Protein phosphatase 2A regulates bim expression via the Akt/FKHRL1 signaling pathway in amyloid-beta peptide-induced cerebrovascular endothelial cell death.

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Abstract

Amyloid-beta peptide (Abeta)-induced death in cerebral endothelial cells (CECs) is preceded by mitochondrial dysfunction and signaling events characteristic of apoptosis. Mitochondria-dependent apoptosis engages Bcl-2 family proteins, especially the BH3-only homologues, which play a key role in initiating the apoptotic cascade. Here, we report that the expression of bim, but not other BH3-only members, was selectively increased in cerebral microvessels isolated from 18-month-old APPsw (Tg2576) mice, a model of cerebral amyloid angiopathy (CAA), suggesting a pivotal role for Bim in Abeta-induced cerebrovascular degeneration in vivo. A similar expression profile was observed in Abeta-treated CECs. Furthermore, Abeta induction of bim expression involved a pro-apoptotic transcription factor, FKHRL1. FKHRL1 bound to a consensus sequence in the bim promoter region and was activated by Abeta before bim expression. FKHRL1 activity was negatively regulated by phosphorylation catalyzed by Akt, an anti-apoptotic kinase. Akt upregulation by adenoviral gene transfer inhibited Abeta-induced FKHRL1 activation and bim induction. In addition, Abeta increased the activity of protein phosphatase 2A (PP2A), a ceramide-activated protein phosphatase. Suppression of PP2A activity by RNA interference or a specific inhibitor, okadaic acid, effectively suppressed Abeta-induced Akt inactivation and FKHRL1 activation, leading to an attenuation of bim expression and cell death in CECs. Coimmunoprecipitation experiments revealed that Abeta enhanced the binding of the PP2A regulatory subunit PP2ACalphabeta to Akt. These results implicate PP2A as an early regulator of Abeta-induced bim expression and CEC apoptosis via the Akt/FKHRL1 signaling pathway. We raise the possibility that this pathway may play a role in cerebrovascular degeneration in CAA.