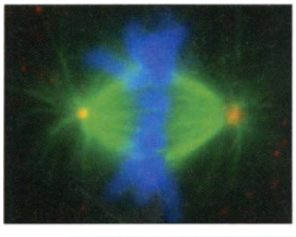
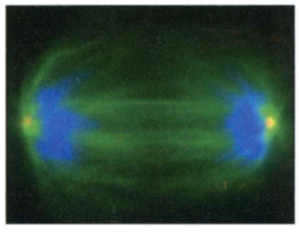
The Unstable Path To Cancer

For a cell, maintaining the integrity of its genome is of paramount importance. If it fails in this task and manages to divide anyway, both of its daughter cells may inherit an abnormal chromosome complement, with potentially dire consequences. In addition to subtle genetic mutations, most cancer cells show dramatic karyotypic changes, including gains and losses of chromosomes, gross chromosomal rearrangements, and amplification or deletion of genetic material, although scientists are still wrestling with the issue of whether this genome instability causes cancer or merely arises after a cell is already well along the path to malignancy. In this special section, *Science* highlights the exciting progress being made in identifying the molecular mechanisms that stabilize the genome and presumably destabilize it when disrupted in cancer cells.

One of the most serious threats to genome stability is unrepaired DNA damage. Rouse and Jackson (p. 547) introduce the section by reviewing the intracellular signaling pathways that activate the "DNA damage response," a critical protective mechanism that delays cell division until damage can be repaired. The wholesale genome rearrangements seen in cancer cells rarely occur in normal cells. The yeast experiments summarized by Kolodner *et al.* (p. 552) reveal why: These rearrangements are suppressed in normal cells by a series of extensive and redundant pathways that include (among other functions) the replication checkpoint proteins that sense defective chromosomes and the recombination proteins that help mediate their repair.





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Several laboratories are also exploring the possibility that genome rearrangements arise when stalled DNA replication forks are processed inappropriately by recombination enzymes; in a Viewpoint, Carr (p. 557) discusses two new Reports (Sogo *et al.*, p. 599, and Cha *et al.*, p. 602) that help to clarify the relationship between replication fork integrity, recombination, and checkpoint proteins. The gains and losses of chromosomes seen in cancer cells (aneuploidy) are almost certainly due to defects in chromosome segregation during cell division. Nasmyth (p. 559) reviews the molecular machinery that ensures the accurate separation of the duplicated chromosomes during mitosis. Finally, Maser and DePinho (p. 565) discuss the accumulating evidence that the dysfunction of telomeres (the structures that protect the ends of chromosomes) is a major driving force in the generation of chromosomal instability in cancer.

The role that genome instability plays in cancer has sparked intense debate in the field. Factions disagree not only about what kind of instability comes into play, but even more fundamentally about whether it causes malignancy or crops up later. A News story by Marx (p. 544) looks at the arguments put forth by the various sides, who are still far from agreement.

Whatever the outcome of these debates, the quest for answers has certainly produced many fascinating insights into the molecular weaponry that enables a cell to defend the integrity of its genome.

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