SUPPLEMENTARY DATA

Cellular Senescence and White-Matter Injury: A Proposed Glial Cascade in AD and Cerebral SVD

Ximing Li, Hanying Xu, Ying Zhang, Dongxu Li, Wenchuan Wang, Yang Wu, Qingjie Li, Hongmei Nan

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SUPPLEMENTARY DATA

Supplementary Table 1. Supporting study details for the evidence summarized in Table 2

Related Table 2 entry	Supporting study details
Aging → microglial senescence	[49] localized p16, p21 and p53 separately to microglia. [13] did not assess senescence. AD cortex: senescence gene sets enriched in microglia, and more GLB1- and p16-immunoreactive glia than age-similar controls [39]. Dystrophic microglia express few conventional markers [137].
Microglial senescence → increased white-matter inflammation	p16-positive microglia incorporated less EdU than p16-negative microglia in old mice [17]. γH2AX increased in microglia isolated from old mice but was not shown in the same p16-positive cells; lysosomal changes and cell-specific secretion were not assessed.
Microglial inflammatory signaling → impaired OPC differentiation or oligodendrocyte maturation	Human microglial supernatants were applied to directly converted human $O4^+$ oligodendrocytes undergoing terminal maturation [62] and cytokines to human OPCs [53].
Age- or disease-altered OPC niche → impaired OPC differentiation	Long-term-cultured astrocytes showed increased p16, p21 and p53 expression and SA-β-gal activity [59]. PPMS NPCs showed increased SA-β-gal activity and p16/p53 transcripts, with cell-cycle analysis no different from controls. Conditioned medium from human PPMS-derived NPCs impaired rat OPC differentiation through HMGB1; the p16-expressing progenitors in MS lesions were SOX2-positive [68]. Senescence was not assessed in the separate aging model [67].
Impaired OPC differentiation → remyelination failure	Aged OPC populations showed higher Cdkn2a expression [64], and p16/Cdkn2a-expressing OPCs increased with age [70]. OPC density in chronic MS lesions was lower than in periplaque white matter [65].
Endothelial senescence → barrier disruption and reduced perfusion	p16-reporter-positive CD31-positive cells and endothelial senescence-related transcriptomic signatures were assessed in separate analyses [19]. Six months after adeno-associated viral vector administration, exogenous human CDKN2A mRNA was undetectable in the cortex, and no evident senescence signatures were detected in the brain [20]. Human endothelial cultures were exposed to hydrogen peroxide [93]. Outcomes differ across disease models [96], and normal aging does not necessarily increase paracellular permeability [94].
Fibrinogen exposure → impaired OPC differentiation and remyelination	Chronic MS lesions showed perivascular fibrinogen with lower Id2, whereas remyelinated lesions showed minimal fibrinogen with control-level Id2 [98].
Reduced perfusion → white-matter injury	Carotid artery stenosis triggered microgliosis, astrogliosis and demyelination confined to cortical layer 6 and the corpus callosum [99].
White-matter injury → cognitive impairment	In rhesus monkeys, intracortical myelin alterations in prefrontal area 46 correlated with the overall cognitive-impairment index, whereas corpus-callosum alterations correlated only with performance on the 2-min delayed nonmatching-to-sample task [74]. A narrative synthesis places white-matter hyperintensities within the spectrum of vascular cognitive impairment [109].

Entries follow the order of the corresponding links in Table 2. These details supplement its findings and limitations; grades are defined in Table 1. Reference numbers follow the main reference list. AD, Alzheimer's disease; CD, cluster of differentiation; EdU, 5-ethynyl-2'-deoxyuridine; GLB1, galactosidase beta 1; HMGB1, high-mobility group box 1; Id2, inhibitor of DNA binding 2; MS, multiple sclerosis; NPC, neural progenitor cell; OPC, oligodendrocyte precursor cell; PPMS, primary progressive multiple sclerosis; SA-β-gal, senescence-associated β-galactosidase.

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