Targeting aged astrocytes may be a new therapeutic strategy in Parkinson's disease

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Parkinson's disease (PD) becomes increasingly common with advancing age. It is therefore possible that cell senescence contributes to its pathophysiology. In a recent paper in Cell Reports, Chinta et al[1] have shown that astrocytes exhibiting an age-associated (senescent) phenotype are toxic to neurons in vitro, and their removal is associated with better outcomes in a mouse model of PD. This finding may be relevant to other neurodegenerative conditions such as Alzheimer's and Amyotrophic Lateral Sclerosis (ALS) in which cellular senescence is also implicated.[2]

Cellular senescence is not necessarily deterimental.[3] It involves the termination of cell growth, followed by development of a senescence-associated "secretory" phenotype (SASP) that recruits immune cells such as macrophages.[3] Nearby progenitor cells are then prompted to engage in repair.[3] In the context of tissue damage this is initially helpful, but can lead to further damage once clearance mechanisms are saturated.

In post-mortem tissue from the substantia nigra of 5 PD patients and 5 controls, Chinta et al show that PD astrocytes have higher expression of senescence markers and elevated levels of inflammatory cytokines and metalloproteinases associated with a SASP. In human cell culture models, astrocytes and fibroblasts show a more senescent phenotype when exposed to paraquat, a herbicide associated with PD risk, and this is associated with the production of factors, including IL-6, which are toxic to dopaminergic neurons. In a mouse model in which senescent astrocytes are selectively depleted, neurodegeneration is attenuated in response to paraquat, with better performance on motor tasks and decreased nigral dopaminergic cell loss.[1]

These findings raise the interesting possibility that astrocyte senescence contributes to PD pathology and as such could represent a novel target for disease-modifying therapy.

However, toxin-based models have important limitations in terms of their ability to replicate the pathology of idiopathic PD, and such models have not been successful to date in identifying effective therapeutic targets. Another important consideration is whether the relevance of astrocyte senescence is restricted to the early pathological stages of PD– in which case 'real-world' disease may present too late for astrocyte modification to succeed as a therapeutic strategy. Hence the critical question to now be addressed is whether astrocyte senescence is associated with faster clinical progression of PD. PET ligands to image reactive astrocytes in vivo are now in development,[4] which, in conjunction with CSF markers of the SASP, may facilitate such studies of the natural history of astrocyte senescence in PD.

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