Molecular and cellular mediators of Alzheimer's disease inflammation

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1. Introduction

A wide range of inflammatory mediators has been demonstrated in the Alzheimer's disease (AD) brain during the past 15 years (for previous reviews, see [6, 279,298,340,343]). Questions nonetheless remain, including even the designation of AD inflammatory mechanisms as a true inflammatory response. Like multiple sclerosis, the cardinal signs of peripheral inflammation, the "rubor et tumor cum calore et dolore" (redness and swelling with heat and pain) that Cornelius Celsus defined as criteria 2000 years ago, are not present in AD. Indeed, AD inflammation does not appear to include even cell-mediated humoral lymphocyte responses, as multiple sclerosis clearly does. Rather, our current understanding of AD inflammation suggests that it is an endogenously-mediated, localized reaction, an innate inflammatory response similar to that mounted in the periphery when localized tissue damage and the chronic deposition of highly insoluble, abnormal material occurs. Such primarily macrophage-mediated reactions have been classed as inflammatory for over a century, and that designation, with glia as the brain intermediaries, certainly should hold for AD.

Henry Wisniewski, who we honor by this special journal issue, was one of the first to come to grips with these simple principles of AD inflammation, and to apply them to other brain disorders. If we understand that localized brain inflammation is likely to arise wherever there is localized brain damage and deposits of highly insoluble, abnormal material, then prion diseases become an obvious research target. Wisniewski and his colleagues therefore looked for and found numerous indices of localized inflammation in prion-infected brain [195,214], just as McGeer and colleagues had done in dopamine-degenerating areas of the Parkinson's disease brain [274]. In fact, among his many studies of multiple sclerosis and experimental allergic encephalitis, Wisniewski pointed out that primary demyelination could be induced as a nonspecific consequence of cell-mediated inflammatory actions in the absence of autoantibodies to myelin [443]. This observation, published in 1975, presaged much of what we now believe about localized inflammatory actions in the AD brain.

A simplified view of AD inflammation also leads to clearer understanding of the roots and roles that inflammatory mechanisms may play in AD. As a localized response to tissue injury and the chronic presence of abnormal, highly insoluble deposits, AD inflammation is unlikely to be an AD etiology, although new data on cytokine susceptibility polymorphisms [88,319] suggest that it could in certain cases be a risk factor. That it is a secondary response, however, does not mean that AD inflammation is unimportant. In brain injury due to head trauma, for example, the etiology, the blow to the head, may cause less damage than the secondary inflammatory response to it. Although eliminating the head trauma is obviously the most satisfactory way to handle the problem, once it has occurred it becomes important to control the inflammatory reaction. Similarly, until we can eliminate the primary insult that causes AD neurodegeneration and the deposition of amyloid β peptide (Aβ) and neurofibrillary tangles, abrogating the initiation of secondary inflammatory damage will continue to be an important therapeutic target. Toward that end, we attempt here to summarize the evidence for a pathophysiologically relevant role of AD inflammation, and to catalogue the many inflammatory mediators present in affected areas of the AD brain.

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2. Cell mediators of inflammation in the AD brain

Although the new data on a vaccination approach to removing Aβ by antibody-antigen mechanisms [355] may yet bring surprises, to date there has been no conclusive evidence that antibodies or peripheral leukocytes are normally involved in AD inflammation. Rather, microglia and astrocytes appear capable of producing nearly every pro-inflammatory component observed thus far in the AD brain (Table 1). Surprisingly, accumulating evidence indicates that neurons also supplement the glial repertoire of pro-inflammatory factors, and oligodendrocytes and vascular endothelial cells may contribute as well. For convenience, these data are summarized in the accompanying table (Table 1).

2.1. Astrocytes

Astrocytes are immunologically activated by various challenges and respond to inflammatory mediators in pleiotropic fashion, including activation of early response genes and expression of various adhesion proteins, cytokines, eicosanoids, proteases, and other cytotoxic molecules in vitro and in situ (Table 1) [93]. In addition to overt inflammatory actions, ectoenzymes secreted by AD astrocytes may also play a role in degrading plaque Aβ [439], removing capillaries with amyloid angiopathy [445], and degrading paired helical filaments (PHF) [334,460].

Activated astrocytes are transformed into "reactive astrocytes" manifesting upregulated glial fibrillary acidic protein (GFAP) expression, astrocytic swelling, hypertrophy, hyperplasia, and gliosis [251,285]. In the AD brain focal and diffuse astrocytosis develops [85, 90,149,252,253,334,354,360,460] and advanced AD may include a nearly four-fold increase in astrocyte numbers [354]. The astrocytes appear around ghost tangles, dark neurons, capillaries ravaged by Aβ, areas of ischemic damage, and Aβ plaques. Astrocytes exhibit distinct morphological characteristics in each of these pathological interactions, possibly indicating a distinct role in each. Astrocytic accrual in plaques appears to be a reaction to focal extracellular Aβ accumulation [85,253,254,444,445] and, with fibrillar Aβ plaque development, is limited to the cerebral cortex and subcortical gray matter. Although a few reactive astrocytes are present in virtually all diffuse (noncongophillic) plaques, their greatest densities occur in neuritic plaques. Astrocytes are seldom associated with dense core, non-neuritic ("burned out") plaques [290].

The position of astrocytes in plaques differs from that of microglia. Astrocyte somas form a corona at the periphery of the neuritic halo that, in turn, may surround a dense core Aβ deposit. Processes from the astrocytes cover and interdigitate the neurite layer [290] in a manner reminiscent of glial scarring, and there is, in fact, recent evidence that plaque-associated astrocytes may be creating barriers: microglial clearance of deposited Aβ in culture is less efficient when astrocytes are plated before the microglia than when microglia alone are used [84,361]. This may be due to the fact that astrocytes deposit proteoglycans that inhibit the ability of microglia to clear plaques [84,361], consistent with the conspicuous localization of proteoglycans to plaques [376].

2.2. Microglia

Microglial cells constitute approximately 10–15% of the cellular population in the brain [31,62,278]. It is generally accepted that microglia have a monocytic origin [31,325,326] and by that derivation possess an inherent macrophage-like phagocytic capacity [134, 206]. Microglial cells typically assume a resting (unactivated) state, having a ramified appearance, expressing virtually no macrophage-like characteristics, and exhibiting a very low turnover [31,205,212]. Activation of microglia causes them to assume an amoeboid morphology, to become phagocytic, and to express MHC II and numerous other macrophage-like pro-inflammatory molecules (reviewed in [31,134,206, 307,427]).

