Figure 1 The greater San Francisco Bay region, showing the course of the San Andreas fault and the main locations discussed in the text. The 1906 earthquake was a consequence of rapid slip along more than 300 km of the San Andreas in this part of California.

vertical fault extending to a depth of 10 km (ref. 11). Thatcher *et al.*¹ investigated a range of plausible fault geometries and show that slip at depth along the Loma Prieta segment must have been between 2.3 and 3.1 m, much more than the 1.5 m of observed surface slip. According to the simple time-predictable model, the next earthquake was not due until well into the next century. It has been suggested that large uncertainties in the geodetic displacements prevent accurate determination of fault slip¹². The computed displacements, however, have larger uncertainties than the estimated fault slip, because the fault model implies additional constraints on the deformation pattern.

The issue of whether or not the Loma Prieta earthquake was anticipated⁷⁻⁹ is further complicated by the observations that it occurred on a dipping fault that many believe to be distinct from the San Andreas fault, and that it had roughly equal amounts of vertical and horizontal slip. Neither of these features was predicted. The previous large earthquake in the region, which occurred in 1865, appears to be distinct from both the 1906 and 1989 events. From seismic intensities¹³ and geodetic displacements¹⁴, it seems that the 1865 earthquake may have occurred on a thrust fault northeast of the San Andreas.

We are left with two messages. First, although the elastic rebound theory implies a basis for long-term earthquake forecasting, the best available data indicate that the history of earthquakes along the southernmost stretch of the 1906 rupture has been more complicated than Reid would have predict-

ed. Second, not only are data collected nearly 150 years ago essential in deciphering the seismic history of the region, but we should look back on the nineteenth-century surveyors with admiration for their thoroughness in archiving and documenting their data. □

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Apoptosis

Placing death under control

David Wallach

Unlike the gloomy connotation of the death of an organism, the death of an individual cell is an integral and continuing part of normal physiology¹. It is also a major form of defence, as sometimes the only way for the immune system to eradicate pathogens is to sacrifice the infected cell. When the timing of cell death is inappropriate, however, havoc may ensue. So understanding the mechanisms that regulate cell death is just as important as understanding those responsible for the actual killing. A newly identified protein, described on page 190 of this issue by Irmeler *et al.*², and in *Immunity* by Shu *et al.*³, appears to act as a regulator of one of the principal ways by which immune mechanisms cause cell death — namely its induction by receptors belonging to the tumour necrosis factor (TNF)-receptor family^{4,5}. This is a highly active research area, as exemplified by the fact that three other groups⁶⁻⁸, including my own, are shortly to publish on the same protein.

Death is a rather uncommon consequence of receptor triggering; usually, the process is concerned with the transmission of life-enhancing signals such as those that stimulate cell growth and division. Nonetheless, the emerging knowledge of induction of cell death by TNF receptors indicates that it happens in the same way as all other receptor-induced effects — that is, through a series of protein–protein bindings. The first involves the binding of specific ligands to the extracellular domains of the receptors. This is followed by sequential binding of cytoplasmic proteins to the intracellular domains of the receptors, leading eventually to activation of enzymatic function in some of these proteins. In the case of death induction, the activated enzymes include caspases, a family of cysteine proteases whose members occur in cells as latent precursors, becoming

activated early in the process of programmed cell death and being central to its development⁹.

The intracellular protein interactions triggered by the death-inducing receptors can be attributed to two structural motifs within the proteins concerned. Both motifs are able to associate with homologous regions in other proteins, and thus prompt binding of such proteins to one another (reviewed in ref. 10). One motif, the ‘death domain’ (DD), is found in several death-inducing receptors of the TNF family, including CD95 (also called Fas or Apo-1), CD120a (the p55 TNF receptor) and others. It also occurs in several cytoplasmic adaptor proteins that bind through this domain both to receptors and to each other (as, for example, in the MORT-1/FADD and TRADD adaptors).

The other motif, the ‘death effector domain’ (DED), is found in MORT-1/FADD upstream of the DD; it also occurs in duplicate in two caspases, caspase 8 (MACH/FLICE/Mch-5) and caspase 10 (Mch-4/FLICE-2). Binding of these two caspases to MORT-1/FADD through association of their DED motifs, and consequent activation of the caspases by their proteolytic cleavage (apparently by self-processing), are thought to be critical steps in the initiation of the killing process.

This multiplicity of interacting proteins provides points of ramification in the signalling pathway, allowing induction of different effects by the same receptor. Thus, several receptors of the TNF family that induce cell death can also activate the transcription factor NF- κ B, thereby turning on genes whose products provide resistance to cytotoxicity by these receptors. This latter activation involves TRAF-2, as well as NIK, a protein kinase that binds to it. TRAF-2 also binds two proteins, c-IAP1 and c-IAP2,

Figure 1 The newly discovered regulatory protein, variously called FLIP², Casper³, FLAME⁶, CASH⁷ and I-FLICE⁸ (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, Irmeler *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). Irmeler *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 Irmeler *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.

