Amyloid beta induces Smac release via AP-1/Bim activation.

許重義
Yin KJ;Lee JM;Chen SD;Xu J;Hsu CY

Abstract

Department of Neurology and Center for the Study of Nervous System Injury, Washington University School of Medicine, St. Louis, Missouri 63110

Insoluble fibrils of amyloid- peptide (A) are the major component of senile and vascular plaques found in the brains of Alzheimer's disease (AD) patients. A has been implicated in neuronal and vascular degeneration because of its toxicity to neurons and endothelial cells in vitro; some of these cells die with characteristic features of apoptosis. We used primary cultures of murine cerebral endothelial cells (CECs) to explore the mechanisms involved in Ainduced cell death. We report here that A25-35, a cytotoxic fragment of A, induced translocation of the apoptosis regulator termed second-mitochondria-derived activator of caspase (Smac) from the intramembranous compartment of the mitochondria to the cytosol 24 hr after exposure. In addition, we demonstrated that X chromosome-linked inhibitor-of-apoptosis protein (XIAP) coimmunoprecipitated with Smac, suggesting that the two proteins bound to one another subsequent to the release of Smac from the mitochondria. A25-35 treatment also led to rapid AP-1 activation and subsequent expression of Bim, a member of the BH3-only family of proapoptotic proteins. Bim knockdown using an antisense oligonucleotide strategy suppressed A25-35-induced Smac release and resulted in attenuation of CEC death. Furthermore, AP-1 inhibition, with curcumin or c-fos antisense oligonucleotide, reduced bim expression. These results suggest that A activates an apoptotic cascade involving AP-1 DNA binding, subsequent bim induction, followed by Smac release and binding to XIAP, resulting in CEC death.

Key words: amyloid- peptide (A); Smac; cerebral endothelial cells; AP-1; BH3-only family; XIAP; cell death; Alzheimer's disease