Although in the normal brain microglia play neurotrophic roles (reviewed in [31,386]), their potential neurotoxic actions have been emphasized in AD research. By numerous criteria microglia in the AD brain, like microglia in a variety of neuropathologic conditions [129,288,289,385,386], are appropriately considered to be activated [31]. These criteria include altered morphology and increased expression of MHC II, cytokines, chemokines, complement, other acute phase proteins, and potential neurotoxins (Table 1), all of which could contribute to localized or more widespread CNS injury [31,307]. In some cases (e.g., complement) microglial production of these mediators in the AD brain has been inferred from studies of isolated culture preparations, where expression can be unequivocally attributed to a particular cell type. Limitations of in situ hybridization – where the hybridization label is not precisely localized due to scattering of the radioactive signal and where the substantially greater mass of

Table 1, continued

Marker	Δ in AD	Pathology	Cell	Method
Nitrotyrosine (and derivatives)	↑	NFTs [140]		HPLC
	↑	Hippocampus, cortical regions, and CSF [152]		IHC
Peroxynitrite	↑	Neurons and NFT bearing neurons [374,391]	N	
nitrotyrosine-modified proteins	↑	[140,152,374,391]		
p22-phox (NADPH subunit)	↑	[415]		IHC
MPO (myeloperoxidase)	↑	Plaques and associated microglia [337]	M	
Iron (Fe)	↑	Multiple brain regions [94,352,405]		
	↑	NFTs neurons vs non-NFT neurons in AD [139]	N	
	↑	Plaques and associated microglia [145]	M	
Ferritin	↑	Plaque associated microglia [145]	M	
	↑	Ferritin has more Fe in AD [117]		
Melanotransferin	↑	Serum, CSF, plaque associated microglia [178,193]	M	
Lipid peroxidation	↑	Multiple brain regions [28,235,317,392]		IHC
iNOS	↑	Hirano bodies, plaques, NFTs [216]	N	
Transcription Factors				EMSA
NF-κB (p65)	↑	Parallel increase with COX-2 mRNA [245]		IHC
	↑	Hippocampus, entorhinal, temporal, and visual cortex neurons [110,187,199,401]	N	IHC
	↑	Nucleus Basalis cholinergic neurons [44]	N	WB
PPAR-γ	↑	Temporal cortex [198]		WB
pCREB	↓	Phosphorylated CREB in hippocampus [461]		IHC
ATF	↑	Cortical neurons [458]	N	ISH
c-fos	↑	Hippocampus neurons [239]	N	IHC
	↑	Hippocampus neurons [255]	N	IHC
	↑	Cortical and plaque associated astrocytes [22]	A	IHC
	↑	PHF-1 expressing neurons [22]	N	IHC
c-jun	↑	Hippocampus neurons [247,255]	N	IHC
	↑	Cortical and plaque associated astrocytes [22,111]	A	IHC
	↑	PHF-1 expressing neurons [22]	N	IHC
	↑	Meningeal and cerebral vessels with CAA [111]		ISH
Krox24	↑	Hippocampus neurons [247]	N	WB
STAT1	↑	Temporal cortex [199]		
Miscellaneous Receptors				
Aβ-binding Receptors	↑	Upregulated on neurons and microglia [464,466]	N,M	IHC
RAGE	↑	Expressed on AD microglia [66,100,101,161]	M	IHC
MSR (macrophage scavenger receptor)	↑	Plaques [66], (review [371])		
FPR (fMLP receptor)	↑	Chemotactic for Aβ [234] (expressed on AD microglia – D. Lorton personal communication)	M	IHC
Other Receptors				
FcγR1	↑	Activated microglia [11,274]	M	IHC
FcγR2	↑	Activated microglia [274]	M	IHC

This table represents those factors that have been specifically detected in the AD brain and its related pathologies to date. It should be noted that many more inflammatory factors and related proteins have been observed in cell culture and animal models. Thus, this list, without a doubt, will continue to grow. Abbreviations: WB, western blot; IHC, immunohistochemistry; ISH, in situ hybridization; ELISA or EIA, enzyme linked immunosorbent assay; PCR, (reverse transcriptase) polymerase chain reaction; EM, electron microscopy; RIA, radio immunoassay; BA, bioassay; NB, northern blot; GC/MS, gas chromatography/mass spectroscopy; HPLC, high pressure liquid chromatography; EMSA, electrophoretic mobility shift assay; N, neuron; A, astrocyte; M, microglia; E, endothelia; O, oligodendroglia; NFTs, neurofibrillary tangles; ND, nondemented; AD, Alzheimer's disease; CSF, cerebral spinal fluid; MAC, membrane attack complex; ↑, increased in AD compared to ND; ↓, decreased in AD compared to ND; ↔, no difference between AD and ND; NC, not compared.

labelled neurons can easily obscure labelling of relatively tiny microglia – have sometimes made it difficult to confirm the culture observations. However, the fact that activated macrophages, close cousins to microglia, are known to express inflammatory mediators such as complement lends confidence to the conclusions from culture studies that microglia do so as well.

As do astrocytes, activated microglia cluster at sites of aggregated Aβ deposition. However, microglia assume a more central position and deeply interdigitate plaques in contrast to the peripheral position of astrocytes. Like astrocytes, microglia are present in virtually all diffuse (noncongophilic) plaques, but the greatest densities of microglia are in neuritic plaques. They

are seldom associated with dense core, non-neuritic ("burned out") plaques [142,144]. This co-localization of microglia and astrocytes with Aβ deposits provides opportunities for intercellular inflammatory signaling. IL-1β secreted by microglia, for example, induces astrocyte expression of S100β protein [367].

The clustering of microglia within plaques is readily explained by chemotactic signaling by Aβ itself [79] and by several inflammatory mediators that are associated with Aβ in senile plaques, including complement activation fragments, cytokines, and chemokines (reviewed in [307]). In addition, AD microglia reportedly upregulate their expression of the macrophage scavenger receptor (MSR) [100] and the receptor for advanced glycation end products (RAGE) [464], both of which appear to have Aβ as ligands [100,464]. Stimulation of the RAGE receptor with Aβ induces M-CSF [466] in microglia just as it does in macrophages. Similarly, adhesion of microglia to Aβ fibrils via class A scavenger receptors leads to immobilization of the cells and induces production of reactive oxygen species [100,101]. It has also recently been demonstrated that the chemotactic formyl peptide receptor (FPR) binds Aβ, triggering G protein dependent calcium mobilization and activation of chemokine signal transduction pathways [234].

