IRAKS MEDIATE MICROGLIAL RESPONSE TO FIBRILLAR AB

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Introduction: Alzheimer's disease is typified by a robust microglial-mediated inflammatory response centered on the amyloid plaques. Microglia are the principal immune effector cells in the central nervous system and interact with fibrillar forms of Aβ through a receptor complex that includes TLR2/4/6. Interleukin receptor-associated kinases are essential intracellular signaling molecules that transduce TLR signals. The role of IRAKs in the microglial response to amyloid are unknown.

Aims: To determine Aβ induced intracellular signaling pathways and cellular responses in microglia that are dependent on IRAKs.

Methods: We have employed primary and N9 microglia and investigated their response to Aβ in the presence or absence of an IRAK1/4 kinase inhibitor. Intracellular signaling pathways and proinflammatory responses were assayed in vitro through various biochemical and cellular techniques. Degradation of Aβ was monitored through ELISA.

Results: We report that IRAK kinase activity is necessary for reactive oxygen species generation in response to Aβ. Interestingly, IRAK kinase activity is not necessary for p38 activation, a canonical proinflammatory signaling pathway. Aβ-induced phagocytosis is reduced in the presence of the IRAK inhibitor. Importantly, blocking IRAK kinase function facilitates degradation of soluble Aβ, suggesting that inflammation regulates an Aβ clearance mechanism.

Conclusions: IRAK kinase activity mediates responses of microglia to Aβ. These responses may be distinct from classical, proinflammatory pathways suggesting they may be individually manipulated.