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Microvascular Pathology and Vascular Basement Membrane Components in Alzheimer's Disease

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Abstract

Several factors have highlighted the vasculature in Alzheimer's disease (AD): Cerebral amyloid angiopathy (CAA) is common, amyloid fibrils emanate from the vascular basement membrane (VBM), and similar forms of β-amyloid are found in vascular and parenchymal amyloid accumulations. The present article discusses the presence of microvascular pathology in AD. Microangiopathy, in addition to neurofibrillary tangles, senile plaques, and CAA, is a common pathologic hallmark of AD. VBM components are associated with amyloid plaques, and nonamyloidotic alterations of the VBM occur in brain regions susceptible to AD lesions. Also, intra-VBM perivascular cells (traditionally called pericytes), a subset of which share the immunophenotype of microglia and other mononuclear phagocytic system (MPS) cells, have been implicated in vascular alterations and cerebrovascular amyloid deposition. Perivascular and parenchymal MPS cells have access to several sources of the β-amyloid protein precursor, including platelets, circulating white cells, and neurons. MPS cells would thus be ideally situated to uptake and process the precursor, and deposit β-amyloid in a fashion analogous to that seen in other forms of systemic and cerebral amyloidoses.

Index Entries: Microangiopathy; β-amyloid; blood–brain barrier; heparan sulfate proteoglycan; collagen type IV; laminin.

Introduction

The term "amyloid" refers to a family of abnormal fibrillar proteins that share specific conformational (β-pleated sheet) and staining (e.g., Congo red and thioflavine) characteristics *(1,2)*. Amyloids derive from the processing of a variety of chemically unrelated precursors, and are deposited as primary or secondary manifestations of a diverse group of systemic and cerebral amyloidoses *(3)*. Amyloidoses have several features in common. Thickening and vacuolization of basement membranes are shared findings, with amyloid fibrils often fusing to this structure *(4–11)*. Two extracellular matrix components, amyloid P component *(12–18)* and heparan sulfate proteoglycan (HSPG) *(19–25)*, are consistently colocalized with amyloid fibrils. Finally, the plasmalemma of resident tissue macrophages, such as Kupffer cells in liver and microglia in brain, form interdigitating channels with the bundles of fibrils that comprise the amyloid core *(26–30)*. Although these macrophages (i.e., cells of the mononuclear phagocytic system, or MPS cells) may be involved in phagocytosis, they have also been shown either to produce amyloid *de novo (3)* or uptake and process an amyloidogenic precursor *(3,31)*. The present article will describe the manifestations of these various amyloidosis-associated alterations in Alzheimer's disease (AD) and will discuss their possible

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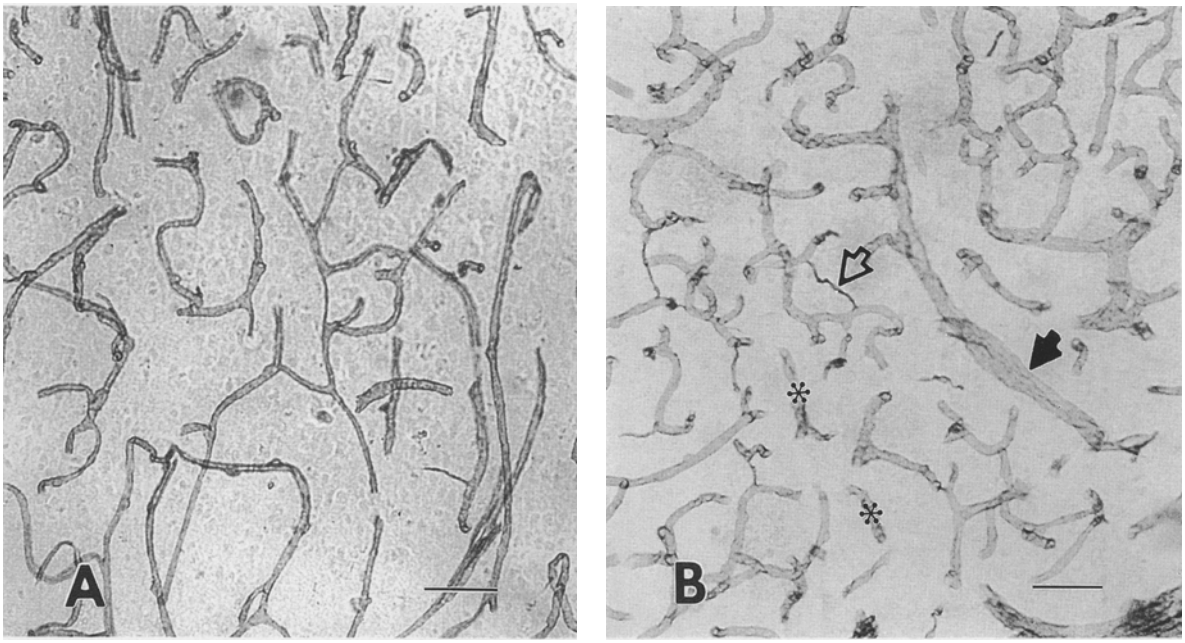