Aβ activates numerous signaling cascades within microglia [67,250,271] that are common to peripheral inflammatory responses. Among these are the tyrosine kinase-based cascades [270,450], calcium-dependent activation of Pyk2 and PKC pathways [67], and p38 and ERKs MAP kinase cascades [67,270]. These, and certainly others, lead to the activation of transcription factors responsible for subsequent pro-inflammatory gene expression. Furthermore, Aβ-stimulated activation of intracellular signaling pathways in microglia leads to production of reactive oxygen species through NADPH oxidase, and to the synthesis and secretion of neurotoxins [68,83,271] and excitotoxins. Excitotoxins released by activated microglia – for example, glutamate [329] and quinolinic acid [104] – can cause significant dendritic pruning as these molecules act preferentially on vulnerable subcellular synaptic and dendritic compartments [265]. Notably, synapse loss is one of the most consistent correlates of AD cognitive impairment [261, 403].

Beyond their chemotaxis and physical proximity to Aβ deposits, the role of microglia in plaque evolution is still incompletely understood. Several hypotheses have been put forward involving synthesis, processing, and catabolism of Aβ by microglia. Of least probability is that microglia play a direct role in the synthesis of amyloid β protein precursor (AβPP) and deposition of Aβ. Although cultured microglia can secrete Aβ and metabolize AβPP in a manner that might favor Aβ deposition [32,39], microglial AβPP mRNA expression is yet to be demonstrated [358]. Conversely, neurons in vivo and neurons in culture exhibit abundant expression of AβPP [213] and are postulated to be the primary source of brain Aβ.

A potential role for microglia in processing AβPP and Aβ is more tenable. Microglial aggregation within amyloid-containing neuritic plaques is nearly universal, whereas it is rare or absent in diffuse plaques in AD, normal aging [74,174,249,348], or AβPP transgenic mice [120,381]. This association suggests that microglia, like peripheral macrophages in systemic amyloidosis [370], may be involved in the conversion of nonfibrillar Aβ into amyloid fibrils. Such a possibility is supported by many studies [76,141,248,353,427], including ultrastructural observations consistent with the possibility that microglia may participate in the laying down of amyloid fibrils within plaques [445].

Finally, catabolism by microglia via phagocytosis and/or degrading of Aβ deposits is another plausible prospect, in keeping with the emerging view that amyloid burden in the AD brain is determined by a dynamic balance between amyloid deposition and removal [168]. Many laboratories have shown that microglia actively phagocytose exogenous fibrillar Aβ in vivo and in culture [26,84,119,241,315,320,361,362, 369]. Although cultured AD microglia phagocytose Aβ [241], it is presently unknown if they degrade it or secrete it in some other form. That they remove Aβ deposits, however, is strongly supported by the recent demonstration of Aβ co-localized with a microglial activation marker, MHC II, in Aβ-immunized PDAPP transgenic mice, where amyloid deposits were apparently cleared [355]. Phagocytosis in these mice likely occurs via the variety of Aβ binding receptors and by opsoninization for complement clearance. Interestingly, however, the first classical pathway complement component, C1q, binds to Aβ [5,63,180,433,435], and has been suggested to block critical Aβ epitopes for Aβ uptake by cultured microglia [438].

Although, phagocytosis of Aβ has generally been considered beneficial, Aβ association with microglia, as previously described, results in extensive activation of signal transduction pathways leading to the formation of numerous pro-inflammatory, neurotoxic, and excitotoxic molecules. Thus, there is also evidence that this process may encourage microglial activation to a neurocytopathic state [3,61,81,86,203,297,411].

2.3. Neurons

In addition to astrocytes and microglia, neurons themselves may exacerbate inflammatory reactions in their vicinity and so contribute to their own destruction in AD. For example, neurons appear capable of producing inflammatory mediators. These include complement [115,323,363,402], cyclooxygenase (COX) [155,303,309,314,407,459], pro-inflammatory cytokines [48,51,138,301,316,394,399,465], the IL-6 receptor signal transducing component gp130 [169], M-CSF [466], and others (Table 1). Virtually all of these mediators are increased in the AD brain and have classical pro-inflammatory roles that could foment neurodegeneration.

3. Inflammatory constituents in the AD brain

3.1. Complement pathways, activation products, defense proteins, receptors

The complement pathways (classical and alternative) are composed of more than 30 proteins, many of them serine proteases that can be sequentially activated as an amplifying cascade. Both pathways converge at the C3 cleavage step and terminate in the pore-forming C5b9 membrane attack complex (MAC) (reviewed in [207, 296,318,441]). The transmembrane channel caused by MAC assembly at the cell surface permits the free diffusion of ions and small molecules into and out of the cell, disrupting cellular homeostasis, especially Ca^{++} homeostasis, and ultimately resulting in cell lysis if a sufficient number of MAC complexes have assembled on the cell. Notably, the MAC can also cause bystander lysis of healthy adjacent tissue [207,296,318,441]. In order to hold the complement cascades in check under normal circumstances, thereby protecting the host from self-lysis of healthy cells, and in order to down-regulate activated cascades during an immune response once the stimulus is depleted [207], tight regulation by a number of regulatory proteins is required [296,318,441]. Virtually all the proteins and respective mRNAs for the classical pathway, most of the alternative pathway, and the majority of complement regulatory proteins have been detected in the brain [115,182,363,388,430,470] and nearly all are up-regulated in AD (reviewed in [307, 341,343,470]).

At the cellular level, three endogenous sources for complement have been suggested. Microglia [146,243, 420,426,428] and astrocytes [123–125,220,429] in situ and in culture appear to synthesize nearly all complement proteins. Remarkably, however, in situ hybridization studies suggest that neurons exhibit more abundant signal for complement mRNAs than any other cell type in the AD brain and express virtually all the proteins of the complement pathways [115,182,208,363,402]. Indeed, based on hybridization results, one study has suggested that complement production in the AD brain may be as great as that in the liver, the primary source of complement in the periphery [470]. Thus, multiple endogenous sources of complement exist in the brain, and at least two of these, neurons and microglia, show complement upregulation in AD.

β-pleated, fibrillar Aβ [4,63,180,339,433,435] and, more recently, tau-containing neurofibrillary tangles [342] have been shown to directly activate the classical complement pathway fully in vitro, and to do so in the absence of antibody. Aβ activates the classical pathway via charge-based binding between Aβ and the collagen-like region of the C1q A chain [130,180,434]. Additionally, the hexameric structure of C1q appears to facilitate further aggregation of Aβ by binding multiple Aβ molecules [434,436,437]. Direct, antibody-independent activation of the alternative pathway by β-pleated fibrillar Aβ has also been demonstrated [50, 388,432]. For the classical and alternative pathway, activation appears to proceed via covalent ester-linked complexes of Aβ with C3 [50], as is characteristic of complement activation reactions.

