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REVIEW ARTICLE

Microglia in the Aging Brain

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Abstract

The aging brain is characterized by a demonstrable decrease in weight and volume, particularly after the age of 50. This atrophy, which affects both grey and white matter, is presumed to result from a loss of neurons and myelinated axons. Glial cells, on the other hand, appear to increase in the aging brain, which exhibits greater immunoreactivity with both astrocytic and microglial markers. This review is focused on the morphologic and phenotypic changes that occur in microglial cells with normal aging. Although there is a consistent aging-related upregulation of microglial activation markers in experimental animals and humans that could be interpreted as aging-related neuroinflammation, it is generally difficult to show a direct correlation between ostensible microglial activation and neurodegeneration. This raises questions about whether aging-related microglial activation indeed represents reactive gliosis in the conventional sense. As an alternative, we discuss the possibility that structural and phenotypic changes that occur in microglia are a direct reflection of the aging process on microglia. Thus, microglia cells themselves may be subject to cellular senescence in the sense that they no longer function efficiently. The concept of microglial senescence offers a novel perspective on aging-related neurodegeneration, namely that neurodegeneration could also occur secondary to microglial degeneration.

Key Words: Aging, Neurodegeneration, Senescence.

INTRODUCTION

Most studies concerned with microglial cells in the aging brain have focused on the potential role(s) of microglia in aging-related neurodegenerative disease, notably Alzheimer disease (AD), to understand the relationship between aging and aging-related neurodegeneration. Although these studies reflect, to some extent, an appreciation of the intricate interrelationship and interdependency of neurons and microglia, the nature of microglial–neuronal interactions remains enigmatic when it comes to explaining pathogenetic mechanisms that lead to neuronal degeneration. Without a doubt, the body of literature published on AD and microglia is large with most studies focused on possible connections between activated microglia and amyloid plaques. Current understanding of the relationship between microglia and amyloid was discussed at length in a recent review (1), which pointed out that although interactions between amyloid and microglia dominate the AD literature, relatively little is known about how microglia may be involved in the characteristic form of neurofibrillary degeneration that is typically seen in the AD brain. Because neurofibrillary tangles are not specific for AD and are also common in the brains of aged, nondemented individuals, our intent here is to review what is known about microglia in the normally aging brain, focusing on a smaller subset of histologic studies that are often lost in the AD literature. The motivation for doing so stems from our hypothesis that microglial cells themselves are subject to aging and an aging-related deterioration of cell function. Thus, neurons that are normally dependent on fully functional, viable microglial cells may be adversely affected by impaired microglial cell function or loss of microglia, which could ultimately contribute to development of neurofibrillary degeneration in the aged brain through vanishing glial support and neuroprotection (2).

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Indirect or Direct Effects of Aging on Microglia?

The effects of aging on microglia are conceivably 2-fold: microglia may react to aging-related changes in their environment, or microglia may be directly affected by the aging process. Regarding the former, a primary function of microglia is surveillance of the central nervous system (CNS) microenvironment, including the monitoring of extracellular chemical changes, debris accumulation, pathogen invasion, and perhaps altered neuronal signaling. Because the CNS parenchyma is subject to some known aging-related changes such as reduction of extracellular volume, increased astrogliosis, and neuronal loss or shrinkage (3–6), it is possible that these changes may affect microglia secondarily. Just as aging-related astrogliosis has been interpreted as a secondary reactive glial cell response to neuronal changes, the microglial activation that reportedly occurs with aging (7–9) may also be considered a secondary glial response. However, there are problems with this interpretation in the sense that the localization of activated microglia has not been correlated with the localization of damaged or lost neurons. In fact, Finch et al state that microglial activation during normal aging is simply "puzzling" because it cannot be correlated with brain pathology (10). Furthermore, positive histopathologic identification of activated microglia and their distinction from nonactivated, so-called resting microglia is quite difficult to achieve in the human brain. Investigators have attempted to do so using specific immunohistochemical

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markers, most notably antibodies directed against human HLA-DR antigens (7, 11) or interleukin-1α (IL-1 α) (12, 13). However, using solely these specific immunoreactivities as identifying markers of activated (reactive) microglia is unreliable. In the case of HLA-DR staining, the LN3 antibody that is often used typically stains large numbers of microglial cells that display great morphologic heterogeneity, including many perfectly ramified (resting) and therefore nonactivated cells (8, 14). We discuss microglial staining for HLA-DR (or major histocompatibility complex [MHC]) antigens in more detail in the next section of this article. One difficulty associated with the use of anti-IL-1α antibodies is that IL-1α-positive cells are scarce compared with LN-3-stained cells (compare [12, 13] with [7, 8, 11]), and thus there are major discrepancies in the number of activated microglia identified with the 2 different markers. As the next section emphasizes, combined evaluation of both cellular morphology and the presence of a biochemical activation marker should be used in any attempts to unequivocally identify activated microglia in human postmortem tissue. All in all, it remains to be determined if and when microglial activation occurs truly as a secondary consequence to aging-related changes that affect other cells in the brain.

