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A Novel TREM2-Mediated Link between Diabetes and Cognitive Impairment: Recent Findings and Future Perspectives

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Abstract

The protein triggering receptor expressed on myeloid cell 2 (TREM2) is a cell surface receptor exclusively expressed on microglia in the brain. Recent extensive studies reveal that the functions of TREM2 as well as the phenotypes of TREM2-expressing microglia are closely implicated in the pathogenesis of neurodegenerative diseases including Alzheimer's disease (AD), one of the most common causes of dementia. Furthermore, several recent studies reported a possible novel pathological implication for TREM2 in cognitive impairment associated with diabetes, one of the several metabolic diseases that are reported risk factors of dementia. In this review, we summarize recent advances and future research directions on the pathophysiological significance of TREM2 in AD and other neurodegenerative diseases as well as in metabolic diseases with increased risk for dementia.

Keywords: Alzheimer's disease; Cognitive impairment; Diabetes; Metabolic disease; Microglia; Neurodegenerative disease; TREM2

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

The 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 significant economic, social and public health burden [1,2]. Development of predictive markers and effective treatments for dementia is thus urgently needed.

Recent epidemiological studies reported diabetes as a risk factor for dementia, including Alzheimer's disease (AD) and vascular dementia (VaD), as well as cardiovascular diseases [2-4]. Possible underlying mechanisms of diabetes-related dementia include multifactorial pathways implicated in hyperglycemic toxicity, microvascular diseases, chronic inflammatory processes, and changes in insulin metabolism, which ultimately lead to small vessel infarcts, neuroinflammation, amyloid-β accumulation and neurodegeneration in the brain [2-5]. Conversely, obesity has also been implicated to play a role in the development of dementia in later life [6]; however, a recent study reported an inverse monotonic association between body mass index (BMI) and dementia incidence [7]. Thus, the potential role of obesity in the development of dementia remains controversial. Although dementia might be prevented or at least delayed in some cases, factors exhibiting preventive effects on dementia remain to be elucidated [8].

Genome-wide association studies recently revealed novel significant associations between variants of the gene triggering receptor expressed on myeloid cell 2 (*TREM2*) and a high risk for AD and other neurodegenerative diseases [9-12]. Following these initial observations, an exponentially growing number of basic and clinical studies have focused on the pathological roles of TREM2 in the development and progression of dementia. More recently, we reported the first study delineating the pathological implications of serum TREM2 in cognitive impairment in non-obese type 2 diabetic patients [13]. Here, we review the characteristics and recent findings regarding TREM2 and discuss the possibility of TREM2 as a novel target to predict and treat cognitive dysfunction.

Structure, Function and Features of TREM2

TREM2 is a 230-amino-acid V-type immunoglobulin domain-containing transmembrane protein consisting of an extracellular domain, a transmembrane domain, and a short cytosolic tail lacking an obvious amino acid-based signaling motif [14]. TREM2 is exclusively expressed on myeloid lineage cells including dendritic cells, tissue macrophages, osteoclasts, and microglia [11,12]. Many potential ligands for TREM2 have been proposed, which are characterized based on the type of anionic and/or lipidic species, such as bacterial components, mammalian cellular membrane components and lipoproteins [15]. TREM2 interacts with the adaptor protein DNAX-activating protein 12 (DAP12)/TYRO protein kinase binding protein (TYROBP) via its transmembrane domain. Following binding to its ligands, TREM2 facilitates DAP12 phosphorylation on tyrosine residues within its immunoreceptor tyrosine-based activation motif region, thereby mediating downstream signaling that leads to various cellular functions including survival, phagocytosis and inflammation [10-12,16]. One remarkable characteristic of TREM2 is the release of its soluble ectodomain fragment, soluble TREM2 (sTREM2), into the extracellular space via proteolytic cleavage at the site in the juxtamembrane region by shaddases such as a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) [17-20]. Although not much is known about the pathophysiological significance of sTREM2 in comparison with TREM2, recent studies demonstrated several novel aspects of sTREM2, which are reviewed in the next section.

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Emerging Implications of TREM2 and sTREM2 in Neurodegenerative Diseases

Pathophysiological significance 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 inflammatory 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 effect 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]. These variants include mutations affecting 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]. Therefore, 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. Therefore, 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-inflammatory roles, mainly based on *in vitro* analyses; however, recent growing evidence highlights the pro-inflammatory roles of TREM2 in *in vivo* disease settings [12] and suggest pathological implications of TREM2-expressing microglia in neuroinflammation and concomitant neurodegeneration, with a shift in microglial phenotypes from homeostasis to disease states.

sTREM2 is detected in human blood and cerebrospinal fluid (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 significance 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 reflect 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 inflammatory responses and prolong survival [33]. These findings hint at the pathological implications of sTREM2 in chronic inflammation, and further elucidation of the pathophysiological roles of CSF and blood sTREM2 will provide significant novel clues on the regulation of central and systemic inflammation by targeting sTREM2 and/or sTREM2-related processes such as proteolytic production.

