The authors found that aneuploidy also strongly affects cell metabolism. The aneuploid strains avidly take up glucose, and many also undergo amplification of genes encoding glucose transporters. However, glucose is used less efficiently in these cells, resulting in lower accumulated biomass per unit of glucose. This is intriguing given that many tumor cells exhibit the “Warburg effect” (12), in which glycolysis (anaerobic metabolism) is emphasized at the expense of mitochondrial (aerobic) respiration. Although S. cerevisiae has a unique physiology that emphasizes fermentation relative to respiration, it will be interesting to determine whether aneuploidy elicits a similar metabolic effect in mammalian cells.

What is the basis for the increased glucose requirement in the yeast aneuploids? Torres et al. propose a simple and intuitive explanation. Although transcripts from the disomic chromosome doubled in abundance, steady-state levels of many proteins encoded by these transcripts did not. The aneuploid strains are also sensitive to compounds that inhibit protein translation or block protein degradation by proteasomes. Thus, the gene expression imbalance leads to compensatory proteolysis, which demands more energy (see the figure). Furthermore, analysis of strains harboring large human genomic DNA fragments as yeast artificial chromosomes, which are not expected to be transcribed or translated to any great extent, did not exhibit a growth delay or drug sensitivities associated with authentic yeast disomes, indicating that these phenotypes are triggered by increases in gene expression rather than the presence of extra DNA.

The results of Torres et al. and earlier studies of fibroblasts obtained from Down syndrome patients (13) indicate that a single extra chromosome can exert a strong antiproliferative effect in both yeast and human cells. If this is the case, then how do aneuploid cancer cells overcome this barrier? There are at least two possibilities. There may be a protective effect of diplody, as Torres et al. found that deleterious consequences of an extra chromosome are less severe in diploid cells than in haploids. This is consistent with previous mathematical analyses showing that increases in the number of sets of chromosomes (ploidy) can buffer the effects of harmful somatic mutations in the short term (14). Some cancers may arise through a tetraploid intermediate (15), which could enhance this buffering effect. This may explain why yeast tetraploids exhibit high rates of chromosome loss but lack detectable delays in cell cycle progression (16). In addition, genes in mammalian cells can be transcriptionally silenced through mechanisms not available in yeast. For instance, most cancer cells exhibit localized chemical modification (hypermethylation) of specific stretches of DNA ( CpG islands) in promoter regions of genes (17). This could lessen the metabolic impact of aneuploidy by silencing genes on a supernumerary chromosome while preserving expression of other genes on the chromosome that confer a selective clonal advantage. Nonetheless, if at least a portion of the transcriptional and phenotypic response to aneuploidy persists in cancer cells, it may be possible to devise inhibitors that arrest or kill such aneuploid cells selectively, with little or no impact on normal diploid tissues (18).

References and Notes
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GEOPHYSICS

The Need to Study Speed
Shamita Das

Rapid ruptures can cause more earthquake damage than slow ones. Lessons from past events indicate which faults may be most dangerous.

The damage earthquakes cause to society depends in part on how fast rock ruptures (1). During the 1960s, owing partly to limited observation and partly to inadequate theory, researchers believed that ruptures could not propagate faster than about 3 km/s, the speed of a transverse (shear) wave moving in rock. Several theoretical studies in the 1970s found that some ruptures could exceed this speed, perhaps reaching 5 km/s (2). Recently, Bhat et al. reported field observations showing that an earthquake in Tibet ruptured faster than the shear wave speed (3). Given the potential for increased destruction, we must take such information into account when planning earthquake-resistant construction worldwide.

The first earthquake that ruptured faster than the shear speed was the 1979 Imperial Valley, California, event (4). No other example was found for two decades, supporting those who resisted the idea of supershear rupture speeds. However, starting in 1999, researchers began to measure fast rupture speeds (5, 6) in the laboratory. The improvement in quality and quantity of seismometers worldwide also led to new reports of supershear rupture speeds (7). Yet, because these reports were based on analysis of very few seismograms, few accepted the possibility of supershear rupture speeds.

Then in 2003, Bouchon and Vallée reported convincing evidence of supershear rupture speed for the 2001 Kunlunshan, Tibet, earthquake (magnitude Mw = 7.8) (8). This earthquake, in which the net slip was in the direction of the surface path of the fault (a strike-slip fault), ruptured a segment longer than 400 km, the longest strike-slip fault rupture (both on land and under water) since the 1906 California earthquake. Robinson et al. (9) showed that the rupture started slowly, accelerated to a supershear wave speed, and then propagated over more than 100 km at a speed of nearly 6 km/s, before slowing and stopping (see the figure, left panel). The region of very high rupture speed coincided with the region of highest earthquake displacement, highest fault slip rate, and highest stress release and occurred on a very straight portion of the fault.

