The Role of C/EBPβ and IL-18 in Neuroinflammation and Early Motor Dysfunction in Alzheimer's Disease

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Neuroinflammation, beyond a reactive process in Alzheimer's disease (AD), actively drives disease progression, with the NLRP3 inflammasome and its downstream cytokine, Interleukin-18 (IL-18), emerging as key mediators. While IL-18's role in AD pathogenesis remains under investigation, its endogenous inhibitor, IL-18 binding protein (IL-18 BP), presents a potential therapeutic avenue. Utilizing postmortem AD brain tissues and multiple AD mouse models (C/EBPβ transgenic, 3xTG, and 5xFAD), we observed heightened IL-18 signaling and related pro-inflammatory activation concurrent with a deficiency in IL-18 BP in both human and murine AD brains. Notably, hippocampal administration of IL-18 BP in 3xTG mice mitigated neuroinflammation and cognitive decline. Furthermore, we investigated the emerging recognition of early motor dysfunction in AD. We found that the inflammation-regulated transcription factor C/EBPβ accelerates pro-inflammatory cytokine activation and motor impairment in young C/EBPβ transgenic mice. Our analysis of postmortem AD brains and C/EBPβ transgenic mice revealed a compromised locus coeruleus (LC)-to-motor cortex noradrenergic pathway. Mechanistically, C/EBPβ-induced IL-18 activation promoted noradrenergic neuronal death, while norepinephrine (NE) modulated IL-18-induced neuroinflammation via adrenergic receptors. Collectively, these findings underscore the critical role of the C/EBPβ-IL-18 axis in driving both neuroinflammation and early motor dysfunction in AD. The therapeutic efficacy of IL-18 BP in alleviating AD pathology and the mechanistic link between C/EBPβ, IL-18, and noradrenergic degeneration highlight these molecules as promising diagnostic and therapeutic targets, particularly for addressing early-stage motor deficits before extensive cognitive decline.

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