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Dystrophic microglia in late-onset Alzheimer's disease

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Abstract

Here, we summarize current understanding of functional involvement of microglial cells in the most common neurodegenerative disease to affect humans, which is sporadic or late-onset Alzheimer's disease (LOAD). Our review narrowly focuses on insights obtained from post-mortem neuropathological examinations of human brains paying particular attention to microglia as these cells have long been implicated as pivotal players in the cellular processes that lead to AD-type neurodegeneration. Although complete understanding of the roles played by microglia in AD neurodegeneration remains elusive, our studies thus far have illuminated microglial involvement in LOAD, showing that microglial dystrophy, the morphological manifestation of senescence, can be integrated with other hallmark pathological features of AD, such as intraneuronal neurofibrillary degeneration (NFD) and extracellular deposits of amyloid-beta (Aβ) protein. We have demonstrated an in situ correlation between microglial dystrophy and presence of NFD suggesting that neurodegeneration is secondary to aging-related microglial deterioration, a concept founded on the notion that proper neuronal function is dependent on presence of healthy microglia. Diseased or weakened glia are detrimental for neuronal well-being because their ability to provide neuronal support may be impaired. Our most recent work also links microglial dystrophy with Aβ deposits by showing that there is a chronic, yet futile microglial reaction to insoluble amyloid deposits. This inability of microglia to remove aggregated amyloid (a foreign body) causes microglial exhaustion and thereby exacerbates already ongoing aging-dependent microglial deterioration. An eventual total loss of functional microglia in advanced LOAD promotes widespread NFD, dementia, and brain failure.

KEYWORDS

aging, dystrophy, late-onset Alzheimer's disease, neurofibrillary degeneration

1 | INTRODUCTION: BASIC POINTS IMPORTANT FOR LOAD PATHOGENESIS

We view microglial cells as essential guardians of the central nervous system (CNS). Their roles are multifaceted and broadly include immunological surveillance as well as a host of activities to support and protect fastidious, vulnerable neurons, which have specific requirements for survival (Streit, 2002). Concisely, microglial functions all serve one common objective: doing whatever is necessary to ensure proper neuronal function. Neurodegeneration occurs because neurons undergo functional impairments for reasons largely unknown. What is clear is that the majority of neurodegenerative diseases are associated with aging, pointing toward the unmistakable fact that the CNS, like any other organ, eventually fails to perform its intended functions. Because not every old person becomes a victim of neurodegenerative disease, an important question is why some individuals do and others do not. This fact of life is most commonly reflected in sporadic or late-onset Alzheimer's disease (LOAD), a neurodegenerative disease that

can affect virtually any human being. Unlike familial, or early-onset Alzheimer's disease (EOAD), which accounts for a rather small percentage of all AD cases, LOAD accounts for more than 95% of all AD cases. It presents a formidable challenge for public health because numbers of affected individuals are increasing at an alarming rate globally, and to date the pathogenesis and etiology of this condition remain unknown. Deciphering the pathogenic processes leading to symptomatic disease is difficult, not only because the disease is sporadic, but also because there are no rodent models that can faithfully mimic the decades-long pathogenesis of LOAD, a disease that spontaneously affects only human beings (Braak & Del Tredici, 2015). Because LOAD is an aging-related disease (Figure 1) and human beings live much longer than most other mammals, especially laboratory rodents, they are at much higher risk of gradually developing aging-related neurodegeneration, which is a very slow process likely involving cellular senescence.

Neurodegenerative diseases are about neuronal survival and degeneration, and pathological lesions affecting neurons directly correlate best with the symptomatology. This means that a substantial amount of neurodegeneration is present before symptoms of cognitive dysfunction become apparent clinically. Specifically in LOAD, the type of neurodegeneration that occurs is known as neurofibrillary degeneration (NFD), which can affect many kinds of neurons but most consequentially those located in the cerebral cortex. NFD involves hyperphosphorylation of the cytoskeletal protein, tau, hence NFD is also known as tau pathology. The spread of tau pathology in LOAD has been analyzed in great detail and been shown to follow a predictable path of spread through well-defined brain regions from allo- to neocortex (Braak & Braak, 1991). However, critical questions remain about what causes NFD in the first place, as well as about its mechanisms of spread. Does NFD occur inevitably? The answer appears to be yes, because 90% of individuals under the age of 30 already reveal tau pathology in subcortical sites (Braak & Del Tredici, 2011). By the time people have reached the age of 40, nearly everybody shows some level of NFD (Braak, Thal, Ghebremedhin, & Del Tredici, 2011). This pervasiveness of tau pathology in the human population suggests that it is due to a ubiquitous influence that affects everybody, the most likely candidate being aging-related oxidative stress. Like NFD, microglial dystrophy first shows up in the young and then slowly progresses as people age thus following a course that seems to parallel development of NFD (Bachstetter et al., 2015; Streit, Braak, Xue, & Bechmann, 2009; Xue & Streit, 2011; Figure 1). As discussed below, some of the structural features of microglial dystrophy suggest oxidative stress as a major contributing factor prompting us to think oxidative stress is the common denominator to account for both neuronal and microglial degeneration. Based on the essential interdependence that exists between microglia and neurons, we hypothesize that microglia weakened by oxidative damage are impaired in their abilities to properly support neurons thus creating a vicious cycle where aging neurons increasingly come to rely on microglial cells that are weakened by aging themselves (Streit, 2002, 2004; Figure 2). Thus, while both neurons and microglia may experience cellular senescence, the neurodegenerative process itself may be triggered by weakened microglial support of neurons.

