News Release

Title

Microglial gene signature reveals loss of homeostatic microglia as a key event for driving neurodegeneration of Alzheimer's disease

Key Points

- **Microglial gene signature in mice revealed that a loss of homeostatic microglia function is correlated with the degree of neuronal cell loss.**
- **In human brains of early Alzheimer pathology, gene expression analyses indicate a loss of microglia and oligodendrocyte function induced by early amyloid pathology.**
- **Results from the present study indicate a correlation between glial phenotypes and severity of neurodegeneration, and also provide important resources to better understand the role of glial dysfunction in progression of Alzheimer's disease.**

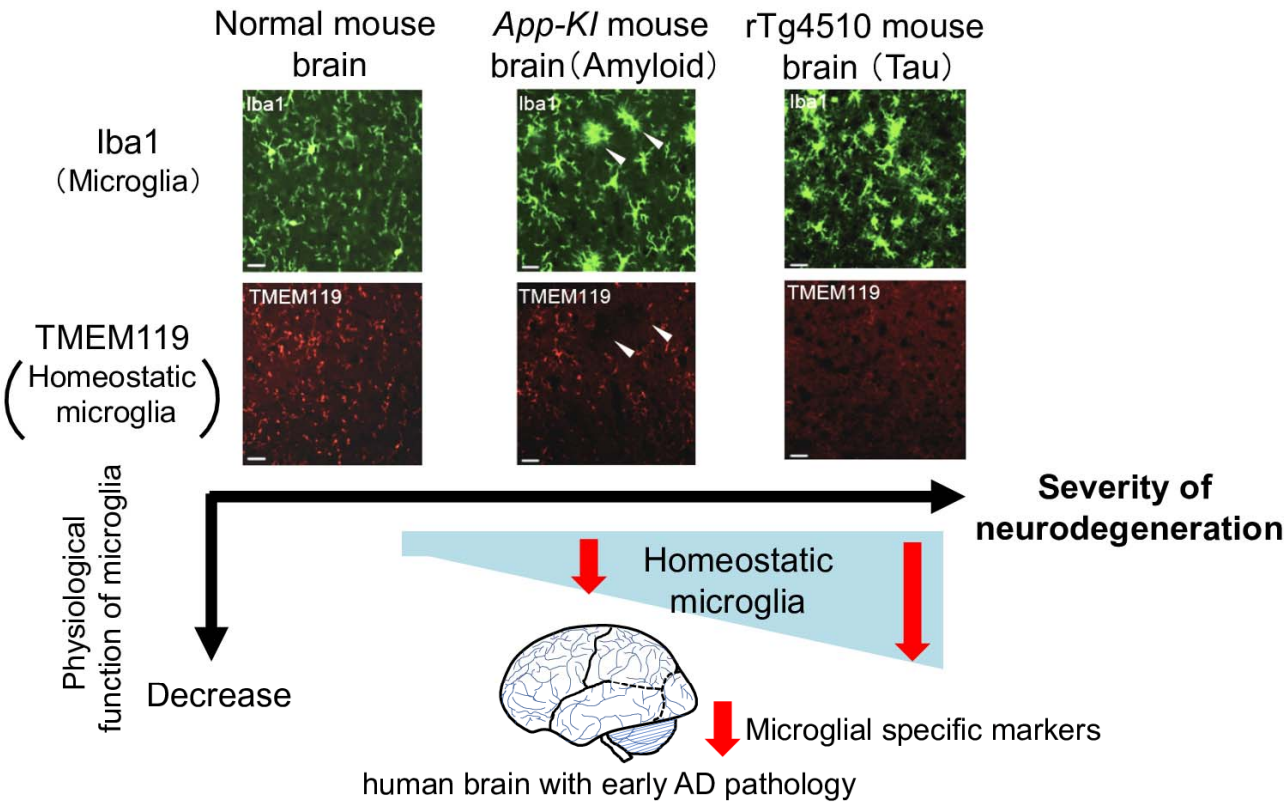

Fig. Microglial gene signature in mice revealed that a loss of homeostatic microglia function is associated with the degree of neuronal cell loss. In human, our analysis of the precuneus of early AD pathology also suggests a loss of microglia and oligodendrocyte function induced by early amyloid pathology.

Summary

Assistant Prof. Akira Sobue and Prof. Koji Yamanaka (Department of Neuroscience and Pathobiology, RIEM / Nagoya University Graduate School of Medicine) found that microglial gene signature reveals loss of homeostatic microglia as a key event for driving neurodegeneration of Alzheimer's disease.

Microglia-mediated neuroinflammation has been implicated in the disease process of Alzheimer's disease (AD) and other neurodegenerative diseases. Microglia in aging and neurodegenerative disease model mice show loss of homeostatic phenotype and disease-associated microglia (DAM), a recently proposed activation phenotype. However, the correlation between those phenotypes and severity of neurodegeneration is not known. Moreover, details of glial phenotype in human brain with early AD pathology are not fully elucidated.

