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Review

The endocytic pathway in microglia during health, aging and Alzheimer's disease

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ABSTRACT

Microglia, the main phagocytes of the central nervous system (CNS), are involved in the surveillance and maintenance of nervous tissue. During normal tissue homeostasis, microglia migrates within the CNS, phagocytose dead cells and tissue debris, and modulate synapse pruning and spine formation via controlled phagocytosis. In the event of an invasion by a foreign body, microglia are able to phagocytose the invading pathogen and process it proteolytically for antigen presentation. Internalized substrates are incorporated and sorted within the endocytic pathway and thereafter transported via complex vesicular routes. When targeted for degradation, substrates are delivered to acidic late endosomes and lysosomes. In these, the enzymatic degradation relies on pH and enzyme content. Endocytosis, sorting, transport, compartment acidification and degradation are regulated by complex signaling mechanisms, and these may be altered during aging and pathology. In this review, we discuss the endocytic pathway in microglia, with insight into the mechanisms controlling lysosomal biogenesis and pH regulation. We also discuss microglial lysosome function associated with Alzheimer's disease (AD) and the mechanisms of amyloid-beta (Aβ) internalization and degradation. Finally, we explore some therapies currently being investigated to treat AD and their effects on microglial response to Aβ, with insight in those involving enhancement of lysosomal function.

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1. Introduction

The mononuclear phagocytic cell population in vertebrates includes monocytes, macrophages, dendritic cells, Langerhans cells, microglia and osteoclasts (Arandjelovic and Ravichandran, 2015 Nakamichi et al., 2013). Phagocytes are responsible for the clearance of infectious agents, dead cells and tissue debris and are involved in immune response. Monocytes circulate in the blood and can enter organs and become macrophages in normal conditions as well as in response to stimuli including infectious agents and inflammatory signals. However, an important fraction of the macrophages is tissue-specific. These tissue-resident macrophages derive from primitive macrophages generated from early *erythro*-myeloid progenitors in the yolk sac, and maintain their presence in tissues by slow self-renewal (Davies et al., 2013; Hoeffel and Ginhoux, 2015). Microglia, the resident macrophages of the CNS, derive exclusively from primitive macrophages in the yolk sac, populate the CNS before and shortly after birth and self-renew locally with a slow turnover rate throughout life (Ginhoux and Prinz, 2015; Gomez Perdiguero et al., 2015; Nakamichi et al., 2013).

Microglia constitute 10–15% of brain cells and play a critical role in tissue surveillance and maintenance of CNS homeostasis. Microglia are very motile within the CNS and engage in the phagocytosis of apoptotic cells and debris, participate in tissue repair, and modulate synapse pruning and spine formation, among other important functions. Microglia also help to initiate the immune response against infectious agents by acting as antigen-presenting cells (Ransohoff and Cardona, 2010).

Generally, phagocytic cells internalize a wide variety of extracellular material via several mechanisms collectively named endocytosis. Internalized material follows branching vesicular transport pathways, and some internalized material is delivered to acidic late endosomes and lysosomes, where degradation occurs. Sorting of internalized substrates and targeting to degradative acidic organelles is regulated by complex sorting mechanisms.

Moreover, as resident CNS phagocytes, microglia play a role in many neurodegenerative diseases. AD, the most common form of dementia, accounts for 60–80% of all cases worldwide. One of the main histopathological hallmarks of AD is the presence of amyloid plaques in specific areas of the brain. However, in the majority of AD cases, it is unclear whether faster production or slower clearance of Aβ species is responsible for plaque accumulation.

In this review, we discuss the endocytic pathway in the context of phagocytic cells, and specifically microglia, with insight into the mechanisms regulating microglial lysosome biogenesis. We also discuss microglial lysosome function in the context of aging and AD, with focus on the various mechanisms of Aβ internalization and degradation. Finally, we explore some therapies currently being investigated to treat AD and their effects on microglial activity and response to Aβ.

2. The endocytic pathway in phagocytic cells

Endocytic processes are involved in the internalization of nutrients, antigen presentation, regulation of cell-surface receptor expression, cellular cholesterol homeostasis, maintenance of cell polarity and removal of pathogens, among other functions (Mukherjee et al., 1997). In the following section we discuss the main endocytic routes in phagocytic cells. Fig. 1 summarizes the various mechanisms of endocytosis in the context of microglia.

2.1. Pinocytosis

Pinocytosis, originally described by Lewis (Lewis, 1931), is a process by which the plasma membrane (PM) forms vesicles that engulf extracellular fluid in a non-selective way. In macropinocytosis, large vesicles (up to 5 μm in diameter) are formed by actin-dependent membrane ruffles whose tips fall back to the PM (Hewlett et al., 1994; Lim and Gleeson, 2011). Fusion of the tips with the PM forms a new vesicle that contains extracellular fluid. Bone-marrow derived macrophages (BMMs) (Norbury et al., 1995), dendritic cells (Sallusto et al., 1995) and microglia (Booth and Thomas, 1991; Fitzner et al., 2011; Mandrekar et al., 2009) are capable of constitutive macropinocytosis. Pinocytotic behavior was described in microglia more than 20 years ago (Booth and Thomas, 1991).

Macropinocytosis allows cells to survey and internalize large amounts of the extracellular milieu in search of cell debris, damaged proteins, apoptotic cells and pathogens, most of which are degraded. For instance, macrophages can internalize up to 200% of their surface area per hour by macropinocytosis (Steinman et al., 1976). Antigens contained in macropinosomes in antigen presenting cells can become associated with major histocompatibility complex (MHC) complexes for antigen presentation (Sallusto et al., 1995). Macropinocytosis has also been associated with pathogen entry (reviewed in (Lim and Gleeson, 2011)).

2.2. Phagocytosis

Phagocytosis is the process by which cells internalize, by vesicular engulfment, large particles (typically ≥5 μm) such as apoptotic cells, foreign bodies and pathogens (Flannagan et al., 2012). Professional phagocytes such as microglia and macrophages are able to migrate to specific areas by chemotaxis and clear foreign bodies by phagocytosis (described in detail in Section 2.6). The phagocytosed particle is recognized by specific receptors on the PM of the phago-

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