An important aspect for understanding LOAD pathogenesis is the fact that the condition is marked by a prolonged preclinical phase during which individuals are nonsymptomatic but develop lesions identical to those seen in clinical, symptomatic disease but to a lesser extent (Braak & Del Tredici, 2015; Price et al., 2009). As shown in Figure 1, the preclinical phase can extend through midlife and is characterized by presence of both NFD and microglial dystrophy, which occur in parallel. Deposition of Aβ is mostly absent during this time but becomes apparent at some point during late to very late midlife. Once Aβ deposits have formed, disease progression likely accelerates because additional pathogenic factors, such as increases in brain iron, also come into play as indicated by increasing numbers of microglial

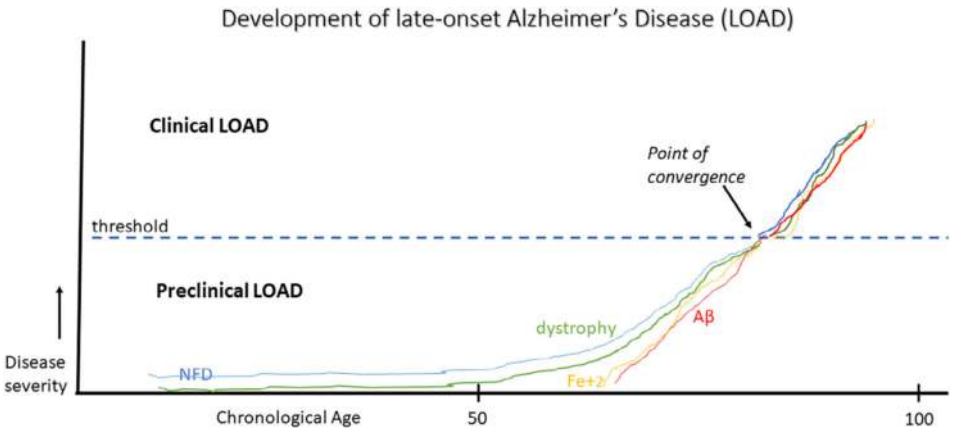

FIGURE 1 Schematic shows development of lesions during late-onset Alzheimer's disease (LOAD) pathogenesis. Throughout the pathogenic course, neurofibrillary degeneration (NFD) and microglial dystrophy progress in parallel, which suggests a common cause, most likely aging and oxidative stress. Deposition of Aβ occurs relatively late (in our cohort, at Age 61) when NFD is already well advanced. The point where key pathological features converge (NFD, Aβ, and neuroinflammation) marks a tipping point where preclinical LOAD transitions into clinical LOAD. At this point, brain iron (Fe^{2+}) levels are elevated as well, as indicated by an upregulation of microglial ferritin expression. Disease continues to progress rapidly after the threshold to clinical LOAD has been crossed

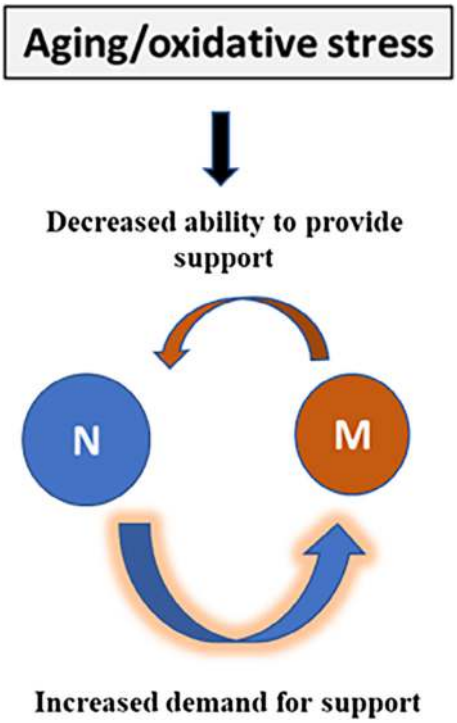

FIGURE 2 Schematic illustrates the dependence of neurons on microglial support, a relationship negatively affected by aging

cells positive for the iron storage protein, ferritin. Increased brain iron likely contributes to increasing levels of oxidative stress and to aggregation of Aβ into amyloid (R. J. Castellani, Moreira, Perry, & Zhu, 2012), which triggers microglial activation. At some point all of the various pathological components (NFD, dystrophy, amyloid, neuroinflammation, iron accumulation) converge to where preclinical LOAD turns into clinical disease thus marking a tipping point in pathogenesis (Streit et al., 2018).