Fig. 1. Examples of HSPG immunostaining in non-AD **(A)** and AD **(B)** cerebral cortices. (A) Note the highly anastomosing array of vessels with smooth contours, constant diameters, and consistent capillary density in this non-AD autopsy sample. (B) The outer capillary surface was ragged and irregular, capillary diameter was both augmented (black arrow) and attenuated (open arrow), and a loss of the interconnected appearance (*) was evident in this sample from an AD case. Scale bar = 30 μm.

relevance to the involvement of the vasculature in disease pathogenesis.

Microangiopathy and AD

The healthy capillary system (Fig. 1A) consists of a highly anastomosing array of vessels with smooth contours, constant diameters, abluminal pericytes, and consistent regional density *(24,32–34)*. In contrast, capillaries from patients with AD are strikingly aberrant (Fig. 1B). There is a loss of the perivascular neural plexus and frequent dramatic pitting of the abluminal membrane, marked variations in capillary diameter, and focal areas of increased capillary density *(24,33–35)*. One study reported a relationship between the density of neurofibrillary tangles (NFT) and regional microvascular pathology *(36)*, and our own preliminary quantitative analyses revealed a significant correlation between disruption of the microvasculature and neuronal loss *(37)*. It would appear that the cerebral micovasculature is specifically targeted in AD, whereas it is spared in other vasculopathies that affect small- and medium-sized vessels *(24)*. Taken together, these findings suggest that microangiopathy, in addition to NFT, senile plaques, and cerebral amyloid angiopathy, is a common pathologic hallmark of AD.

A specific relationship between the microvasculature and senile plaques has been suggested by several lines of evidence. First, a close anatomic relationship has been observed between capillaries and plaque *(8,38)*, although recent quantitative studies may suggest only a chance coincidence *(39,40)*. Second, the amino acid sequences of AD vascular and plaque amyloids are very similar, save a two to four amino acid deletion in the former *(41–43)*. Third, both extrinsic (fibronectin *[44]*; Perlmutter et al., personal observation) and intrinsic (HSPG; *[24,25,45]*; laminin *[46,47]*; collagen type IV *[47]*) components of the VBM have been colocalized with amyloid plaques (Fig. 2). The relationship between amyloid and HSPG is particularly interesting. Binding sites for HSPG have been found on at least three of the alternately spliced forms of the β-amyloid precursor protein *(βAPP) (48)*. In addition, β-amyloid peptide fragments form fibrillar aggregations in the presence of either sulfate ions or heparan, suggesting that HSPG may play a role in the deposition of amyloid fibrils *(49)*.

