Discovery could increase tumors' sensitivity to radiation therapy

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To make tumors more sensitive to the killing power of radiation is a key aspiration for many radiation oncologists. Researchers at Washington University School of Medicine in St. Louis have uncovered new information that leads them closer to that goal.

In an upcoming issue of the journal *Molecular and Cellular Biology*, they report the first extensive study of an enzyme called MOF that helps control how DNA is packaged in cells. The researchers show that MOF is an essential factor for tumor development, and they say it may be possible to manipulate the enzyme to make tumors more sensitive to radiation therapy.

MOF adds a tag 'special chemical group' to the spools that hold the long strands of DNA in the chromosomes. The spools, made of proteins called histones, pack the genetic material into a more condensed form. By adding a tag at a precise location on one kind of histone, MOF helps relax the tight packing of genes and thereby influences how active the genes are.

Although many enzymes are involved in controlling chromosome structure to maintain cells' genetic machinery, MOF is so essential that without it cells inevitably die.

"We think that if we can deplete MOF in tumor cells, but not in healthy cells, we will gain a therapeutic advantage," says Tej K. Pandita, Ph.D., associate professor of radiation oncology and of genetics and a

researcher with the Siteman Cancer Center at Washington University School of Medicine and Barnes-Jewish Hospital. "If we affect MOF in tumor cells, they will be weakened and unable to recover after radiation exposure."

Pandita and his research group at the School of Medicine focus their research on ways to increase the radiation sensitivity of cancer cells to enhance the cure rate of radiation therapy. They became interested in MOF because it was previously found to be involved in genomic instability and defective DNA damage repair.

Other studies have suggested that loss of the histone tag created by MOF is a hallmark of cancerous cells. In contrast, in this study an analysis of more than 300 tumor samples demonstrated that all tumors had either normal or increased amounts of MOF and its histone tag compared to normal samples. When the researchers caused MOF to be more abundant than usual in cells, the cells proliferated faster and showed telltale signs of cancerous transformation. When the same cells were injected into mice, tumors from cells that had an overabundance of MOF grew faster than other tumor cells.

The study also demonstrated that cells with less MOF were more sensitive to radiation exposure. Now the researchers are trying to identify inhibitors of MOF that block its ability to tag histones specifically in tumor cells. "Our research on MOF shows that it is a component that is absolutely needed for cells to proliferate," Pandita says. "It could be the Achilles' heel of cancerous growth."

The research group plans further studies that will clarify how MOF functions and what other cellular components it interacts with. "Using this kind of information, we can more logically approach the issue of making cancerous cells more sensitive to radiation," Pandita says. "Our aim is to achieve a balanced therapeutic adjunct that can keep normal

tissue healthy while weakening tumor cells."

The research also demonstrated that MOF is vital for the development of embryos. It showed that primitive cells, called stem cells, in mouse embryos have high amounts of MOF, and without MOF they stopped growing.

Like cancer cells, stem cells divide rapidly. "Evidence is accumulating to suggest that cancer cells could be considered aberrant stem cells," Pandita says. "MOF is a factor that is common to both embryonic stem cells and cancer cells and ensures their ability to proliferate rapidly."

Source: Washington University in St. Louis