2 | HUMAN MICROGLIA VERSUS RODENT MICROGLIA—DIFFERENCES AND SIMILARITIES

Based on published data in mice (Askew et al., 2017; Lawson, Perry, & Gordon, 1992), microglia represent a long-lived (stable) population of brain immune cells, and we assume that to be the case for humans as well. In mouse bone marrow chimeras, a turnover of microglia by blood-derived mononuclear cells was reported (Priller et al., 2001) but this turned out to be an artifact of the irradiation used to create the mouse chimeras (Mildner et al., 2007). The current view is that microglia derive from yolk sac progenitors (Ginhoux et al., 2010), that is, fetal macrophages that enter the brain early in development when their population is controlled by CSF-1 (Erblich, Zhu, Etgen, Dobrenis, & Pollard, 2011). Thus, in the adult brain microglia are not continuously replaced by bone marrow-derived precursor cells or by blood-borne monocytes, and losses in the resident population are replenished via mitosis (Askew et al., 2017). Human longevity makes it likely that more microglia are lost over time than in rodents, albeit for reasons largely unknown. Their replenishment at various times during the human lifespan creates a microglial population that is considerably more heterogeneous than the microglial population in short-lived laboratory rodents. This fundamental difference between humans and rodents is revealed when studying microglia histopathologically in brain sections from subjects without known or obvious pathology. There is little morphological variability to be found between individual cells in, say, a 12-month-old rodent brain, presumably because most cells are the same age and display the classic ramified morphology of microglia, and all cells typically stain with pan-microglial markers, such as CD11b or Iba1. In contrast, examination of immunostained brain sections from middle-aged human beings often reveals a much more heterogeneous morphology and immunophenotype of microglia producing a mixture of ramified and dystrophic microglial cells (Bachstetter et al., 2015; Streit et al., 2018), but not all of them always stain with Iba1 (Lier et al., 2019). Because humans can experience subtle, nonsymptomatic brain pathology, for example, microinfarcts (Kapasi et al., 2018), activated microglia can also be detected in apparently healthy, nondemented humans without any history of brain disease (Streit & Xue, 2016). Thus, human microglia are different structurally, not only at the level of individual cells but also at the population level showing much greater variabilities in morphology and phenotype than rodents. That said, both rodents and humans reveal evidence of microglial aging. In aged rodents, senescent microglia present primarily as cells containing lipofuscin accumulations (Conde & Streit, 2006; Streit & Xue, 2010; Xu, Chen, Manivannan, Lois, & Forrester, 2008) and perhaps exhibiting small decreases in the complexity of their processes, but in humans decreased complexity is much more advanced and produces dystrophic processes, which includes cytoplasmic fragmentation (see next section). Other, immunological differences between rodent and human microglia are discussed elsewhere (A. M. Smith & Dragunow, 2014).

3 | MICROGLIAL DYSTROPHY IS UNIQUE TO HUMAN AGING AND LINKED TO NFD

Dystrophy of microglia was discovered in human brain (Streit, Sammons, Kuhns, & Sparks, 2004). The term "dystrophy" was selected to refer to a number of morphological abnormalities affecting microglial cytoplasmic extensions, such as spheroidal swellings, de-ramified, beaded, or tortuous processes, and most conspicuously, fragmented processes. The latter probably represent the most advanced stage of cytoplasmic deterioration affecting microglia, and we have used the term "cytorrhexis" to describe specifically microglial cytoplasmic fragmentation (Streit, Xue, Tischer, & Bechmann, 2014). Although at the light microscopic level individual cytoplasmic fragments appear to be completely separated from one another, electron microscopy has revealed that some fragments continue to be connected via very thin cytoplasmic bridges (Tischer et al., 2016). This suggests that many dystrophic cells may still be viable, especially since nuclear morphology appears unaffected by cytorrhexis. The initial discovery of

microglial dystrophy showed that its incidence increased with aging, and thus it was postulated that microglial dystrophy represents a morphological manifestation of cell senescence (Streit et al., 2004). Earlier studies by Samorajski (Samorajski, 1976) had shown that among glial cells microglia reveal the most significant alterations with aging in humans, notably accumulation of lipofuscin pigment. Lipofuscin accumulation in aging microglia also occurs in rodents (Streit & Xue, 2010; Xu et al., 2008) but dystrophy is not apparent in aged rodent microglia. There is evidence to suggest that acute intoxication with manganese can induce dystrophy in nonhuman primates (Verina, Kiihl, Schneider, & Guilarte, 2011).

