingly, in human brain tissue, fragments of aggrecan - a key structural component of PNNs – was found integrated into dense-core Aβ plaques, potentially driving the pathological burden of these structures through a positive feedback loop of microglial activation, PNN loss, Aβ-accumulation and neuroinflammation (Fig. 1).

After PNN degradation or damage, the neurons that they had surrounded become vulnerable to environmental toxicity but are also more plastic and readily form new synapses. It is a possibility that

* Corresponding author.
E-mail address: Areiche4@uwo.ca

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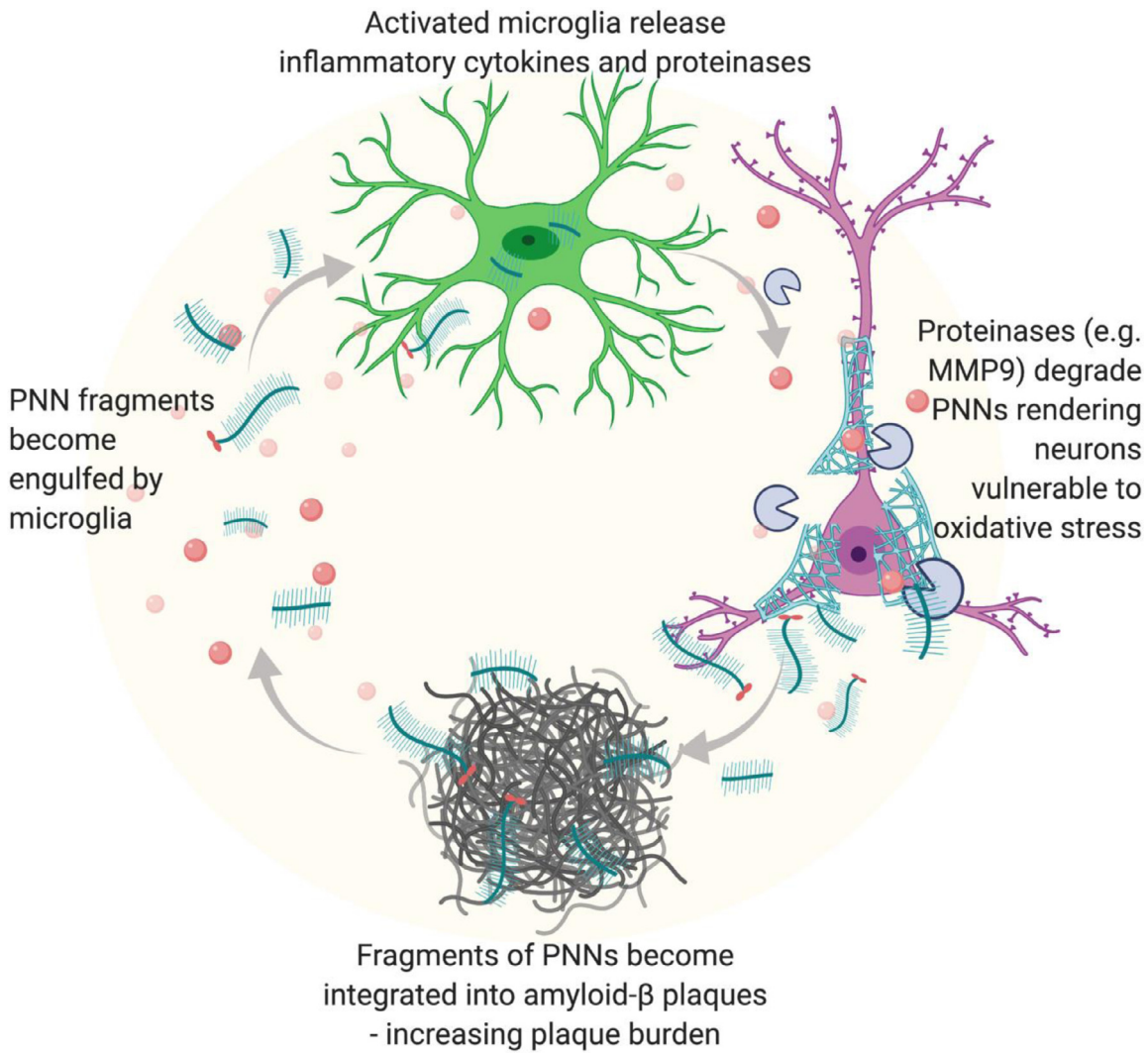

Fig. 1. Positive feedback loop of pathogenesis driven by microglia activation and damage to PNNs in Alzheimer's disease (made in ©BioRender - biorender.com).

the initial loss of PNNs in neurodegenerative disease acts as an endogenous compensatory mechanism to facilitate synaptic plasticity and reduce cognitive decline. Certainly, preclinical studies show that removal of PNNs can restore memory in mouse models of AD-pathologies [10]. However, with extended neuropathological progressions of disease, such as that seen in AD, the damage to neuroprotective PNNs surrounding neurons is likely to accelerate degeneration and exacerbate dementia, leading to advanced cognitive decline.

Author Declaration

The author has no conflicts of interest to disclose.

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