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"DNA Mismatch Repair: From Basic Mechanisms to the Genetics of Cancer Susceptibility"

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Garren Auditorium, Basic Science Building
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If you were to use a word processing program to re-type a page of your favorite book, you would certainly discover that the copy had many spelling mistakes. This would lead you to use a spell-checking program to correct the spelling mistakes. Cells face this problem every time they divide. They must make an exact copy of their genetic material or DNA; however, the genetic equivalent of spelling mistakes, called mutations occur during this process. Just like the person who can't spell, the cell uses its equivalent of a spell-checking program, called DNA mismatch repair, to edit out the spelling mistakes or mutations. DNA mismatch repair involves specialized proteins to eliminate mutations: it involves proteins that bind to the sites of the errors, other proteins to degrade or erase the DNA strand containing the error, and yet other proteins to remake a new correct DNA strand. These sequential steps eliminate the spelling mistake or mutation. The same repair pathways are present in many organisms ranging from bacteria to human cells.

Cancer is called a genetic disease because the normal cells become cancer cells as spelling mistakes, or mutations accumulate in critical genes that are required for normal cell growth or are required to prevent normal cells from acquiring cancer related properties. It has long been thought that the rate of accumulation of these types of errors in normal cells is too low to account for the development of cancer and that cancer cells must have defects resulting in higher than normal rates of accumulating spelling mistakes or mutations. Inherited defects in the genes that encode the cellular spell-checking function increase the cellular rate of accumulating spelling mistakes or mutations and cause a number of different types of common inherited cancer susceptibility syndromes. One of these syndromes, called hereditary non-polyposis colorectal cancer predisposes the affected families to develop colon cancer and many other types of cancer. Yet other such defects cause familial cancers and are found in sporadic cancers. In addition to causing the development of cancer, defects in the genes that encode the cellular spell-checking function also cause resistance to many chemotherapeutic agents. Thus, the human genetics of DNA mismatch repair has important implications for both the development of cancer and how it is treated.