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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 $\epsilon 4$ allele of Apolipoprotein E(ApoE $\epsilon 4$) 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 ApoE $\epsilon 4$. *TREM2* is a receptor expressed on innate immune cells. Using a novel technology called Direct RNA Sequencing we determined 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 A β , 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 A β and produce pro-inflammatory cytokines that promote A β 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 A β 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 or delaying progression of AD.

Keywords

Microglia; Alzheimer's disease; *TREM2*; NeuroImmunology

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 1 and 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, A β 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 ϵ 4 allele of Apolipoprotein E (ApoE ϵ 4) 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 Triggering Receptor Expressed on Myeloid cells 2 protein as causing increased susceptibility to late-onset AD with an odds ratio close to that of ApoE ϵ 4 [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 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 A β

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 A β 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 A β *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 A β *in vivo*, leading to increased A β 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 A β and reduced A β load significantly [25]. Since intracellular A β 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 A β phagocytosis, degradation and clearance. Therefore enhancing their ability to clear A β is a potential therapeutic strategy to stop or delay progression of AD.

6. Microglia/mononuclear phagocytes become neurotoxic and promote A β accumulation

While the data supporting a major role for neuroimmune cells in A β clearance are convincing, these data also raise an important question. With AD progression, the number of accumulating microglia/mononuclear phagocytes increases. It is counterintuitive therefore that A β continues to accumulate, and AD pathology continues to progress despite continued accumulation of neuroimmune cells. It is possible that failure of these cells to stop AD progression is due to an A β -induced phenotypic change that renders these cells more pro-inflammatory and less able to clear A β , resulting in reduced A β uptake and degradation, and increased A β accumulation [20,21]. Indeed we found that interaction of A β with a receptor complex expressed on microglia/mononuclear phagocytes composed of CD36, and the Toll Like Receptors (TLR) TLR4 and TLR6 leads to activation of these cells to produce proinflammatory cytokines and chemokines and neurotoxins [19,27]. These cytokines in turn, downregulate A β phagocytic receptors and A β degrading enzymes in neuroimmune cells [20]. Deficiency in CD36, TLR4 or TLR6 *in vitro* reduces the neurotoxic effects of A β and cytokine production [19,27].

7. Pro-inflammatory molecules produced by A β -stimulated microglia also enhance A β production

A β is generated through proteolysis of APP by the sequential actions of β and γ secretases [28]. In addition to activating microglia and recruiting additional mononuclear phagocytes/microglia, proinflammatory molecules secreted by A β -stimulated microglia, like TNF α , IL-1 β , and interferon (IFN)- γ , stimulate the activity of γ secretase and enhance A β production [29]. Furthermore, IFN- γ IL-6 or TGF- β stimulate β secretase expression also leading to increased A β production [30,31]. Focal glial activation coincides with increased β secretase activation and precedes neuritic plaque formation in AD mice [32], suggesting that cytokine-mediated regulation of A β production may occur *in vivo* before plaque formation, thereby contributing to the pathogenesis of AD. In support of this, blocking microglial-mediated inflammation via non-steroidal anti-inflammatory drugs (NSAIDs) or PPAR γ agonists led to reduced A β production, likely through decreasing β secretase expression and activity [33-36]. Therefore, microglial mediated inflammatory responses promote the

pathogenesis of AD via two pathways. First, they promote neurotoxicity through production of reactive oxygen species, reactive nitrogen species and other neurotoxins. Second, they upregulate the levels and activities of the A β -generating enzymes γ secretase complex and β secretase, and thereby increase accumulation of A β . Blocking A β -induced microglial inflammatory responses is therefore a plausible therapeutic strategy to delay or stop AD progression.

8. How does identification of TREM2 variants as significant risk factors for late onset AD affect our understanding of the role of microglia in AD pathogenesis?

TREM2 encodes an innate immune receptor that is a member of the immunoglobulin family [37]. The exact functions of *TREM2* are not well defined, but it appears to negatively regulate the inflammatory and TLR responses by pairing with a signaling adapter termed DAP12 [38-40]. Deficiency in *TREM2* increased TNF production in macrophages [38,39] and increased TLR induced maturation and rendered dendritic cells more efficient in inducing antigen-specific T-cell proliferation [40]. *TREM2* is also a positive regulator of myeloid cells' phagocytic function. *TREM2* can directly mediate clearance of apoptotic neurons and bacteria [41-43], but it can also regulate phagocytosis without directly interacting with the phagocytized particles, since binding of *TREM2* to its putative ligand Hsp60 stimulated phagocytosis of bacteria [44].

The effects of AD-associated *TREM2* mutations on *TREM2* functions are not well defined yet. However, homozygous loss-of-function mutations in *TREM2* are associated with an autosomal recessive form of early-onset dementia affecting brain and bone termed Nasu–Hakola disease [45] and with a form of frontotemporal dementia without bone involvement [46]. One of the *TREM2* mutations that cause Nasu–Hakola disease is a loss-of-function variant encoding Q33X and predicts synthesis of a truncated *TREM2* protein. Interestingly, the same variant is also one of the recently identified variants that increased the risk for late-onset AD in heterozygous carriers [9] suggesting a similar mechanism in the two diseases.

Based on the discussion above, and since *TREM2* has been shown to positively regulate phagocytosis by myeloid cells and downregulate their inflammatory response, we propose that these mutations predispose to AD by upregulation of the inflammatory response and creating a pro-inflammatory milieu in the brain. This milieu promotes A β production, and reduces A β phagocytic receptors and A β -degrading enzyme expression and activity thereby increasing A β accumulation and disease progression. Since *TREM2* also directly regulates phagocytosis [44], loss-of-function mutations can also negatively downregulate microglial phagocytic abilities thereby reducing their capacity to clear A β . In addition to regulating A β production and clearance, *TREM2* mutations can also contribute to neurotoxicity. Indeed, since A β -induced neurotoxicity is dependent on the CD36/TLR4/TLR6 mediated inflammatory response [27], the pro-inflammatory milieu created by *TREM2* mutations, may directly augment A β -induced, microglia-mediated neurotoxicity further contributing to the pathogenesis of AD.

In addition to potential effect(s) on A β production, clearance and neurotoxicity, the chronic pro-inflammatory milieu that results from *TREM2* mutations may by itself promote neurodegeneration independent of A β . Indeed, chronic neuroinflammation appears to contribute to neurotoxicity in other mouse models of neurodegeneration most notably experimental autoimmune encephalomyelitis model of multiple sclerosis [47].

Interestingly *TREM2* has been shown to increase in AD mice [48], possibly in a failed compensatory attempt by the mice to keep the inflammatory response in check, however, this may suggest that *TREM2* mutations observed in AD patients may be gain-of-function mutations. While this remains a small possibility based on what we know from patients with Nasu–Hakola disease [45] it is crucial to determine whether the effects of *TREM2* variants are due to either loss-of-function, gain-of-function or a novel yet to be defined pathway.

9. Future directions

Identifying the exact mechanism(s) by which *TREM2* mutations increase the risk for AD will certainly be beneficial to the patients carrying these mutations. As importantly, since *TREM2* is highly expressed on neuroimmune cells and regulates specific functions of these cells, identifying *TREM2*-associated pathways that promote or prevent AD development and/or progression, will be useful for patients without *TREM2* mutations. Indeed, identifying the various APP mutations associated with early onset AD, taught us a lot about the role of APP in AD and how pathways involved in APP processing may be useful for treatment of AD in patient without these APP mutations. Similarly, we propose that understanding how *TREM2* causes AD will have a watershed effect on our understanding of the pathogenesis of AD and on development of novel AD therapies.

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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].