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Abbreviations: ADAM10: A Disintegrin and Metalloproteinase Domain-containing Protein 10; AD: Alzheimer's Disease; CSF: Cerebrospinal Fluid; sTREM2: Soluble Triggering Receptor Expressed on Myeloid Cell 2; TREM2: Triggering Receptor Expressed on Myeloid Cell 2; VaD: Vascular Dementia

Introduction

e prevalence of dementia is expanding worldwide, in conjunction with the increase in life expectancy. Dementia is a serious global health issue due to the associated disability and dependence and therefore is a signi cant economic, social and public health burden [1,2]. Development of predictive markers and e ective treatments for

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Emerging Implications of TREM2 and sTREM2 in Neurodegenerative Diseases

Pathophysiological signi cance of TREM2 and sTREM2 in AD and other neurodegenerative diseases

TREM2 is selectively expressed on microglia in the brain, the main cell type responsible for maintaining brain homeostasis that also plays a role in in ammatory response. Accordingly, recent studies reporting that the R47H TREM2 mutation was associated with an approximately 3-fold increase in AD risk in humans [9-12] had a deep impact and ripple e ect based on the possibility that TREM2 and TREM2-expressing microglia might be novel key targets for elucidating mechanisms underlying AD pathogenesis. Recent accumulating evidence reveals an association between a diverse array of *TREM2* variants and risk for AD and other neurodegenerative diseases [10-12]. ese variants include mutations a ecting TREM2 structure/function such as the generation of a truncated protein (W44X or W78X variants) [21], inability to associate with its intracellular adaptor, DAP12/TYROBP (K186N variant) [21], reduction in ligand binding ability (R47H variant) [22-24], alteration of subcellular localization (reduction on cell surface and increase in endoplasmic reticulum in T66M or Y38C variants) [18,25] and accelerated proteolytic loss from the cell surface (H157Y variant) [19,20]. erefore, TREM2-related microglial dysfunction can potentially lead to the impairment of brain homeostasis including amyloid-β clearance, possibly leading to neuronal injury and cognitive dysfunction. erefore, further characterization of TREM2 will allow us to gain a better understanding of its pathological roles in neurodegenerative diseases.

It is increasingly evident that microglia phenotypes are much more complex than previously thought, irrespective of whether they express wild-type or variant TREM2. TREM2 is assumed to exhibit anti-in ammatory roles, mainly based on *in vitro* analyses; however, recent growing evidence highlights the pro-in ammatory roles of TREM2 in *in vivo* disease settings [12] and suggest pathological implications of TREM2-expressing microglia in neuroin ammation and concomitant neurodegeneration, with a shi in microglial phenotypes from homeostasis to disease states.

sTREM2 is detected in human blood and cerebrospinal uid (CSF), and CSF sTREM2 levels are elevated in patients with neurodegenerative diseases compared to healthy controls [18,26-30]. Whereas CSF sTREM2 is a topic of great interest as a potential marker for neurodegenerative diseases, the pathophysiological signi cance of serum blood sTREM2 remains unclear. Additionally, the function of sTREM2 has not been elucidated, although elevated sTREM2 levels in CSF have been suggested to re ect microglial activation in response to neuronal degeneration [27-31]. In this respect, recent studies uncovered sTREM2 as not just an inactive end-product but also a signaling molecule [15] that promotes macrophage survival by preventing apoptosis [32] and activates microglia to ultimately trigger in ammatory responses and prolong survival [33]. ese ndings hint at the pathological implications of sTREM2 in chronic in ammation,

[38,39]. Elucidation of the e ect of ADAM10 mutations on sTREM2 production as well as the impact of TREM2-expressing microglia on their pro-in ammatory status and subsequent sTREM2 release

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