In addition to Aβ aggregates and neurofibrillary tangles, other potential sources for classical pathway activation exist in the AD brain. Neurodegeneration can ultimately expose DNA and neurofilaments to the extracellular environment. DNA [130] and neurofilaments [228] appear to interact with the C1q A chain similar to other antibody-independent activators of complement [130,181]. In addition, oligodendrocyte myelin glycoprotein activates the complement pathway in vitro [181], as do other myelin derived proteins (reviewed in [379]). It is therefore possible that the increased availability of complement in the AD brain might ultimately impact myelinated axons, perhaps helping to account for AD white matter changes that have recently been noted [400].

In summary, Aβ and neurofibrillary tangles, which represent highly insoluble deposits of abnormal proteins, and the exposed cellular byproducts of degeneration, including neurofilaments, naked DNA, and myelin fragments, appear to potently activate complement. This profuse and chronic presence in the AD cortex of multiple complement activating sources, to-

gether with a highly competent endogenous source for complement production, makes it difficult to imagine that a chronic state of complement activation would not occur in the AD brain.

3.2. Cytokines and chemokines and related receptors

Cytokines and chemokines presumably subserve similar intercellular and intracellular signaling processes in microglia and astrocytes as they do in the periphery, although novel cytokine and chemokine mechanisms have been proposed in the CNS. Virtually all the cytokines and chemokines that have been studied in AD, especially the major pro-inflammatory mediators, IL-1, IL-6, TNFα, IL-8, transforming growth factor-β (TGF-β), and macrophage inflammatory protein-1α (MIP-1α), are upregulated in AD compared to ND samples (Table 1) (reviewed in [307,453]).

Both cytokines and chemokines appear to pleiotropically activate numerous inflammatory response genes in AD and most of these proteins are expressed by astrocytes, microglia, and in some cases, neurons. Aβ appears to be capable of inducing the expression of cytokines and chemokines in these cells, and cytokines and chemokines are often detected in Aβ plaques. Concomitantly, exaggerated cytokine levels appear to induce increased expression of AβPP and Aβ.

Cytokine and chemokine expression has been reported to wax and wane with plaque evolution, with highest expression occurring in early diffuse and dense-core neuritic plaques. Many of these factors seem to have dystrophic effects on neurites within and neurons around Aβ plaques, and may thereby play functional roles in plaque evolution. Conversely, paradoxical neuroprotective roles have been suggested for a few of the pro-inflammatory cytokines. These findings have most often resulted from assays of isolated neuron cultures or knockout preparations, and require confirmation under conditions that permit cytokine interactions with other cell types (e.g., glia) and systems (e.g., the vasculature) (reviewed in [307]). Transgenic mice that over express pro-inflammatory cytokines under the control of brain-specific promoters consistently exhibit inflammatory pathology, with little or no evidence of neuroprotection [19,52,153,380].

Two major pathophysiologic consequences of cytokine and chemokine upregulation in the AD brain have been proposed. First, there is the potential for vicious cycles in which cytokines induce Aβ and Aβ induces cytokines. Second, autocrine-paracrine cytokine and chemokine interactions among cells producing cytokines and chemokines are likely to occur, with net effects on cellular responses that can be additive, synergistic, inhibitory, or antagonistic [330]. Interactions among pro-inflammatory cytokines and chemokines, for example, can result in synergistic activities in cytokine production and actions, including effects on Aβ secretion. Low levels of antagonistic anti-inflammatory cytokines and receptors may further compound chronic inflammation. Such a dysregulation in the balance between pro-inflammatory and anti-inflammatory mediators could lead to a deleterious amplification cycle of cellular activation and cytotoxicity [331]. Thus, both cytokine-cytokine interactions and cytokine interactions with existing AD pathology may play critical roles in AD neuroinflammation.

3.3. Cyclooxygenase

Cyclooxygenase (COX) is an enzyme that plays a pivotal role in the arachidonate cascade leading to prostaglandin synthesis. COX helps to mediate production of prostaglandins and other inflammatory factors and is itself upregulated by some of the same pro-inflammatory mediators it induces [106,313,351,462]. Recently, two isoforms of COX, COX-1 and COX-2, have been identified in the periphery and the brain (reviewed in [311]). Many cell types constitutively express COX-1, and the prostaglandins it helps produce are not all pro-inflammatory. In contrast, COX-2 is typically not constitutively expressed but is induced at sites of inflammation, facilitating the induction of pro-inflammatory prostaglandins. Because prostaglandins are so deeply entwined with other inflammatory mechanisms, the inhibition of COX, with its attendant inhibition of prostaglandins, has become a popular therapeutic target in AD.

Accumulating evidence indicates that COX-2 protein levels are increased in several areas of the AD brain and may correlate with levels of Aβ and plaque density [155,198,322]. As well, there is one report of COX-2 protein colocalizing with tangle bearing neurons in AD and Down's syndrome cortex [314].

COX elevations influence multiple downstream mechanisms of inflammation that are well known in the periphery (e.g. cytokine stimulation). Similar downstream mechanisms are likely to occur in the AD brain. This is supported by in vitro culture experiments indicating the production of prostaglandins in response to cytokines [34,284,313], as well as the altered expression of cytokines and other inflammation-related molecules in response to PGE^2 [41,112,177,215] in as-

trocytes and microglia. Other possible roles for COX-2 in AD inflammation involve mechanisms related to glutamate excitotoxicity [192], free radicals [321], and PPARγ expression [179,217,218,307,338].

3.4. *Blood coagulation and fibrinolysis systems*

Originally discovered as mechanisms that regulate the flow and coagulation of blood in the vasculature and at sites of vascular injury, the blood coagulation and fibrinolysis systems have more recently been recognized as playing important roles in inflammatory and tissue repair processes in extravascular tissues. Several molecules of the coagulation cascade, as well as numerous proteases, have been detected in Aβ plaques or are upregulated in the AD brain (Table 1). Interestingly, the actions of several of these mediators are enhanced by heparin binding [356,375]. For this reason, the conspicuous presence of heparin sulfate proteoglycans in Aβ plaques and neurofibrillary tangles in AD brains [376], lends credibility to the active involvement of these proteins in AD neuroinflammation.

3.5. *Adhesion molecules*

As part of the inflammatory response, altered expression of several intercellular adhesion molecules occurs on astrocytes and microglia (Table 1). Such molecules are especially abundant on Aβ plaque-associated astrocytes and microglia. Expression of many of these adhesion molecules is readily induced by upregulated cytokines (reviewed in [27,36,75,299,341]). Integrins are among the better studied adhesion molecules in AD. In particular, the β2 integrins complement receptor 3, complement receptor 4, and LFA-1, a ligand for ICAM-1 on astrocytes [13], are significantly upregulated on AD microglia [347]. Accordingly, these molecules represent another mechanism for glial cell recruitment to inflammatory sites of Aβ deposition.

