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The proteomic study of Ras-induced neuroprotection

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Ras is a universal eukaryotic intracellular G-protein integrating extracellular signals from multiple receptor types. Constitutively activated Ha-Ras was expressed selectively in neurons of a transgenic mouse model named synRas. Earlier it was shown that degeneration of motor neurons was completely prevented after facial nerve lesion in synRas mice, and degeneration of dopaminergic substantia nigra neurons, induced by neurotoxins, was greatly attenuated.

In order to elucidate the mechanisms of neuroprotection, proteins obtained from synaptosomes and perisynaptical mitochondria of murine brains were separated using 2D-DIGE and identified by MALDI-Tof MS. In synRas derived brains there were changes of the expression level and/or post-translational modification of more than 20 proteins. Most of the altered proteins are involved in energy metabolism (oxidative phosphorylation pathway, TCA cycle and ATP transport) and regulation of synaptic vesicular trafficking processes (release of neurotransmitters and vesicle recycling). In synRas brain the expression level of voltage-dependent anion channel 1 (VDAC1, also known as porin), pore-forming protein of the outer mitochondrial membrane, was threefold decreased. Reduction in VDAC1 protein levels were previously shown to result in resistance towards insults by the pro-apoptotic bcl2-family proteins. Thus, down-regulation of VDAC1 could explain the neuroprotective effect of Ras protein.