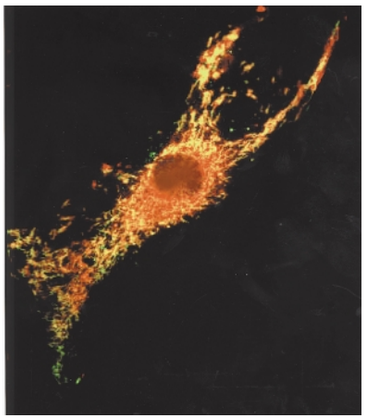
The ARTS of apoptosis

Not only does transforming growth factor-β (TGF-β) regulate cell proliferation, but it is also involved in the control of other cellular processes such as differentiation and cell death. Two principal signalling pathways that activate transcription are initiated by TGF-β — one is dependent on proteins of the Smad family, whereas the other is dependent on mitogen-actiated protein kinase (MAPK). Now, however, there is a new player in the signalling of cell death by TGF-β. In a screen for retroviral-infection-induced insertion mutants that would be resistant to TGF-β-induced cell death, Sarit Larisch, Anita Roberts and Seong-Jin Kim identified apoptosis-related protein in TGF-β signalling pathway (ARTS; *Nature Cell Biol.* **2,** 915–921; 2000). Antisense ARTS mRNA interferes with signalling of caspase activation downstream of the TGF-β receptors and blocks apoptosis in cells that are sensitive to TGF-β-induced cell death. Conversely, overexpression of ARTS, although not toxic in itself, enhances cell death induced by TGF-β, and to a lesser extent by other death stimuli such as TNF-α and Fas-L.

ARTS encodes an alternative transcript of the septin-family gene locus, H5/PNUTL2/hCDCrel-2a/2b. The protein bears some, but not all, of the characteristic features of septins. Interestingly, mutations in the P-loop that is present in all septin-gene products and in the cell-death-regulating protein Apaf-1 and its *Caenorhabditis elegans* homologue CED-4 neutralizes the death-enhancing function of ARTS; the mutant also behaves as a dominant negative inhibitor of wild-type ARTS. Furthermore, unlike other septins that localize to actin-rich regions, ARTS localizes to mitochondria, as shown by the overlap (yellow in the picture) of the staining of endogenous ARTS protein (green) with the staining of the mitochondrial marker MitoTracker (red), and it relocalizes to the nucleus upon induction of cell death by TGF-β, as is the case for CED-4. This indicates that ARTS may be another mitochondrial factor that is involved in the regulation of caspase activation and cell death. Plenty of questions remain unanswered: can ARTS regulate caspase activation directly, as is the case for both CED-4 and Apaf-1? What is its function in the nucleus? How does it fit into either the Smad- or the MAPK-dependent pathway? Is its function specific to TGF-β signalling of cell death? Larisch and colleagues highlight the relevance of unpublished data from Hermann Steller's lab, showing that the *peanut* gene locus encodes an ARTS homologue in *Drosophila*. As mutations at this locus affect the cell-death-inducing function of the *reaper*, *hid* and *grim* genes, the function of ARTS in the regulation of cell death may be evolutionarily conserved.



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