

affected (dominant, semi-dominant, or haploid-insufficient mutations), Siepka *et al.* also included recessive mutations (displaying phenotypes only when both alleles are mutated). Godinho *et al.* identified a mouse with a free-running circadian period length of ~24 hours, about 20 min longer than that of wild-type mice. This phenotype was called *after hours* (*Afh*), and positional cloning revealed *Fbx13* as the culprit gene for the deranged circadian locomotor activity. Sequencing identified a serine residue, rather than a cysteine residue, at position 358 in the mutated *Fbx13* protein. The peptide segment encompassing this mutated amino acid is involved in substrate recognition by *Fbx13*. Indeed, Busino *et al.* found reduced affinity of mutated *Fbx13* for *Cry* proteins.

The importance of this evolutionarily conserved peptide segment is underscored by the study by Siepka *et al.* Again, the mutant phenotype, called overtime (*Ovtm*), was due to a mutation in *Fbx13*. Sequencing revealed a mutation of an isoleucine to a threonine at position 364 of *Fbx13*, six amino acids downstream of the residue change linked to the *Afh* phenotype. The *Ovtm* founder mouse was likely homozygous for the mutation, because it free-ran with a period of ~26 hours; mice homozygous for the *Afh*-associated mutation

free-ran with a period of ~27 hours.

Despite the strong resemblance of the *Afh* and *Ovtm* phenotypes, however, *Ovtm* *Fbx13* bound to *Cry* only slightly less avidly than did wild-type *Fbx13* in cultured mouse cells. Moreover, the reduced abundance of *Cry1* and *Cry2* mRNA in the livers of *Ovtm* mice was not accompanied by equivalent changes in *Cry1* and *Cry2* protein accumulation. Nonetheless, the assignment of two independent mutations affecting circadian physiology to the same gene is unlikely to be a pure coincidence. Although it is difficult to reach statistical conclusions with the few circadian clock genes identified by “forward genetics” (using mutagenesis followed by screening to study gene function) (2, 3, 8, 9), the identification of *Fbx13* in two independent mouse mutant screens indicates that viable mutations affecting circadian clock functions are relatively rare in mammals.

Although groundwork for studying the regulation of *Cry* degradation has now been laid, two interrelated questions will have to be addressed. What signal triggers *Fbx13*-*Cry* interaction? Is it a specific post-translational modification of *Cry*? The other question concerns the temporal regulation of *Cry* degradation rates. At least in liver, *Cry2* protein accumulates with a

markedly higher circadian amplitude than *Cry2* mRNA (10). We do not yet know whether daily fluctuations in protein synthesis or decay rates account for this discrepancy. It may be that free *Cry* proteins are better substrates for *Fbx13*-mediated degradation than *Cry* that is associated with *Per* proteins (see the figure). Now that we know that regulated protein destruction is essential to clock precision, deciphering its exact molecular mechanism is no longer a far cry away.

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## GEOLOGY

# Assessing Landslide Hazards

David K. Keefer and Matthew C. Larsen

On 31 May 1970, a large earthquake shook the highest part of the Peruvian Andes. Millions of cubic meters of rock dislodged from a mountainside and initiated a rock avalanche that traveled more than 14 km in 3 min, burying a city and killing more than 25,000 people (1, 2). On 17 February 2006, a landslide of 15 million m<sup>3</sup> that initiated on a slope weakened by long-term tectonic activity buried more than 1100 people on Leyte Island in the Philippines (3).

Landslides such as these are a hazard in almost all countries, causing billions of dollars of damage and many casualties (4). Landslides also contribute to landscape evolution and erosion in mountainous regions (see the first figure). Here we discuss the latest

strategies used to assess and mitigate landslide hazards.

The basic physics governing the initiation of landslides—the interactions among material strength, gravitational stress, external forces, and pore-fluid pressure—has been well understood for decades. The factors that govern whether landslide movements, once begun, will be catastrophic are less well understood. Nonetheless, much recent progress has been made in understanding those factors, as exemplified by basic research on fracture development in brittle materials (5) and on the properties of flowing material (6, 7).

