TARGETING EARLY EVENTS OF PROGRAMMED CELL DEATH FOLLOWING AXON DAMAGE IN RETINAL GANGLION CELLS

R. Linden*, H. Petrs-Silva*, L.B. Chiarini*, V. Chiodo** & W.W. Hauswirth**
*Instituto de Biofísica da UFRJ, Rio de Janeiro, Brasil e **Department of Ophtalmology, University of Florida College of Medicine, Gainesville, FL, USA. E-mail: rlinden@biof.ufrj.br

Programmed cell death (PCD) may depend on protein synthesis, suggesting that transcription factors can modulate the synthesis of PCD-related proteins. Max, a member of the bHLH-LZ family of transcription factors, regulates cell growth, proliferation and PCD through dimerization with Myc, Mad or Mnt, all of which require Max for DNA-binding, Max can also form a homodimer that represses transcriptional activity following recognition of the same promoter target as the heterodimers. This may be relevant for the control of the activity of c-Myc during PCD. Apoptosis of retinal ganglion cells (RGCs) is the main pathologic hallmark in glaucoma and is responsible for the loss of vision. We have previously shown that Max protein is excluded from the nucleus of RGCs early after axon damage, preceding TUNEL staining and independent of caspase activity (Petrs-Silva et al, J. Cell Physiol. 198:179-87, 2004). To examine the role of Max in RGC death, we modulated gene expression in retinal tissue with a recombinant adeno-associated viral vector (rAAV) containing the *max* gene under the control of a general promoter. Two weeks after intravitreal injection of the vectors, explants from the retina of 15 day-old rats were maintained *in vitro* for 30h. Apoptosis of the axon-damaged RGCs was detected by either chomatin condensation or TUNEL, whereas the content of Max was analyzed with a commercial antibody. The rAAV efficiently transduced ganglion cells, and overexpression of Max decreased ganglion cell death. The data suggest a cytoprotective fuction for the Max transcription factor in the central nervous system. Due to the multiplicity of downstream cell death programs, mechanisms of subcellular protein trafficking, and their early changes upon cell stress or damage, may be both a key to the understanding of programmed cell death and a major target of novel therapeutic strategies related to degenerative diseases.
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