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The pervasiveness of interleukin-1 in Alzheimer pathogenesis: a role for specific polymorphisms in disease risk

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Abstract

Interleukin-1 (*IL-1*) has been implicated as a key molecule in Alzheimer pathogenesis based on findings of an *IL-1* overexpression in Alzheimer brain that is directly related to plaque progression and tangle formation, and on findings that *IL-1* induces excessive synthesis, translation, and processing of neuronal β-amyloid precursor protein (βAPP) as well as synthesis of most known plaque-associated proteins. In addition, *IL-1* activates astrocytes, with the important consequence of over-expression of the neuritogenic cytokine S100β and overgrowth of dystrophic neurites in neuritic plaques. As further evidence of the importance of *IL-1* in Alzheimer pathogenesis, two new genetic studies of inheritance of specific polymorphisms in *IL-1* genes in Alzheimer and control patients show that homozygosity for a specific *IL-1A* gene polymorphism at least triples risk for development of Alzheimer's disease. This increase is associated with earlier age of onset. Homozygosity for this polymorphism plus another in the *IL-1B* gene further increases risk.

Keywords

Alzheimer's disease; Interleukin-1; Genetic risk; Immunogenetics

An understanding of Alzheimer's disease must necessarily commence with an understanding of the pathogenesis of the neuritic β-amyloid plaques that are diagnostic of the disease. Similarly, an understanding of the origins of Alzheimer's disease must commence with identification of pathological changes that precede the appearance of these plaques, and identification of candidate molecules that orchestrate the pathogenic mechanisms culminating in Alzheimer pathogenesis. Our early consideration of a potential role for immune-response generating cytokines as driving forces in pathogenic processes in brain was a departure from more conventional ideas regarding Alzheimer pathogenesis, and our

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early demonstration of interleukin-1 (*IL-1*) overexpression in Alzheimer brain (Griffin et al., 1989) was the first evidence supporting this controversial new idea. This overexpression is principally a manifestation of activated (enlarged) microglia that are found both associated with β-amyloid plaques and located immediately adjacent to neurons. The central and important role of *IL-1* in Alzheimer pathogenesis has been supported by this and numerous subsequent findings, including the observations that *IL-1*: (i) is excessively expressed in Alzheimer brain tissue; (ii) induces excessive synthesis of the β-amyloid precursor protein (βAPP) in neurons (Forloni et al., 1992); and (iii) activates astrocytes (Giulian et al., 1988) with the important consequence of astrocytic overexpression (Griffin et al. 1995) of the neuritogenic (Kligman and Marshak, 1985) cytokine S100β. These findings were the basis for genetic studies showing that specific polymorphisms in *IL-1* genes increase risk for Alzheimer's disease (Nicoll et al., 2000; Grimaldi et al., 2000), lending importance to what we propose as a new area for exploration: the immunogenetics of Alzheimer's disease. These *IL-1* mediated influences in Alzheimer pathogenesis are depicted in Fig. 1.

This review focuses on two lines of investigation delineating the contribution of *IL-1* to Alzheimer pathogenesis. The first is the definition of the molecular events involved in *IL-1*-driven cascades, and their potential to initiate and propagate the neuropathological changes of Alzheimer's disease. The second is the identification of Alzheimer disease risk associated with polymorphisms within the two genes (*IL-1A* and *IL-1B*) encoding the two isoforms of *IL-1*, *IL-1α* and *IL-1β*, respectively.

1. Early evidence for *IL-1* cascades in Alzheimer pathogenesis

An early observation supporting a role for *IL-1* in the pathogenesis of Alzheimer's disease was the overexpression of *IL-1* in Down's syndrome. Florid Alzheimer-type neuropathological changes are virtually inevitable consequences of Down's syndrome (Wisniewski et al., 1985), making this condition a natural model of Alzheimer pathogenesis. *IL-1* is dramatically overexpressed in activated microglia in Down's fetuses and neonates, decades before the inevitable appearance of Alzheimer-like changes (Griffin et al., 1989). This observation suggested that the excessive expression of *IL-1* in Alzheimer brain might be a seminal and continuing driving force, responsible for a cascade of neurodegenerative events that culminate in the neuropathological changes characteristic of Alzheimer disease. By analogy with immune cascades in the periphery (Dinarello and Wolff, 1993), it was logical to conclude that neural cascades include *IL-1*, which is known to activate astrocytes (Giulian et al., 1988), and thus would induce expression of one or more astrocyte-derived secreted neuronotrophic proteins. We proposed that the neuritogenic cytokine S100β (Kligman and Marshak, 1985) would provide a link whereby *IL-1* could contribute to the proliferation of dystrophic neurites and thus to the progression of amyloid deposits into the neuritic β-amyloid plaques diagnostic of Alzheimer's disease. Our subsequent work has confirmed this possibility, as we have shown that *IL-1* does induce astrocytic overexpression of S100β and S100β mRNA (Sheng et al., 1996); that the tissue levels of S100β in cerebral cortex in Alzheimer's disease are directly proportional to the numbers of neuritic β-amyloid plaques (Sheng et al., 1994); and that the numbers of plaque-associated, S100β-expressing astrocytes correlates with the abundance of dystrophic neurites within individual plaques (Mrak et al., 1996).

