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Editorial

The Importance (or Not?) of Perineuronal Nets in Neurodegenerative Diseases

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Editorial

Perineuronal Nets (PNNs) are specialized form of extracellular matrix. They typically form around fast-spiking parvalbumin-positive neurons during development, and are one of the events determining the end of critical periods [1]. Although PNNs are dynamically remodelled during plastic phenomena, their fundamental structure is stable and remains on PNN-bearing neurons for the rest of their lives. In fact, it has been suggested that PNNs and other extracellular matrix components increase with age, potentially accounting for the further loss of plasticity in elderly [2]. PNNs enwrap neuronal bodies and the basal part of their dendrites, and exert several physiological functions [3]. They contribute to regulation of the diffusion properties in the extracellular space [4] and serve as local reservoir of ions for the specific needs of fast-spiking neurons [5]. In continuity with their role in the closure of the critical period, in adulthood PNNs maintain a physiological level of neuronal plasticity, which fails to be achieved when PNNs key components are genetically defective [6,7]. At least part of this function is exerted by a specific action of PNNs and their components on synaptic plasticity. Indeed, PNNs modulate synaptic terminal size and quantity, spines motility, receptors diffusion [8-10]. Given these important roles of PNNs, it is not surprising that defective PNNs are associated with several pathological conditions. Morawski and collaborators have demonstrated the protective role of PNNs against oxidative stress [11]. McRae's group has demonstrated a complex relationship between seizures, PNNs degradation, and the instauration of status epilepticus [12]. Berretta and colleagues have pointed out the involvement of PNNs in schizophrenia [13]. Thus, if on the one hand reducing the PNNs has been suggested as a promising strategy to increase plasticity and improve recovery after CNS injuries [14], on the other hand a general protective role of PNNs against the spreading of misfolded proteins and of oxidative stress is widely recognised [11].

These two contrasting aspects of PNNs functions have to be considered with particular care when searching for therapies against neurodegenerative diseases. A typical example of this dilemma is represented by studies on Alzheimer's Disease (AD). From Bruckner to Morawski, several papers show that PNN-bearing neurons are selectively spared by Tau spreading, thus able to better survive neurodegeneration. A recent paper suggests that Tau associates to the PNNs, which constitute a barrier for Tau penetration inside the neurons. This barrier is far less effective when specific components of the PNNs are lacking, however, neurons enwrapped by defective nets are still more resistant than naked neurons [15]. This line of evidence highly supports the protective function of PNNs. However, key components of PNNs are glycosaminoglycans, which can interact with misfolding proteins and increase their aggregation. It is still debated whether this action of glycosaminoglycans is potentially therapeutic, as fibrils are more stable than oligomers, or it can in fact be detrimental, as also the formation of oligomers from misfolded protein is increased. Moreover, fibrils load is eventually enhanced, increasing the likelihood of neuronal suffering and disease spreading [16]. Further research on AD pathogenesis is needed to clarify this point. To add on this complex scenario, a different line of research has demonstrated that extracellular matrix and PNNs increase in brain areas affected by the pathology and may have a role in memory loss. Degrading extracellular matrix and PNNs with chondroitinase contrasts the symptom onset and even restores learning and memory in animals with clear deficit [2,17]. In contrast with the hypothesized protective role of PNNs, PNNs degradation after chondroitinase does not seem to increase neurons vulnerability. This might be explained with the fact that PNN molecules turnover is not affected, thus neurons remain protected while plasticity is increased. Alternatively, the increased plasticity obtained with PNNs degradation may activate some compensative mechanisms (S.J. Yang, personal communication). While no clear PNNs changes have been found in AD [11], a PNNs decrease has been observed in a non-AD model of Senescence-Accelerated Mouse (SAMP10) [18]. The same strain of mice show increased oxidative stress associated with a decrease in Superoxide Dismutase (SOD) [19]. Unfortunately, it is not clear whether PNNs reduction precedes or follows oxidative stress and neurodegeneration in SAMP10 mice, nor if behavioral deficits are anyhow dependent on this PNNs reduction.

