

Innate immunity and inflammation in Alzheimer's disease pathogenesis

Imunidade inata e inflamação na patogênese da doença de Alzheimer

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Conflict of interest:

There is no conflict of interest to
declare.

Received 18 August 2017

Accepted 25 August 2017



Genetic studies have provided important insights into the pathogenesis of Alzheimer's disease (AD). In the early 1990s, the identification of mutations in the amyloid precursor protein (*APP*), presenilin1 (*PSEN1*) and presenilin2 (*PSEN2*) genes – genes that encode proteins that are involved in the amyloidogenic processing of *APP* – as causative of monogenic AD provided strong arguments for the amyloid cascade hypothesis¹. According to the amyloid cascade hypothesis, amyloid beta ($A\beta$) accumulation and deposition occurs in late onset AD due to failure of clearance mechanisms, and is the initial event that eventually leads to neuronal and synaptic loss¹.

Neuropathological findings brought up the initial clues that the innate immunity system participates in the AD pathogenesis, as activated microglia and astrocytes are found around neuritic $A\beta$ plaques^{1,2}. The interest on the role of neuroinflammation grew after early epidemiological studies indicated that the use of non-steroidal anti-inflammatory drugs (NSAIDs) reduced the risk of developing AD³. Over time, studies in cell and animal models have shown that $A\beta$ oligomers, protofibrils and fibrils are toxic to microglia (thus reducing their ability to promote $A\beta$ clearance) and induce the production of cytokines, and the resulting chronic inflammation promotes neurodegeneration². Genetic association studies have reinforced the idea that microglia and chronic neuroinflammation have a more central role in the disease pathogenesis. Since the mid-2000s, genome-wide association studies (GWAS) and association studies that used whole genome or exome sequencing data, have helped identify genes that are associated with late-onset AD; and by clustering those genes based on the analyses of biological pathways, four major pathways have been identified as implicated in the AD pathophysiology, one of which is immune response (and the others being control of endocytosis, cholesterol metabolism and ubiquitination of proteins)⁴. Genes such as *CRI* (complement C3b/C4b receptor 1), *CD33* (CD33 molecule), and *TREM2* (triggering receptor expressed on myeloid cells 2) are expressed in microglia and encode proteins that participate in the microglial response to $A\beta$ deposition^{1,4,5}. Variants in *TREM2* – despite being less frequent in the population – have a similar effect size on the risk of developing AD to the one associated with the $\epsilon 4$ variant of the *APOE* (Apolipoprotein E) gene, the main genetic AD risk factor^{4,5}. A more recent study that included almost 40,000 AD cases also identified *ABI3* (ABI family member 3) and *PLCG2* (phospholipase C gamma 2), genes that are highly expressed in microglia and encode proteins that participate in the immune response⁵.

Inflammation is a complex and dynamic process, and during the course of AD, it probably has protective and deleterious effects in different phases^{2,3}. The initial accumulation of $A\beta$ triggers microglia activation and $A\beta$ phagocytosis, but the ongoing production of $A\beta$ and release of pro-inflammatory cytokines (such as $TNF\alpha$, interleukin-1, interleukin-12, and interleukin-23) leads to a chronic inflammatory state and microglial dysfunction that hinders $A\beta$ clearance². Anti-inflammatory cytokines, such as interleukin-10 (IL-10), have also been studied in AD, particularly because the modulation of inflammatory processes might be a target for the disease treatment. Its exact role on the neurodegenerative processes, however, still needs more clarification; in transgenic animal studies, IL-10 has shown beneficial effects on cognition in some studies, but more recent research has indicated that IL-10 might worsen $A\beta$ accumulation by inhibiting microglial phagocytosis^{6,7}. Overall, the data currently available indicate that modulation of the inflammatory response in the early stages of the disease rather

than an anti-inflammatory only approach might be a better treatment strategy for AD^{3,6}. This is also supported by the results of clinical trials that used NSAIDs and failed to show clear benefits in patients with AD³.

In this context, Magalhães and colleagues⁶ reviewed the literature on whether single nucleotide polymorphisms (SNPs) that regulate the expression of the *IL-10* gene affect the susceptibility to AD. Even though the findings of the sixteen studies from around the world were conflicting⁶ and a recent meta-analysis did not find a significant association between -1082G>A in *IL-10* and AD risk⁸, interestingly both studies conducted in Brazil showed associations between *IL-10* polymorphisms and AD⁹ or cognitive impairment¹⁰.

The discrepancies across studies might be due to numerous causes, such as different sample sizes, unaccounted

factors that modify *IL-10* expression, and/or the fact that studies were performed in different populations. Indeed, most genetic association studies on AD have been performed in Caucasian populations, and more recently, there have been efforts to also perform those studies in populations with different racial backgrounds. These latter efforts have shown that the effect sizes of gene variants can vary significantly in different populations. Variants in the *ABCA7* (ATP-binding cassette sub-family A member 7) gene, for example, are associated with higher risk of AD among African Americans than in individuals with European ancestry¹¹. It is therefore important to conduct genetic association studies in the highly admixed Brazilian population, to better understand the effects of genetic variants in the risk and phenotype of AD.

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