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Viral FLICE-inhibitory proteins (FLIPs) prevent apoptosis induced by death receptors — Source link

Margot Thome, Pascal Schneider, Kay Hofmann, Helmut Fickenscher ...+10 more authors

Institutions: University of Lausanne, ISREC, University of Erlangen-Nuremberg, German Cancer Research Center

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Topics: Death effector domain, FADD, Fas receptor, Viral replication and Caspase 8

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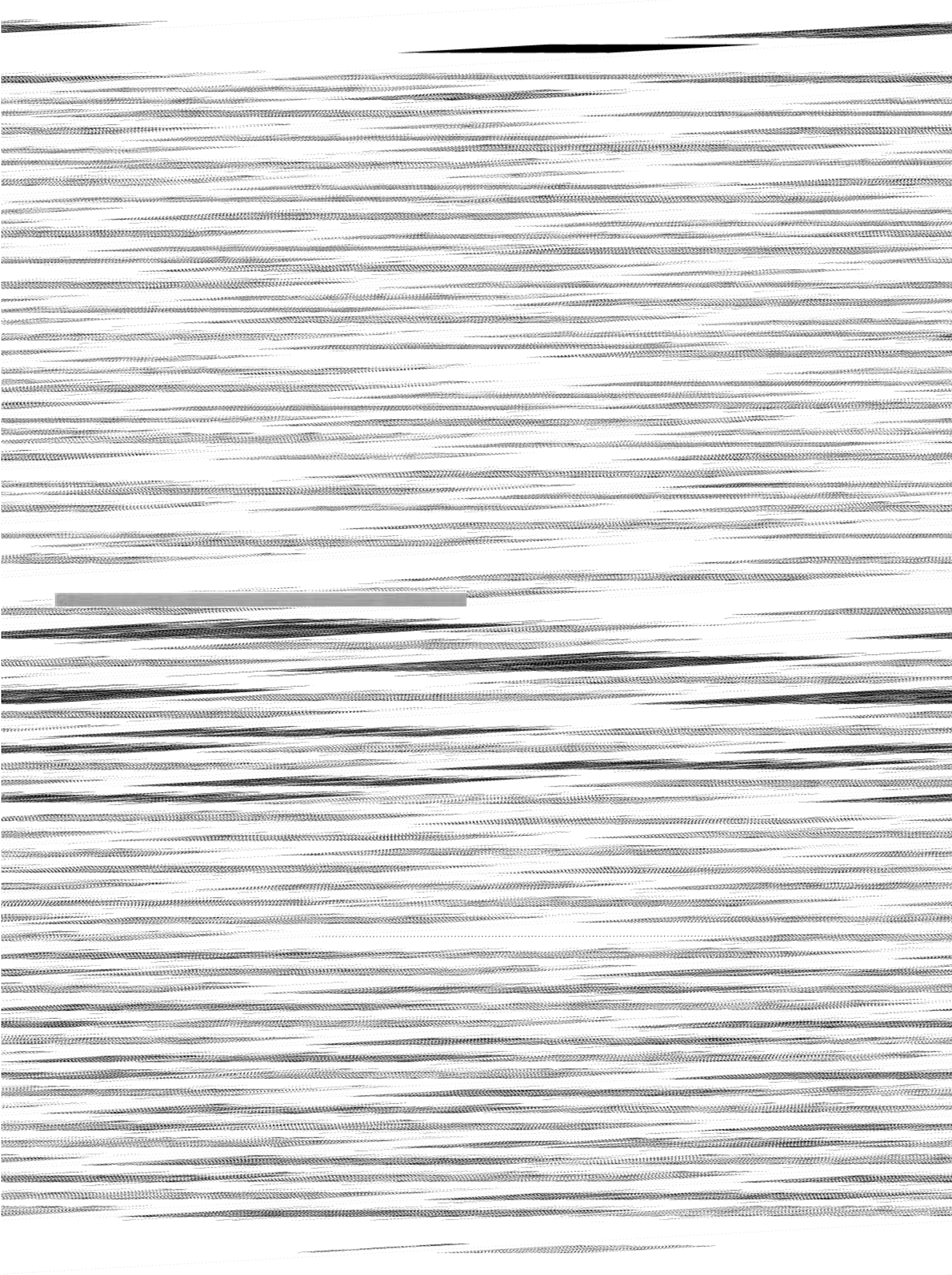
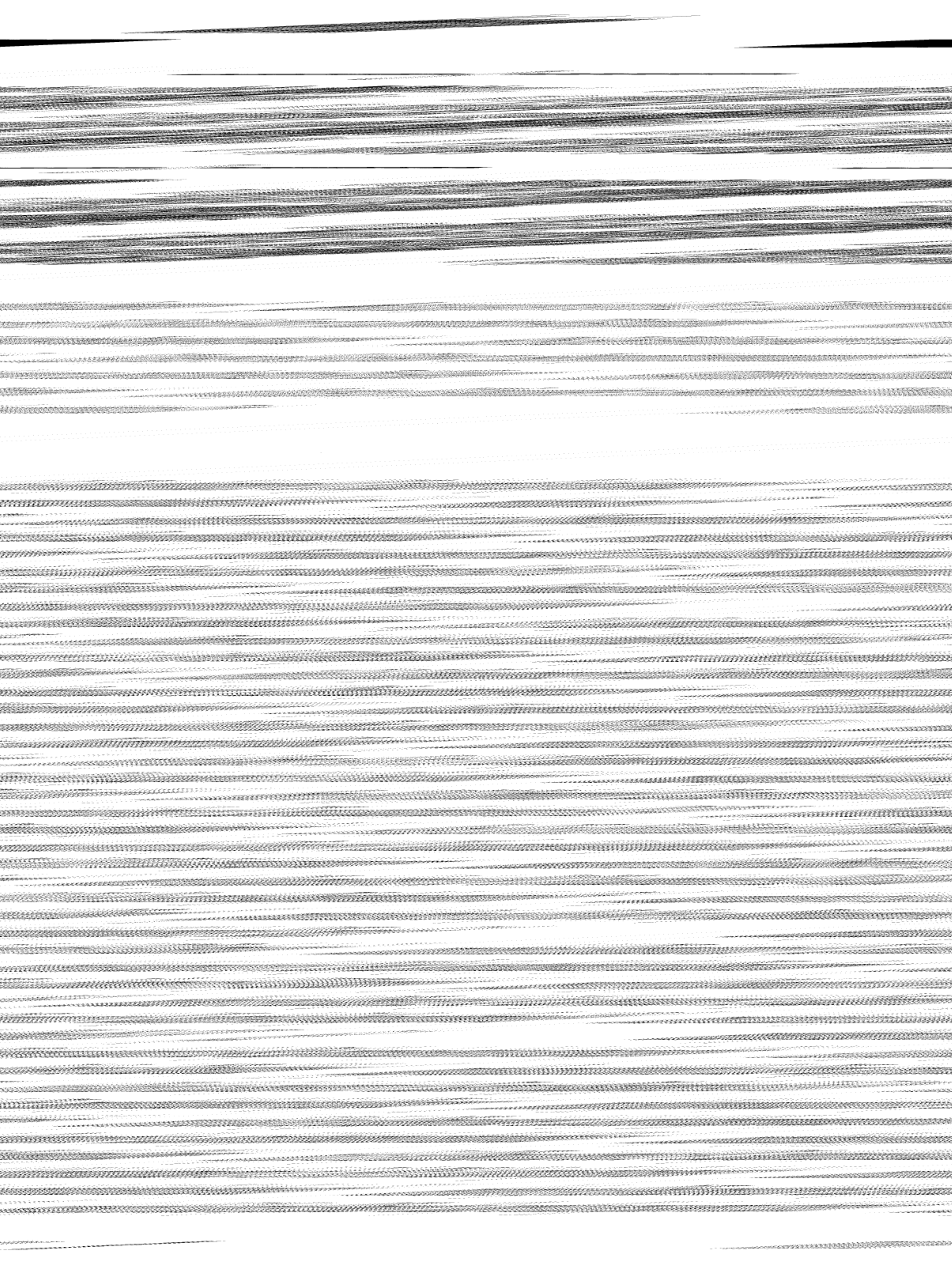




