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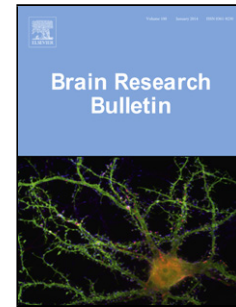
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Emerging Roles of Microglial Cathepsins in Neurodegenerative Disease

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Highlights

- Alzheimer-specific pathological structures cause adverse microglial activation
- Cathepsins B, D and S regulate microglial neuroimmune responses
- Specific inhibitors of cathepsin B may be beneficial in Alzheimer's disease
- Use of cathepsin D and S inhibitors could be limited due to expected side effects
- Use of highly selective cathepsin inhibitors in Alzheimer disease should be explored

Abstract

Alzheimer's disease (AD) is one of the leading causes of dementia, and its prevalence is expected to increase dramatically due to the aging global population. Microglia-driven neuroinflammation may contribute to the progression of AD. Microglia, the immune cells of the central nervous system (CNS), become chronically activated by the pathological proteins of AD including amyloid- β peptides (A β). Such adversely activated microglia secrete mediators that promote inflammation and damage neurons. Cathepsins are proteases that are expressed by all brain cell types, and most of them are found both intra- and extra-cellularly. Microglia express and secrete several different cathepsins, which support various immune functions of microglia, in addition to their involvement in key neuroinflammatory pathways. This review focuses specifically on microglial cathepsins B, D and S, which have been implicated in AD pathogenesis; we identify their roles relevant to microglial involvement in AD pathogenesis. As dysregulated microglial function and neuroinflammation can contribute to AD progression, cathepsins should be considered as potential therapeutic targets for the development of effective AD treatment options. We conclude that the specific inhibition of microglial cathepsin B may lead to neuroprotective outcomes in AD, while the functions of this cysteine protease in neurons appears to be very complex and further studies are required to fully elucidate the pathophysiological role of neuronal cathepsin B. Examination of the CNS roles of cathepsins is

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