

Regulation of Programmed Cell Death in the Nervous System via Survival Signal
Integration at the level of Bcl-2 Family Member Bad

Abstract

Neurons are produced in excess during development and subsequently compete for a limited supply of soluble growth factors to survive. Growth factors interact with receptors at the cell surface and induce changes in the receptor cytoplasmic tails, activating cellular signal transduction cascades. Growth factor-activated cascades and second messengers produced as a result of neuronal activity go on to suppress initiation of the cell-intrinsic program governing physiological death. The Bcl-2 family of proteins regulates activation of the cellular death machinery. The Bcl-2 family includes both members that promote survival and those that promote death. A pro-death family member, Bad, promotes death by localizing to the mitochondrial membrane and antagonizing the activity of the survival-promoting Bcl-XL. The program of cell death is suppressed by growth factors in part through a post-translational modification inactivating Bad. In the presence of growth factors, Bad is phosphorylated on Serines 112 and/or 136. A phosphoserine-binding cytosolic protein, 14-3-3, subsequently sequesters Bad in the cytosol. However, it is unclear how phosphorylation of Bad results in its dissociation from Bcl-XL and relocalization to the cytosol with 14-3-3. Work presented in this thesis identifies a novel Bad phosphorylation site, Serine 155, which lies within a domain through which Bad interacts with Bcl-XL. Phosphorylation of Serine 155 is sufficient to inactivate Bad by abolishing its ability to bind Bcl-XL, and necessary for the mechanism of Bad inactivation through phosphorylation of Serines 112/136. These findings define a mechanism by which survival signals suppress the cell-intrinsic death program through multiple phosphorylation events that inactivate the death promoting protein Bad.