ASK1 in Amyloid ß Peptide-Induced Cerebral Endothelial Cell Apoptosis

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摘要

Abstract

Apathological hallmark of Alzheimer’ s disease is accumulation of amyloid- peptide (A) in senile plaques.A has also been implicated in vascular degeneration in cerebral amyloid angiopathy because of its cytotoxic effects on non-neuronal cells, including cerebral endothelial cells (CECs). We explore the role of apoptosis signal-regulating kinase 1 (ASK1) in A -induced death in primary cultures of murine CECs. A induced ASK1 dephosphorylation, which could be prevented by selective inhibition of protein phosphatase 2A (PP2A) but not PP2B. ASK1 dephosphorylation resulted in its dissociation from 14-3-3. ASK1, released from 14-3-3 inhibition, activated p38 mitogen-activated protein kinase (p38MAPK), leading to p53 phosphorylation. p53, a proapoptotic transcription factor, in turn transactivated the expression of Bax, a proapoptotic protein. Transfection with various dominant-negative mutants (DNs), includingASK1DN and p38MAPK DN, suppressed A -induced p38MAPK activation, p53 phosphorylation, and Bax upregulation and partially prevented CEC death. Bax knockdown using a bax small interfering RNA strategy also reduced Bax expression and subsequent CEC death. These results suggest that A activates the ASK1 – p38MAPK – p53 – Bax cascade to cause CEC death in a PP2A-dependent manner.