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Commentary

Microglia in Alzheimer's Disease and Transgenic Models

How Close the Fit?

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Research on microglia has grown nearly exponentially over the last two decades,[1] fueled in part by the recognition that inflammation plays a role in the pathogenesis of Alzheimer's disease (AD).[2] Whereas their existence as a distinct central nervous system (CNS) cell type was once debated, it is now widely accepted that microglia are monocyte-derived cells that enter the CNS at early stages of development as highly mobile, ameboid cells that are distributed widely throughout the brain and spinal cord, developing a highly ramified phenotype that eventually forms a uniform reticular array in both gray and white matter. Being related to other cells of the mononuclear phagocytic system they are considered to be poised for activation, each cell policing a discrete and nonoverlapping domain and acting as a sentinel to disruption of the normal homeostasis of the neural tissue.[3] Microglia respond rapidly to subtle alterations not associated with any apparent tissue damage such as spreading electrical depression[4] as well as more severe insults such as anoxic-ischemic injury and neuronal loss associated with a host of degenerative disorders with a sequence of antigenic and morphological changes. The latter form is less ramified, with more abundant cytoplasm in soma and cell processes. It has cell markers, such as class II major histocompatibility antigen, that are barely detectable in the ramified form and is referred to as activated. The full repertoire of ramified microglia is not known, but they appear to be long-lived cells with a limited potential to divide, which contrasts with perivascular macrophages.[5] The latter have a more dynamic life cycle and enter and leave the CNS compartment more readily throughout the life of the individual. The perivascular macrophage, which constitutively express class II major histocompatibility antigen (HLA-DR) participates in the immune response and is fully capable of antigen presentation.[6] The phagocytic potential of the perivascular macrophage is not disputed, but whether ramified microglia are phagocytic cells is debated. Progressive transformation of ramified microglia to macrophages has been shown in a limited number of demyelinating conditions, where it appears that at least some microglia may differentiate into brain macrophages.[3,7]

The overwhelming evidence from years of experimental work suggests that brain macrophages are largely derived from blood monocytes that enter the CNS on injury and disruption of the blood brain barrier.[8] Studies of macrophage reaction to amyloid peptides and amyloid particles injected into brain can hardly address the role of intrinsic microglia to amyloid, as can transgenic models where amyloid forms within an intact blood brain barrier. In amyloid injection paradigms amyloid has been demonstrated to be phagocytosed by macrophages and partially degraded, eventually being removed by macrophages that recirculate into the blood stream.[9] Similarly, in studies of amyloid phagocytosis in AD brains with infarcts, macrophages are capable of phagocytosis and slow clearance of amyloid,[10] but once again the macrophages in this setting are blood monocyte-derived macrophages. Finally, amyloid cores have been fed to cultured macrophages and here, again, degraded amyloid is found within phagosomes.[11,12] That such images are not found in the intact human or animal brain is not surprising, because intrinsic microglia have limited capacity for phagocytosis. On the other hand, ramified microglia are likely to have more significant roles as secretory cells, responding to disruption of brain homeostasis by production of trophic[13,14] and possibly toxic factors that can be considered a natural repair mechanism. One of the most important mediators of microglial effects is interleukin-1, which is also among the most potent stimuli for astrocytes.[15,16] Some of the toxic properties of micro-

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glia may actually be ascribed to this dynamic interaction with astrocytes, which in humans are the major source of potentially toxic reactive nitrogen intermediates,[17] for there is virtually never a microglial reaction that is not also accompanied by astrocytic gliosis.

Certainly, the advent of reliable markers for microglia have contributed to their firm establishment as a distinct CNS cell type. Most of the best markers for microglia are cell surface antigens, such as class II major histocompatibility antigens, immunoglobulin Fc receptors, and complement receptors, that are poorly preserved with many routine histopathological methods.[3] Even flash-frozen tissue that is minimally fixed is suboptimal for detection of microglia. These technical factors have contributed to controversy about the presence and degree of microglial reaction to disease processes. The inability to demonstrate microglial reaction to lesions in some of the transgenic mouse models may also represent merely technical factors. For example, it was not until the seminal studies in the late 1980s of the McGeers and their coworkers, who described optimal methods for immunocytochemical detection of microglia,[18] that microglia were widely recognized as important cellular components of the neuropathology of AD.[19,20] The marker used initially by the McGeers was HLA-DR. Several previous studies of the distribution of HLA-DR in human tissue based on unfixed frozen sections had inaccurately interpreted the localization of HLA-DR on endothelial cells and astrocytes.[21] When better preserved tissue was examined using the methods of the McGeers it was clear that HLA-DR was almost exclusively localized to ramified microglia and perivascular macrophages. Soon thereafter, a large number of papers appeared documenting the alterations of microglia in a variety of CNS diseases, most notably AD and acquired immunodeficiency syndrome.[22]