3.6. *Other inflammatory and acute phase proteins*

The acute phase proteins are a diverse set of molecules that arise early in inflammation as the acute phase response. Like many other inflammatory mediators, a wide range of acute phase reactants have been found in association with senile plaques and extracellular neurofibrillary tangles (Table 1).

A few of the acute phase proteins have notable interactions with Aβ. α1-antichymotrypsin (α1-ACT) is consistently colocalized with Aβ deposits in the AD brain, and has been suggested to play a role in plaque formation by enhancing conversion of nonfibrillar forms of the Aβ to Aβ fibrils [103,118,188, 246]. Another acute phase protein, α2-macroglobulin (α2-MAC), is a potent broad spectrum protease inhibitor possessing a bait region that acts as a substrate for a wide variety of proteases [47,378]. Formation of a protease/α2-MAC complex exposes a receptor-binding domain. The complex is removed by endocytosis following binding of this domain to the α2-MAC receptor/low density lipoprotein receptor-related protein (α2-MACR/LRP). In addition to protease inhibition and protease removal, α2-MAC and α2-MAC/LRP function as a clearance system for inflammatory proteins [47,89,165,204,442]. α2-MAC and α2-MAC/LRP have been found in neuritic plaque amyloid and neurofibrillary tangles [33,336,384,408, 447]. Aβ also apparently forms a complex with α2-MAC that is removed through α2-MAC/LRP endocytic clearance mechanisms [305]. α2-MAC may inhibit Aβ aggregation and fibril formation [87], promoting Aβ removal and further implicating α2-MAC and α2-MAC/LRP in several AD pathophysiologic processes. Interestingly, polymorphisms in α1-ACT [188], α2-MAC [40], and α2-MAC/LRP [189,222,332] receptor [189] genes have been reported to be possible risk factors for AD.

Apolipoprotein E (ApoE), particularly, the ApoE4 allele, has been widely documented to play a role in AD. Long-known to be upregulated at sites of inflammation and to play a role in peripheral amyloidosis [197], ApoE first came to light in AD as a susceptibility gene [387]. ApoE4 appears to shorten the onset of AD by some 5–10 years [387] and patients with one and, especially, two ApoE4 alleles tend to have more congophilic amyloid angiopathy [242]. In addition, ApoE can influence microglial expression of several inflammatory factors [209,210], and this effect appears to be isoform dependent [30,233].

Finally, soluble amyloid β precursor protein (sAβPP) bears a number of properties in common with acute phase proteins. It is elevated at sites of tissue damage [29]; its synthesis and release are partly mediated by pro-inflammatory cytokines and stimuli [54, 135]; and it induces NF-κB, stimulating the expression of several inflammatory mediators [30]. The pro-inflammatory activity of sAβPP is inhibited by binding to ApoE, with ApoE3 being more effective than ApoE4. In contrast, it should be noted that sAβPP has also been demonstrated to have neurotrophic actions in many systems [24,262,266,291,292,373,463].

3.7. Free radicals

There has been intense interest in the role of oxygen free radicals as a contributing factor to AD pathology [35,230,256,257]. Many hallmark modifications of oxidative damage have been demonstrated in the AD brain, including proteins modified with advanced glycation end products (AGEs) [396], malondialdehyde, 8-hydroxy-deoxyguanosine, 4-hydroxynonenal [23,257], nitrotyrosine [140,374,391], nitrotyrosine-modified proteins [140,152,374,391], and increased amounts of lipid peroxidation [257]. Free radical-mediated stress not only leads to direct cellular injury, but may also influence neuronal integrity by triggering redox-sensitive, NF-κB-mediated transcription of various pro-inflammatory and/or apoptosis-related genes in surrounding cells [187].

Although the majority of research on AD oxidative stress has focused on neuronal generation of free radicals [35,264,267], the concept of free radical toxicity actually has its roots in inflammation biology, where the secretion of reactive oxygen and nitrogen species by inflammatory cells is a major mechanism for attacking opsonized targets. Activated microglia have the potential to produce large amounts of reactive oxygen species via nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, a complex activated by Aβ peptide. Through such mechanisms, microglia serve as an alternative source of free radicals [83,200,201,271,416,417]. Recent data have also indicated that some plaque-associated microglia may be a source of the enzyme myeloperoxidase (MPO) in AD brains [337]. MPO catalyzes a reaction culminating in the production of hypochlorous acid, which can further react to generate several other reactive oxygen species.

4. Conclusion

The best evidence for the pathophysiologic relevance of AD inflammation is the sheer number of inflammatory mediators that have been found to be upregulated in the AD brain (Table 1). The presence of these mediators defines a localized, innate inflammatory response with roots that are as obvious as those in a peripheral wound: damaged tissue and highly insoluble deposits of abnormal materials. That this localized, innate inflammatory response causes secondary damage to the affected tissue is inarguable if a century of peripheral inflammation biology has any meaning. The salient questions are how much secondary damage occurs due to AD inflammation, and how likely is it that the inflammatory mechanisms invoked, feed back to stimulate AD etiologic processes such as Aβ deposition. Given the recent interest in AD inflammation research, the answers to these questions should not take long to obtain.

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Table 1
Inflammatory markers in AD

