CLINICAL IMPLICATIONS OF BASIC RESEARCH

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TREM2 and Risk of Alzheimer's Disease — Friend or Foe?

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Alzheimer's disease is a genetically complex and heterogeneous disorder. Genomewide association studies aimed at identifying gene variants that influence the risk of Alzheimer's disease have implicated several innate immunity genes, including those involved in microglial activation, neuroinflammation, and clearance of the toxic peptide amyloid-beta 42 (Aβ-42). For example, one of these genes, *CD33*, encodes a protein that, when active in microglia, inhibits microglial uptake and clearance of Aβ-42, thereby promoting the pathological features of Aβ-42,[1] which are characterized by the accumulation of Aβ-42 peptides in plaques. Neurofibrillary tangles, partly made up of the hyperphosphorylated tau protein, constitute another prominent feature of the disease.

TREM2, the triggering receptor expressed on myeloid cells 2 protein, is an innate immune receptor that is expressed on the surface of myeloid cells, such as monocytes, macrophages, and microglia in the brain. Homozygous mutations in the *TREM2* gene have been shown to lead to a form of dementia known as Nasu–Hakola disease, which often involves bone cysts and frequent fractures. One of these mutations, R47H, has also been shown to confer a risk of late-onset Alzheimer's disease when in the heterozygous state.[2,3]

Jay et al.[4] recently found that levels of TREM2 expression are up-regulated in myeloid cells that accumulate around Aβ plaques in two mouse models of Alzheimer's disease and in the brain tissue of persons with Alzheimer's disease. They observed that TREM2 was expressed specifically on a type of macrophage originating from peripheral monocytes that infiltrate the brain parenchyma. They also detected TREM2 in CD45+ macrophages surrounding Aβ plaques, but they did not detect it in resident microglia. Interestingly, knockout of *Trem2* in a specific mouse model of Alzheimer's disease (the APP/PS1 mouse) led to a dramatic reduction in Aβ-associated macrophages but no changes in the numbers of resident microglia (Fig. 1A). These *Trem2*-deficient mice also had less brain inflammation and astrocytosis, fewer Aβ plaques in the hippocampus, and attenuated hyperphosphorylation of the tau protein, as compared with APP/PS1 mice with intact *Trem2*. Together, these results suggest that TREM2+ macrophages contribute to the pathological features of Alzheimer's disease.[4]

These findings contrast with those reported by other groups. Wang et al.[5] found that knockout of *Trem2* in another mouse model (the 5xFAD mouse) led to exacerbation of the disease, with an increased burden of Aβ plaques in the hippocampus due to a dysfunctional response of microglia, in which they fail to accumulate around Aβ plaques while also undergoing apoptosis. *Trem2* deficiency was also reported to lead to a marked reduction in resident microglia around Aβ plaques, which suggests that TREM2 deficiency adversely affects the ability of resident microglia to surround and clear Aβ plaques (Fig. 1B).

Also supporting this conclusion are the results of a study by Hickman and colleagues[6], showing that TREM2 is highly expressed by resident microglia in wild-type mice. And Kleinberger et al.[7] found that the part of TREM2 that extrudes from the cell surface is cleaved by a protease and that soluble TREM2 levels are decreased in the cerebrospinal fluid of patients with Alzheimer's disease and frontotemporal dementia. These findings further suggest that compromised TREM2 function increases the risk of these two forms of dementia. Wang et al. found that TREM2 recognizes a broad array of lipids that accumulate during Aβ deposition and that the R47H mutation impairs TREM2 recognition of lipid ligands,[5] suggesting that TREM2 functions as a microglial sensor for damage-associated lipids and mediates a protective microglial response in Alzheimer's disease. Together, these results suggest that TREM2+ microglia have a beneficial role in patients with Alzheimer's disease.[5,7]