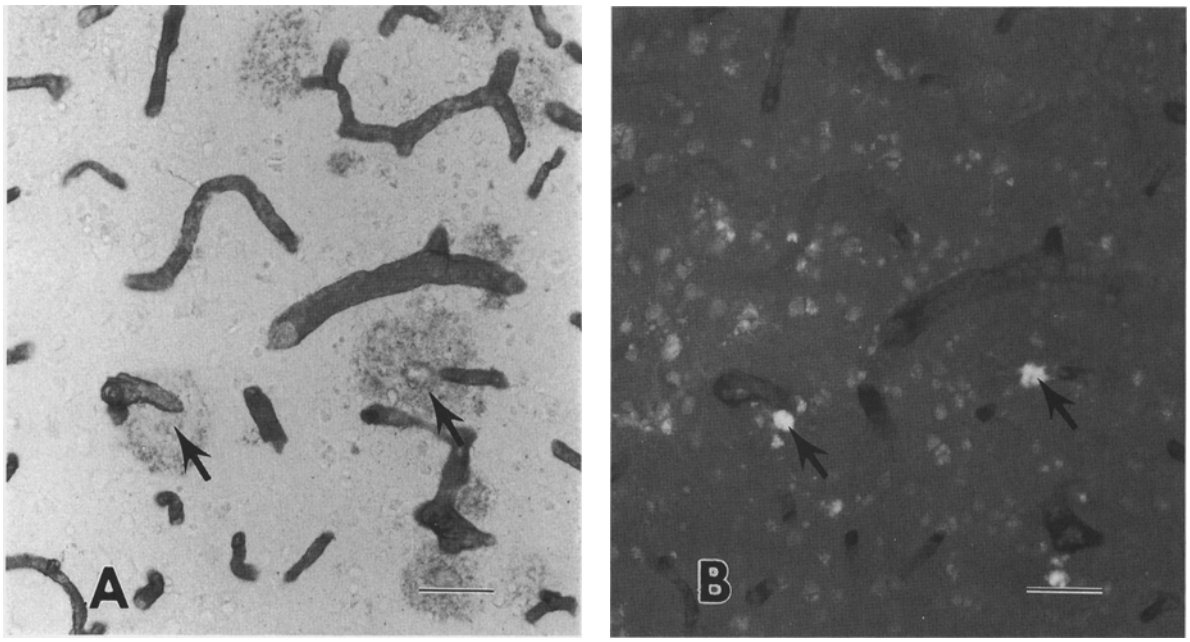

Fig. 2. Tissue section double-labeled for HSPG **(A)** and a fluorescent marker for amyloid (thioflavine S; **B**) from AD cerebral cortex. (A) Capillaries and extravascular accumulations of HSPG immunoreaction product (arrows) are evident (B) Fluorescing amyloid cores (arrows) are seen in the center of these extravascular accumulations. Scale bar = 40 μm.

Although only a subset of capillaries from AD cases is actually associated with obvious accumulations of amyloid fibrils (Fig. 3 *[50,51]*), recent studies have immunocytochemically localized fibrillar β-amyloid within the VBM in AD arterioles and capillaries *(52)* and an amyloidogenic *βAPP* fragment in microvessels of both AD and non-AD cases *(53)*. Thus, a consistent association between β-amyloid/*βAPP* and the VBM has been well established.

Alzheimer's Disease and the Vascular Basement Membrane

Vascular, glomerular, and Schwann cell basement membrane pathologies have been documented in many forms of amyloidoses, including primary localized cutaneous amyloidosis *(7)*, glomerular amyloidosis *(5)*, AA amyloidosis *(11)*, and peripheral neuropathologies *(9,10)*. Nonamyloidotic VBM alterations have consistently been identified in AD as well *(6,50)*. Quantitative analyses comparing the VBM of AD and non-AD cases in a neocortical area severely affected in AD (Brodmann area 22) and a region that is relatively spared (the cerebellum)

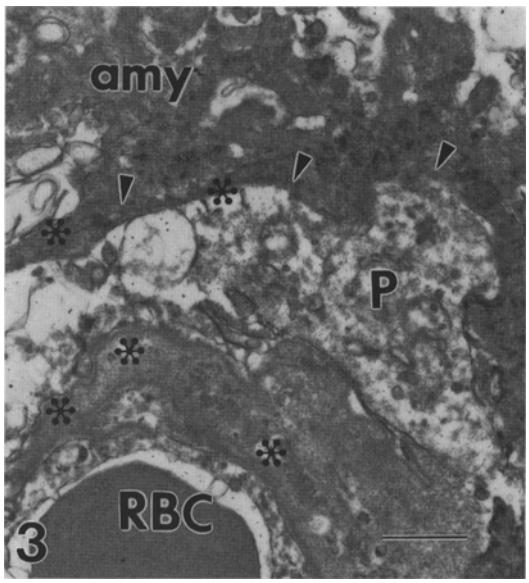

Fig. 3. Only a subset of capillaries from AD cases is actually associated with obvious accumulations of amyloid fibrils. In this amyloidotic vessel from an AD case, amyloid fibrils (amy) appear to fuse (arrowheads) with the VBM (*) and project into the perivascular neuropile. RBC, red blood cell; P, intra-VBM perivascular cell. Scale bar = 1 μm.

