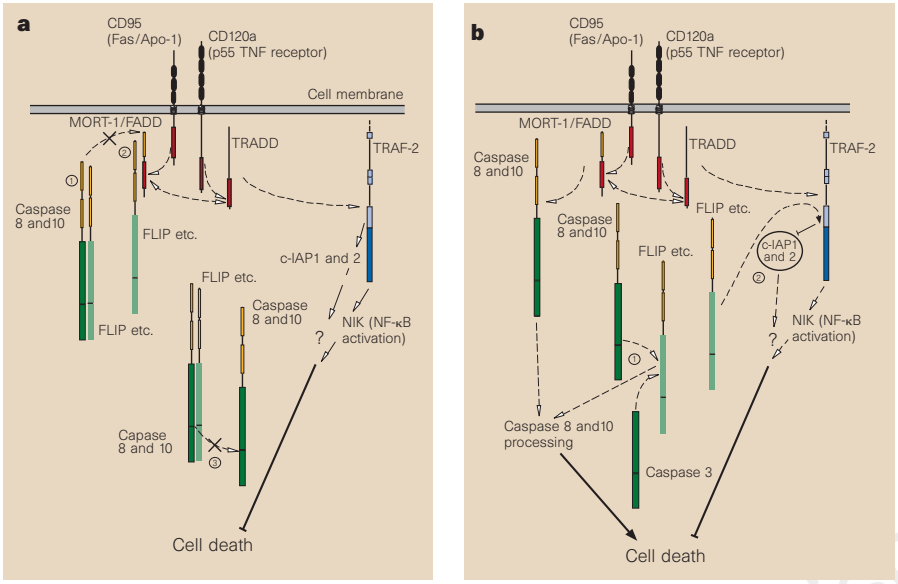

Figure 1 **The newly discovered regulatory protein, variously called FLIP[2], Casper[3], FLAME[6], CASH[7] and I-FLICE[8] (here referred to as FLIP etc. for simplicity), may be involved in blocking the induction of cell death or in activating it. It acts downstream of receptors of the tumour necrosis factor (TNF) family such as CD95 and CD120a.** a, **Proposed mechanisms of blockage of cell-death induction. 1 and 2, inhibition of binding of caspases 8 and 10 to the adaptor protein MORT-1/FADD by the binding of FLIP etc. to any of these proteins; 3, inhibition of caspase 8 and 10 self-processing by the association of their protease-precursor regions with the corresponding region in FLIP etc. Receptors of the TNF family can also activate the transcription factor NF-κB, a process which involves the NIK protein kinase and TRAF-2, and is thought to confer protection against death. In addition, TRAF-2 binds the proteins c-IAP1 and c-IAP2, which may also provide protection against death by an unknown mechanism.** b, **Proposed mechanisms of cell-death activation. 1, triggering of caspase 8 and 10 processing by the simultaneous binding of FLIP etc. to these enzymes and to caspase 3; 2, displacement of c-IAP1 and c-IAP2 from TRAF-2.**

which are thought to provide cells with resistance to death mechanisms.

In seeking additional regulatory proteins that specifically affect the initial event in death induction by members of the TNF-receptor family, Irmler *et al.*[2] and Shu *et al.*[3] concentrated on the terminal point of ramification in the pathway, namely, binding of caspase 8 and caspase 10 to the adaptor protein MORT-1/FADD. Their search led to independent identification of the same protein, which they respectively call FLIP and Casper. This protein contains DED motifs at its amino terminus and through them it can bind to other DED-containing proteins. The gene encoding the protein was localized to region 33–34 of the long arm of human chromosome 2, within 100 kilobases of the caspase 8 and caspase 10 genes (refs 2, 6 and my group's unpublished data).

The FLIP/Casper protein occurs in two sizes (splice variants). The shorter one is essentially composed of the DED motifs. The longer one contains, in addition, a region that closely resembles the carboxy-terminal protease-precursor regions in caspase 8 and caspase 10. In FLIP/Casper, this region lacks several of the sequence features required for protease activity. But it is able to bind directly to the protease-precursor region in caspase 10, as well as to caspase 3, another member of the caspase family that participates in the receptor-induced death process. Surprisingly, it can also bind TRAF-2, displacing the putative death-regulatory proteins c-IAP1 and c-IAP2.

Expression of the long and short splice variants of FLIP/Casper, or of its mutants by introduction of their complementary DNA into cells, had pronounced but varying effects on the cell-death mechanisms activated by TNF receptors. In some cultured cells, it strongly inhibited cell death induction; in others, it triggered cell death.

Perhaps not surprisingly, then, the two groups have quite different views about the physiological role of FLIP/Casper (see Fig. 1). Irmler *et al.* think that the death resulting in some cells from expression of the protein is artificial, and that the protein's sole function is to inhibit cell-death induction. They call it 'cellular FLIP', on the assumption that it acts like virus-produced inhibitors of cell-death induction, vFLIPs (viral FLICE-inhibitory proteins), which also consist of duplicate DED motifs[11–13]. vFLIPs block death induction by interfering with the binding of DED-containing caspases to MORT-1/FADD, and Irmler *et al.* suggest that FLIP/Casper works in the same way. Moreover, they say that the binding of the carboxy-terminal region in FLIP/ Casper to caspase 8 and caspase 10 may constitute a further inhibitory mechanism, preventing the proteolytic self-processing of the caspases.

In contrast, Shu *et al.* propose that

100 YEARS AGO

The chapter on resistance of cycles is very instructive. The conclusions are represented graphically, so that any one non-algebraically-minded can grasp the enormous importance of air resistance at high speeds. Extrapolating from these curves, it is seen that a man who can drive his machine under present conditions through the air at, say, 30 miles an hour, would, if road and machine resistance only had to be met, be able to drive at 330 miles an hour, or if he can actually go 20 miles an hour, he would be able to drive his machine 100 miles an hour. … The writer would like to propose a method to enable great speeds to be attained, which, however, is of spurious interest, since in real cycling the wind resistance must be overcome. All that is necessary is that a large box or small house with glass sides big enough to entirely surround the rider, but with a safe margin, should be dragged by steam or other power along at gradually increasing speeds until the rider shows that he is beginning to lag. Of course, there would be no floor or bottom to the box, and it should be made so that it would clear the ground by any predetermined amount. It might be safer if the house had no back.

From *Nature* 8 July 1897.

50 YEARS AGO

Despite progress in education, the great majority of people seem to have but an inkling of the part played by chemistry and its sister sciences in improving the material conditions of their existence, and very few have any real interest in the subject; they will grasp for an aspirin, grab for a 'nylon' stocking or a coat of many colours, they make full use of the modern rapid means of communication, and relish the margarine that now masquerades as butter, without a thought that these innovations are the outcome of long and patient research in chemistry, physics or biology. One may excuse such ignorance and apathy in those who were born in Victorian days, but there is less excuse for the younger generations, although these also have been handicapped at school in their range of interests by too much concentration on the distant past.

From *Nature* 12 July 1947.