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Soluble Interleukin-6 Receptor Levels and Risk of Dementia: One More Signpost on a Long Road Ahead

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Metti and colleagues' report of an association between high interleukin 6 soluble receptor (IL-6-sR) levels in plasma and lower risk of incident dementia raises several more-tantalizing questions than answers[1]. Although the role of inflammation, peripheral and systemic as well as central, in Alzheimer's disease (AD) have been extensively investigated[2, 3], human studies have largely been cross-sectional and have seldom focused on the oldest-old individuals[4, 5]. In using a longitudinal design to assay plasma cytokines as candidate biomarkers of incident dementia in a much older population than most conventional studies, Metti and colleagues have executed a novel study that plugs several gaping holes in an exciting area of research.

The underlying biology linking higher baseline (and increasing) peripheral IL-6-sR levels with lower risk of dementia is intriguing. In addition to alternative splicing of IL-6R messenger ribonucleic acid, it is known that limited proteolysis of the extracellular domain of membrane IL-6R by metalloproteases such as ADAM10 can generate IL-6-sR[6]. A zinc metalloprotease, ADAM10 is also recognized to be the principal alpha-secretase in neurons, initiating the processing of amyloid precursor protein (APP) into a nonamyloidogenic, nonpathogenic pathway[7]. Previous studies have reported on lower ADAM10 activity within platelets of individuals with AD than in controls, suggesting that lower alpha-secretase activity may be a detectable feature even in early stages of AD[8, 9]. The significance of these findings as a biologically relevant biomarker and the potential for therapeutic manipulation by enhancement of nonamyloidogenic APP processing is obvious[10]. Equally important, all components of the classical IL-6 signaling pathway (IL-6, its membrane-bound receptor (IL-6R), and the signal-transducing component gp130) are detectable in the brain, with evidence of altered cortical immunoreactivity of the functional IL-6R complex in AD[11]. Moreover, IL-6 trans-signaling through the IL-6-sR has been shown to be upregulated in the

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brain during aging[12]. In this context, Metti and colleagues' current findings suggest another plausible biological link between inflammatory cytokine signaling and risk of dementia.

Although predictive blood-based biomarkers of dementia are eagerly sought, this area of research is fraught with many a broken promise because of poor replication of results, inconsistency of analytical techniques, and heterogenous patient populations across studies[13, 14]. It is therefore reasonable to strike a note of cautious optimism that Metti and colleagues' findings, although novel and interesting, must await independent replication in similarly designed studies in comparable populations. Nevertheless, this is not just another biomarker study because it generates several larger questions that merit further consideration.

Do peripheral immune and inflammatory responses reflect core pathological features of AD and vascular dementia?

Are peripheral immune and inflammatory signals initiators of neuropathology in dementia, a consequence, or merely epiphenomena?

Do changing levels of peripheral cytokines and other inflammatory and immune regulatory proteins signal fluxes in host defense responses or recruitment of repair mechanisms?

Can chronic inflammatory states outside the central nervous system be "transmitted" to the brain to influence the onset or progression of AD?

Unbiased proteomic studies, including those from our group, have consistently revealed a peripheral immune or inflammatory signal that is associated with AD. These include associations with disease status and with established endophenotypes of disease pathology such as brain atrophy and amyloid deposition. Examples of such signals include complement-related proteins (complement factors H and I, Complement component 3, clusterin)[15–18], acute phase reactants (alpha2 macroglobulin, haptoglobin, C-reactive protein)[19, 20, 21], cytokines, and cell-signaling proteins[5, 14, 22]. In parallel with these studies, recent large-scale genome-wide association studies of AD have further identified genetic risk variants within genes associated with the immune response including clusterin and complement receptor-1[23, 24]. Together, these findings point to an intrinsic role of the inflammatory and immune response pathways in AD.

Whether a systemic immune response might signal to the brain to initiate or accelerate neurodegeneration or serve to moderate deleterious effects in an inflammatory cascade is a particularly challenging question to address in human studies. It is also unclear whether immune activation within neurons can influence systemic immunity. Although animal studies have suggested that bidirectional immune signaling can occur between the periphery and the central nervous system[25–27], much work remains to be done to understand the cumulative effects of such signaling in humans. Within the context of aging, the net effects of inflammation are likely to depend upon the balance between a stereotyped immune response aimed at fighting invaders (e.g., viruses, bacteria), removing extraneous material or damaged debris, and biological actions promoting tissue repair and regeneration[28–30].

It is especially relevant in this context to consider that a novel variant in the triggering receptor expressed on myeloid cells 2 (TREM2) gene exerts a strong effect on risk for AD[31, 32]. TREM2 is expressed on the cell membrane of many types of immune cells, including microglia. Activation of the TREM2 receptor on microglia has two important functional consequences: stimulation of phagocytosis and decreasing microglial proinflammatory responses[33]. Collectively, TREM2 may therefore function to help aid microglia in clearing damaged or apoptotic cells and cellular debris and help resolve damage-induced inflammation.

A deeper understanding of the regulatory mechanisms underlying the “defense” and “repair” modes of inflammation in aging will be critical if we aspire to turn findings such as those reported by Metti and colleagues into tangible benefits for older individuals at risk of dementia. We therefore propose a roadmap for the comprehensive study of “inflammaging”[34, 35]with the ultimate goal of discerning its role in age-related declines in cognitive and physical function. This effort will require integration of several diverse methodologies in well-characterized and longitudinally followed cohorts of older individuals, including, for instance, multimodal neuroimaging to derive endophenotypes of neuropathology, detailed measurements of changes in domain-specific cognitive trajectories, and the use of “omics” technologies for large-scale unbiased measurements of messenger ribonucleic acid, epigenetic, small metabolite, and protein signatures. The critical milestones on this roadmap include:

Identification of changes in small metabolite, proteomic, and transcriptomic signatures that predict AD risk and brain pathology, cognitive resilience, and frailty.

Delineation of critical time periods before the onset of cognitive decline or frailty when windows of opportunity might exist for specific interventions.

Understanding the genetic and epigenetic regulation of dynamic changes in the immune and inflammatory response.

Mapping the full spectrum of inciting and inhibiting triggers of inflammation during aging.

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