Marker	Δ in AD	Pathology	Cell	Method
Complement Proteins				
Classical Pathway				
C1r	↑	Plaques [402], neurons [402], homogenates [470]	N	IHC,WB
		mRNAs [470]		PCR
C1s	↑	Plaques [402], neurons [402], homogenates [470]	N	IHC,WB
		mRNAs [421,470]		PCR
C1q	↑	3.6X in superior frontal gyrus [49]		WB
	↑	Plaques [4,95,97,98,115,170,272,273,339,402], NFTs [272,273,342], neurons [4,402], dystrophic neurites [272,273], homogenates [402,470]	N	IHC,EM WB
	↑	mRNAs [95,182,363,470]	M,N	ISH
	↑	mRNAs [421]		PCR
	↑	mRNAs – 3.5X in frontal cortex [114,430]	N	NB
C2	↑	Plaques [402], neurons [402], homogenates [402,470]	N	IHC,WB
	↑	mRNAs [363,470]	N	ISH,PCR
	↑	Plaques [96,98,99,170,171,272,273,402,422]		IHC,EM
C3	↔	mRNAs [115]		NB
	↑	mRNAs [114,363,430,470]	N	PCR,ISH
	↑	Homogenates [402,470]		WB
	↑	Plaques [98]		IHC
C3a	↑	Plaques [97,274]		IHC
C3b	↑	Plaques [95,97,98,273,274]		IHC
C3c	↑	Plaques [95,98,273]		IHC
C3d	↑	NFTs, dystrophic neurites [53,57,97,170,272,273]		IHC
	↑	Homogenates [470]		WB
	↑	Oligodendroglial fibers [456]	O	IHC
	↑	Plaques [97,98,136,170,171,272,402]		IHC,EM
C4	↑	mRNAs [86,182,363]	N	ISH
	↑	mRNAs [430,470]		PCR
	↑	NFTs [272], neurons [402]	N	IHC
	↑	Homogenates [402,470]		WB
	↑	Plaques [273]		IHC
C4d	↑	Homogenates [470]		WB
	↑	NFTs [273,357], dystrophic neurites [272,273,342]		IHC
	↑	Degenerating myelin sheaths [456]	O	IHC,EM
Terminal Pathway				
C5	↑	mRNAs [363,470]	N	ISH,PCR
	↑	Plaques [402], neurons [402]	N	IHC
	↑	Homogenates [402,470]		WB
C6	↑	Plaques [274,402], neurons [402]	N	IHC
	↑	mRNAs [363,470]	N	ISH,PCR
	↑	Homogenates [402,470]		WB
C7	↑	Plaques [402], neurons [402], NFTs [174]	N	IHC,EM
	↑	mRNAs [363,470]	N	ISH,PCR
	↑	Homogenates [402,470]		WB
C8	↑	Plaques [402], neurons [402]	N	IHC
	↑	mRNAs [363,470]	N	ISH,PCR
	↑	Homogenates [402,470]		WB
C9	↑	Plaques [402,435], neurons [402]	N	IHC
	↑	Homogenates [402,435,470]		WB
	↑	mRNAs [276,363,435,470]	N	ISH,PCR
	↑	NFTs, dystrophic neurites [435]		IHC
C5b-9 (MAC)	↑	Myelinated and unmyelinated neurons (endocytic vesicles) [202]	N	EM
	↑	Plaques [272,273,435]		IHC
	↑	NFTs, dystrophic neurites [272,273,435]		IHC
	↑	Homogenates [435,470]		WB
Alternative Pathway				
Factor B, Ba, Bb	↑	Plaques, Frontal Cortex [388]	N	IHC,WB

Table 1, continued

Marker	Δ in AD	Pathology	Cell	Method
Factor B, Ba, Bb	↑	Serum AD vs. ND [133]		ELISA
Properdin	↑	Serum AD vs. ND [133]		ELISA
Complement Defense Proteins				
Factor H, FHL-1	↑	Plaques, Frontal Cortex [162,388]	N,M,A	IHC,WB
Factor I	↑	Plaques, Frontal Cortex [388]	N	IHC,WB
CD59 (Protectin, MIRL)	↑	Plaques [276,282]		IHC
	↑	Tangled neurons, dystrophic neurites [282]	N	IHC
	↑	RNA extracts from brain [282]	N	PCR
	↑	Slightly increased in AD vs. ND brains [468]		PCR,WB
	↑	Deficiency in AD brain vs. ND [467]		IHC,WB
Clusterin (APOJ, SP40,40)	↑	Plaques [64,131,150,194,276], pyramidal	N,A	IHC
	↑	neurons [131,226,276], dystrophic neurites [276],		
	↑	neuropil threads [131,276], NFTs [131,276],		
	↑	CAA [423], astrocytes [226]		
	↑	CSF [64],		ELISA
	↑	homogenates [226]		WB
	↑	mRNAs [131,268]	N	ISH
Vitronectin (S-protein)	↑	Plaques [12,99,276,280], NFTs [12,276]	M	IHC
	↑	Dystrophic neurites, neuropil threads [276]		IHC
C4-binding protein (C4BP)	↑	Plaques, CSF, cerebral cortex and microvessels [185,410,477]		IHC,WB
C1-Inhibitor (C1-INH)	↑	Plaques, dystrophic neurites, neuropil threads, pyramidal neurons, astrocytes [419,421,431,468]	N,M,A	IHC,WB PCR
Complement Receptors				
Complement receptor 3 (CR3)	↑	Activated microglia [15,96,99]	M	IHC
Complement receptor 4 (CR4)	↑	Activated microglia [15]	M	IHC
C3a receptor	↑	[80,306]	N,M,A	IHC,ISH
C5a receptor	↑	[126,306]	N,M,A	IHC,ISH
Vitronectin receptor	↑	Activated microglia in classical plaques [12,96,99]	M	IHC
Cytokines				
Interleukin-1α (IL-1α)	↑	Plaque associated microglia [141,364,366]	M	IHC
Interleukin-1β (IL-1β)	↑	Homogenates from frontal cortex, parietal cortex, temporal cortex, hypothalamus, thalamus and hippocampus [55,96]		ELISA
	↑	NFTs associated microglia [367]	M	IHC
	↑	Activated microglia and astrocytes in AD [143]	M,A	IHC
	↑	Plasma [225], CSF [42]		ELISA
ICE (Caspase-1)	↑	Hippocampus and parahippocampus [478]		WB,BA
S100β	↑	Reactive astrocytes around plaques [25,259,290,365,368,413], around NFT [367]	A	IHC,NB
	↑	Activated microglia and astrocytes in AD [143]	M,A	IHC
	↑	Hippocampus and temporal cortex [365]		WB
Interleukin-2 (IL-2)	↑	AD cortex [240,341], Hippocampus [25]	M	IHC,RIA
Interleukin-6 (IL-6)	↑	Plaques [33,164,166,167,384]		IHC
	↑	mRNA [428,476]	M	PCR
	↑	Temporal cortex AD vs. ND [449]		ELISA
	↑	Neurons [384]	N	IHC
	↑	Plasma [186,225,225,372], CSF [42]		ELISA
	↓	CSF [455]		ELISA
Tumor Necrosis Factor (TNF-α)	↑	Serum AD vs. ND [113,397]		ELISA
	↓	Serum AD vs. ND [56]		ELISA
	↑	CSF AD vs. ND [397,398]		ELISA
IFN-α	↑	Subset of neurons [190,457]	N	ISH,IHC
	↑	White matter and activated microglia [9,190,457]	M	IHC,ISH
M-CSF	↑	Microglia [16] and neurons [466] around plaques	M,N	IHC
	↑	CSF (5X) [466]		ELISA
Pleiotrophin (PTN or HB-GAM)	↑	Plaques with dystrophic neurites [446]		IHC
TGF-β	↑	Serum [59,60], CSF [60]		ELISA
TGF-β1	↑	Plaques [324,412]		IHC