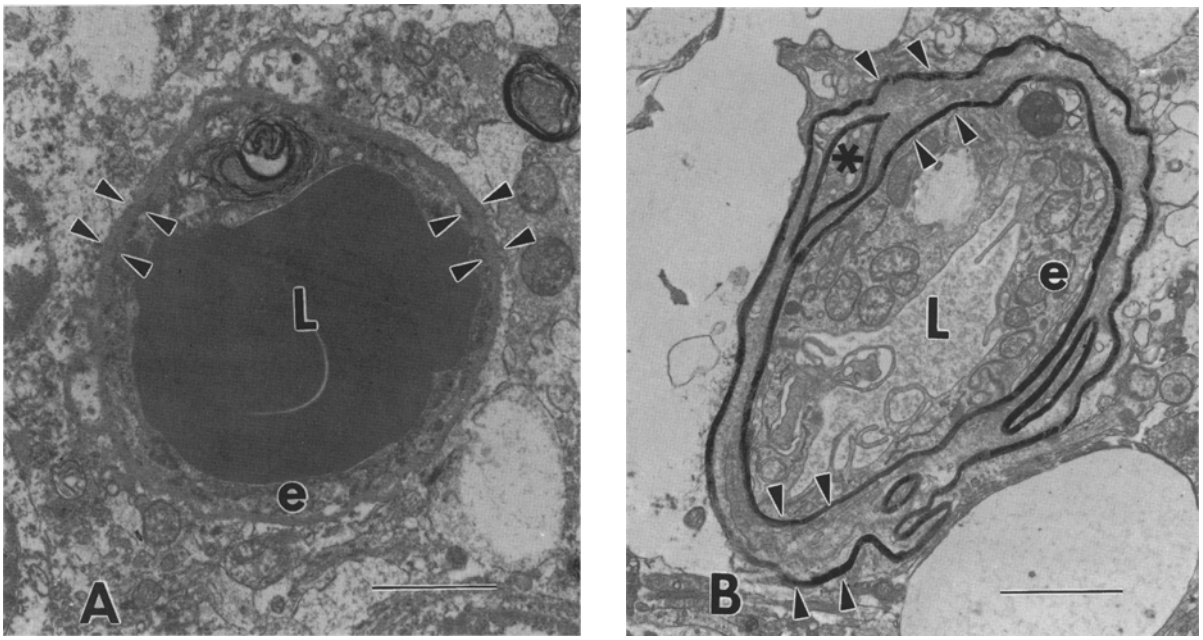

Fig. 4. Comparison of the ultrastructure of capillaries from two brain regions of one AD case. **(A)** Capillary from the cerebellum—a brain region that is relatively spared from the lesions of AD. The VBM (arrowheads) appears as a thin, gray "line" that surrounds the endothelial cell (e). Red blood cells are seen in the capillary lumen (L). **(B)** Capillary from the superior temporal gyrus—a brain region severely affected by the lesions of AD. The outside edge of the VBM has been outlined in black to demonstrate its extent, and arrowheads indicate regional thickenings. Vacuoles (*) at times contain cellular debris. Scale bar = 2 μm.

have recently been completed in our laboratory (Zarow et al., in preparation). The cerebelli of the AD and non-AD cases were qualitatively and quantitatively indistinguishable, whereas the neocortical region in AD cases exhibited significantly greater pathology than all other groups (Fig. 4; Zarow et al., in preparation). It has been suggested that it is not the actual presence of amyloid, but the physicochemical processes of amyloid formation that may be responsible for pathological changes in the VBM *(5)*. These data further support the hypothesis that altered VBM processing may have a specific relationship (whether causal or resultant) to the AD disease process.