Pathophysiological significance of TREM2 and sTREM2 in metabolic diseases with increased risk for neurodegenerative diseases

Not much is known about the pathophysiological significance of TREM2 and sTREM2 in cognitive impairment in patients with metabolic diseases, despite studies demonstrating metabolic diseases as risk factors for AD and VaD. In mouse models of insulin resistance/diabetes, an early study showed elevated TREM2 expression in mesenteric adipose tissue [34]. Further, activated TREM2-expressing microglia/monocytes were found to accumulate in hippocampus in response to a high-fat diet in aging mice and in a mouse model of AD [35]. In humans, a recent study reported that serum sTREM2 levels were associated with the exacerbation of glucose/lipid metabolism in diabetic conditions [36]. However, there are currently no studies elucidating the pathophysiological roles of TREM2 and sTREM2 in cognitive impairment in patients with metabolic diseases.

We recently provided the first report that addressed these issues in a cross-sectional approach using a database of a multicenter prospective observational cohort study [13]. Our analysis revealed that cognitive function was more exacerbated in non-obese type 2 diabetic patients compared to obese type 2 diabetic patients. In addition, whereas serum sTREM2 levels did not differ between the two patient groups, the elevation in serum sTREM2 levels was significantly associated with the risk of cognitive impairment in non-obese diabetic patients. Importantly, no such significant association was found in obese diabetic patients in whom elevated systolic blood pressure was associated with an increased risk of cognitive impairment. Moreover, we found that serum sTREM2 levels were positively correlated with diabetes-associated risk factors of dementia, including hyperglycemia and exacerbation of inflammation, and negatively correlated with adiponectin level in non-obese diabetic patients. However, these correlations were not observed in obese diabetic patients. Overall, these findings suggest that serum sTREM2 levels might be a potential novel marker of the diabetes-associated cognitive impairment in non-obese diabetic patients. Additional studies are critical to elucidate the mechanisms underlying the relationship between sTREM2 and cognitive dysfunction in diabetic patients. In this context, our recent findings provide potential novel strategies for reducing the risk of cognitive impairment and reveal that serum sTREM2 levels might have utility as a marker in prevention and early management hyperglycemia and aggravation of inflammation in non-obese diabetic patients. In addition, early control of systolic blood pressure might be effective in obese diabetic patients.

Future Perspectives

Recent remarkable advances in TREM2 research led to novel insights into the pathological significance of TREM2 and sTREM2 in AD and other neurodegenerative diseases as well as in metabolic diseases with increased risk for neurodegenerative diseases. These revelations further hint at the possible implications of TREM2 and sTREM2 in other cognitive dysfunction-causing diseases such as cerebral amyloid angiopathy [37]. Accordingly, future findings are expected to give prominence to the significance of TREM2 and sTREM2 as key targets in prediction, prevention and/or improvement of cognitive dysfunction.

Emerging pathological roles of TREM2 and sTREM2 raise new issues that need to be addressed. One instance is the mechanistic details underlying the phenotypic shift in microglia from an anti-inflammatory to a pro-inflammatory state, which might trigger chronic neuroinflammation and account for inconsistencies reported regarding the phenotypes of TREM2-expressing microglia. Another important issue is the elucidation of the mechanisms regulating ADAM10-mediated sTREM2 release under steady-state and disease conditions. ADAM10 is also involved in amyloid precursor protein processing to release amyloid-β and ADAM10 mutations confer increased risk of AD

[38,39]. Elucidation of the effect of ADAM10 mutations on sTREM2 production as well as the impact of TREM2-expressing microglia on their pro-inflammatory status and subsequent sTREM2 release should reveal novel pathological implications of ADAM10 in TREM2-expressing microglia-associated neuroinflammation.

Recent findings suggest several directions for future research regarding potential factors affecting microglial phenotypes. Microglial maturation and function were reported to be influenced by gut microbiota-derived metabolites, albeit through unidentified pathways [40]. In addition, the diversity and stability of gut microbiota were shown to alter in conjunction with aging or metabolic diseases such as diabetes [41,42]. These alterations in gut microbiota in turn increase the permeability of gut and blood-brain barriers, thereby triggering systemic and central inflammation and leading to the development of neurodegenerative diseases [42,43]. Accordingly, it remains possible that TREM2 might function as a receptor for gut microbiota-derived molecules during aging or metabolic diseases and might modulate microglial phenotypes to push towards a pro-inflammatory axis. In this respect, gut microbiota-targeted intervention might contribute to TREM2-mediated improvement of microglial phenotypes.

Conclusion

Recent research on TREM2 has provided a deeper understanding of the mechanisms underlying the development and progression of cognitive dysfunction in patients with AD and other neurodegenerative diseases as well as metabolic diseases with increased risk for neurodegenerative diseases. Future basic and clinical research elucidating the pathophysiological significance of TREM2 will reveal new avenues for preemptive medicine for dementia.

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