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TREM2 and the neuroimmunology of Alzheimer's disease

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ABSTRACT

Late-onset Alzheimer's disease (AD) is a sporadic disorder with increasing prevalence in aging. The ε4 allele of Apolipoprotein E(ApoEε4) was the only known major risk factor for late onset AD. Recently, two groups of investigators independently identified variants of the *TREM2* gene, encoding triggering receptor expressed on myeloid cells 2 as causing increased susceptibility to late onset AD with an odds ratio similar to that of ApoEε4. *TREM2* is a receptor expressed on innate immune cells. Using a novel technology called Direct RNA Sequencing wedetermined the quantitative transcriptome of microglia, the principal innate neuroimmune cells and confirmed that *TREM2* is a major microglia-specific gene in the central nervous system. Over the past several years we have shown that microglia play a dichotomous role in AD. Microglia can be protective and promote phagocytosis, degradation and ultimately clearance of Aβ, the pathogenic protein deposited in the brains of Alzheimer's patients. However, with disease progression, microglia become dysfunctional, release neurotoxins, lose their ability to clear Aβ and produce pro-inflammatory cytokines that promote Aβ production and accumulation. *TREM2* has been shown to regulate the phagocytic ability of myeloid cells and their inflammatory response. Here we propose that the mechanism(s) by which *TREM2* variants cause Alzheimer's disease are via down regulation of the Aβ phagocytic ability of microglia and by dysregulation of the pro-inflammatory response of these cells. Based on our discussion we propose that TREM2 is a potential therapeutic target for stopping ordelaying progression of AD.

Late onset Alzheimer's disease (AD) is a sporadic, progressive neurodegenerative disorder characterized by the presence of numerous senile plaques, neurofibrillary tangles, and loss of neurons and synapses particularly in the hippocampus and cerebral cortex [1]. Late onset AD prevalence increases exponentially after the age of 65 [2].

1. Risk factors for AD

In the past two decades several genetic risk factors for familial AD have been identified including mutations in the amyloid precursor proteins (APP), presenilin 1and 2 (PS1 and PS2).These variants appear to be fully penetrant and result in disease onset before the age of 60 [3]. Identifying these mutations has been important to patients carrying them and led to the generation of several rodent models for AD [4–7].These mutations also informed us about pathways that regulate APP processing, Aβ generation and clearance and neuroinflammation in AD. However these mutations do not inform us of risk factors that are associated with the most common late-onset form of AD. Indeed, until recently, mostly low-risk variants have been associated with late-onset AD, and the only two well established major risk factors for late onset AD were the ε4 allele of Apolipoprotein E (ApoEε4) and aging itself [8].

2. TREM2 variants as risk factors for AD

Recently two groups of investigators independently identified several heterozygous variants of *TREM2 gene* encoding **T**riggering **R**eceptor **E**xpressed on **M**yeloid cells **2** protein as causing increased susceptibility to late-onset AD with an odds ratio close to that of ApoEε4 [9,10]. These two groups used genome, exome and Sanger sequencing and identified several rare variants in the coding region of *TREM2* that are associated with higher risk for late onset AD. The most common of these variants rs75932628, which was predicted to result in an R47H substitution, confers significant risk for AD (odds ratio, 2.92; 95% confidence interval [CI], 2.09 to 4.09; $P = 3.42 \times 10^{-10}$) [9,10]. These new findings are highly significant and are likely to have a major impact on how we study AD for two reasons. First, it is obvious that identifying new major risk factors

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for late onset AD could be used to identify patients at risk for developing AD. Second, and as importantly, since the gene involved is *TREM2*, a regulator of the inflammatory response, these findings are especially interesting, because they shed new exciting light on the pathogenesis of AD and on the role of the neuroimmune system in AD as discussed below.

3. TREM2 and microglia

As its name implies, *TREM2* is expressed on myeloid cells including tissue macrophages, dendritic cells and in the brain, microglia the major innate neuroimmune cells. We have recently used a novel technology, termed Direct RNA Sequencing (DRS) [11–14] to quantitatively define the transcriptomes of the whole adult mouse brain, purified microglia, astrocytes, and macrophages isolated from adult animals without the need (and associated bias) for cDNA synthesis or PCR amplification [15]. This approach allowed us to determine the copy numbers of each transcript in microglia and identify a cluster of genes that constitute the microglial transcriptomic signature [15]. This approach also allowed us to identify the cell surface receptors that are highly expressed on microglia. An analysis of our dataset focusing on cell surface receptors shows that *TREM2* is one of the highest expressed receptors in microglia (ranks as no. 31) and is >300 fold enriched in microglia vs. astrocytes (Fig. 1). Since *TREM2* is highly enriched on microglia vs. other brain cells, identifying *TREM2* as a significant risk factor for AD provides new insight into the role of microglia in AD.

