

HIGHLIGHT ADVISORS

CEZMI AKDIS

SWISS INSTITUTE OF ALLERGY
AND ASTHMA RESEARCH,
SWITZERLAND

MARCO BAGGIOLINI

UNIVERSITA' DELLA SVIZZERA
ITALIANA, SWITZERLAND

BRUCE BEUTLER

SCRIPPS RESEARCH INSTITUTE,
USA

ANDREW CHAN

GENENTECH, INC., USA

ANNE COOKE

UNIVERSITY OF CAMBRIDGE,
UK

JAMES DI SANTO

PASTEUR INSTITUTE, FRANCE

TASUKU HONJO

KYOTO UNIVERSITY, JAPAN

GARY KORETZKY

UNIVERSITY OF
PENNSYLVANIA, USA

CHARLES MACKAY

GARVAN INSTITUTE OF
MEDICAL RESEARCH,
AUSTRALIA

FIONA POWRIE

UNIVERSITY OF OXFORD, UK

CAETANO REIS E SOUSA

IMPERIAL CANCER RESEARCH
FUND, UK

ALAN SHER

NATIONAL INSTITUTE OF
ALLERGY AND INFECTIOUS
DISEASES, USA

ANDREAS STRASSER

THE WALTER AND ELIZA HALL
INSTITUTE, MELBOURNE,
AUSTRALIA

ERIC VIVIER

CENTRE D'IMMUNOLOGIE
DE MARSEILLE-LUMINY,
FRANCE

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.

Jennifer Bell

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)