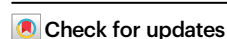


Spatially-restricted inflammation-induced senescent-like glia in multiple sclerosis and patient-derived organoids

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In multiple sclerosis (MS), chronic compartmentalized inflammation is thought to drive relentless clinical deterioration. Here, we investigate the link between unresolved parenchymal inflammation and cellular senescence in MS progression. Single-cell transcriptomic analysis of human brain tissue reveals an accumulation of senescent-like glial cells in diseased white matter, especially in chronic active lesions, and to a lesser extent in the cortex. Spatial transcriptomics show gradients of senescence-like signatures extending from lesion cores to periplaque regions, alongside rewired cellular networks. Experimental induction of senescence in MS hiPSC-derived neural organoids demonstrates that microglia are especially vulnerable to inflammation-induced senescence, which can be partially rescued by CNS-penetrant anti-inflammatory drugs. At the patient level ($n = 466$), increased 3T MRI-estimated brain-age is observed, especially in individuals with more than four chronic active lesions. These findings suggest that chronic inflammation might accelerate senescence-like processes, potentially contributing to disease progression, and that its modulation might help limit further propagation.

Multiple sclerosis (MS) is a lifelong and disabling disease of the central nervous system (CNS) in which waves of peripheral immune attacks on the CNS are accompanied by compartmentalized inflammatory and neurodegenerative processes, leading to cumulative disability¹. While existing disease-modifying treatments effectively control peripheral immune responses and mitigate relapse-associated inflammatory activity, they demonstrate limited efficacy in halting disease progression that occurs independently of relapses (referred to as PIRA or silent

progression)². Growing evidence supports the role of unresolved smoldering CNS inflammation, as occurs at the leading edge of chronic active MS lesions (observable in vivo as paramagnetic rim lesions or PRL on MRI)^{3,4}, in relentless clinical progression^{5–7}. Through single-nucleus RNA sequencing (snRNA-seq) blueprinting, we recently highlighted the coexistence at the chronic active lesion edge of self-sustaining glia-mediated pathological processes as well as, to a lesser extent, resident lymphocyte-driven inflammation⁸.

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