Table 1, continued

Maker	Δ in AD	Pathology	Cell	Method
TGF-β1	↑	NFT [324,412]		IHC
TGF-β2	↑	NFT [116]		IHC
	↑	Neurites, astrocytes, microglia [324]	A,M	IHC
	↑	Cortex (3.2X) [116]		ELISA
TGF-β3	↑	Hirano bodies [324]		IHC
Midkine	↑	Plaques and homogenates [472]		IHC,WB
FGF-a (acidic)	↑↓	Entorhinal cortex neurons [406]	N	IHC
	↑	Plaque associated astrocytes [196]	A	IHC
FGF-b (basic)	↑	Plaques [78,137], NFTs [383], neurons and	N,A	IHC,WB
	↑	astrocytes [78,383], mRNAs [383]		ISH
FGF-9	↑	Dystrophic neurites, neurons, astrocytes [302]	N,A	IHC
IGF (Isulin-like growth factor)	↑	Subpopulation of astrocytes [69]	A	IHC
	↑	Serum and CSF [404]		ELISA
HGF (Hepatocyte growth factor)	↑	Astrocyte, microglia, some neurons [107]	A,M,N	IHC,EIA
VEGF	↑	Astrocytes, vessels, perivascular deposits [183]	A	IHC
PDGF-AA and BB	↑	Neurons (AA,BB), vessels (AA), NFTs (BB) [260]	N	IHC,WB
NGF (nerve growth factor)	↑	Hippocampus [156,359]		ELISA
	↑	Frontal cortex [77,151,156,359]		ELISA
	↑	Temporal cortex [151,359]		ELISA
	↑	Dentate Gyrus [304]		EIA
	↑	Parietal Cortex [105,359]		ELISA
	↑	Superior frontal gyrus [359]		ELISA
	↑	Occipital cortex [77,359]		ELISA
	↑	Amygdala [359]		ELISA
	↑	Putamen [359]		ELISA
Decreased in these structures due	↓	Nucleus Basalis of Meynert [359]		ELISA
to failure of retrograde transport	↓	Nucleus Basalis of Meynert [154]	N	ISH,NB
of NGF in cholinergic neurons.	↓	Cholinergic Basal Forebrain neurons [293]	N	IHC
	↑	CSF [157]		ELISA
BDNF – (Brain derived neurotrophic	↓	Hippocampus and parietal cortex [156]		ELISA
factor)	↓	Entorhinal cortex [304]		EIA
	↓	mRNA parietal lobe [160], hippocampus [327,328]	N	PCR,ISH
	↓	Hippocampus and neocortex neurons [71,108,377]	N	IHC
	↑	Plaques [300]		IHC
	↑	Dystrophic neurites [108]		IHC
Trk -A (NGF receptor)	↓	mRNAs 2X in parietal cortex [158]	N	PCR
	↓	Nucleus Basalis cholinergic neur. [45,46,294,350]	N	IHC
	↓	Nucleus Basalis and frontal cortex [294]	N	BA
	↓	mRNAs in cholinergic neurons of Nucleus Basalis,	N	ISH,PCR
		ventral striatum, and putamen [43,295]		
	↑	mRNAs in hippocampus [70]		ISH
	↑	Plaques associated hippocampal astrocytes [70]	A	IHC
	↑	Plaques in hippocampus and temporal cortex [70]		
Trk -B (catalytic p145)	↓	Temporal and frontal cortex [20]		WB
(BDNF receptor)	NC	Neuronal perikarya of hippocampus and cortex [377]	N	IHC
	↓	Frontal cortex [108]		WB
	↓	Frontal cortex neurons [108]	N	IHC
	↑	Glial cells (especially around plaques) [70,108]	M,A	IHC
	↓	Nucleus Basalis cholinergic neurons [350]	N	
	↑	Plaques in hippocampus and temporal cortex [70]		IHC
Trk -C (NGF receptor)	↓	Nucleus Basalis cholinergic neurons [350]	N	IHC
Cytokine Receptors				
sIL-1R II	↑	CSF [122]		ELISA
IL-1RA	↑	Temporal cortex homogeneates [449]		ELISA
	↑	Plaques, neurons, some microglia and NFTs [471]	M,N	IHC
CSFR-1 (Receptor for M-CSF)	↑	Plaque associated and reactive microglia [16]	M	IHC
IL-6R	↑	CSF AD vs. ND [147]		ELISA
sIL-6R	↑	CSF AD vs. ND [147,148]		ELISA
gp130	↑	CSF AD vs. ND [148]		ELISA
TβR I (type I ser/thr kinase rec.)	↑	Microglia and neurons [229]	M,N	IHC

Table 1, continued

Marker	Δ in AD	Pathology	Cell	Method
TβR II (type II ser/thr kinase rec.)	↑	Microglia and neurons [229]	M,N	IHC
FAS (CD95)	↑	Frontal and temporal lobe homogenates [82]		WB
	↑	Neurons and dystrophic neurites [82,308]	N	IHC
	↑	Plaques and associated astrocytes [308]	A	IHC
EGFR	↑	Neuritic plaques [38], endothelial cells [390]	E	IHC,EM
FGFR-1	↑	Plaque associated astrocytes, neurons, mRNAs [395]	A,N	IHC,ISH
FGFR-3	↑	Plaque associated astrocytes [109]	A	IHC
Chemokines and Receptors				
Chemokines		In AD : Reviewed in [453]		
IP-10	↑	Astrocytes (especially around plaques) [452]	A	IHC
MIP-1α (CCβ)	↑	Neurons, microglia (weakly) [454]	N,M	IHC
MIP-1β (CCβ)	↑	Astrocytes (especially around plaques) [452,454]	A	IHC
MCP-1 (CCβ)	↑	Plaques, microglia [172]	M	IHC
Chemokine Receptors		In AD : Reviewed in [453]		
CXCR3 (IP-10 receptor)	↑	Neurons [452]	N	IHC
CXCR2 (IL-8RB)	↑	Plaques [163,451]		IHC
	↑	Neurons and dystrophic neurites [451]	N	IHC
CCR3	↑	Microglia (especially in plaques) [454]	M	IHC
	↑	Microglia (especially in plaques) [454]	M	IHC
Cell Surface Markers				
MHC I	↑	Endothelial cells [273,409], microglia [281,409]	E,M	IHC
MHCII				
HLA-DR	↑	Activated microglia (concentrated in plaques) [15,96,121,173,240,263,**?**,281,341,409]	M	IHC
	↑	[389]	M	IHC,EM
HLA-DP	↑	[240]	M	IHC
HLA-DQ	↑	[240]	M	IHC
LCA	↑	Activated microglia [15]	M	IHC
Cyclooxygenase (COX) and Eicosanoids				
Cyclooxygenase		COX in AD: Reviewed in [311]		
PLA2 (Phospholipase A2)	↓	Cerebral cortex (multiple areas) [127,128,345]		BA
cPLA2 (cytosolic PLA2)	↑	Cerebral cortex protoplasmic astrocytes [382]	A	IHC
COX-1	↑	Cortical homogenates [198,469]		WB
	↑	Hippocampus and neocortex neurons [469,474]	N	IHC,ISH
	↑	Microglia (especially in plaques) [474]	M	IHC
	↑	mRNAs [244,469]		PCR,NB
COX-2	↑	Frontal [322], hippocampal [155], and temporal		IHC,WB
	↑	cortex [198], neurons [314,469] and NFTs [314]	N	IHC,WB
	↑	mRNAs [244,245,469]		PCR,NB
PGHS-2 (COX-2)	↓	mRNAs [58,312]		NB
Eicosanoids				
Prostaglandin D2 (PGD2)	↓	Cortex AD vs. ND [175,448]		BA
Prostaglandin E^2 (PGE^2)	↓	Frontal cortex AD vs. ND [448]		BA
	↑	5X in CSF [287]		GC/MS
Prostaglandin F1((PGF1()	↓	4X in CSF [287]		GC/MS
Prostaglandin F2((PGF2()	↓	Frontal cortex AD vs. ND [448]		BA
Isoprostanes	↑	CSF [286,287,333], cortex [310,333]		GC/MS
Thromboxane B2 (TXB2)	↓	Cortex AD vs. ND [175,448]		BA
Coagulation and Fibrinolysis Systems				
Prothrombin	↑	In areas of vascular damage [37]		IHC
Thrombin	↑	Plaques, Tangles [7,8,11,277]		IHC
Antithrombin III	↑	Plaques, tangles, paired helical filaments, dystrophic neurites, some astrocytes, mRNAs [184]	A	IHC,WB EM,PCR
Tissue factor (thromboplastin)	↑	Plaques [269]		IHC
Tissue factor pathway inhibitor-1	↑	Plaques and microglia [159]	M	IHC,WB
Hageman factor	↑	Plaques, mRNAs [473]		PCR,WB
TPA	↑	Plaques [335]		IHC

