APOPTOSIS

FLIP-side

At physiological levels, cellular FLICE-inhibitory protein (c-FLIP$_L$) — a caspase homologue that is thought to be an inhibitor of death-receptor-mediated apoptosis — is actually an activator of apoptosis, according to a report in *The EMBO Journal*, which describes an entirely new mechanism of cell-death regulation.

After ligand binding, death receptors such as FAS recruit the death adaptor FAS-associated via death domain (FADD) and procaspase-8 to form a death-inducing signalling complex (DISC). The activation of procaspase-8 in the DISC triggers a cascade of caspase activity that leads to cell death. c-FLIP$_L$, which is highly homologous to procaspase-8 but has no protease activity, is also recruited to the DISC, but its role is controversial. The overexpression of c-FLIP$_L$ can inhibit apoptosis, but this effect has not been shown at physiological levels of expression and there is some evidence that c-FLIP$_L$ can, in fact, promote apoptosis.

As c-FLIP$_L$ is known to be recruited to the DISC, Chang and co-workers asked if dimerization of procaspase-8 with c-FLIP$_L$ might have a role in its activation. An inducible dimerization system was used to pair-up procaspase-8 and c-FLIP$_L$ *in vitro* and in transfected cells. The cleavage and activation of procaspase-8 *in vitro* was markedly enhanced after dimerization with c-FLIP$_L$ compared with procaspase-8 homodimerization. Also, enhancement of procaspase-8 processing by c-FLIP$_L$ in the DISC was observed using cell lines that stably or inducibly express c-FLIP$_L$. This indicates that c-FLIP$_L$ can catalyse the processing and activation of procaspase-8.

By transfecting HeLa cells with various amounts of c-FLIP$_L$ DNA, and using stable and inducible transfectants, the authors show that the cell-death-sensitizing effects of c-FLIP$_L$ are highly dependent on expression level; maximum sensitivity to FAS-mediated apoptosis was seen when levels of exogenous c-FLIP$_L$ approximated physiological endogenous levels. So, it is probable that c-FLIP$_L$ functions *in vivo* to promote death-receptor-mediated apoptosis.

But, the level of endogenous c-FLIP$_L$ is typically only 1% of that of procaspase-8. How can such a small amount of c-FLIP$_L$ regulate death-receptor-mediated apoptosis? When the authors quantified the amounts of c-FLIP$_L$ and procaspase-8 in the cytosol and DISCs of FAS-stimulated cells, they found that the amount of c-FLIP$_L$ is increased 18-fold in the DISCs, so that the ratio of c-FLIP$_L$ to procaspase-8 is approximately 1 to 5.

This new dimension to c-FLIP$_L$ makes it an attractive target for therapies that seek to inhibit or promote death-receptor-mediated cell death.

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References and links

ORIGINAL RESEARCH PAPER Chang, D. W. *et al.* c-FLIP$_L$ is a dual function regulator for caspase-8 activation and CD95-mediated apoptosis. *EMBO J.* **21**, 3704–3714 (2002)

FURTHER READING Thome, M. & Tschopp, J. Regulation of lymphocyte proliferation and death by FLIP. *Nature Rev. Immunol.* **1**, 50–58 (2001)