Cancer in a single catastrophe

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Most of the time cancer seems to creep up gradually over time; cells become premalignant, then increasingly abnormal before they become cancerous. But sometimes cancers seem to pop up as if out of nowhere. Now, researchers reporting in the January 7th issue of the journal *Cell* have new evidence to explain how that can happen. Based on the DNA sequences of multiple cancer samples of various types, they show that cancer can arise suddenly in the aftermath of one-off cellular crises involving tens to hundreds of genomic rearrangements.

"We think this process happens as a part of life to produce chromosomal damage on a spectacular scale," said Peter Campbell of Wellcome trust Sanger Institute and the University of Cambridge. "Probably almost always the cell dies, but sometimes the cell tries to rescue itself. It repairs itself incorrectly and a genome emerges with incredible cancerous potential."

The researchers report that this stamp of the phenomenon they call chromothripsis (meaning chromosome shattering) can be seen in at least two to three percent of all cancers, and some 25 percent of bone cancers. Given the prevalence of cancer, that's quite a significant number, they say.

Campbell's team started out studying the patterns of DNA rearrangements in cancers in general. Those sequencing studies turned up cases in which there were massive rearrangements in tightly circumscribed regions of the genome, involving one to a few chromosomes. They attempted to come up with a scenario to reconstruct a series of events that might lead up to such a massive rearrangement and "it was impossible to do," Campbell said.

That led to the notion that those chromosomes had instead been shattered in a single catastrophe and then patched back together in "higgledy piggledy" fashion. "The cell should say, 'That's it,' and give up but instead it tries to piece the chromosomes back together like a valuable piece of porcelain," Campbell explained. "They attempt to reconstruct the un-reconstructable and they wind up with a disastrous genome that shortens the road to cancer."

Campbell said they don't yet know what might cause such large-scale rearrangements, but he suspects single pulses of ionizing radiation might play a role. Ionizing radiation is well-known to induce double stranded DNA breaks that could cut a swathe through a condensed chromosome and, depending on whether the angle of the path relative to the long axis of the chromosome is transverse, oblique or longitudinal, generate breaks involving a band, an arm or the whole chromosome, according to the researchers.

One of the key things they intend to do now is identify potential causes for the damage. "If we can understand its roots, then we may learn how to prevent that kind of damage from happening," he said. They will look at cancers in people with known exposure to ionizing radiation in search of evidence of these sorts of rearrangement.

"Whatever the mechanism of damage, the consequences are profound," the researchers write in conclusion. "Faced with hundreds of DNA breaks, the cell's DNA repair machinery attempts to rescue the genome. The resultant hodgepodge bears little resemblance to its original structure, and the genomic disruption has wholesale and potentially oncogenic effects."

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