Published in final edited form as:
J Leukoc Biol. 2002 August ; 72(2): 233–238.

Interleukin-1 in the genesis and progression of and risk for development of neuronal degeneration in Alzheimer's disease

W. Sue T. Griffin[*,†] and **Robert E. Mrak**[‡]

[*]Department of Geriatrics, Medicine, and Psychiatry, University of Arkansas for Medical Sciences, Little Rock

[‡]Department of Pathology, University of Arkansas for Medical Sciences, Little Rock

[†]Geriatric and Mental Health Research Education and Clinical Centers, Veterans Affairs Medical Center, Little Rock

Abstract

Interleukin-1 (IL-1), a key molecule in systemic immune responses in health and disease, has analogous roles in the brain where it may contribute to neuronal degeneration. Numerous findings suggest that this is the case. For example, IL-1 overexpression in the brain of Alzheimer patients relates directly to the development and progression of the cardinal neuropathological changes of Alzheimer's disease, i.e., the genesis and accumulation of β-amyloid (Aβ) plaques and the formation and accumulation of neurofibrillary tangles in neurons, both of which contribute to neuronal dysfunction and demise. Several genetic studies show that inheritance of a specific IL-1A gene polymorphism increases risk for development of Alzheimer's disease by as much as sixfold. Moreover, this increased risk is associated with earlier age of onset of the disease. Homozygosity for this polymorphism in combination with another in the IL-1B gene further increases risk.

Keywords

brain; neurodegenerative disease; Down's syndrome; head injury; aging; epilepsy; genetic risk; immunogenetics

INTRODUCTION

More than a decade ago, we proposed that immune response-generating cytokines are driving forces in pathogenic processes in the brain in Alzheimer's disease. This idea was a departure from accepted ideas about Alzheimer pathogenesis, and our early demonstration of interleukin-1 (IL-1) overexpression in Alzheimer brain and very early on in the life of those with Down's syndrome [1] was the first evidence supporting this controversial new idea. We also proposed that this idea is not confined to Alzheimer's disease and Down's syndrome, a recognized precursor for Alzheimer's disease, but rather may be a generalization that applies to other conditions exhibiting IL-1 overexpression and neuronal injury and loss. In support of this, subsequent studies have shown IL-1 overexpression within hours after head injury [2], in chronic, intractable epilepsy [3], and in AIDS [4]; each of these conditions has been associated with Alzheimer's disease itself or precocious development of Alzheimer pathology [2, 5, 6]. Recent microarray studies, assessing gene

Correspondence: Professor Sue Griffin, Donald W. Reynolds Center on Aging, 629 South Elm Street, Little Rock, AR 72205. griffinsuet@uams.edu.

expression of many immune and Alzheimer-related, cytokines, show selective overexpression of IL-1 and S100B in Alzheimer's disease [7]. These and other findings provided the rationale for recent genetic studies, which show, in the main, that specific polymorphisms in IL-1 genes increase risk for Alzheimer's disease [8–13], lending importance to what we propose as a new area for exploration: the immunogenetics of Alzheimer's disease.

This review focuses on three lines of investigation delineating the contribution of IL-1 to Alzheimer pathogenesis. The first is the identification and characterization of IL-1 temporal and spatial overexpression patterns and their relation to Alzheimer neuropathological changes. The second 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 third is the identification of Alzheimer's disease risk associated with polymorphisms within the two genes (*IL-1A* and *IL-1B*) that encode the two isoforms of IL-1, IL-1α and IL-1β, respectively.

IL-1 OVEREXPRESSION IN ALZHEIMER'S DISEASE

In Alzheimer's disease, IL-1 overexpression is differentially distributed to the activated (enlarged) microglia found associated with β-amyloid (Aβ) plaques and immediately adjacent to neurons, in particular those bearing tangles [14, 15]. This and numerous subsequent findings have supported a central role for IL-1 in Alzheimer pathogenesis. These include observations that IL-1 is excessively expressed in Alzheimer brain tissue [1, 16], that excessive expression of IL-1 is related to the pathological involvement in a given brain region, and that IL-1 overexpression is correlated with the spread of Alzheimer pathology across cortical regions. Human postmortem studies, of course, cannot provide definitive proof that IL-1-mediated events, shown experimentally, occur in the development of Alzheimer's disease, Down's with Alzheimer's disease, head injury, or in precocious development of Alzheimer changes in epilepsy or AIDS. However, such human studies actually demonstrate that experimental results are relevant to human disease. These human studies, together with the established functions of IL-1 (Fig. 1), strongly implicate IL-1 in neuropathogenesis.