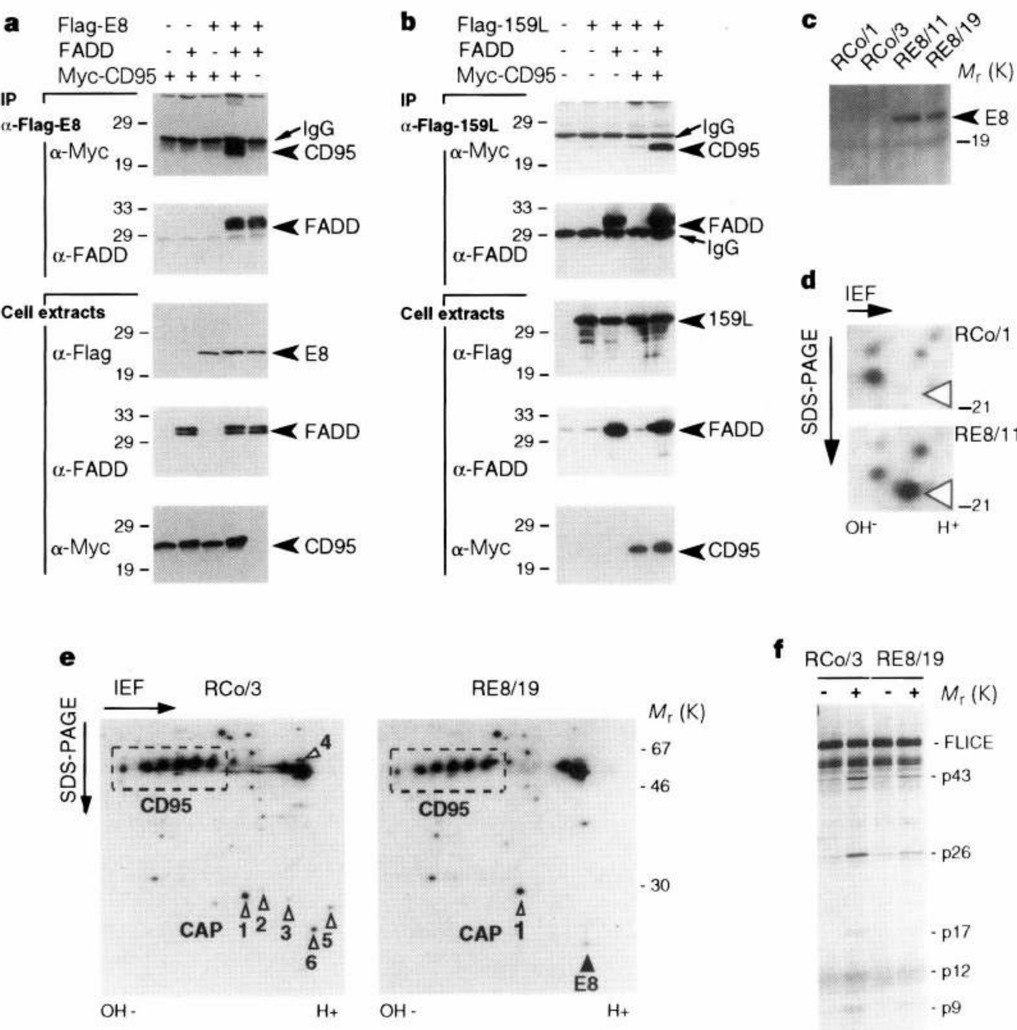
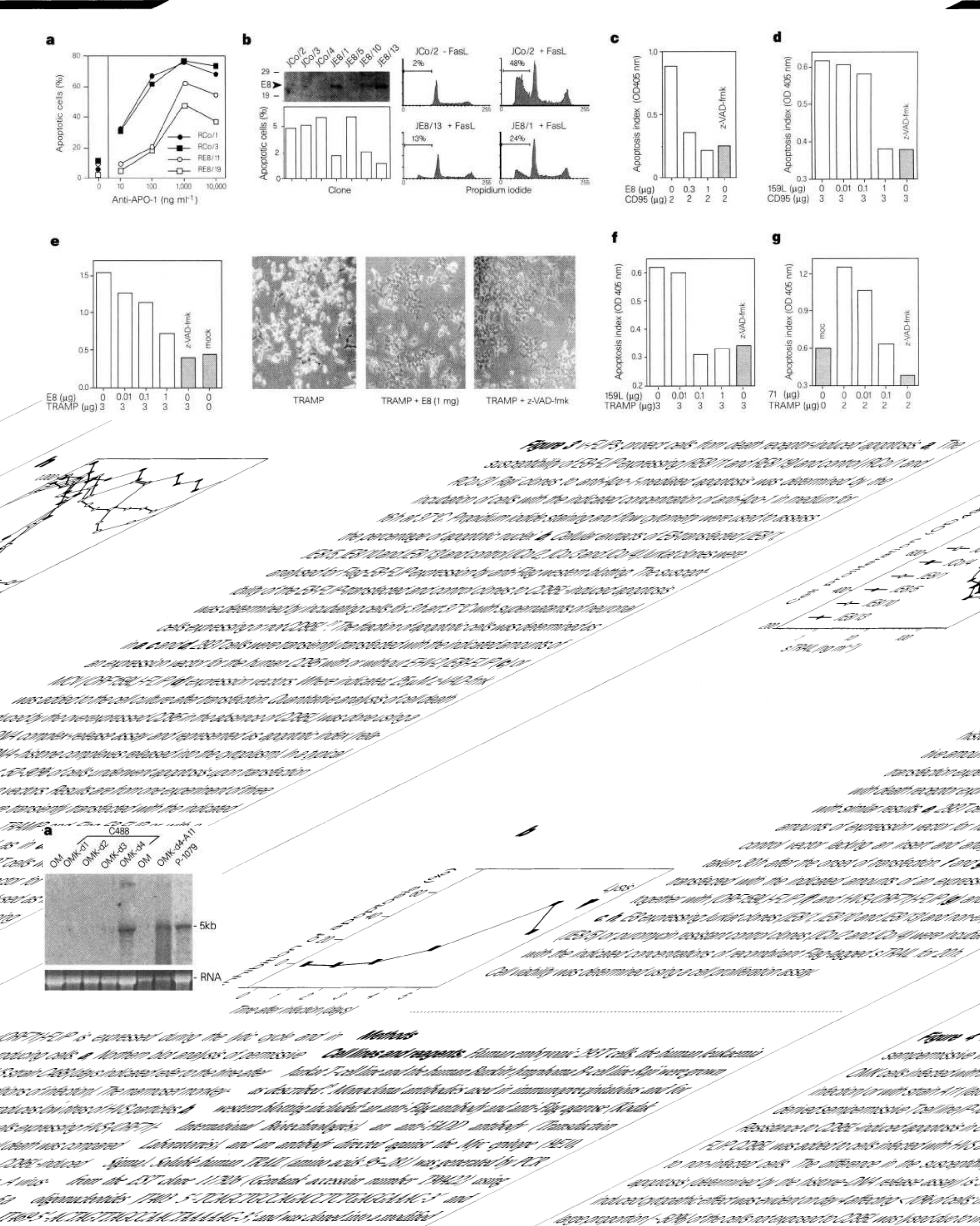


