Journal of Molecular and Genetic Medicine
ISSN: 1747-0862

Reitz and Tosto, J Mol Genet Med 2013, 7:2
DOI: 10.4172/1747-0862.1000060

Review Article Open Access

Inflammation, Immune System and Alzheimer's disease: A Review of the Findings from the Major GWAS Studies

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Abstract

A role for inflammation in the pathogenesis of Alzheimer's disease (AD) has been a matter of debate since the beginning of AD research in 1907. Over the past three decades immunohistochemical studies demonstrated that amyloid plaques are co-localized with activated microgliaas well as a broad spectrum of inflammation-related proteins (complement factors, acute-phase proteins, pro-inflammatory cytokines) spurring the hypothesis that amyloid plaques may benests of a non-immune mediated inflammatory reactions induced by fibrillar Aβ deposits. However, molecular studies also suggest that inflammation-related proteins are involved in Aβ generation and clearance, gliosis and increased phosphorylation of tau with accelerated tangle formation, i.e. several events considered key pathogenic steps in AD. In line with both notions, neuropathological studies show a close relation between fibrillar Aβ deposits, inflammation and neuroregeneration in relatively early stages preceding extensive tau-related neurofibrillary changes. Genetic studies address the issue of reverse causation and thus can help clarify the temporal relation between inflammatory changes and AD. In this review article we summarize the findings on inflammatory genes from the large scale genetic studies in AD and discuss directions for future research.

Keywords: Inflammation; Immune system; gene; Alzheimer's disease; Genome-wide association study; Sequencing

Introduction

A role for inflammation in the pathogenesis of Alzheimer's disease (AD) has been a matter of debatesince the beginning of AD research. In 1910, although lacking the tools to pursue this hypothesis experimentally, Oskar Fischer suggested that senile plaques form as the result of an extracellular deposition of an abnormal substance in the cortex. He proposed that accumulation of this substance induces a local inflammatory reaction followed by an attempted but doomed regenerative response of the surrounding nerve fibers. Seven decades later, the presence of complement factors and activated microglia in plaques has been demonstrated using monoclonal antibodies stipulating the notion that Aβ itself can stimulate a local inflammatory response [1]. This views supported by *in vitro* studies showing that fibrillar Aβ can bind complement factor C1 and activate the classical complement pathway in an antibody-independent fashion [2]. Such activated early complement factors could play an important role in the local recruitment and activation of microglial cells expressing the complement receptors CR3 and CR4 [3]. Aβ activates microglia by binding to the receptor for advanced glycation end products (RAGE) [4] as well as other scavenger receptors [5]. In addition, the LPS receptor, CD14, interacts with fibrillar Aβ [6] and microglia destroys $Aβ_{1–42}$ damaged neurons by a CD14 dependent process [7]. Fibrillar Aβ has been shown to increase cytokine and nitric oxide production in microglia dependent on CD14, TLR2 and TLR4 [8]. Aβ also triggers inflammatory signaling through heterodimer formation of Toll-like receptor 4 and 6 [9]. However, molecular studies also suggest that inflammation-related proteins are involved in several events considered key pathogenic steps in AD [10]. Chronic inflammation and cytokine up-regulation induce tau hyperphosphorylation in prepathological 3xTg-AD mice [11]. In addition, studies [12-14] indicate that inflammatory processes are involved in clearing or degrading Aβ depositions. The deficiency of CCR2, a chemokine receptor, impairs microglia accumulation and increases Aβ deposition in amyloid precursor protein (APP)-transgenic mice, indicating a role for microglia in regulating Aβ accumulation [15,16]. On the other hand, chronic lipopolysaccharide (LPS)–induced neuroinflammation increases intraneuronal Aβ load in transgenic mice, [17] possibly through the release of proinflammatory cytokines and other toxic speciesand the subsequent exacerbation of AD-related pathological features.

Based on these findings, inflammation could be both cause or consequence of the disease process. Clinicopathological studies show that the presence of activated microglia and inflammation-related mediators in the cerebral neocortex of patients with a low Break stage for AD pathology precedes extensive tau-related neurofibrillary pathology [18]. Studies using positron emission tomography (PET) with the peripheral benzodiazepine receptor ligand PK-11195 as a marker for activated microglia indicate that activation of microglia occurs before cerebral atrophy in AD patients [19]. In line with this notion of an early involvement of inflammation and immune response in the disease etiology, aPET study using the Pittsburg compound B (PIB) for visualization of fibrillar amyloid and the PK-11195 ligand for microglia activation detected amyloid deposition with microglia activation in ~50% of patients with mild cognitive impairment [20]. Of note, there is evidence that brain Aβ loadas measured by PIB labeling is correlated with peripheral acetylcholinesterase (AChE) levels [21]. Elevated AChE levels, in turn, are prevalent in AD and lead to the commonly seen decreased acetylcholine levels. The fact that

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Received July 06, 2013; **Accepted** July 22, 2013; **Published** July 25, 2013

Citation: Reitz C, Tosto G (2013) Inflammation, Immune System and Alzheimer's disease: A Review of the Findings from the Major GWAS Studies. J Mol Genet Med 7: 60. doi:10.4172/1747-0862.1000060

acetylcholine blocks inflammatory mechanisms suggests that ACH inhibitors, which constitute four out of the five drugs approved for treatment, may also be beneficial through an effect on this this pathway. In summary, it is likely that some components of the molecularly and cellularly inflammation pathway are promoting pathological processes leading to AD, whereas other components serve to do the opposite (in more detail reviewed in [22,23]).