Major causes of landslides are also well known, and these include rainfall, seismic shaking, human construction activities, landscape alteration, and natural processes of erosion that undermine slopes. Yet predicting just where and when a landslide will occur continues to be a complex proposition, because the properties of earth materials and slope condi-

Despite their widespread occurrence and often deadly nature, it remains difficult to predict when and where landslides are likely to occur.

tions vary greatly over short distances, and the timing, location, and intensity of triggering events—such as storm precipitation or earthquake shaking—are difficult to forecast.

Two landslides at La Conchita in California illustrate the complexity of landslide occurrence and behavior. In 1995, a landslide consisting of a relatively coherent block of earth at La Conchita caused property damage but no fatalities. Ten years later, another landslide remobilized from the 1995 deposit, transformed rapidly into a highly fluid debris flow, and traveled downslope at a speed of 5 to 10 m/s, causing 10 fatalities (see the second figure) (8).

Current landslide hazard analyses and mitigation strategies tend to concentrate at one of two scales: intensive, site-specific analyses of individual slopes or landslide bodies, and regional-scale evaluations that seek to identify hazardous zones that are best avoided when construction is planned.

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**Landslides in mountain regions.** These rock avalanches were triggered by the 1980 Mammoth Lakes earthquake sequence. Several thousand rock falls and slides were associated with this event in central California.

In a site-specific landslide evaluation, instruments may be installed into the slope to determine water pressures, measure subsurface slippage, and monitor surface deformation. Materials may be sampled for laboratory testing of shear strengths and other properties such as mineralogy and density. Because these methods are expensive, extensive and site-specific analyses are commonly restricted to slopes where the costs of construction, potential for damage, or risk to population justify the expense.

A range of analytical techniques is used to evaluate the potential for landslide initiation at the site-specific scale. The decades-old and generalized limit-equilibrium method envisions a landslide as a rigid sliding block, and this has proved useful for many engineering and construction applications. Some newer, more sophisticated methods are specialized for the analysis of such processes as volcano-flank collapses (9) and initiation of debris flows (6, 7). In the case of volcano-flank collapses, for example, these new methods incorporate coupled numerical modeling of heat and groundwater flow to analyze the potential for landslide initiation involving steep volcano flanks due to hydrothermal pressurization. Such modeling predicts the occurrence of deep-seated landslides that match the dimensions of many observed landslides, whereas more traditional slope-stability analyses predict that the landslides would be shallow (9).

Regional-scale evaluations of landslide hazards also use a range of analytical techniques. For example, modeling that combines analysis of groundwater flow with slope-stability calculations has been used to predict

the timing and location of shallow, precipitation-triggered landslides (10), and the Newmark analysis (which combines slope-stability calculations with seismic ground-motion records) is widely used to evaluate the potential for landslides that could be triggered by earthquake shaking (11, 12). Regional-scale analyses may also include empirical methods based on mapping landslide occurrences and developing statistical correlations among landslide occurrence, material and slope properties (such as rock type and slope steepness), and the strength of triggering events such as seismic shaking (13) or rainfall intensity and duration (10, 14–17).

Regional-scale landslide analyses took a leap forward with the advent of high-resolution remote-sensing imagery and the use of geographic information systems (GIS) technology. The first automated event-based mapping of landslides from satellite imagery was carried out after the 1999 Chi-Chi earthquake

in Taiwan (18). More recently, landslides triggered by the 2004 Niigata Ken Chuetsu earthquake in Japan were mapped using a similar technique (19). Further automated landslide mapping of this kind would greatly extend the database on which regional-scale hazard and risk models may be constructed.

Several other techniques also have promise for increasing the accuracy, precision, and effectiveness of landslide hazard evaluation. For example, synthetic aperture radar interferometry can be used for early detection of landslide movements (20). Models are being developed to predict landslide motion based on detailed analyses of motion-induced changes in pore-fluid pressures and material properties in landslide shear zones (21, 22). Finally, landslide warning systems can be used to issue public alerts and warnings for a particular region when accumulated and/or forecast amounts of rainfall equal or approach those amounts that have triggered landslides there in the past (23, 24).