The other possibility, that aging has a direct impact on microglia, seems more likely. That is, why would aging not affect microglia when it affects all other cells and tissues in the body? However, current textbooks of neuropathology do not even mention such a possibility, likely because relatively little is known about the effects of aging on microglia. What is known, specifically from histopathologic studies, concerns aging-related changes in microglial morphology and immunophenotype, and these studies are summarized in the following sections.

Phenotypic Changes That Occur in Microglia With Aging

The vast majority of studies of aging-related immunophenotypic changes in microglia have demonstrated a steady increase in the expression of markers usually found to be upregulated on activated microglia after acute CNS injuries. Most notable is an aging-related increase in microglial expression of MHC class II antigens, which has been reported in humans (7–9), monkeys (15, 16), and rats (17–19). The increases in MHC II expression very likely represent immunophenotypic changes in the existing microglial population, because there is no clear evidence of increased microglial cell numbers in old compared with young rat brains (20). Because expression of MHC II antigens seems to steadily increase on existing microglial cells as the brain ages, one should therefore consider the possibility that MHC II expression is a marker of cell maturation or cell senescence in addition to, or instead of, being an activation marker. In studies that compared grey and white matter, the aging-related increase in MHC II expression was much more significant in white matter (15–17, 19), which is known to constitutively harbor greater numbers of MHC II-positive microglia than grey matter (21, 22). Increased prevalence of MHC II-positive microglia could suggest a correlation between aging-related myelin breakdown and microglial activation. It is known that microglia have the ability to phagocytose myelin (23, 24) and become activated by myelin in vitro (25). A recent study also demonstrated that activated microglia in the white matter of rhesus monkeys had an aging-related increase in the expression of active calpain-1 (26), a proteolytic enzyme that was previously proposed to have a role in aging-related myelin protein degradation (27); thus, age-dependent increases in calpain-1 expression may be a reflection of increased degradation of phagocytosed myelin fragments by microglia. Aging-related increases in the breakdown of myelin and other cellular components, and the subsequent phagocytosis of these substances by microglia, may account for the substantial increase in inclusions within microglia reported in aged monkeys (28–30) and rats (31).

In addition to MHC II antigens, molecules such as the ED1 macrophage antigen, leukocyte common antigen (LCA), and CD4 antigen are present with increasing frequency on microglia in the aging CNS of the rat (19, 32). In humans, an aging-related increase in the number of IL-1α+ microglia has been reported in the temporal lobe (12), but these findings are not paralleled by similar studies in other brain regions or in experimental animals. Studies on age-related expression of complement receptor 3 (CR3; also known as Mac-1 or CD11b) have had more varied results. Increases in the number of CR3 expressing microglia were reported in the aging rat spinal cord white matter (32, 33) and brain (18, 32), but other studies found no difference in the number or density of CR3+ microglia in the mouse hippocampus (20) or rat brain (17, 19). The reason for this incongruity in observations is likely found in the fact that there is considerable regional variability in the density and distribution of microglia within the normal brain (34).

Morphologic Changes That Occur in Microglia With Aging

In addition to age-related increases in the expression of antigenic markers of microglial activation, several studies have reported significant changes in microglial morphology, including the presence of cytosolic inclusions already mentioned. These membrane-bound inclusions have been described in monkeys (28–30) and rats (31, 35) as heterogeneous, foamy, or dense, generally filling the microglial perikarya and often pushing the nucleus off to the side. Lamellar inclusions filled with phagocytosed myelin sheaths have been described in microglia of the monkey optic nerve (30). Vaughan and Peters (35) also demonstrated extension of these heterogeneous inclusions into the microglial processes of older rats, and they suggested other possible sources of the aging-related accumulation of material, including phagocytosis of degenerating axon terminals and dendritic spines, and pinocytosis of plasma proteins, metabolic waste, or other material. Perry et al reported vacuolated processes in MHC II-positive (OX-6 antibody) microglia in aging rats, and although they found no aging-related difference in the density of CR3-positive (antibody OX-42) microglia, they described CR3-positive microglia in old rats as having abnormal morphology and a higher incidence of clumping, particularly in and around white matter

