CLINICAL IMPLICATIONS OF BASIC RESEARCH

# Neuroinflammatory Cytokine Signaling and Alzheimer's Disease

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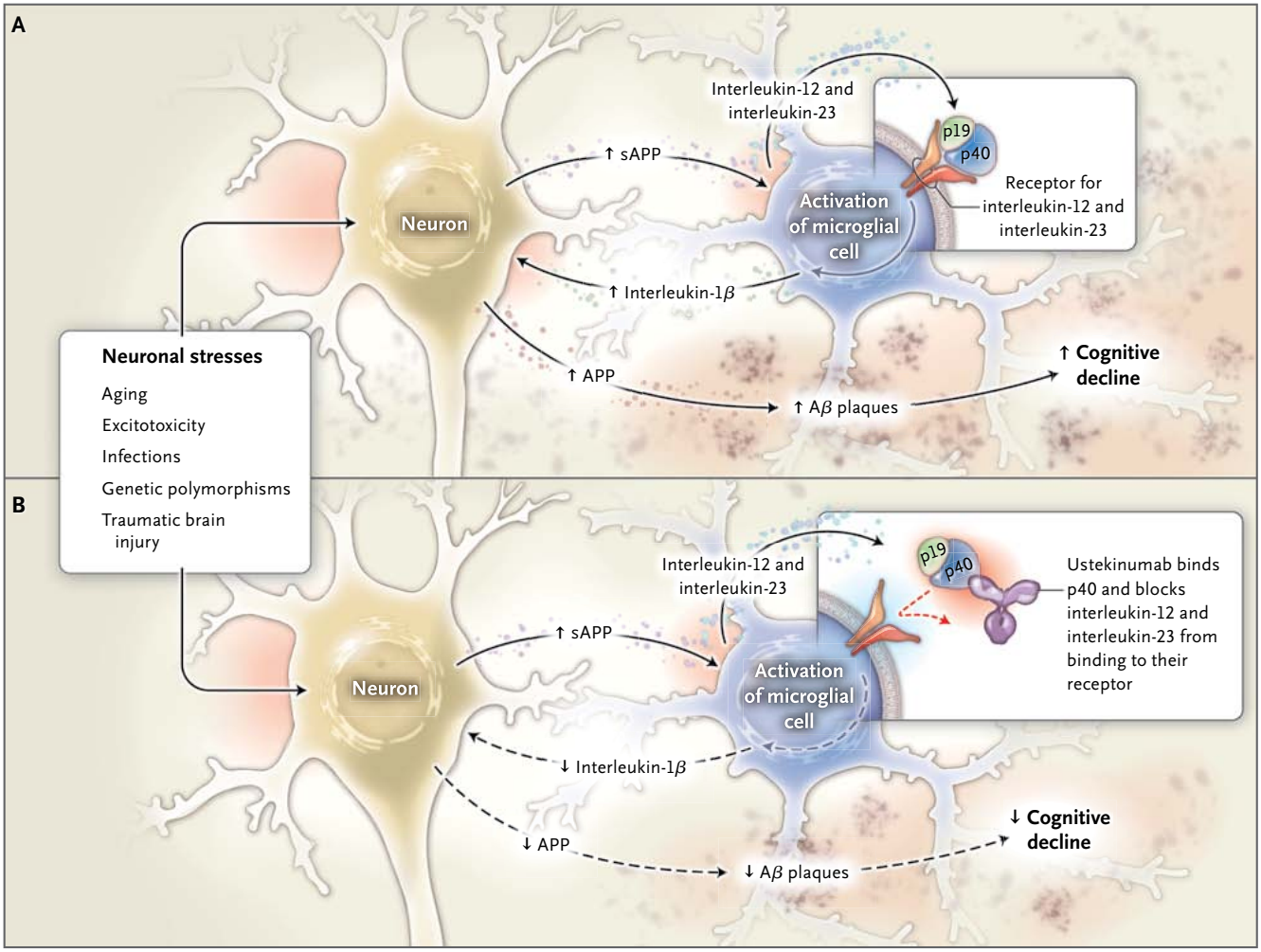
Neuroinflammation, expressed as frank microglial activation with excessive expression of immune cytokines, is fast acquiring the status of "principal culprit" in the unresolved connection between an elevated risk for the development of sporadic Alzheimer's disease and traumatic brain injury, systemic infections, normal aging, and several neurologic disorders. Neuroinflammation also appears to be a substantial contributor to Alzheimer's disease in persons with Down's syndrome (owing to the excess gene dosage that is characteristic of the syndrome) and in persons with genetic mutations that affect the amyloid precursor protein (APP) or presenilin.[1]

