EDITORIALS

Variant *TREM2* as Risk Factor for Alzheimer's Disease

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Current knowledge about the pathogenic mechanism of Alzheimer's disease is based mainly on rare, high-penetrance variants in genes encoding amyloid precursor protein, presenilin 1, and presenilin 2, which result in familial early-onset Alzheimer's disease. However, Alzheimer's disease is predominantly a sporadic late-onset disease with exponentially increasing prevalence starting at the age of 65 years. Genomewide association studies have recently identified several risk variants for late-onset Alzheimer's disease, but aside from the well-known ε4 allele of apolipoprotein E, these variants are generally associated with very low risk; in addition, such variants are noncoding and more challenging to link to molecular function. It has been suggested that lower-prevalence coding variants that have been missed in genomewide association studies might contain functional variants with an increased effect, although early returns from exome-sequencing studies have been modest at best.

Pursuing the hypothesis that low-prevalence variants cause Alzheimer's disease with a moderate-to-high effect size, two groups of researchers[1,2] convincingly show in the *Journal* that rare variants in *TREM2*, encoding triggering receptor expressed on myeloid cells 2 protein, cause susceptibility to late-onset Alzheimer's disease, with an odds ratio similar to that of the apolipoprotein E ε4 allele. Although the most compelling *TREM2* variant (encoding a substitution of arginine by histidine at residue 47 [R47H] of the TREM2 protein) is rare, with an allelic prevalence of 0.63% in Iceland,[1] these findings implicate a gene and naturally arising perturbation that may generate new insights into the pathogenesis of late-onset Alzheimer's disease.

The two groups of investigators used a combination of direct sequencing in some study participants and imputation (genotypic inference of untyped markers) in data from genomewide association studies to implicate the R47H variant of *TREM2* in late-onset Alzheimer's disease. Jonsson et al.[1] derived additional statistical power by using the highly homogeneous population of Iceland, where R47H is somewhat more common and more accurately imputed from data from genomewide analysis studies than it is elsewhere in the world, although as expected, the biologic effect of the variant was consistent across the many populations studied by the two groups. Not surprisingly, the more heterogeneous population studied by Guerreiro et al.[2] appears to contain a broader spectrum of alleles.

TREM2 is an innate immune receptor expressed on the cell membrane of a subset of myeloid cells — namely, immature dendritic cells, osteoclasts, tissue macrophages, and microglia. TREM2 is a member of the immunoglobulin family and has been shown to act as a phagocytic receptor of bacteria.[3] It recognizes anionic lipopolysaccharides in the cell wall of bacteria and signals through a transmembrane adapter protein called TYROBP (also called DAP12) (Fig. 1). When a bacterium binds to TREM2 on macrophages, activation of the signaling pathway triggers the phagocytic uptake of bacteria and the release of reactive oxygen species.[4]

Furthermore, TREM2 on microglia is critical to the clearance of neural debris of the lesioned central nervous system.[5] The endogenous ligand of the lesioned neural tissue that is recognized by TREM2 is still unknown. TREM2 signaling through TYROBP creates an antiinflammatory

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cytokine milieu while mediating the clearance of apoptotic neural tissue. TREM2 can thus be described as a receptor that clears the damaged or degenerated tissue and resolves damage-associated inflammation.

Patients with near-complete loss of function of either *TREM2* or *TYROBP* have an autosomal recessive disorder called polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, or Nasu–Hakola disease, a disorder affecting both brain and bone.[6,7] Patients with Nasu–Hakola disease show progressive presenile inflammatory neurodegeneration and formation of multifocal bone cysts. They often present with bone fractures or psychiatric symptoms in the second decade of life, which is followed by severe dementia with premature death in the fourth or fifth decade of life. Although patients with Nasu–Hakola disease carry two homozygous mutations, heterozygous carriers of the same *TREM2* mutation (a variant encoding Q33X) are now known to be at increased risk for late-onset Alzheimer's disease,[2] suggesting a similar mechanism in the two diseases. Although Q33X, a mutation that predicts the synthesis of a truncated protein, very likely confers loss of function on the TREM2 protein, the effect of the other mutations, including R47H, on protein function is not known.

Another neurodegenerative disease could be linked to TREM2 or TYROBP. Patients with partial loss-of-function mutations in *CSF1R*, encoding colony-stimulating factor 1 receptor, have a corticobasal syndrome called hereditary diffuse leukoencephalopathy with spheroids.[8] CSF1R is a microglial receptor that binds CSF1 and has also been shown to cosignal through TYROBP.[9] Thus, the innate immune-receptor complex consisting of TREM2, CSF1R, and the signaling molecule TYROBP in microglia, when dysfunctional, contributes to chronic neurodegeneration. Furthermore, several other genes (*CR1*, *CD33*, and *MS4A4A*/*MS4A6A*) that have been shown to be associated with a low risk of late-onset Alzheimer's disease are related to microglial function.[10] Amyloid plaques have not been reported in patients with Nasu–Hakola disease, suggesting that the *TREM2* variants associated with late-onset Alzheimer's disease do not act through dysfunctional amyloid clearance. However, the three diseases that are related to TREM2, CSF1R, and TYROBP have shown increased microgliosis and neurodegeneration, indicating an overshooting release of inflammatory mediators and reactive oxygen species from microglia. We therefore suggest that the degeneration of neurons in these diseases and in TREM2-associated Alzheimer's disease is driven by a chronic inflammatory process with dysfunction in the microglial phagocytosis or inflammatory pathway. These studies provide a new path for experimental inquiry into the biologic roots of Alzheimer's disease.

