The Scientist: NewsBlog:
Stress strikes cytogenetics
Posted by Elie Dolgin
[Entry posted at 14th November 2008 03:23 AM GMT]
View comment(1) | Comment on this blog

Cellular stress during replication induces many small deletions and duplications in the genome, adding fuel for human diversity and disease, researchers reported today (Nov. 13) at the *American Society of Human Genetics* meeting in Philadelphia.

Replication stress is known to be hazardous for the cell, and is thought to contribute to ageing and cancer. But exactly how stress causes DNA damage has remained unclear. Last year, a team led by Thomas Glover, a human geneticist at the University of Michigan, Ann Arbor, showed that human-mouse hybrid cells exposed to aphidicolin -- an antibiotic that inhibits DNA polymerase and induces mitotic stress -- led to a high frequency of submicroscopic deletions at a particular genomic site with elevated susceptibility to DNA damage (*PNAS*, 105: 246-251, 2007).

Now, Glover's team exposed human fibroblasts to the same stressful conditions, and compared the stressed out cells with their normal counterparts using array-based comparative genomic hybridization. Their results revealed a suite of sequence copy number changes -- deletions and duplications -- between the stressed sample and control DNA.

They found that eight of their 14 stressed cell populations had at least one copy number change, compared to only one of 11 control populations. On average, each stressed cell population had 2.2 copy number changes after three days of aphidicolin-treatment -- about 10 times more changes than the control -- with no apparent patterning between chromosomes. "Numbers of deletions and duplications are just scattered across the genome," Martin Arlt, the study's lead author, said in a presentation.

The deletions varied from 25 to around 1,300 kilobases, while the duplications were slightly larger, ranging from 143 to around 2,800 kilobases. In one instance, the researchers observed the same deletion in two independent cell lines, indicating that there might be a predictable pathway to stress-induced DNA damage.

Glover's team sequenced the deletions' breakpoint junctions, and discovered that they were all characterized by short equivalent DNA sequences called microhomologies. This pattern is consistent with a particular form of DNA repair that uses microhomologies to mend DNA damage, known as non-homologous end joining, rather than other

genetic fix-it methods that rely on matching DNA templates, the researchers concluded.

Since the observed deletions and duplications closely resembled copy number variants seen in screens of human diversity, as well as spontaneous DNA changes implicated in diseases such as cancer, stress during cell division is likely a major contributor to both normal and aberrant genomic copy number changes, Arlt said.

Rate this article

Rating: **4.47**/5 (19 votes)

Comment on this blog

Return to Top
comment:
Stress or poison?
by null null

[Comment posted 2008-11-18 03:56:14]

I would not consider this "stress", it is a deliberate poisoning of the DNA replication machinery. Is it any wonder that it causes DNA damage and error in repairs? A small bullet in heart muscle would impair circulation, but isn't generally termed "stress".
HF

Comment on this blog