Abstractions

LEAD AUTHOR

Roger Bilham is on a mission to improve earthquake forecasts in the Himalayan region. The geophysicist and his student Nicole Feldl, from the University of Colorado, Boulder, braved high altitudes and Maoist guerillas to gather GPS points in the Himalaya. Using these data and a subsurface model of the northern Indian region helped clarify the seismic significance of the squishy Tibetan plateau that has confounded modelling efforts up to now. On page 165, the model represents how time lag between earthquakes, the length of ruptures and their magnitude are linked.

How soon could the Himalaya experience a massive earthquake?

Our calculations show that two-thirds of the Himalaya are ready today for an earthquake of magnitude 8 or greater. Some parts of the Himalaya are apparently long overdue.

Describe your model.

By assuming that most of the Tibetan plateau is elastic, or able to return to its original shape following temporary stress, we calculated how earthquake magnitude grows with rupture length. Using data from past earthquakes, we calibrated our results by adjusting the time interval in our models that's necessary to obtain the observed geologic movement. Unfortunately, it's not useful for accurately predicting earthquakes.

How does this work change assumptions about plate activity in the region?

It brings a new perspective, with a couple of unexpected consequences. For example, if you have a devastating magnitude 7.6 earthquake (like in Kashmir, 2005), we find that it doesn't drain the system's energy, and the same area can have another, bigger earthquake soon afterwards. This contradicts seismic gap theory, which says if you've recently had a big earthquake you shouldn't expect another for a long time.

If pressure is released by smaller earthquakes, how can conditions for a megaquake still exist?

Short ruptures are unable to tap deep into the Tibetan plateau's cumulative reservoir of strain energy. It requires megaquakes to do this. We've had four fairly substantial earthquakes in the past 200 years, but they haven't been big enough to release much of this cumulative strain.

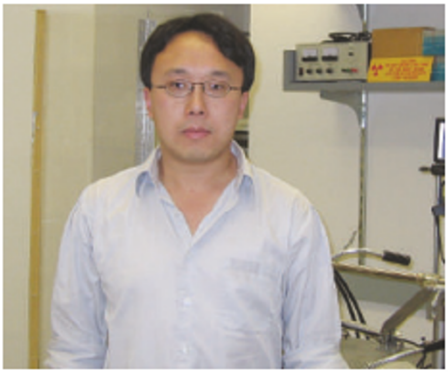
How serious is the threat of earthquake in the region?

Quite frankly, the countries bordering the Himalaya are in terrible trouble. We estimate that one million people could die in a single event unless city structures are made earthquake-resistant. ■

MAKING THE PAPER

Ya Ha

Understanding how proteases cut inside the cell membrane.



Scientists have long puzzled over the workings of membrane-spanning proteases, the molecular scalpels that cleave other membrane proteins into smaller segments. Their interest is due, in part, to the fact that this group of enzymes includes γ-secretase, the protease responsible for producing the amyloid β-peptide that forms damaging plaques in the brains of Alzheimer's sufferers. Understanding how γ-secretase works may lead to ways to stop its function and hinder the disease. On page 179 of this issue, Ya Ha of Yale University School of Medicine, New Haven, determines the crystal structure of another intramembrane protease from *Escherichia coli*. Although unrelated to γ-secretase in amino-acid sequence, the protease he describes is likely to act in the same way.

Proteases cleave proteins into smaller segments using water molecules to break amino-acid bonds. Thus, they typically operate in a watery environment. But the proteases embedded in the cell's membrane are an exception. They do the cutting inside the cell membrane.

Ha heard about this group of enzymes as a postdoc at Harvard University five years ago while searching for a project for his own lab. The intramembrane proteases seemed to fit the bill. "This area was ideal for a structural biologist like myself because there is no other way to figure out how these proteases work," he explains. "You need direct visualization to do so."

After setting up his lab at Yale in 2001, he set out, with the help of Yongcheng Wang and Yingjiu Zhang, to determine the crystal structures of several intramembrane proteases, including γ-secretase. He followed standard laboratory practice, engineering the genes encoding these proteases so that they were expressed in bacteria. He purified each protein to make crystals from it, and then bombarded the crystals with X-rays to reveal the relative positions of the protein's atoms.

"We were stuck at almost every step of the process," laughs Ha. "It was a risky project." Most of the proteins he had started with had to be discarded at various stages of the purification process because they did not yield either sufficient amounts or sufficiently pure or stable protein. But he persevered. "Structural biologists have a number of tricks to use," he says. In the end, he was able to crystallize a bacterial rhomboid protein called GlpG.

With crystals in hand, he quickly obtained the protein's structure. Ha discovered that the amino acids involved in cleaving target proteins reside in a cavity smack in the middle of the protein, along with several water molecules. Although the membrane keeps water out, inside the enzyme there's a little watery pool where the proteins are cut. In the absence of a protein, the opening to this cavity is blocked by a string of amino acids shaped into a loop, which may act as a molecular gate.

Ha plans to use his experience to unravel the structure of other intramembrane proteases, including γ-secretase. "Now we know how difficult the project is, but that it can be done," he says, while acknowledging that the process may not be any easier the second time around. "I have been in the field long enough to know that experience does not always translate into making things go faster." ■

KEY COLLABORATION

Chimpanzees are recognized as the primary primate reservoir for simian immunodeficiency viruses (SIV) — the most closely related virus to HIV-1, which causes AIDS in humans. Earlier this year, the origins of both a pandemic and non-pandemic form of HIV-1 were traced to distinct chimpanzee groups in southern Cameroon. The same research team found that wild gorillas in western Cameroon were infected with a variant of SIV that is more closely related to a strain of HIV-1 (see page 164).

The ten-year collaboration of researchers — from France, the United States, the United Kingdom and Cameroon — collected fecal samples from chimpanzees and gorillas in the remote regions of Cameroon. "It is key to have a local team involved in such research efforts," says Martine Peeters, a virologist at the University of Montpellier, France.

The samples were sent to labs in France and Alabama equipped to extract fecal RNA.

Peeters stresses that the gorilla findings don't negate previous chimpanzee work. "Chimpanzees could have transmitted the newly found virus to gorillas and humans independently, or they could have been transmitted first to gorillas, who transmitted it to humans," she says.

The team will soon perform analyses at a molecular-biology lab to be built in Cameroon. ■