Because microglial dystrophy was linked to aging, an immediate question arose concerning its prevalence in aging-related neurodegenerative diseases, notably AD and other human tauopathies. Our published work has shown that in advanced AD (Braak Stages V and VI), as well as in Down syndrome, microglial dystrophy is widespread and is frequently colocalized with NFD (Streit et al., 2009; Xue & Streit, 2011). Therefore, microglial dystrophy increases as NFD increases, and both of these degenerative processes are driven by aging (Figures 1 and 3). Subsequently, findings from other laboratories have reported reductions in microglial process lengths and arborizations occurring with aging and in AD (Davies, Ma, Jegathees, & Goldsbury, 2017), and most recently a loss of healthy microglia (Paasila, Davies, Kril, Goldsbury, & Sutherland, 2019). These results dovetail with earlier studies showing widespread microglial apoptosis in AD brain (Jellinger & Stadelmann, 2000; Lassmann, Schmied, Vass, & Hickey, 1993; Sugaya, Reeves, & McKinney, 1997; Yang et al., 1998). Thus, the big picture emerging is that both microglial and neuronal degeneration progress gradually, and in parallel with aging and with preclinical development of LOAD. This implies substantial microglial malfunction (Hickman, Allison, & El Khoury, 2008; Mhatre, Tsai, Rubin, James, & Andreasson, 2015), which is supported by the fact that phagocytosis of degenerating neurons by microglia is not detectable histopathologically in advanced LOAD or Down syndrome, and that phagocytosis of Aβ by blood monocytes from AD patients is defective (Fiala et al., 2005; Fiala, Cribbs, Rosenthal, & Bernard, 2007). It seems clear that impairments in CNS innate immune function play a major role in the onset and progression of LOAD, perhaps mirroring the general decline in immunological ability that occurs during aging. The fact that microglia in the CNS serve a dual role as both endogenous immune cells and neuroprotective glia supports the thought that microglial malfunction has adverse consequences for neurons. Because microglial dystrophy appears to precede NFD, it may be a key factor in triggering neurodegeneration in the cerebral grey matter (Streit & Xue, 2014).

Interestingly, microglial dystrophy is consistently seen also in the cerebral white matter where its presence appears to be unrelated to the intensity of tau pathology in grey matter. Although microglial dystrophy in white matter confirms ubiquity of microglial deterioration throughout the CNS, it raises questions about underlying biology because of absence of neurons in white matter. Recent work by Safaiyan et al. (2016) illuminates this issue from the perspective of myelin degradation and associated burden on microglial clearance functions. These authors show that in mice age-dependent fragmentation of myelin places a phagocytic burden on microglia causing formation of lipofuscin-like lysosomal inclusions in microglia, a clear indicator of cellular aging and senescence. Accumulation of these inclusions was linked to lysosomal dysfunction and associated with increased expression of MHC-II antigens in microglia. The latter observation explains the well-known fact that microglial MHC-II expression in human brain is greatest in white matter (Hayes, Woodroofe, & Cuzner, 1987), and it also illuminates MHC-II expression from the perspective of cell senescence. Because major histocompatibility complex (MHC) expression was originally observed in the context of microglial activation, its increased expression with aging in humans and other species has been interpreted to indicate increased neuroinflammation (Ogura, Ogawa, & Yoshida, 1994; Perry, Matyszak, & Fearn, 1993; Rogers, Luber-Narod, Styren, & Civin, 1988; Sheffield & Berman, 1998; Streit & Sparks, 1997). In light of what we know now about microglia and associated dysfunction, we would be