POTENTIAL IL-1-INDUCED CASCADES IN ALZHEIMER PATHOGENESIS

Down's syndrome is a natural model of Alzheimer's disease as virtually all Down's patients develop marked Alzheimer-type neuropathological changes in middle age. IL-1 is overexpressed early in Down's syndrome, decades before the appearance of the florid Alzheimer-type, neuropathological changes [1]—the Aβ plaques and the neurofibrillary tangles—that characterize Down's syndrome at middle age [17]. As early as the second trimester, activated microglia of Down's fetuses dramatically overexpress IL-1; this overexpression continues throughout life with the inevitable appearance decades later of Alzheimer-like changes that include activated microglia colocalizing with Aβ plaques and tangles [1]. These findings, together with IL-1 functions established in vitro and in animal experiments, suggest that early and persistent overexpression of IL-1 in Down's syndrome may explain, in part, the early and excessive synthesis (i.e., greater than the 1.5× that is expected from gene loading), translation [18], and processing [19] of the precursor of the principle protein in plaques, Aβ precursor protein (βAPP) in neurons [20]. By analogy, we have proposed that in Alzheimer's disease itself, the pathology is initiated and driven, in part, by early and sustained overexpression of IL-1 with consequent overexpression of products of IL-1-driven cascades. It may also explain the intense, early, and persistent activation of astrocytes [21] with accompanying overexpression of astrocytic S100B [22], a cytokine known to promote dystrophic growth of neuronal processes [23]. In Alzheimer's

disease, astrocyte activation with overexpression of S100B correlates with the number of neuritic plaques in a given region [24] as well as with the density of dystrophic, neuronal processes in individual neuritic plaques [25]. Taken together, such events are consistent with our idea that microglial activation with overexpression of IL-1 is an early, important event in the generation of the neuritic Aβ plaques, which themselves are associated with neuronal dysfunction and loss. The latter is based on findings showing that neuronal DNA damage worsens with plaque progression from amyloid deposits to the neuritic plaques diagnostic of Alzheimer's disease [26]. In the dense core end-stage plaque, there are few associated microglia, astrocytes, or neurons. All of the remaining plaque-associated neurons show evidence of DNA damage. We have shown that neuronal damage is associated with microglial activation and overexpression of IL-1 [27, 28], providing feedback from damaged neurons that may act as a continuing driving force for amplification of IL-1-driven cascades. All such cascades shown in Figure 1 can result in neurodegeneration. The basis for the idea that these cascades may be important in the human brain and lead to neurodegenerative events lies in the existence of analogous IL-1-driven cascades in the periphery [29–31] and the production of IL-1 by glial cells of a type that respond to injury in the brain [32]. The finding that IL-1 activates astrocytes [21] and induces overexpression [22] of the neurite growth-promoting cytokine S100B [23] suggests a link whereby IL-1 could contribute to the proliferation of dystrophic neurites and thus to the conversion of Aβ deposits into the more complex neuritic Aβ plaques diagnostic of Alzheimer's disease. In addition, S100B overexpression may contribute to the initial deposition of Aβ, as S100B induces the increased synthesis of its precursor, βAPP [33].

IL-1 induction of excessive expression of the βAPP [34] provides a further link between the overexpression of IL-1 in Alzheimer's disease and its principal neuropathological feature, deposition of Aβ. The importance of IL-1 regulation of βAPP expression was subsequently expanded to include regulation of its translation [18] and processing into amyloidogenic secreted fragments (sAPP) [19]. These results suggest that IL-1 overexpression is an important factor in driving Aβ production, deposition, and thus plaque formation, as well as through astrocyte activation and overexpression of S100B to the growth of dystrophic neurites and formation of neurofibrillary tangles.

