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Review Article

The roles of inflammation and immune mechanisms in Alzheimer's disease

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Abstract The Alzheimer's Association's Research roundtable met in April 2015 to explore the role of neuroinflammatory mechanisms in the progression of Alzheimer's disease (AD). The ability of innate immune cells, particularly microglia and astrocytes, to mediate neuroinflammation in AD has been implicated as a significant contributor to disease pathogenesis. Adaptive immunity, which plays an important role in responding to injury and some diseases of the central nervous system, may contribute to neuroinflammation in AD as well. Communication between the central and peripheral immune systems may also be important in AD. An increased understanding of the physiology of the innate immune system may aid the identification of new therapeutic targets or mechanisms. The development of predictive animal models and translatable neuroinflammation biomarkers for AD would also facilitate the advancement of novel treatments for innate immunity. Important challenges impeding the advancement of new therapeutic agents and strategies to overcome them were discussed.

Keywords: Microglia; Astrocyte; Innate immunity; Neuroinflammation; Alzheimer's disease; Adaptive immunity

1. Introduction

When Alois Alzheimer peered through a microscope at histologic sections of Auguste D's brain over a century ago, he saw not only the characteristic amyloid plaques

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and neurofibrillary tangles that have become the hallmarks of Alzheimer's disease (AD), but also glial cells clustered around the plaques [1]. These innate immune cells that mediate neuroinflammation in AD—primarily microglia and astrocytes—are now thought to play an important role in disease pathogenesis, possibly providing novel therapeutic targets that may ultimately be as important as the amyloid and tau proteins that make up the plaques and tangles themselves [2]. Adaptive immunity also plays an essential role in responding to disease or injury in the central nervous system (CNS), although adaptive immune-system driven effects, mediated by T and B cells, appear at present to be far more important in neuroinflammatory diseases such as multiple sclerosis (MS) than in AD, where innate immunity appears to drive neuroinflammation.

In the early 2000s, the finding that individuals receiving various nonsteroidal anti-inflammatory drugs (NSAIDs) for diverse systemic inflammatory disorders had a reduced incidence and prevalence of AD was noted fairly consistently in a number of epidemiologic studies [3]. This observation in part led to trials of NSAIDs in both mild cognitive impairment (MCI) and AD dementia; however, the results of these studies were negative, dampening further investigation of this therapeutic strategy for almost a decade. Interest in the role of neuroinflammation in AD has increased dramatically in recent years, however, driven by important findings in neurobiology and genetics, and the topic has been the focus of several recent international symposia and reviews [2,4,5]. In April 2015, the topic was addressed by the Alzheimer's Association's Research roundtable, a partnership of experts from academia, industry, and regulatory agencies. Participants at the meeting examined what is currently known, including research gaps, therapeutic opportunities, and barriers for clinical development. This article aims to contribute to the evolving understanding of inflammatory and immune mechanisms in AD and their potential as therapeutic targets by summarizing key aspects of those discussions.

2. Cells and mediators of inflammation in neurodegenerative disease

There is increasing appreciation that AD pathogenesis and progression are not a consequence solely of neuronal dysfunction but also involve glia-dependent neuroinflammatory mechanisms. Microglia and astrocytes are the major glial cell types that respond to disease stressors by innate immune responses such as production and release of inflammatory mediators. In addition, perivascular macrophages and peripheral myeloid cell populations that can enter the diseased brain also participate in neuroinflammatory signaling. If not kept in check, these neuroinflammatory responses can contribute to pathology and disease progression. Microglia were historically viewed as mainly protecting the brain from exogenous insults, and astrocytes were seen as primarily providing nutritive and structural support for neurons. However, both cell types are now known to play multiple roles in brain health. During neurodegenerative disease processes their function may be adversely affected through inflammatory signaling responses.

2.1. Microglia

Microglia, derived from primitive hematopoietic cells in the yolk sac, seed the brain during fetal development, expand in numbers dramatically after birth, and are self-renewing throughout adult life. They are the resident phagocytes of the CNS and though sharing many properties with peripheral tissue macrophages and monocytes, they are autonomous from peripheral monocytes, which normally do not enter the brain. Although phagocytosis is perhaps their best known property, recent research has revealed multiple roles and distinct functions for microglia in development and adult life. In development, they remove excess synaptic connections and modulate circuit development—a role that is critical for proper brain development [6].

In the adult brain, microglia play an important role in regulating synaptic plasticity and remodeling neuronal circuits. Another key function of microglia is to act as sentinels, surveilling the parenchyma for danger signals, especially the intrusion of pathogens, and contribute to homeostasis. This capacity is facilitated by their numerous extensions (filopodia) that maintain close contact with neurons, perivascular cells, and astrocytes. They may also participate in neurogenesis and synaptogenesis in brain regions where this occurs, as well as in the removal of debris resulting from (non-neuronal) apoptotic cell death [6]. Importantly for AD, given its preponderant onset in late-life, aging-associated changes in the quality of these functions have been increasingly appreciated as well.

In the face of injury and neurodegenerative disorders, however, microglia assume a radically different phenotype. They are rapidly activated in response to acute injury, for example, trauma or stroke, becoming "nurturers" and "warriors" as well as sentinels [7]. This phenotypic alteration involves both chemical and morphologic changes. Morphologically, filopodia retract and microglia can become actively phagocytic, participating in the resolution of tissue damage. However, process retraction by microglia will eliminate their ability to monitor synaptic activity, thereby compromising the microglial contribution to network homeostasis. The ability of microglia to change their phenotype dramatically on activation has led to their being referred to as a "double-edged sword."

In AD brain, microglia (or peripherally-derived macrophages) have long been noted to cluster around neuritic plaques but appear to have a loss of phagocytic capacity and possibly a gain of toxic function as well [8,9]. It is important to note that AD is a very slow process, with the interval between the onset of amyloid β (Aβ) deposition (the leading hypothesized etiologic culprit) and dementia being approximately 20 years [10]. Also, as far as is known, the pathophysiological processes are endogenous; therefore,