

## Appendix A14.18

### The Bcl-2 family of proteins: arbiters of life and death

Bcl-2 (an acronym for the B-cell lymphoma/leukemia-2 gene) was the first identified member of a large family of cellular and viral apoptosis-regulating proteins (Merry and Korsmeyer, 1997; Adams and Cory, 1998; Bruckheimer et al., 1998). The Bcl-2 family is the best characterized protein family involved in the regulation of apoptotic cell death, and consists of both anti-apoptotic (e.g. Bcl-2 and Bcl-XL) and pro-apoptotic members (e.g. Bax and Bad), several of which are expressed in the rodent and mammalian CNS. Bcl-2 attenuates apoptosis by sequestering proforms of death-driving cysteine proteases (called caspases), by preventing the release of mitochondrial apoptogenic factors such as calcium, cytochrome c and AIF (apoptosis-inducing factor) into the cytoplasm, and by enhancing mitochondrial calcium uptake (reviewed in Adams and Cory, 1998; Bruckheimer et al., 1998). Increasing evidence suggests a critical role for the mitochondria in the process of apoptosis, and studies have shown that mitochondria undergo major changes in membrane integrity before classical signs of apoptosis become manifest, leading to a disruption of the inner transmembrane potential ( $\Delta\psi_m$ ) and the release of intermembrane proteins through the outer membrane. Chemically-induced opening or closing of the permeability transition pore (also called mitochondrial megachannel) can induce or prevent apoptosis respectively. Bcl-2 acts on mitochondria to stabilize membrane integrity and to prevent opening of the permeability transition pore, and has been shown to protect neurons from a variety of insults both in vitro and in vivo (reviewed in Adams and Cory, 1998; Bruckheimer et al., 1998). Overexpression of bcl-2 in transgenic mice has been shown to prevent motor neuron and retinal ganglion death, to protect cells from the deleterious effects of MPTP or focal ischemia, to protect photoreceptor cells from inherited retinal degeneration, and to prolong survival and attenuate motor neuron degeneration in a transgenic animal model of amyotrophic lateral sclerosis (discussed in Merry and Korsmeyer, 1997; Adams and Cory, 1998; Bruckheimer et al., 1998; Manji et al., 1999 and references therein).

It is also noteworthy that recent studies have demonstrated that bcl-2 may mediate many of the downstream effects of several neurotrophic factors. Neurotrophic factors (e.g. nerve growth factor and brain derived neurotrophic factor) are now known to promote cell survival by binding to membrane receptors (such as Trk A and Trk B) and regulating intracellular signal transduction pathways that can control apoptosis. The signal transduction cascades that have been identified include the mitogen activated protein (MAP) kinase cascade and the phosphatidylinositol-3 kinase (PI-3K)/Akt pathway (Segal and Greenberg, 1996; Tao et al., 1998). Recent studies have demonstrated that the activation of the MAP kinase pathway can inhibit apoptosis by inducing the

phosphorylation of Bad and increasing the expression of Bcl-2, the latter effect likely involves the cAMP response element binding protein (CREB) (Ricchio et al, 1999; Bonni et al., 1999).

Phosphorylation of Bad occurs via activation of a downstream target of the MAP kinase cascade, ribosomal S-6 kinase (Rsk). Rsk phosphorylates Bad and thereby promotes its inactivation.

Activation of Rsk also mediates the actions of the MAP kinase cascade and neurotrophic factors on the expression of Bcl-2. Rsk can phosphorylate the cAMP response element binding protein (CREB) and this leads to induction of Bcl-2 gene expression. Moreover, in addition to its neuroprotective effects, Bcl-2 overexpression has also been shown to promote regeneration of axons in the mammalian CNS and regulate neurite sprouting (Chen et al., 1997). Thus, it has been convincingly argued that pharmacological means of increasing CNS bcl-2 levels may represent a very effective therapeutic strategy for the treatment of many neurodegenerative diseases (Chen et al., 1997).

Table A14.18a

Neurotrophic and Neuroprotective Effects of Bcl-2

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Protects against the lethal effects of a variety of reactive oxygen species

Protects against MPTP and AMPA neurotoxicity

Protects against growth factor deprivation

Protects against the effects of ionizing radiation

Protects against glucocorticoid toxicity

Reduces neuropathology after focal ischemia

Reduces neuropathology after traumatic brain injury

Prevents axotomy-induced motor neuron death.

Attenuates motor neuron degeneration in a transgenic animal model of ALS

Regulates neurite sprouting and outgrowth, and increases axonal growth rate

Promotes regeneration of axons in the mammalian Central Nervous System

MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. AMPA:  $\alpha$ -amino-5-methyl-3-hydroxy-4-isoxazole propionic acid. ALS: amyotrophic lateral sclerosis

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