Through Mendelian randomization, genetic studies address the issue of reverse causation and thus can help clarify the causal and temporal relation between inflammatory changes/immune response and AD. In this review article we summarize findings on inflammatory genes from large scale genetic studies in AD and discuss directions for future research.

Findings from Genetic Studies

In the beginning of the century, thousands of candidate-gene-based association studies aiming to identify susceptibility loci for late-onset AD were performed but only one gene, the sortilin-related receptor (*SORL1*) which is implicated in intracellular trafficking of APP, could be consistently replicated in independent datasets and implicated in the disease. The main reasons for these inconsistencies between studies are sample heterogeneity with differences in linkage disequilibrium (LD) patterns and allele frequencies, and small sample sizes leading to limited power to detect small or moderate effect sizes. In the past five years, technological advances in high-throughput genome-wide arrays allowed the hypothesis-free simultaneous examination of thousands to millions of polymorphisms across the genome.Large collaborative efforts capitalizing on this technology have significantly advanced the knowledge on the genetic underpinnings of late-onset Alzheimer's disease (LOAD) and pathways involved by identifying several novel risk loci. Of note, besides genes clearly clustering in the lipid metabolism, intracellular trafficking and APP metabolism pathways, several of the identified genes cluster in the inflammation/immune response pathway.

Most genome-wide association studies (GWAS) contributing to this gained knowledge were performed in non-Hispanic Whites of European ancestry. The first set of studies identified four genes (*CLU*, *PICALM*, *CR1* and *BIN1)* as AD susceptibility loci [24-26]. While CLU, also known as a polipoprotein J (ApoJ), is similar to APOE involved in lipid transport [27] and is also hypothesized to act as an extracellular chaperone that influences Aβ-aggregation and receptor-mediated Aβ clearance by endocytosis [28], and BIN1 [29] and PICALM [30] are involved in clathrin-mediated endocytosis, CR1 is a cell-surface receptor that is part of the complement system.It has binding sites for complement factors C3b and C4b and is involved in clearing immune-complexes containing these two proteins. Since Aβ oligomers can bind C3b as described above, CR1 may participate in the clearance of Aβ and play a role in neuroinflammation in AD [31]. Interestingly, Clu may play a role in this process as an inhibitor [32].

The second set of large GWA studies identified five additional susceptibility genes (*CD33, MS4A4A/MS4A4E/MS4A6E cluster*, *ABCA7*, *CD2AP* and *EPHA1* [33,34] out of which all are likely involved in the immune system (Table 1). The *CD33* gene encodes a protein that is a member of a family of cell surface immune receptors that bind extracellular sialylatedglycans and signal via a cytoplasmic domain called the immune receptor tyrosine inhibitory motif [33,34]. CD33 has primarily been studied in the peripheral immune system where it is expressed on myeloid progenitors and monocytes and also in the brain.

Gene	Chr	Position	Disease-associated SNP
CR1	1	207692049	rs6656401
CD2AP	6	47487762	rs10948363
EPHA1	7	143110762	rs11771145
CLU	8	27467686	rs9331896
MS4A6A	11	59923508	rs983392
ABCA7	19	1063443	rs4147929
CD33	19	51727962	rs3865444
TREM2	6	41129252	rs75932628

Table 1: Inflammatory pathway genes associated with Alzheimer's disease.

In the periphery, CD33 appears to inhibit proliferation of myeloid cells [35]. The *MS4A4A/MS4A4E/MS4A6E* locus is part of a cluster of 15 *MS4A* genes on chromosome 11 and encodes proteins with multiple membrane-spanning domains that were initially identified by their homology to CD20, a B-lymphocyte cell surface molecule. Little is known about the function of MS4A4A gene products; however, like CD33, MS4A4A is expressed on myeloid cells and monocytes and likely has an immune-related function. *EPHA1* encodes a member of the ephrin family of cell surface receptors which interact with ephrin ligands on adjacent cells to modulate cell adhesion, migration, and axon guidance and synapse formation and plasticity. While there is a substantial body of research on the function of ephrin receptors in general, little is known about the *EPHA1* gene product. Like other ephrin receptors, it regulates cell morphology and motility [36] and early work implicated this receptor in regulating vascular morphogenesis and angiogenesis [37]. *EPHA1* knockout in mouse results in abnormal tail and reproductive tract development, [38] but no effects on the brain. Consistent with this notion, in mouse, expression is restricted to epithelial tissue. In humans, EPHA1 is expressed by CD4-positive T- lymphocytes [39], monocytes, [40] intestinal epithelium, and colon. Combined with the lack of evidence for brain expression this may suggest that, like CD33, *CR1*, and *MS4A4/MS4A6E*, the role of the *EPHA1*gene product in AD may be mediated though the immune system.The CD2 associated protein gene (*CD2AP*) encodes a scaffolding protein that binds directly to actin [41], nephrin and other proteins involved in cytoskeletal organization. In the immune system, CD2AP is required for synapse formation [42] in a process that involves clathrin-dependent actin polymerization. *ABCA7* is an integral transmembrane ATP-binding cassette transporter belonging to the ABC family proteins that mediate the biogenesis of high-density lipoprotein with cellular lipid and helical apolipoproteins [43]. It binds APOA-I and functions in apolipoprotein-mediated phospholipid and cholesterol efflux from cells [44]. However, *ABCA7*also affects the transport of other important proteins, including APP, [44] through the cell membrane and is involved in host defense through effects on phagocytosis by macrophages of apoptotic cells [43].

