had three-fold or greater energy than the accepted structures, and most had multiple ϕ,ψ angles in the unallowed regions of the Ramachandran plot. The remaining 30 unaccepted structures had the same overall fold and similar overall energies, but contained one or more NOE violations.

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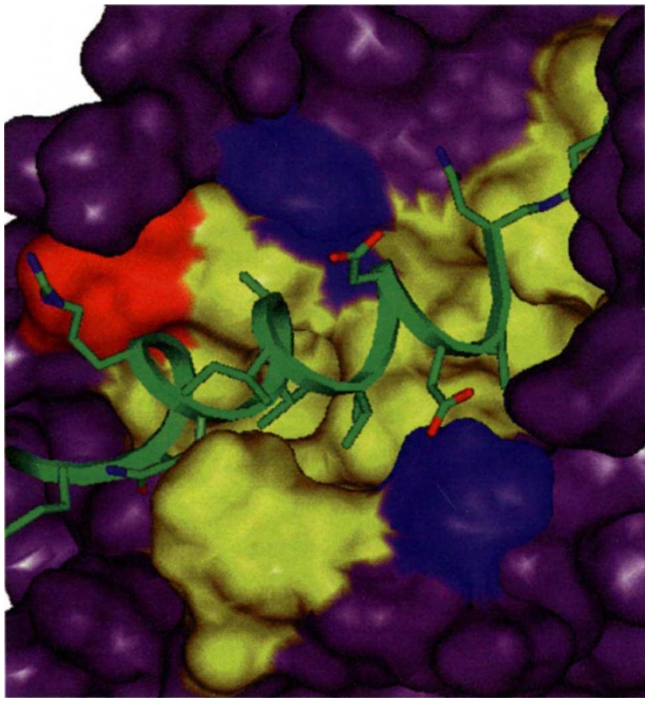
picture story

Death grip



Cells lie poised between continued life and the deliberate death of apoptosis. While this may lead us to ponder existential questions, for cells this appears to be an evolutionary exigency to deal with pressing questions of normal development and daily insult. The improperly placed cell, as well as the damaged one, must sacrifice itself for the good of the organism. A malfunction of apoptosis leads to disease; for example in most (if not all) cancer cells, cell death is inhibited, leading to survival of tumour cells that should otherwise perish.

The mutually antagonistic embrace between members of the Bcl-2 family of proteins, which promote life, and Bax or Bak, which promote death, controls the balance between continued existence and apoptosis. A recent NMR structure of the Bcl-x_L complex with a Bak peptide (M. Sattler *et al. Science*, **in the press**) reveals the details (Bcl-x_L in surface representation, Bak peptide in green ribbon). The Bak peptide is a 16-mer derived from the minimal region of Bak sufficient to induce death; the peptide can compete with the full-length protein for binding to its companion. The NMR structure of the complex shows the hydrophobic and charge interactions between the partners that are likely to be important for binding. In the view of the binding region shown in the figure, hydrophobic residues of Bcl-x_L are highlighted in yellow, while those potentially involved in electrostatic interactions are shown in red and blue. This picture is confirmed by alanine mutagenesis of the Bak peptide: a substantial reduction in binding affinity is produced by mutating the hydrophobic Bak peptide residues that face into the cleft, and also by mutation of charged residues Arg 76 (upper left, blue stick) and Asp 83 (upper middle, red stick) (but curiously, not Asp 84, lower right). Interestingly, in the intact Bak protein, the hydrophobic residues of this helix face into the protein core, so it is proposed that a conformational change is necessary for binding *in vivo*. **AF**