As transgenic animal models were developed for AD, it was inevitable that microglia should be the object of intense scrutiny. The reports of Stalder and her coworkers in this issue of *The American Journal of Pathology*[23] and Frautschy and coworkers in the January 1998 issue[24] of the *Journal* are noteworthy studies of microglia in transgenic mouse models of AD. Stalder characterized transgenic mice (APP23) generated by Sommer from animals that carried the human APP gene with a double mutation of Swedish familial AD under a neuron-specific promoter,[25] whereas Frautschy characterized mice originally generated by Hsiao from animals that carried the same mutation in APP under a different promoter, the PRP promoter,[26] which is expressed in both neurons and glia. The Swedish mutation is associated with elevated levels of production of Aβ in brain, plasma, and fibroblasts of affected and at-risk individuals and in a variety of cells transfected with such constructs.[27] Both studies document aggregation and phenotypic activation of microglia associated with dense amyloid deposits, but limited or no association of microglia with diffuse amyloid deposits. Both studies use double immunocytochemical methods to simultaneously label amyloid and microglia, but different methods to detect microglia. Frautschy used an antibody to phosphotyrosine, whereas Stalder used an antibodies to β2-integrin (Mac-1). Similar antibodies have been used to detect microglia in human brains, but arguably the best marker for human microglia is HLA-DR. The association of microglia was greatest with dense or reticular amyloid deposits that contained Aβ40. Similarly, Aβ40 deposits are also the ones most clearly associated with microglia in humans.[28,29] Frautschy used image analysis to document the increased concentration of microglia in the vicinity of the dense cored amyloid deposits, whereas Stalder used immunoelectron microscopy to characterize the lesions.

Based on the electron microscopic findings, Stalder suggested that microglia might be the source of amyloid that is deposited in tissue. Similar conclusions have been suggested from electron microscopic studies of human and other animal models by Wisniewski and coworkers.[30] Dense brain amyloid deposits in both humans and mice are encased in microglia, this being beautifully illustrated in the three dimensional reconstruction experiments of Weigel and Wisniewski.[31] At high magnification amyloid and cell membranes are closely apposed and there are many interdigitations of cell processes between amyloid fibrils as well as invaginations of macrophage cytoplasm that give the impression of amyloid being intracytoplasmic. This has lead to the suggestion that microglia produce amyloid. The highly convoluted and infolded cytoplasm of macrophages has been known for many years; the channels are referred to as labyrinths.[32] The convoluted cell surface with its many cytosolic vesicles form structures in which it is difficult to determine which face of the vesicle is extracellular. Many apparent vesicles in the cytoplasm of macrophages are actually found to be invaginations of cell membrane when serial sections are performed[32] or the extracellular surface is labeled with methods such as tannic acid that bind to the glycocalyx on the outer surface of the plasmalemma.[33] The complicated membranous structures of macrophages is a byproduct of the highly dynamic nature of macrophage cell membranes, which continually recycle lipid from plasmalemma to intracellular vesicles during movement, formation of pseudopods, and phagocytosis. It is known that macrophages in the context of engaging a foreign target display abundant microfilaments, short stacks of rough endoplasmic reticulum and free polysomes in the cytosolic domain adjacent to the site of plasmalemmal contact with the target.[34] Membranous vesicles are also frequently disposed at the periphery of this region, as they are needed to extend pseudopods. The electron micrographs of Stalder display many of these same features as the microglial cell interacts with the extracellular amyloid fibrils. The phenotype illustrated does not necessarily support either synthesis of amyloid or phagocytosis, but merely engagement of macrophage with a large indigestible extracellular target.

Although microglia have been shown to express the precursor protein to β-amyloid (βAPP),[35–38] it is unlikely that microglia are the major source of amyloid fibrils that are deposited in the extracellular space. One of the forms of APP that microglia express, APP-L, is an alternatively spliced form of APP that alters expression of the Aβ domain.[36] Furthermore, cell culture studies show that microglia are deficient in production of Aβ compared to

neurons and astrocytes.[35,38] On the other hand, it remains possible that microglia process neuron-derived APP or truncated forms to produce Aβ. This would seem to be the only possibility in the APP23 mice studied by Stalder, because the promoter used is expressed only in neurons. An intriguing hypothesis we first proposed in 1988 and one that remains viable might account for the distribution of amyloid plaques in gray matter areas known to be highly plastic. If microglia produce Aβ from neuronal APP, they may acquire neuronal APP, which may be a synaptic protein,[39] from synapses that are undergoing remodeling.[40] Although microglia have limited phagocytic capabilities, they have been shown to engulf dendritic spines in denervated and axotomized neurons in a process that has been referred to as synaptic stripping by Kreutzberg and his coworkers.[41] It is unknown if ramified microglia have this capability under normal conditions of learning and memory. This could account for the fact that although APP expression is high in many brain areas, amyloid is deposited only in select regions,[25,26] such as the limbic gray matter, a region that has the greatest potential for synaptic remodeling.