Figure 2 v-FLIPs interfere with CD95 signaling by binding to FADD. **a**, 293T cells were transiently transfected with 4 μg of each expression vector encoding Flag-E8-FLIP, FADD and Myc-CD95 as indicated, or empty vector to keep the total amount of plasmid constant. Cells were lysed 30 h after transfection, and anti-Flag immunoprecipitates or total cell extracts were analysed for the presence of FADD, Flag-E8 or Myc-CD95 by western blotting as indicated. **b**, The association of MCV-159L-FLIP with FADD and CD95 was analysed as described in **a**. **c**, Flag-E8-FLIP expressing Raji clones RE8/11 and RE8/19, as well as the control clones RCo/1 and RCo/3 were tested for E8 expression by western blotting using an anti-Flag antibody. **d**, Analysis of anti-Apo-1 immunoprecipitates from ^{35}S-labelled control (upper panel) or Flag-E8-FLIP-expressing (lower panel) Raji clones by 2D gel electrophoresis and autoradiography. The arrow indicates the migration position of a 23K protein of p*I* 5.0 found in the E8-FLIP-expressing clone RE8/11 and absent in the control clone RCo/1. **e**, Apo-1 immunoprecipitates from ^{35}S-labelled, anti-Apo-1-treated clones RCo/3 and RE8/19 were analysed by 2D gel electrophoresis and autoradiography. Numbers refer to CAP proteins: CAP1 and CAP2 (FADD), CAP3, CAP4 (FLICE), CAP5 and CAP6 (the prodomains of FLICE as a result of proteolytic cleavage). A filled arrowhead indicates the position of E8. **f**, FLICE-processing activity associated with the DISC in E8 expressing and control Raji cells. Cells were treated with anti-Apo-1 for 5 min, and Apo-1 immunoprecipitates from treated (+) or untreated (−) cells were analysed for FLICE processing activity by incubation with *in vitro* translated ^{35}S-labelled FLICE. FLICE-specific cleavage products (p43, p26, p17, p12 and p9)[17] were detected by SDS-PAGE and autoradiography.