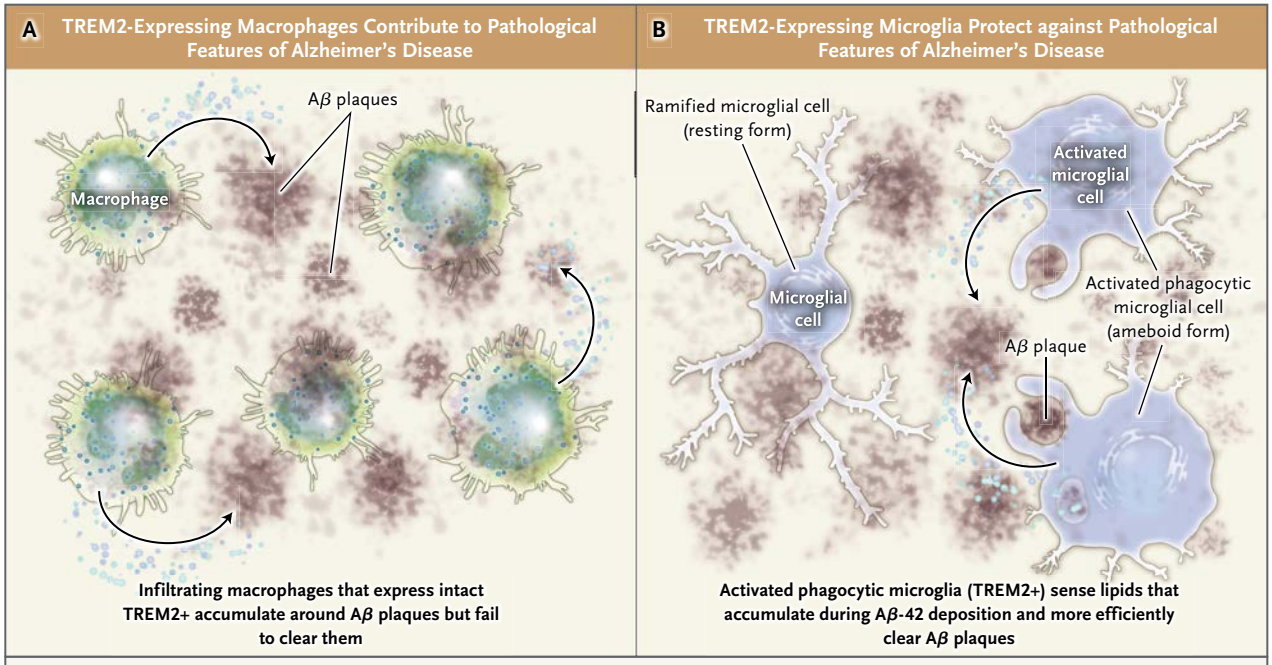

Figure 1. Different Takes on TREM2.

How variant *TREM2*, the gene encoding the triggering receptor expressed on myeloid cells 2 protein, confers susceptibility to Alzheimer's disease is not clear. Experiments with the use of mouse models indicate different potential mechanisms. Jay et al.[4] recently found that infiltrating macrophages in the brain (Trem2+ and CD45+) accumulate around amyloid-beta (Aβ) plaques but fail to efficiently clear them — that is, macrophages expressing intact TREM2 may contribute to the pathological features of the disease. In contrast, Wang et al.[5] found that TREM2+ microglia, resident in the brain, sense lipids that accumulate during Aβ-42 deposition and thereby more efficiently clear pathologic plaques.

Thus, different studies indicate opposite effects of TREM2 ablation on neuroinflammation and the Aβ plaque burden in the hippocampus in the pathogenesis of Alzheimer's disease. These different outcomes could be due to the use of different mouse models of Alzheimer's disease and *Trem2* knockout, as well as to analyses performed at different time points. In any event, TREM2 has been shown previously to play an important role in the clearance of injured and dying neurons,[8] which could suggest a common mechanism for TREM2 function in various neurodegenerative disorders, such as Alzheimer's disease, frontotemporal dementia, Parkinson's disease, and amyotrophic lateral sclerosis. Future research with the use of *Trem2* conditional knockout mice and behavior analyses, as well as the identification of TREM2-mediated microglial gene-expression signatures, should provide a better understanding of TREM2 action in microglial cells and will hopefully lead to the development of new therapeutics for the prevention and treatment of Alzheimer's disease and other neurodegenerative disorders.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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