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(19). Our own most recently published studies using lectin staining (36, 37) confirm that aging produces dramatic changes in the morphology of so-called resting microglia (i.e. cells present in nonpathologic normal brain tissue). As shown in Figure 1, microglia in the aged brain are characterized by significant hypertrophy of their cytoplasm and dense lectin staining. Others have used lectin histochemistry to show microglial hypertrophy in the aging rat retina (38) and cytoplasmic vacuoles in aged mouse brain (39). Microglial structural changes such as bulbous swellings, long stringy processes, and cytoplasmic fragmentation found in a mouse model of Huntington disease were mirrored with aging in wild-type mice (40). Abnormalities in the cytoplasmic structure of microglia in the aged human cerebral cortex were described in a recent study by our laboratory (14). These abnormalities, collectively referred to as microglial dystrophy, were characterized by cell processes that appeared stripped of fine ramifications (deramification), showed excessive beading and formation of spheroidal swellings, as well as fragmentation or tortuosity. Another instance in which similar changes have been reported was in a study by von Eitzen et al examining microglia in 11 cases of Creutzfeldt-Jakob disease (41). These authors provided a link between abnormal microglia and spongiform encephalopathy suggesting that microglia themselves could become a target of disease. We support this hypothesis, because additional evidence is emerging from our own ongoing studies in the aging and AD brain, as well as from recently published work in schizophrenia (42), showing that microglial cells are subject to degenerative changes. Although these types of changes are only beginning to be documented and analyzed, there are implications that could fundamentally change the way we contemplate the pathogenesis of potentially many neuropathologic conditions. A summary of the reported phenotypic changes that occur in microglia with aging is provided in Table 1.

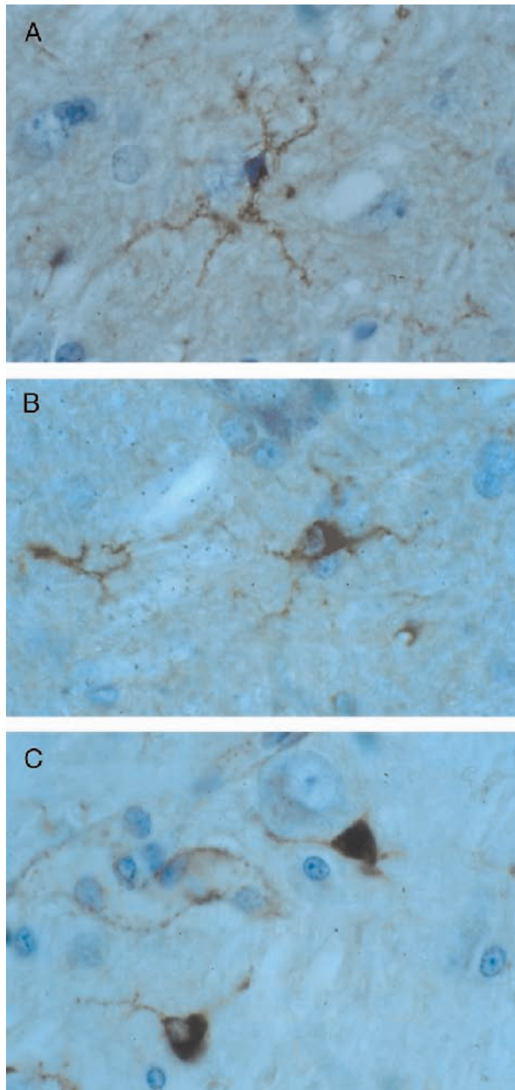

FIGURE 1. Morphologic changes occur in microglia with normal aging. Shown are microglial cells in the brainstem of rats aged **(A)** 3 months, **(B)** 15 months, and **(C)** 30 months. Note the increasing hypertrophy of the perinuclear cytoplasm and decreasing ramification of cell processes. Cells are visualized with lectin histochemistry in paraffin sections, as described in (36). Magnification: 750×.

Effects of Aging on the Microglial Response to Injury

Whether or not, and to what extent, aging affects the ability of microglia to respond to neuronal injury is not entirely clear from the limited number of studies that have investigated this question. Similar to observations already described here, the retina in aged rats showed greater lectin reactivity for microglia than young rats, and transient retinal

TABLE 1. Summary of Reported Microglial Changes in the Normal Aging Brain

Microglial marker	Observed change with aging	Species	References
Ultrastructural phenotype	↑ Heterogeneous inclusions	Monkey	(28–30)
		Rat	(31, 35)
	↑ Number/density	Monkey	(29, 30)
		Rat	(35)
MHC class II	↑ Number/density/area	Human	(8, 9)
		Monkey	(15,16)
		Rat	(17–19)
	Morphologic changes	Human	(14)
		Rat	(19)
Complement receptor 3 (CR3)	↑ Number/area	Rat	(18,33)
	Phenotypic changes	Rat	(19,32)
	No change	Rat	(17)
		Mouse	(20)
ED1 macrophage marker	↑ Number	Rat	(19,32)
GSA I-B4 lectin	Phenotypic changes	Rat	(38)
	↑ Density/intensity, cytoplasmic vacuoles	Mouse	(39)

MHC, Major histocompatibility complex.