The molecules and pathways that mediate the inflammation associated with Alzheimer's disease have recently come under scrutiny. An advance in this area has been described by Vom Berg et al.,[2]



who used a mouse model of Alzheimer's disease to investigate the role of proinflammatory cytokines in disease pathogenesis (Fig. 1). Their results show that damping the expression and signaling of the cytokines interleukin-12 and interleukin-23 in the mouse model is associated with decreases in microglial activation, in the level of soluble $\beta$-amyloid (A$\beta$), and in the overall A$\beta$ plaque burden. These findings are consistent with earlier studies that linked microglial activation with excess expression of interleukin-1 (which regulates interleukin-12–interleukin-23 signaling[3]) and expression of APP (which when cleaved generates A$\beta$), the development of A$\beta$ plaques, and the activation of microglia in the brains of patients with Alzheimer's disease.

Vom Berg et al. also observed that intracerebroventricular delivery of an antibody against p40 — a subunit common to both interleukin-12 and interleukin-23 — reversed the age-related cognitive decline in mice and that this reversal was accompanied by a reduction in levels of soluble A$\beta$. These observations suggest that the suppression of signaling by interleukin-12, interleukin-23, or other inflammatory cytokines may prevent or delay the onset of Alzheimer's disease and, for patients already undergoing the cognitive decline of Alzheimer's disease, may halt such decline.

These findings raise the question of whether monoclonal p40 antibodies (ustekinumab and briakinumab), which have already been approved by the Food and Drug Administration for the treatment of psoriasis, should be tested in randomized, controlled trials for the treatment of Alzheimer's disease. Also of interest is a large epidemiologic study[4] in which the rate of incident Alzheimer's disease decreased by almost 50% among persons who took the common nonsteroidal antiinflammatory agent (NSAID) ibuprofen for 5 years, a finding that suggests that experimental investigation of NSAIDs as preventive agents is warranted. Given the mounting sociological, economic, and personal costs of Alzheimer's disease, the lack of a perfect understanding of its mechanisms should not stop researchers from conducting clinical studies of a variety of strategies intended to reduce the risk of development of the disease and of experimental approaches to expedite its treatment.

**Figure 1 (facing page). Inflammatory Events and Alzheimer's Disease.**

Neuronal stresses are associated with an increased risk of the development of sporadic Alzheimer's disease by triggering the expression of $\beta$-amyloid precursor protein (APP) by neurons, resulting in the release into the extracellular milieu of a soluble fragment of APP (sAPP) (Panel A). In turn, sAPP activates microglia and induces the synthesis and release of the proinflammatory cytokine interleukin-1$\beta$. This action elicits a further increase in neuronal APP expression and induces the expression of interleukin-23 and interleukin-12, two other proinflammatory cytokines that share a common subunit p40. Expression of these interleukins leads to binding to their common receptor, interleukin-23R–12R$\beta$1. Such binding is associated with increased concentrations of soluble A$\beta$, elevation of A$\beta$ plaque density, and cognitive decline in a mouse model of Alzheimer's disease. Using p40 as a target for preventing interleukin-23 and interleukin-12 from binding to their receptor, Vom Berg and colleagues[2] have found that there is not only a decrease in A$\beta$ plaque density in the mouse model of Alzheimer's disease but, remarkably, a halting of the behavioral changes associated with cognitive decline (Panel B). Experimental siRNA suppression of subunit p40 precluded the binding of interleukin-23 and interleukin-12 to the microglial receptor, interleukin-23R–12R$\beta$1,which resulted in reduced levels of soluble A$\beta$ and fewer A$\beta$ plaques. Most relevant as a possible therapeutic strategy for Alzheimer's disease in humans is the finding that treatment of the mice with a neutralizing antibody to p40 (ustekinumab) reversed the adverse behavioral changes associated with cognitive decline in mice.

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

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DOI: 10.1056/NEJMcibr1214546