Oxidative stress and PNNs play also a role in motor neuron diseases. The most known kind of Amyotrophic Lateral Sclerosis (ALS) is in fact determined by mutations in SOD1. As the superoxide dismutase cannot catalyse reactive oxygen, oxidative stress can induce neurodegeneration [20]. It has been demonstrated that rats in the presymptomatic stage have normal PNNs and even up regulated extracellular matrix molecules [21]. However, as the disease proceeds, this pattern changes, and toward the terminal stage the PNNs surrounding motor neurons result attenuated [22]. Since PNNs decrease appears at a stage when neurons are already suffering from oxidative stress, it is tempting to suggest that PNNs loss is not causally involved in the disease progression. In fact, it could be a secondary effect of the disease. Indirect evidence corroborates this hypothesis. Neurons selectively degenerating in SOD1 mutants express the enzyme MMP9. MMP9 activity mediates the onset of neuronal stress and protein misfolding, which eventually lead to neuronal death

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[23]. However, as member of the metalloproteinases family, MMP9 activity is also responsible for extracellular matrix degradation [24], which could account for the late PNNs loss in neurons affected by ALS. If PNNs decrease is not directly involved in the pathogenesis of ALS, it is nonetheless possible that it exacerbates the disease progression. Indeed, it has recently been demonstrated that exogenous administration of another protease able to degrade PNNs components, ADAMST4, promotes further neurodegeneration. Interestingly, endogenous ADAMST4 is downregulated in SOD1 mutants, suggesting a tentative compensation from the affected neurons [25].

On the contrary, PNNs loss is an early event in prion diseases. Interestingly, parvalbumin interneurons do not express the native form of prion protein, but die after the spreading of the insoluble form. It has then been suggested that PNNs surrounding these neurons are somehow affected by the pathological form of prion protein [26]. Microglia activation at the beginning of the infection could participate in PNNs degradation. PNNs and Concomitant synapses loss seem to account for the onset of behavioral anomalies in prion diseases [27]. Moreover, after PNNs disappearance, the protease-resistant form of prion accumulates on the surface of parvalbumin interneurons which subsequently die [28]. Surprisingly, this model sharply contrasts with morphological data collected from scrapie affected sheep. In this species, indeed, PNNs are not affected at any point during the disease, whereas the infective prion is associated with a decrease of parvalbumin expression before neuronal death [29]. The difficult interpretation of these results could be due to the high individual variability in prion infections. A recent paper [30] sheds some light on the mechanisms accounting for different susceptibility of distinct cell populations to the infection. It seems that a complex network of extracellular matrix molecules is involved in neuronal resistance, and anomalies in each of them increase prion propagation. Thus PNNs may not be directly involved in prion diseases, but rather be affected within the scenario of a generally perturbed homeostasis of the extracellular matrix. Interestingly, as mentioned for AD, also in this case specific glycosaminoglycans more than the PNNs seem to be involved in transformation and aggregation of prions [16].

Summarising, it is not possible to draft any conclusion about a causal relationship between the presence or absence of PNNs and the progression of the considered neurodegenerative diseases. In AD, PNNs are stable and enwrapped neurons survive; PNNs degradation may introduce a risk factor for neuronal survival, but can also contrast memory loss thanks to increased terminal plasticity. In ALS, PNNs decrease in the terminal stage when neuronal death is already substantial; PNNs degradation is not causing neuronal death, but it can accelerate the pathology progression. In prion diseases, PNNs decrease early, but this phenomenon seems to be unrelated to neuronal death; prion infections have high intrinsic variability and may affect in parallel neurons and nets. In other neurodegenerative diseases, such as Parkinson's, Huntington's, Pick's Diseases, PNNs do not seem to be involved at all. Thus, PNNs as specialized structures have a clear role on terminal plasticity, but, relatively to neurodegenerative diseases, specific PNNs and extracellular matrix components are differentially involved and should be studied better separately.

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