The early landmark study (Goldgaber et al., 1989), showing that *IL-1* induces excessive expression of the β-amyloid precursor protein (βAPP), confirmed a link between the overexpression of *IL-1* in Alzheimer's disease and the deposition of β-amyloid that is so characteristic of the disease. The importance of *IL-1* regulation of βAPP expression was subsequently expanded to include regulation of its translation (Rogers et al., 1999) and processing into secreted fragments (sAPP) and β-amyloidogenic fragments (Buxbaum et al.,

1992). These results suggest that *IL-1* overexpression is an important factor in driving β-amyloid production, deposition, and thus plaque formation.

1.1. Interleukin-1 and neuronal dysfunction

In addition to putative effects of *IL-1* overexpression on the genesis and progression of plaques in Alzheimer's disease, there is considerable evidence of direct neurotoxic effects of *IL-1*, with potential contributions to neuronal dysfunction and loss in Alzheimer's disease. Although *IL-1* is trophic to neurons at low concentrations, higher concentrations are neurotoxic (Brenneman et al., 1992a,b). *IL-1* induces overexpression and phosphorylation of neurofilament proteins and *tau* (Sheng et al., 2000), and activated microglia, overexpressing *IL-1*, are intimately associated with neurons bearing neurofibrillary tangles in Alzheimer's disease (Sheng et al., 1997).

Recent findings suggest that *IL-1* may have a more direct role in the cholinergic dysfunction and decline that is characteristic of Alzheimer's disease. In response to both toxic and sub-toxic stress, neurons synthesize βAPP and increase release of sAPP, and this neuronal stress-induced sAPP activates microglia and induces excessive expression of *IL-1* (Barger and Harmon, 1997). This interaction, by which neurons may signal their distress to microglia, and the consequent microglial overexpression of *IL-1*, results in increased neuronal activity and expression of acetylcholinesterase both in vivo and in vitro (Li et al., 2000). These findings suggest that the increase in concentration of *IL-1* in Alzheimer brain contributes to the decrease in acetylcholine by upregulating acetylcholinesterase.

Recent work has elucidated, in part, the intracellular regulation of *IL-1* synthesis and activation as well. *IL-1β* converting enzyme (ICE) is responsible for converting *pro-IL-1β* to active *IL-1β*, and the activity and expression of ICE is increased in Alzheimer's disease (Chan et al., 1999; Zhu et al., 1999). In addition to its role in activating *IL-1β*, ICE may also contribute directly to neuronal toxicity and death. ICE is the first described member of a caspase family (caspase I), and its activation is associated with, and necessary for, neuronal and astrocyte apoptosis (Keane et al., 1997). This suggests that the overexpression of ICE by plaque-associated and neuron-associated microglia might contribute to the DNA damage observed in neurons within and adjacent to neuritic β-amyloid plaques (Sheng et al., 1998a) and in non-plaque-associated neurons bearing neurofibrillary tangles in Alzheimer's disease (Sheng et al., 1998c).

1.2. IL-1 and β-amyloid plaque formation and progression

Microglia show a characteristic laminar distribution pattern in normal brain, and the laminar distribution of β-amyloid plaques in Alzheimer brain mirrors that pattern (Sheng et al., 1998b). There is also a correlation between the number of activated microglia overexpressing *IL-1* and the number of neuritic β-amyloid plaques across brain regions (Sheng et al., 1995). These findings suggest that *IL-1* is a principle driving force in the initiation and spread of β-amyloid plaque pathology in Alzheimer's disease.

IL-1 promotes astrocytic expression of a number of important, Alzheimer-related proteins, in addition to S100β. These include *IL-6* (Bauer et al., 1991), α_1-antichymotrypsin and apolipoprotein E (Das and Potter, 1995), and some complement proteins (Barnum and Jones, 1995). All of these proteins are found co-deposited with β-amyloid in the plaques of Alzheimer's disease. This, together with the effects of *IL-1* on synthesis and processing of βAPP, suggests a powerful role for *IL-1* in driving deposition of protein within β-amyloid plaques. *IL-1* may also contribute to the formation of dystrophic neurites within these plaques—and thus to the conversion of diffuse amyloid deposits into neuritic β-amyloid

plaques—through regulation of astrocytic S100β expression (Sheng et al., 1996) and through the consequent neuritogenic actions of S100β (Marshak et al., 1991).