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TABLE 2. Aging-Related Differences in the Response of Microglia to Injury: Varying Results Based on Injury Model, Marker, and Method of Analysis

Injury paradigm, species	Microglial marker, data compared	Aging-related difference after injury?	Aging-related difference in ratio of lesioned to control	Reference(s)
Intracerebral hemorrhage, rat	CR3, cell density	Old ↑	Not stated	(44)
Stroke, rat	ED-1, qualitative	Old ↑	Not stated	(46, 47)
Transient retinal ischemia, rat	GSA I-B4 lectin, qualitative	Old ↑	Old ↑	(38)
Cortical stab injury, rat	ED1, qualitative	Old ↑	Not stated	(45)
MPTP-induced neurotoxicity, mouse	CR3, cell counts	Old ↑	Old ↑	(43)
Facial nerve axotomy, rat	MHC II, CR3, area ratio	No	No	(48)
	Lectin, area ratio	Old ↑	No	(36)
	^{3}H-thymidine, cell density	Old prolonged ↑	N/A	(36)
Sciatic nerve constriction, rat	CR3, area ratio	Old ↑	Old ↓	(33)

ischemia produced a greater increase in the reactive microgliosis in aged rats (38). However, aged rats also showed a greater loss of retinal ganglion neurons after ischemia, which could account for the increase in reactive gliosis. Similarly, microglial CR3 expression was increased and prolonged in aged mice after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced dopaminergic neurodegeneration, and the increase in this expression over control was greater than in young mice (43). In contrast, although baseline microglial expression of CR3 was higher with aging in the primary afferent terminations and motoneuron columns of the rat sciatic nerve, sciatic nerve injury did not increase CR3 expression as much in old as in young animals (33). CR3 expression was higher in aged versus young rats 3 days after intracerebral hemorrhage (44), but in that study, it was not stated if the net increase over control was different between age groups. Immunoreactivity for the ED-1 macrophage marker was found to be greater with aging after cortical stab injury (45) and stroke (46, 47). These studies also did not indicate the ratio of lesioned to control immunoreactivity, yet they showed that the time course of postinjury ED-1 reactivity changes with aging with ED-1 reactivity peaking earlier in old rats. Hurley and Coleman did not find age-related differences in microglial CR3 or MHC II expression in either the control or axotomized facial nucleus, although they did note that basal CR3 expression was increased in other areas of the aging brainstem (48). Our own findings in the facial axotomy paradigm show a dysregulation of the microglial mitotic response during axotomy-induced activation as well as the aforementioned changes in cellular morphology affecting primarily nonactivated resting cells (36). Thus, overall, the literature on acute microglial activation with aging (summarized in Table 2) does not reveal entirely consistent findings, in large part as a result of the diversity of injury models, species, anatomic regions, microglial markers, and methods of analysis used. If any conclusive statement was to be made, it would be that there is no obvious aging-related impairment in the ability of microglia to respond to CNS injury. Of course, this statement applies only to experimental animals, primarily rodents, in which it is possible to perform time course studies of acute microglial activation. The situation in humans is likely to be different and considerably more complex as a result of their extended lifespan.

CONCLUSIONS

The available histopathologic evidence from a variety of species, including humans, strongly supports the fact that microglia undergo aging-related changes in cell morphology and cell surface antigen expression. The physiological significance of these structural and biochemical changes in terms of microglial cell function remains to be further investigated. For now, we have accepted the working hypothesis that over time, a changing phenotype at the cell level, similar to an altered appearance of the aged brain at the organ level, reflects a change in function. Specifically, if the aged brain shows atrophy with an associated decline in cognitive and memory function, then morphologic changes in microglia may indicate impaired cellular function. Furthermore, if we accept the idea of microglial senescence, then an important question arises about whether or not aging-related microglial dysfunction contributes to neuronal dysfunction and if perhaps the former precedes the latter. If one views microglia primarily as neuroprotective elements, as we do, it would be reasonable to hypothesize that a weakening of microglia-mediated neuroprotection could have negative consequences for neurons and may indeed contribute to aging-related neurodegenerative changes. This, of course, raises the possibility that any intervention targeted specifically at preserving proper microglial cell function may be beneficial for preserving brain function and slowing brain aging.

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