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Review - Part of the Special Issue: Alzheimer's Disease - Amyloid, Tau and Beyond

Microglial dysfunction in brain aging and Alzheimer's disease

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ABSTRACT

Microglia, the immune cells of the central nervous system, have long been a subject of study in the Alzheimer's disease (AD) field due to their dramatic responses to the pathophysiology of the disease. With several large-scale genetic studies in the past year implicating microglial molecules in AD, the potential significance of these cells has become more prominent than ever before. As a disease that is tightly linked to aging, it is perhaps not entirely surprising that microglia of the AD brain share some phenotypes with aging microglia. Yet the relative impacts of both conditions on microglia are less frequently considered in concert. Furthermore, microglial "activation" and "neuroinflammation" are commonly analyzed in studies of neurodegeneration but are somewhat ill-defined concepts that in fact encompass multiple cellular processes. In this review, we have enumerated six distinct functions of microglia and discuss the specific effects of both aging and AD. By calling attention to the commonalities of these two states, we hope to inspire new approaches for dissecting microglial mechanisms.

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1. Introduction

In the original 1907 article in which he first described the disease that would come to bear his name, Alois Alzheimer observed an inflammatory component to the diseased brain, writing that the glia had developed "numerous fibers" and "adipose saccules" (translated by ref. [1]). Over 100 years later, it is now well accepted that Alzheimer's disease is marked by neuroinflammatory events involving glia, including astrocytes and, in particular, microglia. A recent PubMed search with the key words "microglia", "Alzheimer's disease", and the Boolean connector "AND" returned 2397 citations. Interestingly, the first of these PubMed articles, published in 1976, is a review article of which the primary focus is not in fact Alzheimer's disease but rather an assessment of how the human brain responds to aging [2]. Alzheimer's is, after all, a disease of the aged brain. While aging mechanisms and microglial activity clearly play some role in

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Alzheimer's disease, the intersection of these two components has not been thoroughly explored. Microglia also undergo striking morphological and molecular changes with age, yet our understanding of the consequences of these changes within simply normal aging is also limited. In this review, we discuss the significance of microglial aging in Alzheimer's disease (AD). We begin by first reviewing certain genetic factors that have been of particular interest recently in the AD field, and which specifically implicate microglia. We then examine how specific microglial functions are altered in aging and AD, and whether there may be mechanistic connections between these altered states.

2. What are the typical functions of microglia in the adult brain?

Before we attempt to foray into a discussion of what may go wrong in microglial physiology during aging and AD, it will be helpful to first define what the expected role of microglia should be in the normal, healthy adult brain. Since their discovery nearly 100 years ago, and indeed as suggested in their very definition as the innate immune cells of the central nervous system, it is of general consensus that microglia exist in the adult brain as a protective agent. How do microglia protect and defend the brain from pathological insult? Here, we briefly introduce the major physiological effector functions of microglia, which for the purposes of this review we place into six broad categories: (1) Proliferation; (2) Morphological transformation; (3) Motility and migration (4) Intercellular communication; (5) Phagocytosis; and (6) Proteostasis (Fig. 1). In the following sections, we will consider both aging and AD microglial phenotypes within each of these main effector functions. We have termed these changes the "hallmarks of microglial aging", a concept that we borrow from an influential review by Lopéz-Otín et al. [3] who have attempted to identify and categorize the "hallmarks of aging". Our Fig. 1 is also modeled on a schematic in this review.

