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RESEARCH HIGHLIGHT

TREM2 enables amyloid β clearance by microglia

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In a recent paper published in *Cell*, Wang *et al*. report that deficiency of triggering receptor expressed on myeloid cells 2 (TREM2) augments amyloid β accumulation and neuronal loss in a mouse model of Alzheimer's disease. TREM2 acts as a signaling receptor involved in innate immunity for the natural clearance of this toxic protein by microglia.

Although Alzheimer's disease (AD) is not a classical inflammatory disease, Genome-wide association studies on hundreds of thousands of subjects have yielded several genetic markers for predisposition and most of them play a dominant role in immunological processes. The high levels of inflammatory cytokines measured in the cerebrospinal fluid and in post mortem analysis of the cortex of AD patients have skewed the field toward limiting neuroinflammation instead of harnessing its power. However, this idea was proven wrong with the crushing failure of non-steroidogenic anti-inflammatory drugs in clinical trials showing that blocking all forms of inflammation is highly detrimental to patients, even accelerating disease progression in some cases. In mouse models of AD, systematic gene deletion of key signaling molecules of the innate immune system has almost always resulted in worsening of symptoms, augmenting amyloid deposition and cognitive decline [1]. As such, it is now better accepted that receptors of the innate immune system are involved in the removal of amyloid β (Aβ) and may act as a natural defense mechanism to prevent Aβ accumulation in the neurovascular system and brain parenchyma. On the other hand, innate immune molecules and cells can also have detrimental effects in advanced stages of the disease. Moreover, while microglia can be effective to clear Aβ, they alone cannot resolve the problem as amyloid production surpasses their capacity for its clearance while the disease is progressing. These effects are exacerbated due to their polarization toward an anti-inflammatory phenotype rather than being pro-inflammatory. Accordingly, blocking the signaling cascades of the immunosuppressive cytokine TGF-β1, IL-4 and IL-10 significantly improved AD-like pathology in mice [2].

In a recent paper published in *Cell,* Wang *et al.* [3] provide new molecular insights into the innate immune mechanisms involved in the ability of microglia to prevent Aβ accumulation. They investigated the role of triggering receptor expressed on myeloid cells 2 (TREM2), which is a cell surface receptor of the Ig superfamily expressed on myeloid cells, such as monocytes, macrophages and microglia in the brain. They investigated the role of this receptor since a rare R47H mutation of TREM2 is associated with a substantial increase in the risk of developing AD. TREM2-deficient 5XFAD mice exhibited higher hippocampal amyloid burden and neuronal loss than 5XFAD animals. A significant increase of the insoluble form of $A\beta_{40}$ and $A\beta_{42}$ was also found in the hippocampus, but not in the cerebral cortex. Microglia are the key immune cells of the brain and they play a critical role in the phagocytosis of Aβ. TREM2 is strongly expressed by these cells, especially in mouse models of AD including the 5XFAD. The global transcriptome analysis of microglia revealed that TREM2 plays a critical role in the regulation of proinflammatory genes and that TREM2-deficient microglia behaved more similarly to WT microglia. These data indicate that TREM2 is essential for microglia to react against Aβ and engage in the clearing process.

Microglia have previously been shown to be closely associated with senile plaques and restrict their formation. Here TREM2-deficient mice had reduced number of microglia, particularly in the areas surrounding senile plaques, which suggests a lower microgliosis near amyloid deposits. Microglial survival is also affected by TREM2. In a series of *in vitro* experiments, Wang *et al*. provided evidence that TREM2-deficient microglia are not able to sustain reactive microgliosis and undergo apoptosis rather than becoming activated and expanding. This may be the critical mechanism underlying the failure of TREM2-deficient microglia to clear Aβ and explains the amyloid burden in this mouse model of AD. The survival of microglia affected by TREM2 is quite relevant in the context of the very hostile environment in the brain of AD. They next investigated the ligand(s) that may trigger TREM2 signaling in the process of Aβ deposition. Membrane phospholipids are exposed by damaged neurons and glial cells, and anionic and zwitterionic non-phosphate lipids are released by damaged myelin. TREM2 is a sensor for these myelin lipids that also interact with fibrillar Aβ. As mentioned earlier, the rationale behind this study

was that R47H mutation of TREM2 is a major risk factor of developing AD. To determine how this mutation affects microglia in these processes, TREM2 R47H reporter cells were generated and exposed to anionic ligands. The results show that TREM2 recognition of lipid ligands was less effective in the presence of the R47H mutation. These data provide mechanistic insights into the ability of endogenous lipids to trigger TREM2 and the inflammatory signaling cascade in microglia in order to clear Aβ from the CNS.

We have previously shown that it is possible to affect the CNS milieu by targeting cells of the periphery. In this regard, injecting macrophage colony-stimulating factor (M-CSF) to transgenic mice that spontaneously develop AD on a weekly basis prior to the appearance of learning and memory deficits prevented cognitive loss [4]. The treatment also restored the number of Ly6Chigh (e.g., M1) monocytes in the blood and greatly decreased Aβ levels [5]. M1 monocytes being the most efficient at clearing Aβ from the brain parenchyma, M-CSF treatment resulted in the stabilization of the cognitive decline state in transgenic mice that already had Aβ pathology. In another recent paper, Jay and colleagues suggest a role of TREM2 in the capability of monocytic cells to eliminate Aβ [6]. They show that TREM2 is expressed in monocyte-derived macrophages in the brain of another mouse model of AD APP/PS1. However, this interpretation was only based on indirect markers such as CD11b and CD45, which are also regulated in resident microglia during brain injury and diseases. One should therefore be cautious to interpret these data as pure cells of systemic origin. A chimeric approach is absolutely needed to identify cells of systemic origin. Surprisingly and in contrast to the previous paper, TREM2-deficient APP/PS1 mice seem to have a lower hippocampal Aβ deposition than APP/PS1 mice.

Although these two studies used a different mouse model of AD, such discrepancies are very difficult to reconcile. It is also possible that while TREM2 affects microglia and macrophages, this may not be translated to significant functional consequences. Indeed, both of these papers are lacking of the most critical piece of data, behavior analyses of the cognitive decline and improvement. These data are absolutely essential to conclude that TREM2 is indeed involved in the regulation of innate immune cells to modify cognition and other behavioral functions that are affected by this disease.

Serge Rivest[1]

[1]*Neuroscience Laboratory, CHU de Québec Research Center, Department of Molecular Medicine, Faculty of Medicine, Laval University, 2705 Laurier Blvd., Québec, Canada*
Correspondence: Serge Rivest
E-mail: Serge.Rivest@crchudequebec.ulaval.ca

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