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PERSPECTIVES
Fast breaks. (Left) Vertical bars show the slip on the Main Kunlun fault for the 2001 Tibet earthquake [adapted from (9)]. (Upper and lower right) The fault slip for the 1906 California earthquake [adapted from (15)]. The fault segment ruptured is shown by the thick red line; the black star on this line marks the region where rupture commenced. The fault rupture for the 1857 California earthquake is indicated by the red dashed line, the black star indicating region of rupture commencement. If the next earthquake here follows this pattern, a superfast rupture propagating southward would strongly focus shock waves on Santa Barbara and Los Angeles.

High slip rate (the relative speed of the two sides of the fault) may drastically lower the friction on the fault (10, 11), allowing much higher rupture speed (the speed at which the two sides separate at the leading edge of the fault). In the Kunlun earthquake, the region of large displacement has been separately confirmed from satellite measurements (12). In addition, field observations, made several months later by Bhat et al., showed a ~25-km-wide region to the south of the superfast rupture section of the fault with many off-fault open cracks (3). Calculations show that as the rupture moves from sub- to supershear speeds, large perpendicular stresses develop in the off-fault regions, as the shock wave passes through, which could explain these cracks (3). These off-fault open cracks are seen in only that portion of the fault that was found to have the very high rupture speed (9). This is independent corroboration that the earthquake did actually reach supershear speeds in this long, straight section of the fault, the first earthquake for which such direct evidence is available.

The Tibet earthquake suggests that long, straight strike-slip faults are necessary for ruptures to propagate at supershear speeds. Re-examination of earlier reports of supershear rupture also show that such speeds generally occur on the straight section of faults (7, 13), although not all straight portions of faults reach supershear speeds. Thus, straightforwardness of the fault is only a necessary (but not sufficient) condition for very fast rupture. Fracture mechanics studies show that long, straight faults are more likely to reach the high rupture speeds. The faults start from rest, accelerate to the maximum permissible speed, and continue at this speed provided there are no obstacles along the way and fault friction is low (2).

What can the 2001 Tibet earthquake teach us about, for example, the 1906 and the 1857 California earthquakes? Any repeats of these events may lead to fewer deaths but will certainly produce greater financial cost than the 2004 Sumatra-Andaman earthquake and tsunami. The 2001 Tibet earthquake is very similar to the 1906 San Francisco earthquake, both being vertical strike-slip faults and having similar magnitude, fault length and width, and hence similar average slip and average stress drop. The 1906 earthquake rupture started south of San Francisco (see the figure, upper right panel) and propagated both to the northwest and to the southeast. Geodetic measurements (14) show that the largest displacements were to the north of San Francisco, which is in agreement with results obtained by inversion of available seismograms (15). This northern segment may have reached supershear rupture speeds (16). The fact that the high fault-displacement region is also here, where the fault is very straight, would provide additional support for this notion, assuming the 1906 and the 2001 earthquakes behaved similarly. Unfortunately, due to heavy rains and rapid rebuilding following the 1906 earthquake, no information is available on whether off-fault cracks appeared in this region. Fortunately, the cold desert climate of Tibet had preserved the off-fault open cracks from the 2001 earthquake, uncovered during the winter months, until the scientists visited.

Of course, no seismograms are available for the 1857 Fort Tejon earthquake (see the figure, upper right panel), which was a strike-slip earthquake with a rupture length greater than 300 km. Trenching across the fault revealed that the largest slip occurred in the Carrizo Plain, where the fault is very straight (17). One can speculate that the 1857 earthquake may have propagated at supershear speeds in the Carrizo Plain, and slowed as it went around the “Big Bend,” just as the 2001 Tibet earthquake slowed at a bend in the fault strike.

The 1857 and 1906 California earthquakes may have propagated faster than was believed. If so, we need to apply the same analysis to other great strike-slip faults around the world, such as the more than 10,000-km-long Himalayan-Alpine seismic belt. We also need to develop a measure of the “straightness” of faults and the length of the straight portion required for such fast rupture speeds. Observations of off-fault open cracks can be used as a diagnostic tool for supershear rupture, and it would be useful to search for and document them.

References and Notes