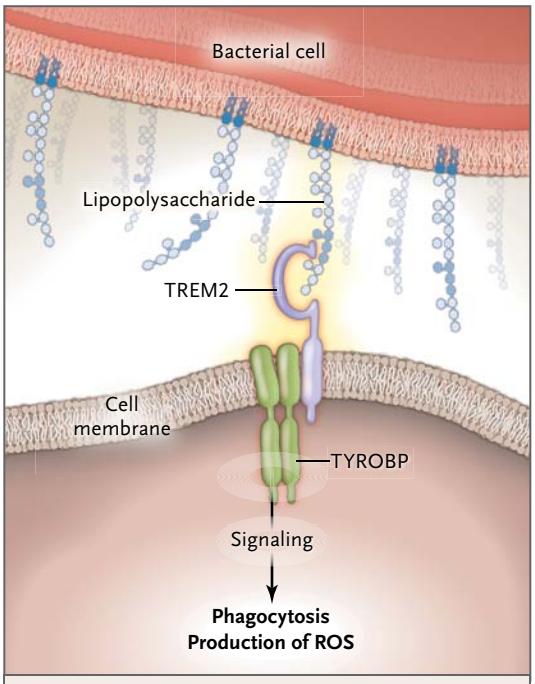

Figure 1. Phagocytosis and TREM2.
The receptor molecule TREM2 is expressed on the surface of the microglial cell and is known to mediate phagocytosis of bacteria. Binding of TREM2 promotes signaling through the molecule TYROBP, resulting in phagocytosis and elevated short-term production of reactive oxygen species (ROS).

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

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Levonorgestrel Intrauterine System — First-Line Therapy for Heavy Menstrual Bleeding

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Heavy menstrual bleeding, or menorrhagia, affects up to 30% of women during their reproductive years, negatively affecting their quality of life[1,2] and exacting a high price from the health care system.[3] Several studies have assessed the effectiveness and cost-effectiveness of various medical and surgical therapies,[4-6] but a clearly superior approach to management of heavy menstrual bleeding remains elusive.

In this issue of the *Journal*, Gupta et al.[7] provide data from a multicenter, randomized, controlled trial showing the superiority of the levonorgestrel intrauterine system (levonorgestrel-IUS) over other usual medical treatments in improving quality of life for women who sought medical care from their primary care physicians for heavy menstrual bleeding. As compared with women assigned to usual medical therapies, those assigned to the levonorgestrel-IUS had significantly greater improvement on the primary quality-of-life measure, the Menorrhagia Multi-Attribute Scale (MMAS), which measures the effect of menorrhagia on social life, work routine, and family life. Women assigned to the levonorgestrel-IUS also had more improvement on several other quality-of-life measures and were almost twice as likely (64% vs. 38%) to have continued the assigned treatment at 2 years. In addition, half the women who changed from usual medical treatments switched to the levonorgestrel-IUS.

"Usual medical treatments" in this trial comprised a variety of therapies, including antifibrinolytics (tranexamic acid), nonsteroidal antiinflammatory drugs (mefenamic acid), combined oral contraceptives, high-dose progestin, depot medroxyprogesterone acetate injections, and combinations of these methods. Meta-analyses of randomized, controlled trials suggest that these treatments do reduce menstrual blood loss but are less effective than the levonorgestrel-IUS.[4] The majority of women in this study (75%) received tranexamic acid, mefenamic acid, or both. Clinicians in the United States rarely use these agents, preferentially prescribing oral contraceptives as first-line medical therapy. The few studies that compare the use of oral contraceptives with other treatments for reducing heavy menstrual bleeding suggest that these agents may be inferior to tranexamic acid.[8]

Assessment of the effectiveness of therapies for heavy menstrual bleeding has evolved from a focus solely on quantity of bleeding to one focused on patient-based outcomes as well — specifically, measures of quality of life. Identifying the most effective treatments is complicated because of heterogeneity among studies in terms of outcome measures and the definition of heavy menstrual bleeding. Many treatment trials have used menstrual blood loss as the primary outcome measure; however, about half the women who seek care for heavy bleeding lose less than 80 ml of blood per menstrual cycle; losses of 80 ml or more are traditionally considered the criterion for menorrhagia.[9,10] In addition, satisfaction with treatment does not always correlate with reduction in blood loss.[11] Clinical guide-

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