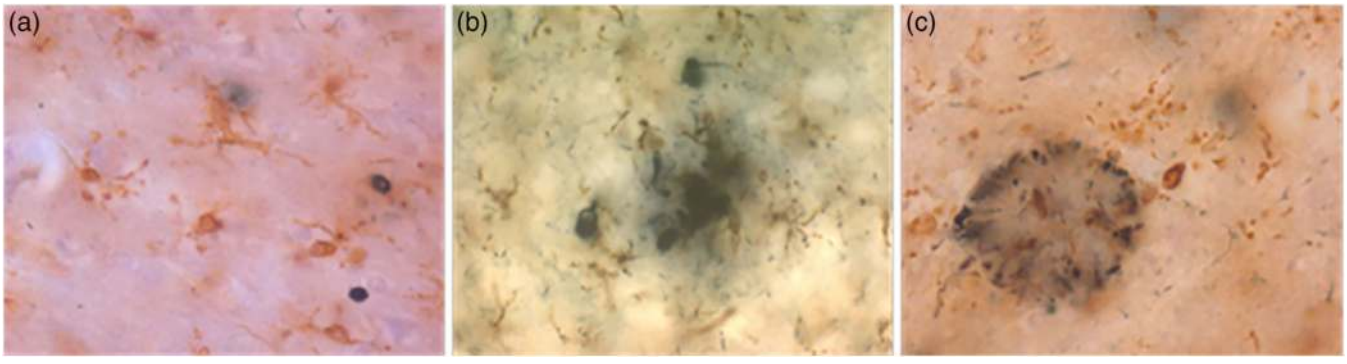

FIGURE 3 Microglia become increasingly dystrophic as neurofibrillary degeneration advances. Double immunohistochemical staining for microglia (Iba1, brown) and phospho-tau (AT8, black) in three individuals at Braak Stages III (a), IV (b), and V (c). The subject in panel (a) was not cognitively impaired, but subjects in (b) and (c) had clinical dementia. Microglia in (a) remain largely intact and are only beginning to show cytoplasmic fragmentation, a hallmark feature of dystrophy. Tau pathology is moderate and evident in a few neurofibrillary tangles. In contrast, microglia in (b) and (c) are highly dystrophic showing extensive fragmentation and are seen in association with neuritic plaques (black). Seventy-three-year-old female in (a); 87-year-old male in (b); 89-year-old female in (c)

inclined to re-interpret age-related increases in MHC expression as a sign of cell senescence rather than of increased inflammation. Thus, microglia in cerebral white matter may age more rapidly than those in the grey matter.

4 | MICROGLIAL DYSTROPHY IS PIVOTAL AND LIKELY CAUSED BY OXIDATIVE STRESS

The discovery of microglial dystrophy has offered an alternative to the long-held view that chronic neuroinflammation (microglial activation) is responsible for NFD in LOAD (Streit, 2002, 2004; Streit et al., 2004). Astonishingly, despite the fact that microglial activation in AD was always known to occur in response to amyloid (McGeer, Itagaki, Tago, & McGeer, 1987), microglial activation was interpreted as a detrimental reaction directed toward neurons without compulsory evidence to support that notion (McGeer & McGeer, 2001). Today, with the benefit of two decades of hindsight, we know that microglial activation does not cause or aggravate NFD. We also know that treatment with anti-inflammatory drugs in clinical trials does not halt the aging-related progression of neurodegeneration and cognitive decline, and thus it is clear that NFD in AD has been frequently misrepresented as a condition characterized by an inflammatory etiology (Streit, 2010). Although there is an inflammatory component to AD, neuroinflammation in LOAD represents a very focal and targeted response of microglia to abnormal extracellular amyloid deposits that occurs late during preclinical LOAD when NFD is already well established (Braak et al., 2011; Streit et al., 2018). Moreover, microglial activation (neuroinflammation) triggered by amyloid formation may not be as chronic as commonly thought, because our work shows that even amyloid plaque-associated, activated microglia undergo dystrophic degeneration (Streit et al., 2009, 2018). These observations suggest that immune exhaustion rather than chronic inflammation is more consequential in terms of LOAD pathogenesis, and thus future therapeutic strategies should perhaps be guided by this insight. However, in order to devise meaningful approaches toward treatment or prevention, we need to understand the factors that drive microglial senescent degeneration, one of which appears to be aggregated amyloid, as discussed.

Another, potentially very important factor is iron. Although it has been known for many years that increased levels of free iron in the brain are associated with neurodegeneration (R. J. Castellani et al., 2012; Honda, Casadesus, Petersen, Perry, & Smith, 2004; M. A. Smith & Perry, 1995; M. A. Smith et al., 2010; Zecca, Youdim, Riederer, Connor, & Crichton, 2004), a clear mechanistic explanation (other than neuronal oxidative stress) has been missing. Once again, consideration of microglial dystrophy and the concept of neuron–microglial interactions (Figure 2) offer a plausible and more detailed mechanism for how iron can accelerate development of neurodegeneration. Microglial cells in their efforts to provide a microenvironment supportive of neuronal function will upregulate expression of ferritin in order to sequester excess free iron in the CNS (Lopes, Sparks, & Streit, 2008). In so doing, they are being neuroprotective by preventing or attenuating iron-mediated oxidative damage to neurons. The downside is that iron-sequestering microglia themselves are susceptible to iron-mediated oxidative damage, as evidenced by the fact that many ferritin-positive microglia reveal dystrophic morphologies (Lopes et al., 2008; Simmons et al., 2007). Thus, excess CNS iron further damages microglial cells already exhibiting dystrophy, and in that way exacerbates aging-related microglial degeneration that may contribute to NFD. Furthermore, iron has been linked to the aggregation and oxidation of amyloid (Dong et al., 2003; Head et al., 2001; Lovell, Robertson, Teesdale, Campbell, & Markesbery, 1998), which also contributes to progression of microglial dystrophy. Thus, free iron and amyloid together create a toxic brew that greatly increases oxidative stress on all brain cells, including microglia (Chiziane et al., 2018).