2. *IL-1* polymorphisms in Alzheimer pathogenesis

The postulated role for *IL-1* as a key orchestrating cytokine in Alzheimer pathogenesis suggested that variations in the genes for *IL-1* might confer differential risk for development of Alzheimer's disease. One common polymorphism in the promoter region of the *IL-1A* gene (allele 2) has already been shown to confer increased risk for juvenile rheumatoid arthritis (McDowell et al., 1995). Another common polymorphism (also known as allele 2) in the coding region of the *IL-1B* gene has been associated with increased production of *IL-1β* (Pociot et al., 1992). In a study of a group of neuropathologically confirmed Alzheimer patients from four centers in the US and UK (Nicoll et al., 2000), the prevalence of the *IL-1A* 2,2 genotype was 12.9% in Alzheimer patients, compared to 6.6% in control patients. Patients homozygous for the *IL-1A* 2 allele thus carry three times the risk of developing Alzheimer's disease. Furthermore, homozygosity for both *IL-1A* allele 2 and *IL-1B* allele 2, was associated with a 10-fold increased risk of developing Alzheimer's disease in this study. Another study of a large cohort of clinically assessed patients in the Italian Longitudinal Study was directed toward the possible effects of *IL-1* polymorphisms on age at onset of Alzheimer's disease (Grimaldi et al., 2000). Homozygosity for the *IL-1A* allele 2 strongly influenced age at onset of Alzheimer's disease (yielding an odds ratio of 4.74): the age at onset of *IL-1A* 2 homozygous patients was, on average, 61 years, compared to 68 years for hemizygous patients, and 70 years for *IL-1A* 1,1 patients. In this generally younger population of clinically assessed Alzheimer patients, there was an *IL-1A* genotype dose effect: an odds ratio of 6.33 for *IL-1A* 2,2 and 1.84 for *IL-1A* 1,2. Another polymorphism located in the promoter region of the *IL-1B* gene also increases risk for developing Alzheimer's disease. Homozygosity for this polymorphism confers twice the risk for developing Alzheimer's disease, and the risk is for late-onset, rather than early-onset, disease. In both of these studies, the increased risk for development of Alzheimer's disease with specific polymorphisms in *IL-1* genes was independent of *ApoE* genotype.

We have proposed (Nicoll et al., 2000) that these *IL-1* gene polymorphisms act by increasing the gain of an *IL-1* driven cycle, referred to as the *cytokine cycle* (Griffin et al., 1998), that acts through the *IL-1* mediated cascades discussed here to favor plaque formation and progression, dystrophic neurite proliferation, and neuronal dysfunction and loss in Alzheimer's disease. These neurodegenerative consequences of *IL-1* overexpression, in turn, engender further activation of microglia, through stress-induced overexpression of neuronal βAPP and β-amyloid deposition, and further amplification of *IL-1* overexpression. In this way, the *cytokine cycle* becomes self-propagating, a requisite for cycles that give rise to and maintain the progression of degenerative diseases.

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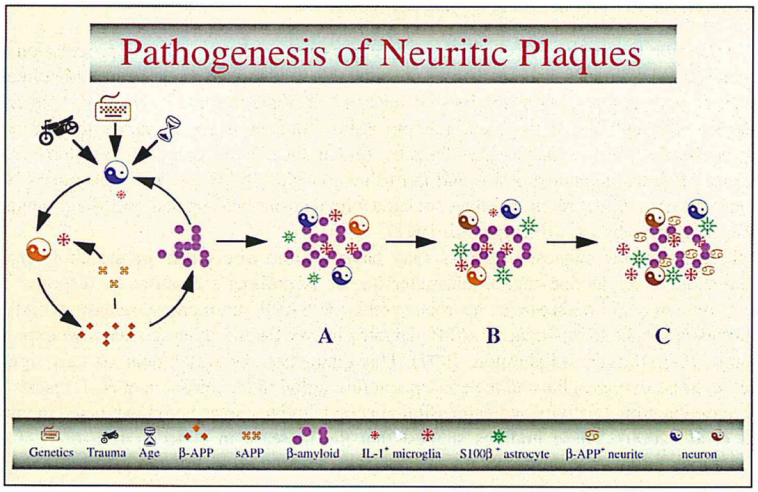

Fig. 1.

This is a schematic diagram demonstrating pathogenesis of neuritic plaque as a consequence of neuronal injury, activation of microglia with overexpression of *IL-1*, and subsequent initiation of *IL-1* driven cascades. (A), (B), and (C) represent progressive stages of β-amyloid plaque evolution.