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Review

Myeloid Cells in Alzheimer's Disease: Culprits, Victims or Innocent Bystanders?

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Several recent genome-wide association studies (GWAS) in patients with neurodegenerative disorders have shed new light on the brain immune system, suggesting that it plays a pivotal role in disease pathogenesis. Mononuclear phagocytes are blatantly involved in Alzheimer's disease (AD) of the central nervous system (CNS), but the specific functions of resident microglia, perivascular or meningeal macrophages, and circulating myeloid cells have not yet been fully resolved. Next-generation sequencing, high-throughput immune profiling technologies, and novel genetic tools have recently revolutionized the characterization of innate immune responses during AD. These studies advocate selective and non-redundant roles for myeloid subsets, which could be a target for novel disease-modifying therapies in AD.

Introduction

Age-related processes in the brain can be considered as a crime scene: individuals on the sidewalk ('neurons') chatting with each other away from the curb ('blood–brain barrier', BBB) are suddenly attacked by cruel predators ('insoluble amyloid') thereby causing the death of the individuals ('neurons' again). This dramatic act involves numerous participants such as eye-witnesses ('astrocytes'), local guards ('microglia, macrophages') and new arrivals from the street ('blood-derived monocytes'). Whether all myeloid cells (microglia, macrophages, monocytes) involved in the drama of neurodegeneration act as victims, culprits, or guiltless spectators is still uncertain. In this review we summarize our current view of myeloid cells as brain-specific immune cells and highlight recent developments in the field, with a focus on their function in AD.

The Family of Myeloid Cells in the Brain

Myeloid cells in the CNS encompass a diverse group of mononuclear cells that mediate the local immune response in the CNS during development, health, and particularly neurodegenerative diseases [1]. As such, they are crucial effectors and regulators of inflammation and innate immune responses, the immediate arm of the immune system. They all have a common origin in hematopoietic stem cells and develop along distinct differentiation pathways in response to internal and external signals.

The healthy CNS hosts several myeloid populations. In addition to the parenchymal microglia, this family includes perivascular, meningeal, and choroid plexus macrophages [2] (Figure 1). Upon breakdown of the BBB that may occur during neurodegenerative disorders, blood-derived myeloid cells, especially monocytes, can enter the affected brain. On the basis of their differential expression of the chemokine (C-C motif) receptor CCR2 and the surface molecule Ly-6C, inflammatory monocytes ($CCR2^{+}Ly\text{-}6C^{hi}$), which are highly mobile and rapidly recruited to the

Trends

Myeloid cells differ in their kinetics (long-lived versus short-lived) and localization. This should be taken into account when targeting myeloid cells during neurodegenerative diseases.

Microglia are recruited to and cluster around newly formed Aβ plaques, indicating that they are not directly involved in the initial stages of amyloid plaque formation.

Microglia are phagocytic cells in the brain equipped with several receptors that play a role in the clearance of Aβ. Downregulation of these immune-receptors results in compromised phagocytotic capacity of microglia.

Morphological alterations such as dystrophic (senescent) microglia have been observed in the aged human and AD brain. Emerging data suggest that microglia deteriorate with age and are dysfunctional during AD.

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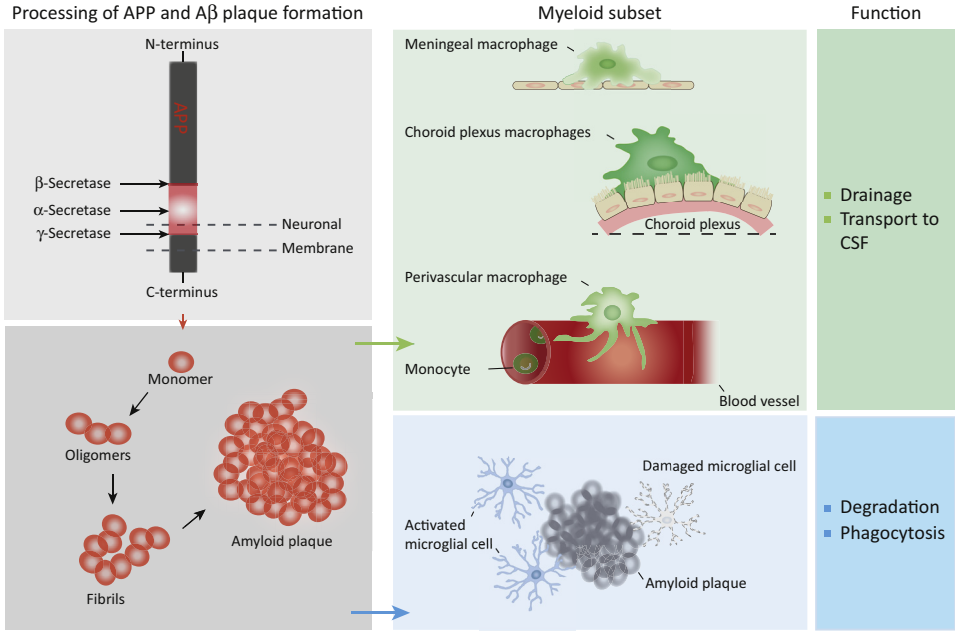

Figure 1. APP is Processed Either by α-, or β-, and γ-secretase. The β-secretase pathway constitutes the first step in the formation of the Aβ peptide (top left box). Aβ monomers assemble into oligomers, fibrils, and finally mature into amyloid plaques (bottom left box). Immune cells such as monocytes and perivascular macrophages can approach Aβ and clear Aβ by shuttling it out via the perivascular space (green upper middle box). Under some circumstances microglia that are already present in the brain are able to degrade or phagocytose Aβ (blue bottom middle box). Abbreviation: APP, amyloid precursor protein.

inflamed brain [3,4], can be distinguished from patrolling monocytes (CCR2^{-}Ly-6C^{lo}), which are larger in size and are thought to be important for patrolling along blood vessels [5,6]. Despite the fact that all these myeloid populations hosted by the CNS during neurodegenerative conditions share numerous myeloid- and macrophage-specific markers [such as ionized calcium-binding adapter molecule (IBA1/AIF1), F4/80 antigen, also known as EMR1 (EGF-Like module receptor 1)/ADGRE1, and the fractalkine receptor CX3CR1 (chemokine C-X3-C motif receptor 1)] and exhibit similar immune regulatory functions (such as local immune surveillance and removal of debris), recent results suggest that they have clearly distinct origins and cellular dynamics [7,8].

The precise source of microglia and other myeloid cells in the brain has been a matter of controversy for decades. In 2010 it was discovered that, under homeostatic conditions, the microglia population is generated from immature yolk-sac precursors rather than from adult bone marrow (BM)-derived precursors that are, by contrast, the source of circulating monocytes [9,10]. In a more detailed study, it was shown that adult microglia originate from non-committed c-Kit^{+}F4/80^{-}CX3CR1^{-} erythromyeloid progenitors in a c-Myb-independent manner during primitive hematopoiesis (via c-Kit^{lo} yolk-sac populations and immature c-Kit^{-}F4/80^{hi}CX3CR1^{+} macrophage populations, termed A1 and A2, respectively) [11,12]. At later stages, when fetal liver-derived monocytes are released into the circulation and definitive hematopoiesis yields myeloid cells, the brain already seems uncoupled from the circulation by the closing BBB. The forming CNS is thus established as a defined and restricted environment that excludes any substantial immigration of peripheral myeloid cells under non-diseased conditions [13].

Furthermore, results of parabiosis experiments, which involve the surgical fusion of the blood circulation of two animals, clearly demonstrated that BM-derived cells such as monocytes do not

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