Current landslide research efforts around the world are generally small relative to the costs of landslide damage. A recent report by the U.S. National Research Council recommended a 15-fold increase in funding for landslide research and development in the United States (25). Although landslide hazard evaluation and mitigation strategies are



**Dangerous complexity.** This landslide at La Conchita, California, on 10 January 2005 destroyed 13 houses, severely damaged 23 others, and killed 10 people (8).

advancing in many fundamental areas, the loss of life and destruction of property by landslides around the world will probably continue to rise as the world population increases, urban areas of many large cities impinge more on steep slopes, and deforestation and other human landscape alterations affect ever-larger areas.

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## CELL SIGNALING

# A Touching Response to Damage

John H. J. Petrini

There are many things in day-to-day life that have the potential to cause mutations. Environmental exposure to chemicals and sunlight, and assaults from within such as free radicals produced when cells use sugar to make energy, all share the property of causing mutagenic damage to DNA. Despite this, the genetic information stored in DNA is remarkably stable. This is largely attributable to the existence of a complex cellular signaling network called the DNA damage response. Its role in maintaining genome integrity requires the integration of three general processes: sensing the damage, regulating the cell division cycle, and repairing DNA. The effectiveness of each, and their integration, relies heavily on the proper spatiotemporal dynamics of the components of this signaling network. Four papers in this issue—by Matsuoka *et al.* (1) on page 1160, Wang *et al.* (2) on page 1194, Sobhian *et al.* (3) on page 1198, and Kim *et al.* (4) on page 1202—collectively underscore that these dynamics are influenced by modifications of proteins that are catalyzed, and subsequently recognized, by components of the network itself.

The DNA damage response is loosely analogous to signal transduction networks activated by extracellular stimuli such as hormones and growth factors. Just as such factors (ligands) are bound by receptors on the cell surface to initiate the appropriate signal, damaged DNA engages proteins that

sense genetic lesions. In both scenarios, the interaction of ligand with the receptor initiates a signaling cascade that leads to the phosphorylation of proteins functioning in the pathway. And in both cases, this chain of events culminates in the alteration of cellular processes.

Within the context of the DNA damage response, this general scheme also implicitly provides a critical piece of information: the location of the DNA damage. This feature is a consequence of the fact that DNA damage sensors recruit specific protein-phosphorylating enzymes (kinases) to the sites of damage. Among these kinases are ataxia telangiectasia mutated (ATM), ATM and Rad3-related kinase (ATR), and DNA-dependent protein kinase. This recruitment is a requisite first step in activating the DNA damage response.

Matsuoka and colleagues cataloged substrates of ATM and ATR, the major signal-transducing kinases of the DNA damage response, through the large-scale identification of peptides that are phosphorylated in response to ionizing radiation. For this approach, they used a panel of 68 phospho-specific antisera to purify, and ultimately identify the peptides in question from cells treated with ionizing radiation, a DNA damaging agent. Although the antisera were raised against 68 known ATM and ATR substrates, 700 additional targets were found; hence, almost 10 novel peptides were recovered for each phospho-specific reagent used. This suggests that sites phosphorylated by ATM and ATR are structurally similar.

An extensive network of proteins, and their combinatorial diversity, account for biological functions that are regulated in response to damaged DNA.

From a biological perspective, this presumptive similarity suggests that phosphorylation “marks” inscribed by the transducing kinases may be recognized by protein domains common to mediators of the DNA damage response to facilitate protein interactions (see the figure). This idea is supported by the fact that the breast cancer C-terminal (BRCT) domain and forkhead-associated (FHA) domain—both phosphopeptide binding motifs—are commonly found in members of the DNA damage response signaling network. On the other hand, from a technical perspective, it’s hard to imagine a more eloquent word of caution regarding the interpretation of immunofluorescence data obtained using those cross-reactive antisera to assess the disposition of DNA damage response proteins.

The central issue, and the major advance that Matsuoka *et al.* provide, is that the targets identified represent a comprehensive catalog of ATM and ATR substrates. To assess whether their approach accurately identified bona fide members of the DNA damage response network, Matsuoka *et al.* picked 37 of the new ATM and ATR targets and depleted them from human osteosarcoma cells with small interfering RNA. Although these proteins had not previously been implicated in the DNA damage response, more than 90% of the new targets queried in this manner exhibited defects in one or more indices of DNA damage response functions such as the activation of cell cycle checkpoints and DNA repair. These validations illustrate that this data set provides a solid foundation for

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