The Blood–Brain Barrier

Structural alterations of the cerebral microvasculature are a common feature of AD. Increased tortuosity *(33,54,55)*, attenuated vessels *(24)*, possible gaps in endothelial cell tight junctions *(56)*, loss of HSPG from the VBM luminal surface (Perlmutter et al., in preparation), and VBM thickening and vacuolization *(6,24,33,34,50)* have all been reported. However, imaging and permeability studies provide no clear functional evidence to support leakage through the blood–brain barrier (BBB) *(57–59)*. A variety of serum proteins, including amyloid P component, prealbumen, albumen, immunoglobulins, and complement factors *(60–64)*, have been detected in plaque amyloid. However, a similar pattern of diffusion of serum proteins is seen in AD and non-AD aged cases *(57,58)*, and immunocytochemistry consistently fails to detect the serum proteins C-reactive protein and serum amyloid A in the brain parenchyma *(16,65)*. Finally, a specific impairment of the glucose transporter in isolated brain microvessels from lesion-affected areas of AD brain has been described *(66)*. Taken together, these data suggest that BBB disturbances might be in the form of microleaks or problems in transport, rather than a severe loss of BBB integrity. Future studies must determine whether these changes are primary or secondary to the disease process.

The Role of the Pericyte in AD Cerebrovascular Lesions

The cerebral microvasculature is comprised of three cell types—each of which has potential

