Title: The Jekyll and Hyde of TREM2

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Abstract:

In a recent paper, Gratuze et al. demonstrate a putative neuroprotective role of a key Alzheimer risk variant, the TREM2^{R47H}, against tau-mediated neurodegeneration in a mouse model of tauopathy. This study highlights the context-dependent response of microglia, and proposes antagonistic roles of TREM2 in Aβ- versus tau-mediated pathology.

Main Text:

Genetic risk variants for Alzheimer's disease (AD) have implicated microglia as a critical component in the disease pathology. Among the goals of current research is to identify how immune risk factors modulate microglial function and possibly alter the risk for dementia. It is becoming increasingly clear that microglia cannot be classified as simply reactive or homeostatic, but that they wear many hats as required by changes in their local milieu. As tissue-resident macrophages of the brain, microglia constantly monitor changes in their neighboring neuronal environment. Key regulatory hub genes expressed by microglia, such as Triggering Receptor Expressed on Myeloid cells 2 (*TREM2*), appear critical in modulating microglial functions including their energy metabolism and lipid homeostasis, which in turn affect brain homeostasis. While microglial TREM2-mediated functions have often been categorized as either beneficial or detrimental, a recent paper by Gratuze et al. [1] cautions against this simplistic view. The authors address the role of a key AD-associated TREM2 variant, R47H, in the relatively understudied context of tau-mediated neurodegeneration. The results challenge the general perception that TREM2^{R47H} is detrimental to brain health, as has been suggested in various amyloid-centric models.

Current knowledge on TREM2 in AD mouse models, which have been mostly β-amyloid (Aβ)-centric, suggests that TREM2 is critical for microglial sensing of danger: for instance, mice with defective TREM2 signaling display impaired microglial response to injury and AD pathology, including clustering around plaques and tau seeding [2]. In the peripheral immune system, TREM2 signaling promotes macrophage phagocytosis and restrains myeloid cytokine secretion. As a key regulatory gene for tissue-resident macrophages, TREM2 acts as a sensor of tissue metabolic state and appears critical in regulating lipid homeostasis. Importantly, TREM2 regulates microglia to adopt a disease-associated microglia (DAM) profile in response to amyloid, tau and other pathological features [2]. What functional roles DAMs play in the diseased and aged brain remain unclear. Importantly, little is known about the role of TREM2 when aggregates of hyperphosphorylated tau accumulate in neurons, another pathological hallmark of AD. Interestingly, levels of soluble TREM2 in AD patient cerebrospinal fluid correlate with tau pathology, rather than with changes in pathological Aβ levels [3]. Tau aggregation typically occurs a decade or more after the onset of Aβ deposition in patients. Thus, understanding how TREM2 variants modulate tau-related pathology is critical to elucidate how microglia contribute to neurodegeneration in AD. This is especially important considering the microglia's role as a sensor of tissue homeostasis, as degenerating neurons afflicted with tangles likely present a different neural environment and a distinct challenge for microglia, versus during earlier stages of AD when Aβ starts aggregating in the brain parenchyma.

In their study, Gratuze et al. reported an elegant model to address the function of TREM2 in tau pathology [1]. As some context, it should be mentioned that rodent models of the TREM2^{R47H} variant have been a focus of debate. In particular, a caveat of the knock-in R47H variant mouse models is the altered expression level of Trem2 [4], which complicates the interpretation of these studies. Gratuze et al. elegantly bypassed this challenge by introducing the variants of human TREM2 on a mouse *Trem2* knock-out background. This approach nicely revealed phenotypic alterations not previously observed in P301S mice lacking Trem2 [5]. Perhaps most notably, Gratuze et al. showed that, unlike in amyloid-centered pathology, mice with TREM2^{R47H} variant have an attenuation of tau-mediated neurodegeneration, as displayed by reduced tau spreading, synapse loss and brain atrophy.

Furthermore, the findings by Gratuze et al. suggest that TREM2 may be critical for microglial synaptic engulfment in disease. Loss-of-function mutations in *TREM2* or *DAP12* (the latter encoding an adaptor protein for TREM2 signaling) underlie Nasu-Hakola disease where patients display progressive presenile dementia. Recent work has investigated TREM2 in microglia-mediated synaptic refinement in the developing brain [6]. Similar to complement, a key developmental pruning pathway reactivated in AD models to mediate synapse loss [7, 8], Gratuze et al. suggest that TREM2 plays a role in synaptic engulfment by microglia in AD. The expression of TREM2^{R47H} variant leads

to fewer engulfed synaptic elements by microglia both in brains of the P301S mouse model and AD patients carrying R47H or R62H variants as compared to those carrying TREM2 common variant. Interestingly, there were also less synaptic markers co-localized with complement protein (C1q) and decreased levels of phagocytic ($CD68^{+}$) microglia in the tau mouse model with $TREM2^{R47H}$ versus controls. These data raise an intriguing question of whether TREM2 works upstream of the classical complement pathway to mediate synapse loss in AD models. Further experiments are necessary to delineate this link. Altogether, these data confirm the relevance of the complement pruning pathway in microglia in AD models. A critical question that remains is whether microglia target specific synapses for elimination, and if so, which ones. Furthermore, detailed behavioral assessment in AD models with different TREM2 variants will be needed to understand better the implications of TREM2 on cognitive function. This appears particularly critical in tauopathies, as current genetic data do not suggest any particular association of TREM2 with tangle diseases.

Neuroinflammation is a double-edged sword, the consequences of which appears to be highly context-dependent. An example of this is the role of the complement pathway in mediating synapse loss in early stages of pathology (i.e., possibly detrimental role of complement) [7] versus clearing neurotoxic extracellular Aβ aggregates in later stages (i.e., possibly beneficial role of complement) [9]. Along similar lines, the study by Gratuze et al. suggests opposing roles of TREM2 in Aβ- versus tau-mediated AD pathology. This apparent dichotomy needs to be considered when thinking about the potential therapeutic relevance of TREM2-mediated signaling in AD, as it raises important questions about when and how to therapeutically target this pathway. Of note, in a mouse model of Aβ-mediated pathology, a recent immunotherapy that activates TREM2 signaling has provided valuable results, and a Phase I clinical trial has shown safety and tolerability of the compound [10]. However, the therapeutic approach of activating TREM2 signaling in AD may not come without caveats, for TREM2 could promote detrimental tau-mediated neurodegeneration, as warned by Gratuze et al. Development of effective biomarkers for pathological tau progression, for instance using a tau PET tracer, will be critical to define the ideal therapeutic window for potential TREM2-based treatments such as immunotherapy. In a chronic neurodegenerative disease such as AD, a disease stage-specific therapeutic approach may be necessary.

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