In the largest GWAS performed to date in Caribbean Hispanics [45] associations in *CLU,PICALM*, and *BIN1* were replicated and several additional loci on 2p25.1, 3q25.2, 7p21.1 and 10q23.1 - which could be replicated in an independent cohort of non-Hispanic Whites of European ancestry from the National Institute on Aging Late-Onset Alzheimer's Disease Family Study (NIA-LOAD) were observed. In the largest GWAS of African Americans performed to date, Reitz et al. [46] identified *ABCA7* as a major susceptibility locus in this ethnic group and replicated *CR1*.

Based on genotyping chip and quality control design, GWAS by definition capture mostly common genetic variation with small to moderate effect sizes. In line with this notion, all abovementioned AD-associated variants outside the *APOE* locus that have been identified by GWAS are common and have small effect sizes (1.0<OR<1.2) leaving a large part of the genetic contribution to the disease unexplained. It is likely that much of the 'missing heritability' is explained by rare genetic variants with a minor allele frequency (MAF) below 1% [47]which are commonly excluded from GWAS. Moreover, imputation, which is used to infer non genotyped variants, often fails to show acceptable accuracy at low MAF (i.e. MAF<0.3) [48].

In line with this notion, two recent studies that performed genome sequencing followed by imputation of identified variants in independent datasets implicated the triggering receptor expressed on myeloid cells 2 (*TREM2*) gene in AD by identifying a causative rare missense mutation (rs75932628) which results in an R47H substitution and confers a threefold increase in risk. The *TREM2* gene istranslated into a type-I membrane protein with an extracellular Ig-like domain and was first described as potentially involved in chronic inflammation response [49]. TREM2 is widely expressed in the brain, on myeloid and natural killer cells, some T and B cells and osteoclasts. Its signaling capacity is carried out through coupling with DAP12, a cytosolic adapter with dual function (activation and inhibition of several immune cell types)resulting in cytokine production regulation [50]. This regulatory effect is thought to be fundamental for regulating microglia activity which in turn enhances development ofamyloid plaques, the key pathological hallmark in AD [51]. Of note, a loss of function of *TREM2* had been previously described to be associated with an autosomal recessive form of early-onset dementia presenting with bone cysts and quasi-spontaneous fractures called "polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy" or "Nasu–Hakola disease" [52]. Other homozygous *TREM2* mutations have been described in patients presenting with frontotemporal-like dementia [53]. Besides implicating this gene in the disease, these two studies provided significant confirmation that not only common but also rare variants are involved in late-onset AD.

Conclusions and Future Perspective

The genetic studies from the past decade have added a significant body of evidence for a causative involvement of inflammation and the immune system in AD etiology through identification of several disease-associated genes functioning in this pathway. The recent advances in next generation whole exome (WES) and whole genome sequencing (WGS) will help to identify specific disease-associated alleles in these genes. In addition, it is likely that, besides identifying additional genes that are part of other pathways involved including lipid metabolism, intracellular trafficking and APP metabolism, they will identify further common and rare variants in inflammation- and immune response-related genes that will explainpart of the heritability still missing.

It is important to note that before the known information on genes involved is used in clinical settings several additional issues have to be clarified. First, it has to be clarified at what stage of the AD disease process the inflammation-related risk genes might exert its effect. Recent high throughput transcriptome studies based on hippocampal neurons indicate an early-stage involvement of inflammatory regulators [54]. Second, more functional validation of these genes is needed. Before any of the identified genes can be safely used as a target for prevention, treatment or diagnostic testing, it has to be fully clarified through which mechanisms theyexert their effects on AD risk, in which other pathways they are involved and interact with, and which effects a modulation of their function would have.

Acknowledgements

Dr. Reitz was supported by a Paul B. Beeson Career Development Award (K23AG034550). Dr. Tosto was supported by Whole Exome Analysis of Early Onset Alzheimer's Disease Grant (W81XWH).

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