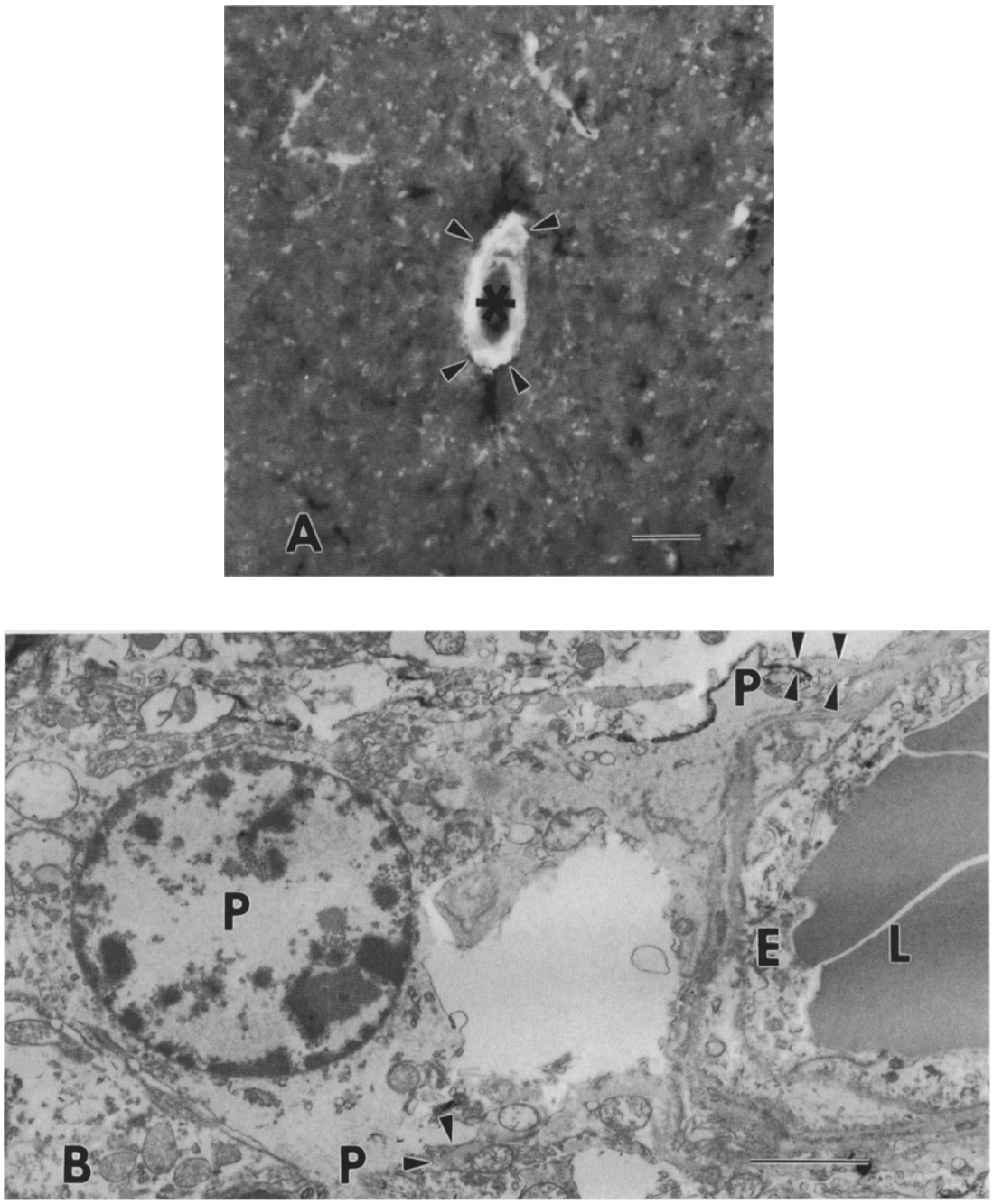

Fig. 5. Involvement of perivascular cells in AD. **(A)** Light micrograph of thioflavin S-positive amyloidotic vessel (*) surrounded by processes of perivascular cells (arrowheads) immunopositive for MPS cell marker (MHC class II). Scale bar = 20 μm. **(B)** Electron micrograph of an intra-VBM perivascular cell possibly moving into the neuropile. Note the disruption of the VBM (arrowheads) and the extension of the perivascular MPS cell process (P) into the brain parenchyma. Amyloid P component immunolabels a portion of the perivascular cell surface (black immunoreaction product). E, endothelial cell. L, capillary lumen. Scale bar = 2 μm.

involvement in AD pathogenesis (Fig. 5). First are the specialized endothelial cells of the brain, which form the BBB. These cells contain few pinocytotic vesicles, epithelial-like tight junctions with no fenestrations, and an unusually high density of mitochondria as compared to endothelial cells elsewhere

in the body *(67–69)*. Cultured endothelial cells have been shown to exhibit enhanced expression of the *βAPP* gene in the presence of interleukin (IL)-1 *(70)*. The second cell type of the microvasculature is the astrocyte, whose endfeet form a discontinuous sheath on the abluminal surface of the VBM. Although their function is unclear, they are thought to influence endothelial cell expression of brain-specific features (e.g., tight junctions) *(67,71,72)*. Astrocytes express *βAPP* in response to lesion in rat brain *(73)* and have recently been shown to contain paired helical filaments *(74,75)*.

The third cell type making up the microvasculature is the pericyte, which appears as a flattened cell whose processes encompass the capillary wall. Pericytes inhibit endothelial cell growth in culture *(76,77)* and may regulate capillary tone *(78)*. Controversy surrounds the origin and nomenclature for these cells *(79–83)*. Animal lesion models have revealed that a subset of "pericytes" actually expresses the same cell-surface markers as microglia and macrophages (i.e., MPS cells) *(84–86)*. In response to lesion, these "perivascular MPS" cells appear to migrate into the brain parenchyma *(87,88)*. We and others *(79,89,90)* have recently shown that human perivascular MPS cells express MHC class II molecules and apparently break through the VBM to enter the brain parenchyma during the course of AD (Fig. 5 *[90,91]*). Selective and highly significant loss of pericytes occurs in diabetic humans and mice, and has been associated with VBM vacuolization *(78,92)*. In fact, the cellular debris seen in the VBM vacuoles has been called "pericyte ghosts" by one researcher *(78)*. In addition, the plasmalemma of both pericytes (i.e., perivascular MPS cells) and microglia (i.e., parenchymal MPS cells) form interdigitating channels with the bundles of fibrils that comprise the amyloid deposit at the vasculature or the senile plaque, respectively *(29,90,91,93,94)*. Perivascular and parenchymal MPS cells have access to several sources of *βAPP*, including platelets, circulating white cells, and neurons *(95–101)*. MPS cells would thus be ideally situated to uptake and process *βAPP* and deposit β-amyloid in an analogous fashion to the macrophages associated with other forms of amyloidosis *(1)*.

Exposure of MPS cells to basement membrane components activates C1 and C3 receptors *(102)*, enhances Fc receptor-mediated phagocytosis by MPS cells *(102)*, and regulates gene expression of cytokines *(103)*. IL-1, a cytokine produced by microglia *(104)*, has been shown to enhance the expression of the *βAPP* gene in both cultured neuroblastoma and endothelial cells *(70,105)*. Likewise, β-amyloid stimulates the secretion of IL-1 from microglial cultures *(106)*, and secreted forms of *βAPP* stimulate the release of IL-6 in fibroblast cultures *(107)*. Thus, the VBM and its components, MPS cells and their secretory products, and *βAPP* and its breakdown products may work synergistically in a complex AD pathogenetic cascade.

Acknowledgments

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