FLIP/Casper acts solely as a death activator, prompting activation of caspase 10 upon binding to it simultaneously with the binding to caspase 3, and perhaps also further enhancing death by displacement of the putative death-inhibiting c-IAPs from TRAF-2.

What of the work of the other three groups? Like Irmeler *et al.*, Alnemri and his colleagues⁶ observed an inhibitory effect of the protein on both CD95- and CD120a-induced cytotoxicity, and, similarly, suggest that it acts as an anti-apoptotic protein. They call it FLAME. In our own tests⁷, however, the protein (which we call CASH) exhibited both protective and marked cytotoxic effects, depending on the cell line examined. Finally, Dixit's group⁸ call the protein I-FLICE and see inhibition only.

Taken together, the data in the five reports indicate that the marked variations observed in the levels of FLIP/Casper/CASH/ FLAME/ I-FLICE in cells, depending on their states of differentiation and activation, constitute an important determinant of the effectiveness of cell killing by members of the TNF-receptor

family. But the markedly different interpretations of the various groups involved underscores a severe limitation in our ability to infer the physiological function of a newly discovered gene from its *in vitro* function. Clearly, further work is necessary to clarify not only what is happening *in vitro* but how these observations relate to the cell death that occurs in the body during health and disease. □

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X-ray astronomy

How one galaxy can be a cluster

Richard Mushotzky

On page 146 of this issue¹, Hattori *et al.* report the discovery of a distant cluster of galaxies that is massive and bright in X-rays, but surprisingly dark optically — containing only one visible galaxy, it has extremely anomalous optical properties (Fig. 1). In most theories of structure formation, massive clusters at high redshift should be rich in galaxies.

Clusters of galaxies are the largest gravitationally bound systems in the Universe. They

were originally found by searching for large numbers of galaxies in a small patch of sky, but they are also luminous X-ray sources. Most of the visible matter is in the hot X-ray-emitting gas between galaxies, rather than in the stars². In nearby clusters, the gas has about three to ten times the mass of the stars, and is enriched in heavy elements such as silicon and iron to roughly a quarter to a half of solar levels³. Because these elements are produced in stars, and stars are thought to

lie only in galaxies, there should be a close connection between the total amount of starlight in a system and the total mass of heavy elements⁴.

These objects are interesting not just in themselves, but for what they tell us about the Universe. The heavy elements probably can't escape the deep gravitational potential well of the cluster, so changes in the composition of the cluster gas with redshift (and thus with distance and look-back time) constrain the history of star formation in the Universe⁵. Also, clusters probably form in a 'bottom-up' fashion⁶, such that massive clusters form out of smaller clusters and galaxies. If the Universe is dense enough to be closed, massive clusters should form relatively late and so should evolve strongly with cosmic time.

Clusters of galaxies are strong gravitational lenses⁷, and their distortion of the images of background galaxies provides a measurement of the mass and mass distribution in the cluster. Another mass measurement can be derived from the X-ray temperature and density profile, assuming that the gas is in hydrostatic equilibrium. Both the X-ray and lensing data show that most of the mass in any cluster is some form of dark matter. For several well-studied clusters^{8,9} the optical light is a fairly accurate tracer of the dark matter, and therefore there is a strong connection between dark matter and the galaxy distribution. X-ray and gravitational-lens mass measurements of several nearby clusters, with redshifts $z < 0.4$, give mass-to-light ratios of $\sim 100\text{--}300h_{50}^{-1}$ (where the value for the Sun is 1, and h_{50} is the Hubble constant in units of $50\text{ km s}^{-1}\text{ Mpc}^{-1}$). This is only about a quarter of that required to close the Universe¹⁰ and so is used as an argument for an open Universe.

The discovery by Hattori *et al.* of a distant cluster ($z \sim 1$) with a very high mass-to-light ratio whose gas is considerably enriched in iron is a significant break with expectations, contrary to all these apparently established ideas.

The authors looked for X-ray emission from the region of a gravitationally lensed quasar, MG2016+112, using two X-ray satellites: ASCA, an X-ray astronomy spectroscopic mission; and Rosat, which has considerably better spatial resolution than ASCA. The large angular separation of this lensed quasar had led Narasimha *et al.*¹¹ to predict that the splitting was due to a massive gravitational lens, on the scale of a cluster mass. But sensitive optical searches showed no evidence for a cluster¹². So the discovery by Hattori *et al.* of a luminous X-ray-emitting cluster is unexpected.

In X-ray emission, this cluster is very similar to lower-redshift ($z < 0.4$) clusters, having similar size, luminosity, temperature and iron abundance. Using the X-ray data to obtain a mass via the equation of hydrostatic

Figure 1 An empty cluster. In X-rays (countours), MG2016 appears as a massive galaxy cluster; but at optical wavelengths (false colours) only one obvious galaxy is present. It also has a high content of heavy elements, presumably produced by stars — but what stars?