As mentioned, dystrophic microglia are absent in the brains of aged wildtype rodents, and are also not found in transgenic mouse AD models. However, in prior work with a rodent model of motor neuron disease, the $SOD1^{G93A}$ transgenic rat, we did encounter widespread presence of dystrophic microglia during end stage disease (Fendrick, Xue, & Streit, 2007). These animals develop CNS pathology in three identifiable stages, presymptomatic, early symptomatic (onset), and late symptomatic (end stage). The early symptomatic stages of motor neuron disease in this model are characterized by massive microglial activation in the spinal cord ventral grey matter, but this neuroinflammatory response wanes during end stage disease when microglia transition from activated to dystrophic cells and the spinal cord grey matter becomes inundated with fragmented microglia (Fendrick et al., 2007; Streit & Xue, 2009). Thus, there is a parallel situation to what we have observed in LOAD, namely, that microglial activation occurring in response to amyloid eventually converts to microglial dystrophy (Streit et al., 2018), illustrating how immune activation can lead to immune exhaustion in pathological situations. The fact that this transition from activation to dystrophy occurs in rats bearing a Cu/Zn superoxide dismutase mutation strongly suggests that genetic defects in antioxidant enzymes contribute to microglial dystrophy, and that dystrophy is therefore likely caused by oxidative damage. Additional evidence in support of oxidative damage comes from electron microscopic studies in the $SOD1^{G93A}$ transgenic rat showing that dystrophic microglia are marked by severe mitochondrial abnormalities, such as flocculent densities, swelling, and bizarrely shaped mitochondria (Streit & Xue, 2013). These observations are shifting attention from being focused primarily on neuronal oxidative damage (R. Castellani et al., 2002) toward the possibility that microglial oxidative damage also plays a major role in neurodegeneration. Although microglia are known for their strong antioxidative potential characterized by high levels of glutathione and numerous antioxidative enzymes, such as dismutase, catalase, glutathione peroxidase and others (Dringen, 2005), it appears that this potential becomes rapidly exhausted in advanced neurodegenerative diseases.

Oxidative stress and damage associated with aging are not only inevitable but also cumulative, and it is conceivable that neurodegenerative diseases develop once oxidative damage becomes so great that even cells with superb antioxidative potential, such as microglia, lose their resilience. An example of a scenario where a temporary, but sudden rise in oxidative stress causes microglial dystrophy can be

found in experimental strokes performed in young rodents. A most recent study shows presence of microglial dystrophy and microglial cell loss in the early ischemic core created by permanent occlusion of the middle cerebral artery, MCAO (Otxoa-de-Amezaga et al., 2019). Although these authors discuss their findings primarily in the context of microglial phagocytosis of neutrophils, our own studies of microglia after transient MCAO in rats show that presence of fragmented microglia immediately after ischemia is short-lived and that these dystrophic cells are replaced with activated microglia 2 days after ischemia. We attribute this replacement to the fact that the ischemic animals were young adults capable of generating new microglia quickly to compensate for the initial loss. Nevertheless, the initial dystrophy occurring shortly after ischemia induction is most likely due to the enormous oxidative stress produced by the experimental stroke. A concomitant disruption of the blood brain barrier also triggers expression of ferritin immunoreactivity in the dystrophic microglia (Figure 4). These findings seem to show a reiteration of parts of the same process that occurs during LOAD pathogenesis and they offer support for our hypothesis that dystrophy is largely the result of oxidative stress. Although ferritin expression in microglia shortly after experimental stroke may be triggered by iron leaking into the CNS parenchyma via a damaged blood brain barrier, additional factors are likely to also contribute to iron accumulation in the aging and AD human brain. The findings can help explain why blood–brain barrier disruption and cardiovascular disease are likely major contributors to dementia (Montagne et al., 2015; Zipser et al., 2007).