Interestingly, all FLIP encoding γ-herpesviruses also have a Bcl-2 homologue. The anti-apoptotic Bcl-2 family members block cell death induced by growth factor deprivation, γ-irradiation and cytotoxic drugs[23,24]. However, in contrast to the v-FLIPs, these proteins have a less potent effect on CD95-mediated apoptosis of lymphoid cell lines. Some viruses may thus take advantage of two complementary anti-apoptotic functions provided on the one hand by a Bcl-2 homologue and on the other by v-FLIP.

Tissue homeostasis is maintained through the delicate balance of cell growth and apoptosis. Recent evidence indicates that tumour cells such as melanomas and hepatomas do not respond to CD95L-mediated apoptosis owing either to the downregulation of CD95 expression or to a blockade in the CD95 signalling pathway[25,26]. Thus, by interference with CD95 and other death-receptor-mediated signals, we propose that v-FLIPs may not only facilitate viral spread and persistence, but that they also contribute to the transforming capacity of some herepesviruses. This possibility is supported by the fact that MCV produces slow-growing epidermal neoplasms that persist for long periods with little immune response. HVS causes tumours in New World primates, and tight epidemiological links indicate that HHV-8 is an infectious cofactor for Kaposi's sarcoma and primary effusion lymphoma[13]. Future investigations should address the possible presence of v-FLIPs in tumours caused by viruses.

Note added in proof: Related findings have been reported by J. Bertin *et al.*[30]. □


a
Apoptotic cells (%)
Anti-APO-1 (ng ml-1)
RCo/1
RCo/3
RE8/11
RE8/19
b
JCo/2
JCo/3
JCo/4
JE8/1
JE8/5
JE8/10
JE8/13
E8
Apoptotic cells (%)
Clone
JCo/2 - FasL
JCo/2 + FasL
JE8/13 + FasL
JE8/1 + FasL
2%
48%
13%
24%
Propidium iodide
c
Apoptosis index (OD405 nm)
z-VAD-fmk
E8 (μg) 0 0.3 1 0
CD95 (μg) 2 2 2 2
d
Apoptosis index (OD 405 nm)
z-VAD-fmk
159L (μg) 0 0.01 0.1 1 0
CD95 (μg) 3 3 3 3 3
e
z-VAD-fmk
mock
E8 (μg) 0 0.01 0.1 1 0 0
TRAMP (μg) 3 3 3 3 3 0
TRAMP
TRAMP + E8 (1 mg)
TRAMP + z-VAD-fmk
f
Apoptosis index (OD 405 nm)
z-VAD-fmk
159L (μg) 0 0.01 0.1 1 0
TRAMP (μg) 3 3 3 3 3
g
Apoptosis index (OD 405 nm)
moc
z-VAD-fmk
71 (μg) 0 0 0.01 0.1 0
TRAMP (μg) 0 2 2 2 2
a
C488
OM
OMK-d1
OMK-d2
OMK-d3
OMK-d4
OM
OMK-d4-A11
P-1079
5kb
RNA