INTERLEUKIN-1 AND NEURONAL DYSFUNCTION

The overexpression of IL-1 observed in Alzheimer's disease could potentially contribute directly to the neuronal dysfunction and loss seminal to the disease. With regard to direct toxicity, elevating concentrations of IL-1 in vitro are toxic to neuronal explant cultures [35]. As for dysfunction, experimental elevation of IL-1 in the brain in vivo [36] induces the overexpression and phosphorylation of neurofilament proteins and of the microtubule-associated protein *tau* and the paired helical filaments, which are present in the neurofibrillary tangles of Alzheimer's disease. Moreover, elevation of IL-1 in vivo is associated with excessive growth of dystrophic neurites [36]. Activated microglia overexpressing IL-1 and activated astrocytes overexpressing S100B are intimately associated with neurons bearing neurofibrillary tangles in Alzheimer's disease [15]. Such neurons in Alzheimer brains also overexpress mitogen-activated protein kinase-p38, which phosphorylates tau at the sites that are phosphorylated in neurofibrillary tangles [16].

A further role for IL-1 overexpression in neuronal dysfunction may arise from IL-1 effects on cholinergic systems, as the cholinergic decline characteristic of Alzheimer's disease is thought to contribute to memory loss. IL-1 released from activated microglia directly induces increases in the acetylcholine-degrading enzyme, acetylcholinesterase, production, and activity in neurons [28]. In experiments showing this IL-1-induced increase, microglia were activated in response to neuronal release of sAPP. Both toxic and subtoxic stress to

neurons results in synthesis and release of sAPP, which in turn activates microglia and induces excessive microglial expression of IL-1 [27]. These findings suggest that the increased concentration of IL-1 in Alzheimer brain may contribute to the observed decreases in tissue acetylcholine levels by increasing synthesis and activity of neuronal acetylcholinesterase.

The increased tissue levels of IL-1 and the neuronal dysfunction in Alzheimer's disease may be attributable in part to increased production and activity of the IL-1β-converting enzyme (ICE), which converts pro-IL-1β to mature IL-1β. ICE activity and expression are increased in Alzheimer's disease, and this increase is related to neuronal DNA damage as well as to compromised, neuronal function [37, 38]. Overexpression of ICE by plaque- and neuron-associated microglia may contribute to neuronal DNA damage associated with neuritic Aβ plaque progression [26] and with neurons bearing neurofibrillary tangles in Alzheimer's disease [39].

IL-1 AND Aβ PLAQUE FORMATION AND PROGRESSION

The overexpression of IL-1 by plaque-associated, activated microglia dramatically increases with progression of plaques from non-neuritic, diffuse Aβ deposits to the neuritic Aβ plaques characteristic of Alzheimer's disease [14]. As discussed above, this conversion from diffuse deposits to the more complex, neuritic plaque may be, in part, a result of IL-1 promotion of astrocytic expression of S100B [40, 41]. IL-1 also induces astrocytic expression of other plaque-associated proteins that may contribute to this progression. These include IL-6 [42], α_1-antichymotrypsin, apolipoprotein E [43], and some complement proteins [44]. These findings suggest that IL-1 contributes to plaque progression through increased synthesis of astrocyte-derived proteins as well as through IL-1 effects on synthesis and processing of βAPP, which may directly contribute to the genesis and deposition of amyloidogenic fragments.