In this study, the research group analyzed gene expression profiles of microglia isolated by magnetic activated cell sorting (MACS) from three mouse models for neurodegenerative diseases: $App^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ mice that display an amyloid pathology, rTg4510 mice with tauopathy, and $SOD1^{G93A}$ mice with motor neurodegeneration by RNA-sequencing. Despite robust neuroinflammation with microglial responses in all mouse models, $App^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ mice do not show neuronal death, whereas rTg4510 and $SOD1^{G93A}$ mice show a substantial loss of neurons.

The group found that the reduction of homeostatic microglial genes was correlated with severity of neurodegeneration, whereas DAM genes were uniformly upregulated in all mouse models. Moreover, in human precuneus with early AD pathology, reduced gene expressions of microglia and oligodendrocytes were observed, although DAM genes were not upregulated.

Results from the present study indicate a correlation between glial phenotypes and severity of neurodegeneration, and also provide important resources to better understand the role of glial dysfunction in progression of Alzheimer's disease.

Research Background

Alzheimer's disease (AD) is the most common form of dementia, characterized by accumulation of amyloid β (Aβ) and phosphorylated Tau in brain. Microglia, immune cells of brain, surround and contact Aβ deposits in the brains of patients and animal models of AD. Microglia-mediated neuroinflammation has been implicated in the pathogenesis of AD. Although microglia in aging and neurodegenerative disease model mice show a loss of homeostatic phenotype and activation of DAM, a correlation between those phenotypes and the degree of neuronal cell loss has not been clarified. Moreover, details of glial phenotype in human brain of early AD pathology are not fully elucidated.

Research Results

The research group performed RNA sequencing of microglia isolated from three representative neurodegenerative mouse models, $App^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ with amyloid pathology, rTg4510 with tauopathy, and $SOD1^{G93A}$ with motor neuron disease by magnetic activated cell sorting. In parallel, gene expression patterns of the human precuneus with early Alzheimer's change and control brain were also analyzed by RNA sequencing for the first time. Precuneus, located in an inner side of parietal lobe of brain, is known as a

component of a default mode network and a lesion where Aβ accumulates in preclinical stage of AD. The group found that a substantial reduction of homeostatic microglial genes in rTg4510 and SOD1^{G93A} microglia, whereas DAM genes were uniformly upregulated in all mouse models. The reduction of homeostatic microglial genes was correlated with the degree of neuronal cell loss. In human precuneus with early AD pathology, reduced expression of genes related to microglia- and oligodendrocyte-specific markers was observed, although the expression of DAM genes was not upregulated. Our results implicate a loss of homeostatic microglial function in the progression of AD. Moreover, analyses of human precuneus also suggest loss of microglia and oligodendrocyte functions induced by early amyloid pathology in human.

Research Summary and Future Perspective

Microglial gene signature in mice revealed that a loss of homeostatic microglia function is associated with the degree of neuronal cell loss. In humans, our evaluation of the precuneus of early AD pathology also suggests a loss of microglia and oligodendrocyte function induced by early amyloid pathology. Results from the present study indicate a correlation between glial phenotypes and severity of neurodegeneration, and also provide important resources to better understand the role of glial dysfunction in progression of Alzheimer's disease.

Publication

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Akira Sobue[1,2], Okiru Komine[1,2], Yuichiro Hara[3,4,5], Fumito Endo[1,2], Hiroyuki Mizoguchi[6,7], Seiji Watanabe[1,2], Shigeo Murayama[8,9], Takashi Saito[1,10], Takaomi C Saido[11], Naruhiko Sahara[12], Makoto Higuchi[12], Tomoo Ogi[3,4], Koji Yamanaka[1,2*]

Institutions:

[1]Department of Neuroscience and Pathobiology, Research Institute of Environmental Medicine, Nagoya University, Aichi, 464-8601, Japan.

[2]Department of Neuroscience and Pathobiology, Nagoya University Graduate School of Medicine, Aichi, 466-8550, Japan.

[3]Department of Genetics, Research Institute of Environmental Medicine, Nagoya University, Aichi, 464-8601, Japan.

[4]Department of Human Genetics and Molecular Biology, Nagoya University Graduate School of Medicine, Aichi, 466-8550, Japan.

[5]Research Center for Genome & Medical Sciences, Tokyo Metropolitan Institute of Medical Science, Tokyo 156-8506, Japan.

[6]Research Center for Next-Generation Drug Development, Research Institute of Environmental Medicine, Nagoya University, Aichi, 464-8601, Japan.

[7]Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine, Aichi, 466-8550, Japan.

[8]Brain Bank for Aging Research, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo,

173-0015, Japan
[9]Brain Bank for Neurodevelopmental, Neurological and Psychiatric Disorders, United Graduate School of Child Development, Osaka University, Osaka, Japan.
[10]Department of Neurocognitive Science, Institute of Brain Science, Nagoya City University Graduate School of Medical Sciences, Aichi, 467-8601, Japan.
[11]Laboratory for Proteolytic Neuroscience, RIKEN Center for Brain Science, Saitama, 351-0198, Japan
[12]Department of Functional Brain Imaging, National Institute of Radiological Sciences, National Institutes for Quantum and Radiological Science and Technology, Chiba, 263–8555, Japan

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