5 | MICROGLIA AND Aβ

The amyloid cascade theory (Hardy & Selkoe, 2002) has dominated AD research for decades, but has yielded no tangible results in terms of effective preventions or treatment (Herrup, 2015; Joseph et al., 2001; Morris, Clark, & Vissel, 2014). Based primarily on the genetics of rare conditions, such as EOAD and Down syndrome, where there are penetrant genetic mutations and duplications of amyloid precursor protein (APP) alleles, the amyloid cascade theory states that Aβ is responsible for subsequent NFD by triggering microglial activation and concomitant production of neurotoxic inflammatory mediators. This has resulted in numerous approaches directed toward Aβ removal and toward reducing inflammation, most developed in transgenic mouse models overexpressing human APP. None of these approaches

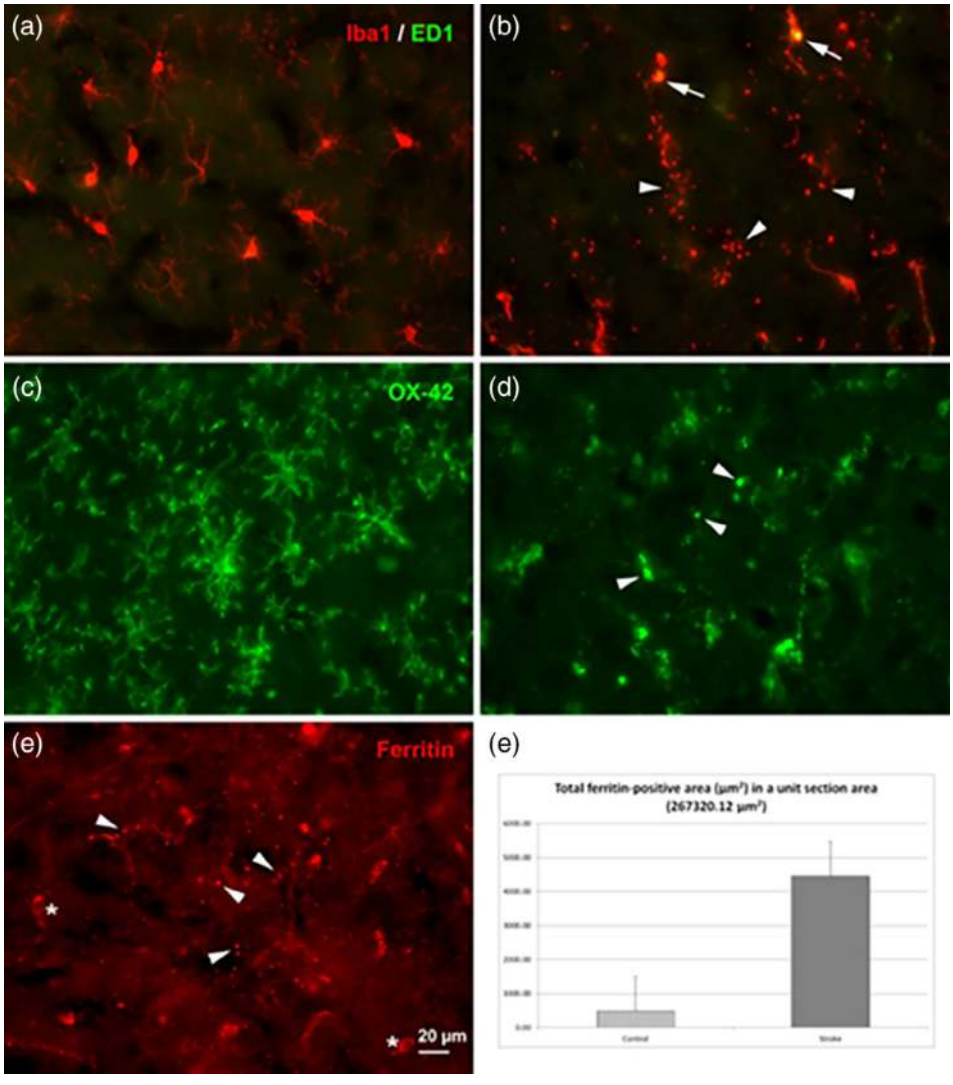

FIGURE 4 Microglial dystrophy (fragmentation) is detectable 24 hr after MCAO with different microglial markers. (a, c) Contralateral somatosensory cortex shows presence of normal, ramified microglial cells with Iba1 and OX-42 immunostaining. Ipsilateral ischemic cortex shows presence of numerous microglial fragments with Iba1, OX-42, and antiferritin labeling (arrowheads in [b], [d], and [e]). Double-label immunostaining with Iba1/ED1 (a, b) shows no ED1 immunoreactivity in control and minimal ED1 in ischemic tissue (arrows in [b]), indicating relative absence of brain macrophages at this early survival time. Ferritin immunolabeling is strongly upregulated in the ischemic cortex and is present in both oligodendrocytes (asterisks in [e]) and in cellular fragments derived from cytorrhectic microglial cells (arrowheads). The quantitative difference in ferritin immunoreactivity between the ipsilateral ischemic and the contralateral control cortex is shown in panel (f). Scale bar in (e) applies to (a)–(e)

has proven effective for halting or slowing neurodegeneration in human clinical trials. These negative results are not surprising given that, (a) transgenic AD mouse models do not recapitulate the sequential development of lesions occurring in human AD; (b) it cannot be rationally assumed that mice poorly modeling rare genetic disorders, such as EOAD or Down syndrome (DS), will yield therapies effective for the common sporadic form of AD that affects humans (i.e., LOAD). For those interested in trying to understand LOAD pathogenesis, it seems the best way to proceed is to continue studying humans. There is no rodent model for LOAD.

