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HIF-1α hinders mismatch repair

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A newly found mechanism that promotes the appearance of mutations under hypoxic conditions is reported in the March 18 issue of Molecular Cell. In the oxygen-deprived microenvironment of certain tumors, the genetic instabilities that ensue stimulate tumor progression and metastasis.

Eric Huang, from the National Cancer Institute in Bethesda, Md., and colleagues were studying HIF-1α, the hypoxia-induced transcription factor, which is known to upregulate a variety of hypoxia-related genes. HIF-1α is often overexpressed in tumors because different factors induce its expression.

Huang's team found that, under certain cellular conditions, HIF-1α is also responsible for hindering the cell's mismatch repair (MMR) system, crucial for maintaining a cell's genetic integrity. "Cancer cells already divide more frequently than others, so they develop more mutations," said Franklin Bunn, from Harvard Medical School, Cambridge, Massachusetts, who did not participate in the study. "Impairing the MMR system further enhances the potential for genetic instabilities."

Working with a variety of human cancer cell lines, Huang and colleagues identified the steps involved in the pathway. HIF-1α acts by displacing Myc, the transcriptional activator of two nuclear proteins, MSH2 and MSH6. In the absence of HIF-1α, Myc activates the expression of the two compounds, which then dimerize to form the MutSa complex—one of the mammalian versions of the MMR system. In the presence of HIF-1α, Myc cannot reach the promoters, and the expression of MutSa is inhibited.

Most importantly, the team found that the presence of wildtype tumor oncogene *p53* is an essential condition for this pathway to occur. "While less than half of all human cancers involve a wildtype version of *p53*, the findings nonetheless explain an important aspect of the biology of cancer. Here we discover the conditions in which a particular transcription factor, which is known to be induced in a majority of cancers, works to the tumor's advantage," said Peter Glazer, a professor of therapeutic radiology and genetics at Yale University, New Haven, Conn., who did not participate in the study. "We've already found other pathways that affect the MMR system under different conditions. The DNA correction system is a very complex business, and there are a number of factors that are involved in its regulation."

The question arises as to whether oxygen deficiency could induce the development of cancer. "HIF-1α–induced mutations may occur in the very early stages of the development of a tumor, when all cancer cells still express the wildtype *p53*," said Huang. "However, because it may take a few decades before a non-cancer cell acquires the combination of genetic mutations that will make it metastatic, it would be a pretty daunting challenge to try to demonstrate that hypoxia plays a role in carcinogenesis."

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