Researchers identify new cell source for microgliosis in neurodegenerative diseases

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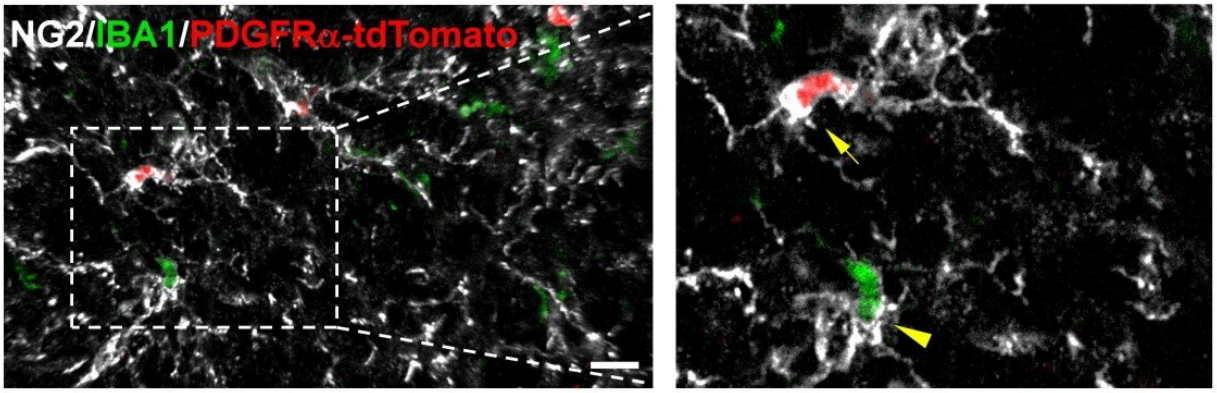

Cspg4^{+} microglia in Pdgfra:tdTomato double transgenic mice. Immunohistochemical stainingfor NG2 and IBA1 in Pdgfra:tdTomato mice. Scale bar 20 μm. Arrows indicate NG2^{+}/PDGFRα-tdTomato OPC. Arrowheads indicate NG2^{+}/IBA1^{+} microglia. Credit: *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2210643120

In a study published in *Proceedings of the National Academy of Sciences*, a research team led by Dr. Zhou Jiawei at the Institute of Neuroscience, Center for Excellence in Brain Science and Intelligence Technology of the Chinese Academy of Sciences found that Cspg4^{high} microglia is a new cell source for microgliosis in neurodegeneration, and they unraveled the molecular characteristics and functions of Cspg4^{high} microglia, which showed high cell proliferation in neurodegenerative

diseases, thus providing a new insight into the pathogenesis of neurodegenerative diseases.

Emerging evidence has strongly suggested that microglia are a key player in the pathogenesis of neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease. Upon pathological stimulation, microglia, resident immune cells in the brain, are rapidly activated and migrate toward the injured brain sites. Activated microglia play crucial roles in neuroinflammation, protein deposition and phagocytosis. Aberrant activation of these cells is believed to contribute significantly to the initiation and progression of neurodegenerative diseases.

It has been suggested that microglia may be used for early diagnosis and treatment of neurodegenerative diseases. However, the origin of the activation of microglia during neurodegeneration remains incompletely understood. Traditionally, activated microglial cells in the brain have been believed to originate from themselves and the bone marrow-derived precursor cells. Understanding their origin is essential for controlling deregulated microglial activity.

The researchers identified chondroitin sulfate proteoglycan 4 (Cspg4, also known as neural/glial antigen 2) expressing microglia as a specific subset of microglia with proliferative capability during neurodegeneration.

The percentage of $Cspg4^{+}$ microglia was increased in mouse models of Parkinson's disease. Transcriptome analysis of $Cspg4^{+}$ microglia revealed that the subcluster $Cspg4^{high}$ microglia displayed a unique transcriptomic signature, which was characterized by enrichment of orthologous cell-cycle genes and a lower expression of genes responsible for neuroinflammation and phagocytosis. Their gene signatures were also distinct from that of known disease-associated microglia.

The proliferation of quiescent Cspg4^{high} microglia was evoked by pathological a-synuclein. Following transplantation in the adult brain with depletion of endogenous microglia, Cspg4^{high} microglia grafts showed higher survival rates than their Cspg4^{-} counterparts.

Consistently, Cspg4^{high} microglia were detected in the brain of Alzheimer's disease patients and displayed the expansion in animal models of Alzheimer's disease.

These findings suggest that Cspg4^{high} microglia are one of the origins of microgliosis during neurodegeneration and may open a new avenue for the treatment of neurodegenerative diseases.

More information: Ya-jing Liu et al, Cspg4^{high} microglia contribute to microgliosis during neurodegeneration, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2210643120

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