IL-1 GENETICS IN ALZHEIMER PATHOGENESIS

The potential role of IL-1 as a key orchestrating cytokine in Alzheimer pathogenesis focused interest on the possibility that polymorphisms in IL-1 might confer risk for development of Alzheimer's disease. A polymorphism in the promoter region of the IL-1α gene as well as one in the coding region of the IL-1β gene have been shown to confer increased risk for peripheral immune diseases, and both polymorphisms are associated with overexpression of IL-1 [45, 46]. Five groups have now shown that the polymorphism in the IL-1α gene increases risk for Alzheimer's disease [8–12]. Patients homozygous for this IL-1α polymorphism carry at least three times the risk of developing Alzheimer's disease. In addition, homozygosity for the IL-1α gene polymorphism was associated with earlier onset of disease, lowering the average age of onset from 68–70 years to 61 years [9]. Furthermore, homozygosity for both of these polymorphisms was associated with a tenfold increased risk of developing Alzheimer's disease [8]. This increased risk is independent of the ApoE genotype, another risk-conferring polymorphism for Alzheimer's disease. That these polymorphisms increase expression of IL-1 suggests that they increase risk for Alzheimer's disease by increasing the gain of an IL-1-driven cycle such as we propose in the cytokine cycle [47], acting through IL-1-mediated cascades that favor plaque formation and progression, dystrophic neurite proliferation, and neuronal dysfunction and loss. Neurodegenerative consequences of IL-1 overexpression, in turn, engender further activation of microglia through stress-induced overexpression of neuronal βAPP and Aβ deposition, thus inducing self-amplification of the cycle, a requisite for cycles that give rise to and maintain the progression of degenerative diseases.

A ROLE FOR IL-1 IN HEAD INJURY AND ITS RISK FOR LATER DEVELOPMENT OF ALZHEIMER'S DISEASE

Epidemiological observations implicate a previous head injury as a significant environmental risk factor for the subsequent development of Alzheimer's disease [48, 49], and this is now supported by a variety of neuropathological findings. Pathological changes that are similar to those seen in Alzheimer's disease, i.e., large numbers of diffuse Aβ plaques and numerous neurofibrillary tangles, are present in boxers who develop dementia pugilistica ("punch-drunk syndrome") [50]. Diffuse Aβ plaques are even found in the brains of approximately 30% of individuals who die shortly after a single, severe head injury [51, 52]. Genetic analyses of the latter head injury patients with Aβ show an overrepresentation of the ApoE ε4 allele [53], suggesting a synergism between head injury and ApoE genotype in conferring increased risk for Alzheimer's disease [54].

The mechanisms underlying the association between head injury and Alzheimer's disease are not clear. However, in head-injured patients [55] and in experimental models of head injury [56, 57], there is increased, acute expression of βAPP, suggesting that head injury may initiate prolonged overexpression of βAPP. In addition, activated microglia overexpressing IL-1 are intimately associated with the neurons that are overexpressing βAPP in such head-injured patients [2]. This overexpression of IL-1 and βAPP may ultimately lead to the development of Alzheimer-type, neuropathological changes, as predicted by the increased risk for development of Alzheimer's disease in such patients through actions illustrated in the cytokine cycle. These studies demonstrate fundamental molecular similarities between acute-phase responses to head injury and those responses characteristic of Alzheimer's disease. Acute head injury may thus be viewed as a natural model [58] for the early (acute) stages of the later (chronic) inflammatory processes thought to underlie Alzheimer's disease.

A ROLE FOR IL-1 IN PROGRESSIVE NEURODEGENERATION WITH AGING

Alzheimer's disease is not an inevitable consequence of aging, but aging may, like head trauma, represent another priming process. The characteristic laminar distribution pattern of microglia expressing IL-1 observed in normal brain mirrors that of Aβ plaques in Alzheimer's disease [59], suggesting that age-related activation of these microglia with overexpression of IL-1 could be such a priming process. Neurologically intact patients do show a progressive, age-associated increase in brain expression of IL-1 and IL-1 mRNA [60] as well as of S100B and S100B mRNA [61]. These increases in expression of IL-1 and S100B, both of which make multiple contributions to the neurodegenerative cascades we propose, may act synergistically with additional risk factors such as head injury and inheritance of genetic risk factors in order to precipitate the neurodegenerative changes characteristic of Alzheimer's disease.