On the other hand, studies of presumably the earliest amyloid deposits in humans, so-called diffuse plaques, have demonstrated wisps of amyloid filaments in the extracellular space between synaptic and cellular elements of the neuropil, with no obvious contribution of microglia.[42] It must, however, be acknowledged that immunoelectron microscopic studies of microglia in diffuse plaques have yet to be reported. Until these studies are performed the origin of diffuse amyloid from microglia remains in doubt. At the light microscopic level early diffuse amyloid deposits are often found around neuronal perikarya;[43,44] it must be recalled that as many as 20% of the satellite cells associated with neuronal perikarya are microglial.[45] Thus, microglia or their cell processes are present in sites of early diffuse amyloid deposition. Unfortunately, diffuse amyloid deposits are not a prominent feature of either of the transgenic mouse models in which microglia have been studied. Quite unlike its behavior in humans, amyloid appears in these models to form as an initial dense cored plaque. This makes it difficult to study diffuse deposits in transgenic mice. The other major APP model, for which detailed studies of microglia have not yet been reported, is the PDAPP model. These animals have a greater diversity of amyloid deposits, including diffuse deposits.[45] Immunoelectron microscopy of diffuse plaques in the PDAPP mice may provide insights on the relationship of microglia to early lesions that are difficult to interpret in human postmortem tissue samples. Another animal model that may be exploited in immunoelectron microscopic studies of diffuse plaques is the aged beagle, where compact amyloid deposits are uncommon and most lesions are diffuse amyloid plaques.[46]

A question that remains to be solved is why diffuse amyloid deposits may have an attenuated microglial response. One factor that needs to be considered in this regard is the possibility that there may be different predominant amyloid peptides in these lesions. Biochemical studies by Roher and coworker of brains with predominantly diffuse amyloid deposits[47] revealed that the most abundant amyloid species was actually a 3-kd amino-terminally truncated Aβ peptide referred to as p3. p3 may be derived from APP by a different mechanism than Aβ.[48] In any event, the missing amino acid residues in p3 are also the residues that are felt to be critical for complement[49] and microglial binding.[50] p3 may also have a decreased propensity for glycation because it has fewer lysine residues than Aβ.[44] If diffuse plaques contain predominantly p3, then the paucity of microglia may be a consequence of the fact that the amyloid is deficient in microglial chemotactic and activation signals.

The bulk of the evidence suggests that cells reacting to amyloid deposits are intrinsic microglia and that the response is an effete or abortive phagocytic engagement. The interaction of macrophages with amyloid may be mediated by macrophage receptors, such as the scavenger receptor[51,52] or the receptor for advanced glycation end products.[53] Interaction of ligands with these macrophage receptors leads to a signal cascade that leads to production of a number of molecules, including interleukins and growth factors.[54] The activated macrophage also undergoes respiratory burst, which could generate reactive oxygen intermediates.[55] Given the fact that complement is codeposited with amyloid,[56] complement receptors may also be occupied. The process of interaction is likely to produce a number of factors that could be potentially toxic to the surrounding.[57] For example, macrophages and microglia are known to produce proteases that degrade extracellular matrix when they contact surfaces with these substances.[58,59] Glycosaminoglycans have been shown to be present in amyloid[60] and these macromolecules may also be involved in the stabilization of the extracellular deposit.

The final assessment is that the transgenic animal model is a good fit for only one particular type of amyloid deposit seen in AD, the plaque with a dense amyloid core. It is not, however, a good fit for the more challenging early lesions or diffuse plaques. Unfortunately, the available transgenic animal models do not permit study of the interrelationships between the various forms of amyloid deposits that are common to the human brain in aging and AD. Plaque types in the human brain have consistent regional anatomical variability that is missing in the transgenic models. For example, diffuse deposits are consistently found in the molecular layer of the cerebellar hemisphere and dense core deposits in the Purkinje's cell layer of the cerebellar vermis in AD. These regional differences appear to be unique to the human. Local tissue pathology is clearly most apparent in plaques with dense amyloid and a microglia reaction, whereas it is subtle in diffuse plaques. The transgenic models offer a means to study mechanisms of local tissue pathology associated with dense deposits. They may also provide experimental means of manipulating the microglial reaction (eg, anti-inflammatory drug treatments) to monitor the effects on the local tissue pathology. On the other hand, neuronal pathology in AD is far more widespread than that associated with dense amyloid deposits, and most of the neurofibrillary pathology in AD appears to be an independent process of neurodegeneration in selectively vulnerable neurons that often

show no apparent relationship with any type of amyloid deposit. To date transgenic mice have failed to provide a good model for these more complicated pieces of the AD puzzle.

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