Stress-induced genomic instability facilitates rapid cellular adaption in yeast

January 29 2012

Cells trying to keep pace with constantly changing environmental conditions need to strike a fine balance between maintaining their genomic integrity and allowing enough genetic flexibility to adapt to inhospitable conditions. In their latest study, researchers at the Stowers Institute for Medical Research were able to show that under stressful conditions yeast genomes become unstable, readily acquiring or losing whole chromosomes to enable rapid adaption.

The research, published in the January 29, 2012, advance online issue of *Nature*, demonstrates that stress itself can increase the pace of evolution by increasing the rate of chromosomal instability or aneuploidy. The observation of stress-induced chromosome instability casts the molecular mechanisms driving cellular evolution into a new perspective and may help explain how cancer cells elude the body's natural defense mechanisms or the toxic effects of chemotherapy drugs.

"Cells employ intricate control mechanisms to maintain genomic stability and prevent abnormal chromosome numbers," says the study's leader, Stowers investigator Rong Li, Ph.D. "We found that under stress cellular mechanisms ensuring chromosome transmission fidelity are relaxed to allow the emergence of progeny cells with diverse aneuploid chromosome numbers, producing a population with large genetic variation."

Known as adaptive genetic change, the concept of stress-induced genetic variation first emerged in bacteria and departs from a long-held basic

tenet of evolutionary theory, which holds that genetic diversity —evolution's raw material from which natural selection picks the best choice under any given circumstance—arises independently of hostile environmental conditions.

"From an evolutionary standpoint it is a very interesting finding," says graduate student and first author Guangbo Chen. "It shows how stress itself can help cells adapt to stress by inducing chromosomal instability."

Aneuploidy is most often associated with cancer and developmental defects and has recently been shown to reduce cellular fitness. Yet, an abnormal number of chromosomes is not necessarily a bad thing. Many wild yeast strains and their commercial cousins used to make bread or brew beer have adapted to their living environs by rejiggering the number of chromosomes they carry. "Euploid cells are optimized to thrive under 'normal' conditions," says Li. "In stressful environments aneuploid cells can quickly gain the upper hand when it comes to finding creative solutions to roadblocks they encounter in their environment."

After Li and her team had shown in an earlier *Nature* study that aneuploidy can confer a growth advantage on cells when they are exposed to many different types of stress conditions, the Stowers researchers wondered whether stress itself could increase the chromosome segregation error rate.

To find out, Chen exposed yeast cells to different chemicals that induce various types of general stress and assessed the loss of an artificial chromosome. This initial screen revealed that many stress conditions, including oxidative stress, increased the rate of chromosome loss ten to 20-fold, a rate typically observed when cells are treated with benomyl, a microtubule inhibitor that directly affects chromosome segregation.

The real surprise was radicicol, a drug that induces proteotoxic stress by

inhibiting a chaperone protein, recalls Chen. "Even at a concentration that barely slows down growth, radicicol induced extremely high levels of chromosome instability within a very short period of time," he says.

Continued growth of yeast cells in the presence of radicicol led to the emergence of drug-resistant colonies that had acquired an additional copy of chromosome XV. Yeast cells pretreated briefly with radicicol to induce genomic instability also adapted more efficiently to the presence of other drugs including fluconazole, tunicamycin, or benomyl, when compared to euploid cells.

Interestingly, certain chromosome combinations dominated in colonies that were resistant to a specific drug. Fluconazole-resistant colonies typically gained an extra copy of chromosome VIII, tunicamycin-resistant colonies tended to lose chromosome XVI, while a majority of benomyl-resistant colonies got rid of chromosome XII. "This suggested to us that specific karyotypes are associated with resistance to certain drugs," says Chen.

Digging deeper, Chen grew tunicamycin-resistant yeast cells, which had adapted to the presence of the antibiotic by losing one copy of chromosome XVI, under drug-free conditions. Before long, colonies of two distinct sizes emerged. He quickly discovered that the faster growing colonies had regained the missing chromosome. By returning to a normal chromosome XVI number, these newly arisen euploid cells had acquired a distinctive growth advantage over their aneuploid neighbors. But most importantly, the fast growing yeast cells were no longer resistant to tunicamycin and thus clearly linking tunicamycin resistance to the loss of chromosome XVI.

Provided by Stowers Institute for Medical Research