not seem to end there. The basic targeting signals can also bind to the inner face of the outer membrane[4], and the authors cite their unpublished data which confirm that part of this binding is to an acidic Tom22 domain that protrudes into the intermembrane space[5]. Tom7 may contribute yet another *trans*-binding site. So, as sketched by the black arrows in Fig. 1, protein transport across the outer membrane may be driven by binding of the targeting signal to a series of strategically placed acidic binding sites of increasing avidity. A binding relay mechanism could also mediate transfer of the precursor to the inner membrane — the awaiting outer mouth of the Tim channel has exposed acidic domains on Tim23, which bind targeting signals[6]. Even the cytosol may be part of this proposed binding array, as the acidic cytosolic protein Mft2 (whose 'acid bristles' resemble those of Tom20) controls the import of some artificial mitochondrial precursors *in vivo*, and binds mitochondrial targeting signals *in vitro*[7].

The binding relay model begs two questions. First, why do precursors not short-circuit this array by binding immediately to Tom5? Some short-circuiting may, in fact, be tolerated, because yeast cells lacking either Tom5 or Tom20 can still grow slowly at room temperature. In other words, they can probably still import proteins into their mitochondria. But massive short-circuit on the mitochondrial surface may be prevented by the cytosolic chaperone to which the precursor is bound[8]. Ordered binding to the intramitochondrial sites might be safeguarded by the topological arrangement of these sites. Second, what clears the bound precursor from the last member in the array? Logical candidates are the potential across the inner membrane and the ATP-driven protein-import motor on the matrix side of the inner membrane. Viewed in this light, Tom5 is the newest and smallest link in an 'acid chain' that guides basic mitochondrial-targeting signals to their final destination. □

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Seismology

New insights into old earthquakes

Paul Segall

Geodetic survey measurements conducted in the late nineteenth and early twentieth centuries continue to improve our understanding of the great San Francisco earthquake of 18 April 1906. These data are crucial to understanding the seismic strain history of the greater San Francisco Bay region, as exemplified in the latest work from Wayne Thatcher and colleagues, published in the *Journal of Geophysical Research*[1].

The 1906 earthquake was a milestone in the history of seismology. To many Californians it is the archetypal Big One, although amongst twentieth-century earthquakes it is not even close to being the biggest — the 1960 Chilean earthquake, the largest instrumentally recorded earthquake, had a seismic moment 350 times greater. Nevertheless, the 1906 earthquake was critical for what it revealed about the physics of earthquakes. Geologists quickly recognized that over 300 km of the San Andreas fault had slipped up to 6 m during the quake[2] (see map, Fig. 1). This observation helped to establish that fault slip caused earthquakes, rather than being a manifestation of secondary ground failure.

The transient seismic waves unleashed by the slip in 1906 devastated San Francisco. Permanent displacements of the Earth's crust, which remained after the shaking stopped, caused other, albeit less dramatic, problems. For example, roads were beheaded by the fault. Permanent ground displacement distorted precise survey networks which had been painstakingly measured to map the coastline of California and San Francisco Bay. These surveys, begun in the 1850s, determined the relative latitude and longitude of landmarks with a precision of a few parts in a million (a few decimetres over a distance of 100 km). With earthquake displacements of many metres occurring in the quake, it was "decided to repair the old triangulation, damaged by the earthquake, by doing new triangulation"[3].

The 1906 epicentral region was resurveyed by triangulation in 1906 and 1907 by the US Coast and Geodetic Survey. When the data were analysed they revealed that fault-parallel motions extended tens of kilometres from the San Andreas. The horizontal gradient in these displacements showed a decrease in shear strain acting on the fault. Furthermore, the measurements made between the 1850s and 1880s showed that shear strain had been building up on the fault in the decades before the earthquake. From these data, Harry Fielding Reid formulated the elastic rebound theory[4], in which earthquakes are caused by sudden release of shear strain resulting from fault slip, following years of slow strain accumulation. Elastic rebound remains a central tenet of modern theories of earthquake generation.

The triangulation measurements central to Reid's analysis remain invaluable, because advances in our understanding of earthquake mechanics and vastly improved computational capabilities allow use of the data in modelling of the earthquake in ways that were not imaginable in his day. Thatcher and his colleagues at the US Geological Survey have been at the forefront of this research, and have now refined[1] earlier modelling of the slip that occurred on the San Andreas on 18 April 1906.

This study adds previously unanalysed data at the northern end of the 1906 rupture near Cape Mendocino (Fig. 1). The San Andreas is located offshore between Point Arena and Shelter Cove, and the interpretation of the fault geometry near Shelter Cove has been controversial[5]. Assuming the main trace of the fault runs through Shelter Cove, the triangulation data suggest 8.6 m of fault slip in this region, the maximum slip anywhere along the 1906 rupture.

But it is data from the southeastern end of the rupture that yield the most significant results, for this is the location of the magnitude-6.9 1989 Loma Prieta earthquake. In this region it is possible to compare the strain released in the 1906 earthquake with strain accumulation in the years between 1906 and 1989. Geological and geodetic measurements suggest that the San Andreas fault in this region slips 19±4 mm yr^{-1} when averaged over many earthquake cycles[6]. Mapping indicated 1.5 m of slip in this area during the 1906 event, leading to some forecasts of a high probability of a moderate earthquake on this segment of the fault[7–9].

The reasoning was quite simple: if the San Andreas slips 19 mm yr^{-1} on average, and if the 1906 slip in this region was 1.5 m, then the strain released by the 1906 earthquake should have recovered by 1985. However, there is, of course, considerable uncertainty associated with both the long-term slip-rate and the 1906 co-seismic slip. Furthermore, our understanding of earthquake physics does not require the earthquake to occur when the earthquake strain-drop recovers. The so-called time-predictable model[10] is nonetheless widely used in long-term forecasting, and deserves careful testing. It is for this reason that the slip in 1906 near Loma Prieta is so important.

Although the surface mapping indicated 1.5 m of slip, the fault trace in this area is complex and it is possible that additional slip was distributed over a fault zone a few hundred metres wide, and was thus missed. Here is where the triangulation measurements are crucial. These data show that the Loma Prieta moved 1.2 m to the southeast in 1906, consistent with 2.5 ±0.4 m of slip on a

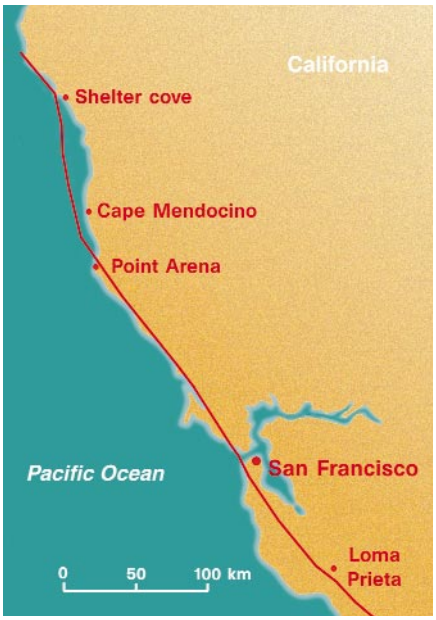

Figure 1 **The greater San Francisco Bay region, showing the course of the San Andreas fault and the main locations discussed in the text. The 1906 earthquake was a consequence of rapid slip along more than 300 km of the San Andreas in this part of California.**

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 slip[12]. 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 anticipated[7–9] 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 intensities[13] and geodetic displacements[14], 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 predicted. 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 physiology[1]. 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 Irmler *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 groups[6–8], 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 development[9].

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-κB, 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,