When it comes to microglia, the only obvious feature transgenic amyloid mouse models have in common with human AD patients is the response to amyloid—microglia respond to amyloid deposits by clustering around them and attempting phagocytic removal of the insoluble substance. NFD does not develop in transgenic mice overexpressing human APP and showing microglial activation, and microglia do not undergo dystrophy. The use of young or middle-aged mice to model AD essentially takes off the table the most important AD risk factor, which is aging. It is therefore no surprise that aging-related neuronal and microglial degeneration do not happen in these animals. Even if some of the mouse models did develop microglial dystrophy, it would only be momentary because the young mice would be able to quickly replace degenerated microglia with new ones, as suggested by the stroke findings mentioned above (Figure 4). The microglial response to amyloid also seems to be much stronger in mice than in humans (Navarro et al., 2018), speaking to the existence of a robust and vital microglial population in these animals and standing in stark contrast to the fragility of microglia that exist in aged human brains. Lastly, as discussed before (Streit et al., 2014), it is obvious that mice simply do not live long enough to develop neuronal and glial degeneration in the same way humans do, and are therefore unlikely to ever yield authentic AD models.

The excitement surrounding neuroinflammation in AD, and by proximity, other neurodegenerative diseases has been overstated, and has misrepresented neuroinflammation as a causative etiology for neurodegeneration. Treatment with nonsteroidal anti-inflammatory drugs has not slowed the progression of neurodegeneration in humans (Breitner et al., 2011; ADAPT Research Group et al., 2008; Martin et al., 2008). We have previously discussed the reasoning and data that have contributed toward this notion and concluded that the supporting evidence is weak at best (Streit, 2010). The thought that AD is a condition with an inflammatory etiology can be traced back to the earliest descriptions of microglial clusters forming around amyloid deposits. What most researchers failed to realize and take into consideration is the extraordinary specificity of the microglial reaction to amyloid, namely, that inflammation is spatially confined only to the immediate vicinity of amyloid. Microglia located in the neuropil between amyloid plaques are nonactivated and ramified (Prokop, Miller, & Heppner, 2013; Streit et al., 2018). This kind of highly localized neuroinflammation is consistent with a targeted cellular response to a foreign body (amyloid) by showing microglia acting as macrophages wanting to clear out an undesirable, insoluble substance. The idea that attempted clean-up by macrophages causes widespread neurodegeneration throughout the brain is bizarre and speculative, but in the search for a culprit activated microglia have been promoted nevertheless (Heneka et al., 2015; Kempermann & Neumann, 2003). Similarly, proinflammatory cytokines and chemokines have been falsely portrayed as neurotoxic substances that cause NFD in AD without direct evidence to support this claim. Recent studies on age/AD-related gene expression did not reveal proinflammatory cytokines to be increased (Erraji-Benchekroun et al., 2005; Mathys et al., 2019; Soreq et al., 2017). However, cell senescence is associated with a phenomenon known as senescence-associated secretory phenotype, senescence associated secretory phenotype (SASP) (Campisi & d'Adda di Fagagna, 2007), which refers to the fact that aging cells alter their production of cytokines. Given the large extent of cell senescence that characterizes LOAD it is highly likely that dystrophic microglia develop a SASP, which may lead to increased production of various cytokines in the CNS. The concept of SASP is compatible with the idea of dementia being the result of microglial senescent malfunction as a central event in its pathogenesis. It may well apply to other aging-related neurodegenerative diseases (Bachstetter et al., 2015; Streit & Xue, 2016).

6 | CONCLUSIONS

LOAD, the common form of AD, is without a doubt an aging-related condition, and aging is inextricably linked to oxidative stress and damage. We have developed and promulgated the microglial dysfunction hypothesis of AD (Streit, 2004) because it takes these known facts into account. The brain's immune system is subject to aging-related decline just as peripheral immunity weakens with aging. The difference is that brain immune cells are also neuron-supporting glia and when they undergo aging-related degeneration both their immunological and neuroprotective abilities decline gradually, and this produces the gradually progressive neurodegeneration that characterizes LOAD. Efforts to rejuvenate or otherwise strengthen microglial vitality would seem like a good generic strategy toward reducing the incidence or LOAD and other dementing disorders.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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