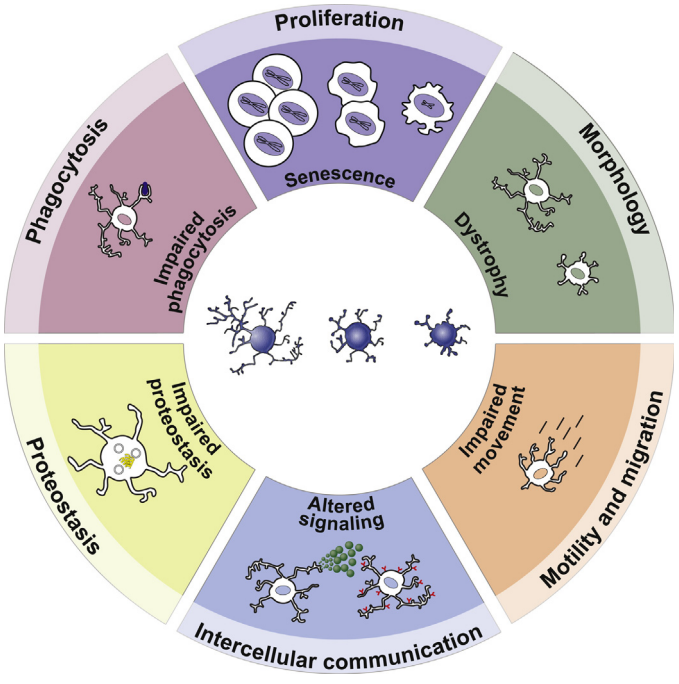

Fig. 1. The hallmarks of microglial aging. The six major effector functions/phenotypes of microglia that are the focus of this review are highlighted at the outer ring of this schematic: proliferation, morphology, motility and migration, intercellular communication, proteostasis, and phagocytosis. Within the inner ring of the circle we describe the effects of aging on each of these functions.

The execution of microglial responses to injury or disease via the above effector functions has collectively been termed "microglial activation", though it has been argued that this terminology incorrectly implies that microglia in the healthy, adult CNS are latent bystanders [4]. In fact, microglia are quite dynamic cells even in an apparently healthy brain, as exemplified through studies of motility and migration functions. *In vivo* two-photon microscopy studies several years ago revealed that microglia endlessly sample the extracellular space by extending numerous ramified processes, which seems to enable the cells to monitor the brain parenchyma, maintain tissue homeostasis, and react rapidly to brain injury or insult [5,6].

Though microglial activation may protect the brain through much of life, the efficacy of these functions seems to deteriorate with age. However, the effects of age on microglia do not necessarily always present as a loss of these functions. The hallmarks of microglial aging may also sometimes be characterized as dysfunctional and even hyper-reactive responses. The immune system in general undergoes an imbalanced shift toward a proinflammatory status with aging, a concept termed "inflammaging" [7]. If this is also true for microglia, then these cells may shift from a protective role in youth to a state in which some protective mechanisms are lost and others are even detrimental to brain health. Systemic infections and inflammation also activate microglia and drive and exacerbate neurodegeneration [8,9] (and reviewed in refs. [10,11]). As such, it has been suggested that microglia may age, in part, as a result of cumulative activation in response to systemic infections over the course of a lifetime (reviewed in refs. [11,12]). Thus, systemic inflammaging itself could also drive microglia aging, priming the cells to eventually react with exaggerated responses that actually contribute to neurodegeneration (see Graphical Abstract). Accordingly, it may be that AD phenotypes represent an exaggerated state of microglia dysfunction beyond that observed during normal aging. AD-associated genetic variations could also exacerbate these age-related changes, along with other predisposing factors such as cigarette smoking, high blood pressure, and type 2 diabetes [13]. Obesity, for example, has been linked to AD and is promoted by aging (reviewed in ref. [14]). Adipocytes can produce proinflammatory factors, and in the obese state adipose tissue may be infiltrated by immune cells (reviewed in ref. [15]). Recent studies have also found that obesity stimulates microglia and enhances the recruitment of peripheral monocytes to the CNS [16,17]). Obesity could therefore also contribute to low-grade chronic inflammation peripherally and within the brain. Thus while aging and AD microglial phenotypes are by no means equivalent, chronic stimulation over time, combined with certain genetic mutations and other risk factors, could push aging microglia towards an AD state.

3. Genetic evidence that microglia are important in Alzheimer's disease

In the past year, a number of studies have brought more attention to microglia in AD research than ever before by demonstrating strong genetic implications for microglial molecules and the immune system in general. Most recently, a genome-wide association study (GWAS) identified a novel association for late onset Alzheimer's disease (LOAD) in the *HLA-DRB4-DRB1* region (encoding for major histocompatability complex, class II, DRβ4 and DRβ1, respectively) [18]. Earlier this year, Griciuc et al. [19] demonstrated that microglial functions in AD may be modified by *CD33*, another gene with a role in immune response [20] that has been linked to AD in some (though not all) recent GWAS [18,21–23]. And perhaps most prominent were the two GWAS published concurrently in the *New England Journal of*