4. Dichotomous role for microglia/mononuclear phagocytes in AD pathogenesis

Microglia/mononuclear phagocytes are the principal innate immune cells of the brain. They phagocytose and clear debris, pathogens and toxic substances, but they also can be activated to produce proinflammatory cytokines, chemokines and neurotoxins [16]. Over the past decade, work in our lab and other labs significantly enhanced our understanding of the role(s) of microglia/mononuclear phagocytes in AD. Based on these studies, we proposed that these cells play a dichotomous role in the pathogenesis of AD [17–22].

5. Microglia/mononuclear phagocytes are neuroprotective and clear Aβ

Microglia/mononuclear phagocytes accumulate in AD brains in a manner dependent on the chemokine receptor Ccr2. Preventing such accumulation in Ccr2-deficient AD transgenic mice, led to a significant increase in Aβ deposition and increased mortality in these mice [17,18]. More recent data from our lab indicate that *Scara1*, a scavenger receptor expressed on microglia/mononuclear phagocytes that promotes binding and phagocytosis of Aβ *in vitro* [23,24], also promotes such phagocytosis *in vivo* in a mouse model of AD [25]. Deficiency in *Scara1*, while not affecting the number of microglia/mononuclear phagocytes, reduced the ability of these cells to clear Aβ *in vivo*, leading to increased Aβ accumulation and early mortality in an AD mouse model [25], similar to what we found with Ccr2 deficiency [23,24]. Restoring *Scara1* expression pharmacologically using a small molecule termed Protollin [26] increased the ability of microglia/mononuclear phagocytes to clear Aβ and reduced Aβ load significantly [25]. Since intracellular Aβ deposits have been observed in microglia in AD brains, it appears that early in the disease process microglia/mononuclear phagocytes play a neuroprotective role by promoting Aβ phagocytosis, degradation and clearance. Therefore enhancing their ability to clear Aβ is a potential therapeutic strategy to stop or delay progression of AD.

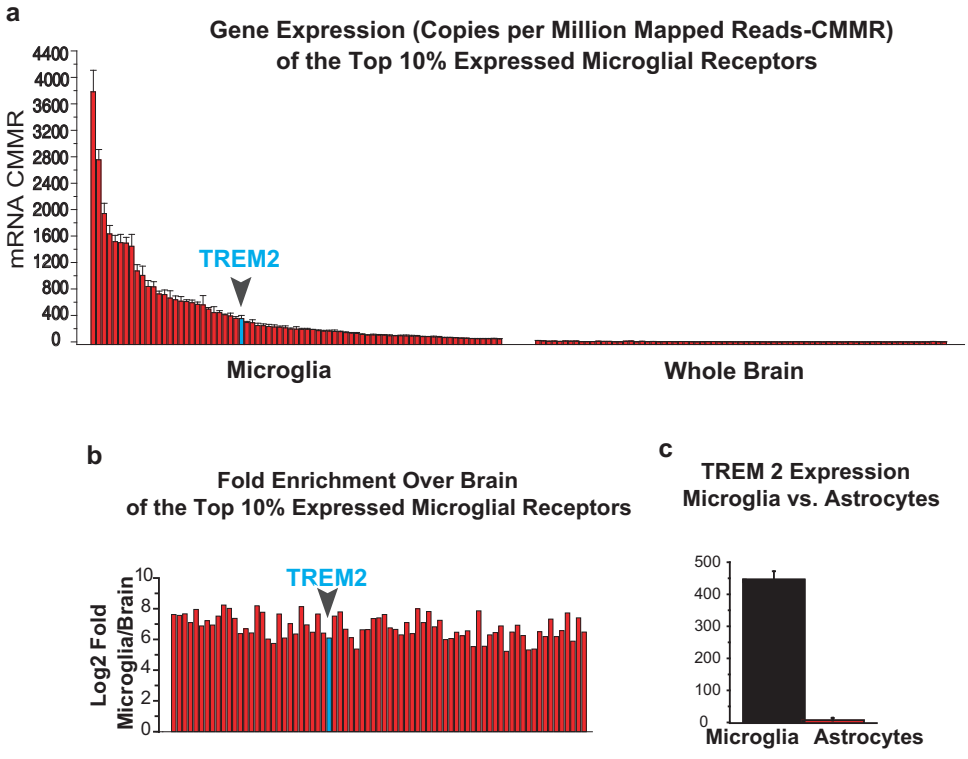

Fig. 1. Expression levels of the top 75 microglial receptors show that TREM2 is highly expressed in microglia (a) and highly enriched in microglia compared to whole brain (b), and to purified astrocytes (c). These data represent a reanalysis of a recently published dataset by the authors [15].