Table 1, continued

Marker	Δ in AD	Pathology	Cell	Method
UPA	↑	Plaques [335], Serum activity and conc. [21]		IHC,BA
PAI I	↑	Plaques [335], CSF [393]		IHC,BA
PAI II	↑	Activated microglia [10]	M	IHC
Protease nexin-1 (PN-1)	↓	Activity decreased ≈ (85% , AD homogenates [425]		BA,WB
	↓	Immunoreactivity and number of blood vessels [418]		IHC
	↓	Cortical homogenates and immunoreactivity [65]		IHC,WB
	↑	Plaques, NFTs [344,425]		IHC
Protease nexin-1/ thrombin complex	↑	AD homogenates [425] (increased complexes but decreased free PN-1)		WB
Protease Nexin-2 (PN-2 or AβPP)	↓	Cortical homogenates and immunoreactivity [65]		IHC,WB
XIIIa	↑	Expressed in AD microglia [14]	M	IHC
Adhesion Molecules				
ICAM-1	↑	Plaques [99,121,347,424]		IHC
	↑	Cerebrovascular endothelial cells [121]	E	IHC
	↑	Plaques and associated astrocytes [13]	A	IHC
ICAM-2	↑	Activated microglia [424]	M	IHC
NCAM	↔	Astrocytes, Cortical homogenates [132]	A	IHC,WB
	↓	Frontal cortex neurons [475]	N	IHC
PSA-NCAM	↑	Hippocampal formation		IHC
LFA-1 (CD11a)	↑	Activated microglia [11,15,121,347]	M	IHC
VLA (very late antigen)				
α3	↑	Plaque corona [99]		IHC
α6	↑	Plaque corona [99]		IHC
β1	↑	Plaque corona [99]		IHC
LeuCAM (β2 integrin)	↑	Activated microglia [99]	M	IHC
CD44	↑	Astrocytes AD vs. ND [17]	A	IHC
Acute Phase And Other Proteins		In AD : Reviewed in [211]		
α1-Antichymotrypsin (α1-ACT)	↑	Plaques [1,2,136,346,349,477], tangles [136]		IHC
	↑	Astrocytes [2,136] , some neurons [2]	A,N	IHC
	↑	Serum [?], CSF [224]		ELISA
	↑	Serum [227]		RIA
α2-Macroglobulin (α2-MAC)	↑	Plaques [33,335,384,414], microglia bordering plaques [414], hippocampal neurons [33,384]	N,M	IHC
	↑	2X in AD vs. ND [449]		ELISA
ApoE (Apolipoprotein E)	↑	Plaques [150,194,335,477]		
LRP (ApoE and α2-MAC receptor)	↑	Plaques [335,408], NFTs [408], neurons [335,408,447], astrocytes [408,447], microglia [408]	N,M,A	IHC IHC
α1-antitrypsin	↑	Plaques, tangles, astrocytes [136]	A	IHC
	↑	Serum [133,440]		ELISA
Serum amyloid A	↑	Homogenates [221], mRNAs [221], serum [102]		WB,PCR
Serum amyloid P (pentraxin)	↑	Plaques, CAA [18,73,92,185], NFTs [18,92,357]		IHC
C-reactive protein (pentraxin)	↑	3X in AD vs. ND [449]		ELISA
	↑	Plaques [176,384], NFTs [91]		IHC
Ceruloplasmin	↑	CSF [231]		ELISA
	↑	Homogenates, plaques, neurons, astrocytes [232]	N,A	EIA,IHC
	↓	Temporal cortex [72]		WB
ApoA-I	↑	Plaques [150]		IHC
ApoA-IV	↑	Plaques [150]		IHC
ApoD	↑	Plaques [150]		IHC
Receptor Associated Protein	↑	Neuronal soma (inhibitor of LRP) [335]	N	IHC
Lipoprotein Lipase	↑	Plaques [335]		IHC
Lactoferrin / Lactotransferrin	↑	Plaques [335]		IHC
	↑	Plaques, neurons, NFTs, glia [176,176,191,219]	N,M,A	IHC
Free Radicals and By-Products		In AD: Reviewed in [35,256,257]		IHC
AGEs	↑	Colocalized with astrocytes and microglia [396]	A,M	
Malondialdehyde	↑	[257]		
8-Hydoxy-deoxyguanosine	↑	mtDNA of parietal cortex [283], CSF [237]		IHC
4-hydroxynonenal	↑	Plaques [23], ventricular fluid [236]		
	↑	Multiple brain regions [258]		
Glutathione S transferase	↓	Multiple brain regions and CSF [238]		IHC