IL-1-MEDIATED CHANGES IN EPILEPSY AND PRECOCIOUS DEVELOPMENT OF SENILE CHANGES

Chronic, intractable epilepsy is not an established risk factor for the later development of Alzheimer's disease, but epileptic patients do show accelerated appearance of Alzheimer-type "senile" changes [5]. These Alzheimer-type histological changes are accompanied by expression of Alzheimer-associated proteins in the brain of epileptic patients. We have shown overexpression of microglial IL-1, astrocytic S100B, and neuronal βAPP in resected temporal lobe tissue from patients with intractable, complex, partial seizures [3, 62]. The neuronal βAPP overexpression is particularly dramatic, appearing in fields of cortical neurons. Neuronal βAPP overexpression in epilepsy is correlated with increased tissue levels

of βAPP, increased numbers of activated microglia overexpressing IL-1, and localization of these activated microglia adjacent to neurons overexpressing βAPP. As is the case with head injury [53], the accelerated Alzheimer-type changes seen in epilepsy are more common and more pronounced in patients carrying the Alzheimer-associated ApoE ε4 allele [63]. Chronic microglial activation and IL-1 overexpression may thus provide a pathogenic explanation for the increased incidence of “senile” changes observed in patients with chronic epilepsy.

SUMMARY

It is now an accepted clinical tenet that immune-system imbalances, perhaps as a result of interactions of multiple cytokines, cause or contribute to many diseases and age-related changes. IL-1 is a preeminent factor in immune function, as a regulator of intricately controlled, normal immune responses and as a participant in degenerative events arising from inappropriate activation of the immune system. The association of polymorphisms in IL-1 genes with risk for several diseases further underscores a role for IL-1 in pathology [64–71]. Similar to observations from systemic diseases, several brain degenerative conditions involve overexpression of IL-1. Alzheimer’s disease, in particular, shows overexpression of IL-1 that conelates with the neuronal dysfunction and loss associated with plaque and tangle formation. Again, similar to the case with systemic diseases, several studies have demonstrated a positive association between inheritance of specific polymorphisms in IL-1 genes and increased risk for Alzheimer’s disease [8–12]. The overexpression of IL-1 that occurs in systemic and neural diseases amplifies established IL-1-driven cascades, which, because of the excessive expression of IL-1, become degenerative and self-propagating. Such a process is illustrated in the cytokine cycle depicted in Figure 1.

Acknowledgments

This work was supported in part by National Institutes of Health grant AG12411. We thank the donors and our technical staff who made this work possible and Ms. Pam Free for secretarial support.

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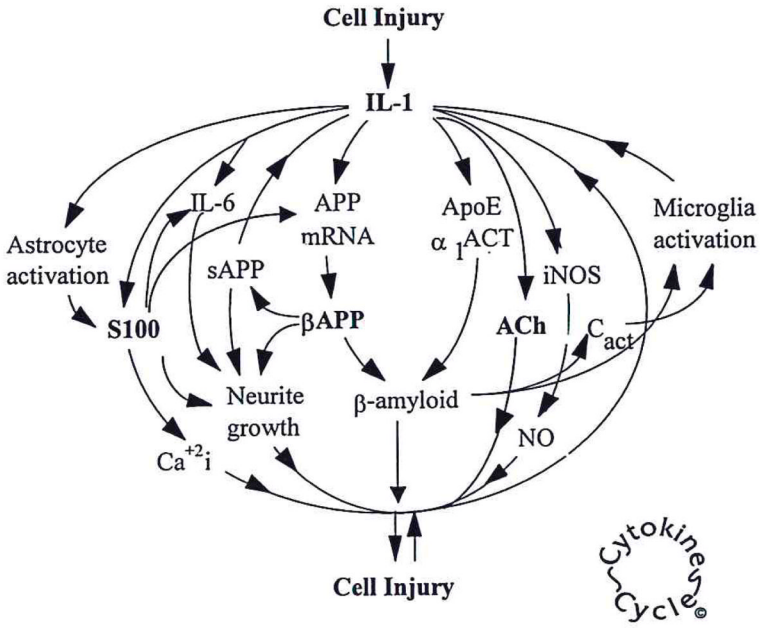

Fig. 1.

Depiction of the ways in which IL-1 may be induced and amplified by and contribute to cellular injury. NO, nitric oxide; iNOS, inducible NO synthase. © University of Arkansas for Medical Sciences.