Medical Xpress

Lower levels of key protein influence tumor growth in mice, study shows

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Tumors need a healthy supply of blood to grow and spread. Researchers at the Stanford University School of Medicine have identified a molecule that regulates blood vessel growth that is often found at less-than-normal levels in human tumors. Blocking the expression of the molecule, called PHD2, allows human cancer cells to grow more quickly when implanted into mice and increases the number of blood vessels feeding the tumor.

"It appears to be acting as a tumor suppressor by negatively controlling blood vessel formation," said cancer biologist Amato Giaccia, PhD, the Jack, Lulu and Sam Willson Professor and professor of radiation oncology. He and his colleagues are hopeful that targeting the downstream molecules activated when PHD2 levels are low may be an effective treatment for a variety of human cancers.

Giaccia is the senior author of the research, which will be published in the June 2 issue of the journal *Cancer Cell*. He is also a member of Stanford's Cancer Center.

The finding was particularly surprising because PHD2 was already known to play a less-direct role in blood vessel formation: that of destabilizing another important cancer-associated protein, HIF-1. HIF-1, which stimulates blood vessel development, is induced by the low oxygen levels found in many solid tumors. Although the HIF-1 molecule is rarely modified in human cancers, its levels are often elevated as compared to normal tissue. Giaccia and his colleagues wondered if the

higher levels of HIF-1 could be explained by decreases in the level of PHD2.

The researchers measured PHD2 levels in several human tumor samples, including breast and colon cancers, and compared them with surrounding tissue. They found that, in many cancers, the tumors did have lower-than-normal levels of PHD2. They then inhibited the expression of PHD2 in a variety of human cancer cells in the lab, transplanted these cells into mice with compromised immune systems and examined the tumors that resulted. Those arising from cells in which PHD2 expression had been blocked grew more quickly and were more highly vascularized than the unmodified control cells.

Surprisingly, however, these effects of PHD2 inhibition were evident even in cells engineered not to express HIF-1. "Nobody expected this," said Giaccia. "It's always been thought that the major role of PHD2 was in regulating HIF-1 activity. But now we've learned that it seems to control tumor growth through blood vessel formation in a variety of different cell types on its own."

Upon further investigation, the researchers learned that blocking PHD2 expression increases the levels of two other important proteins involved in vessel formation: IL-8 and angiogenin. The researchers believe that blocking the activity of these proteins may be a good way to stunt tumor growth. "Prior to this study," said Giaccia, "it was unclear which of the many proteins involved in vessel growth, or angiogenesis, should be targeted. But now we know they play a predominant role in tumor growth."

He and his colleagues are planning to continue their studies in laboratory mice engineered to develop breast cancer. They will investigate whether a version of the mice lacking PHD2 expression develops more aggressive tumors, and whether blocking IL-8 or angiogenin slows tumor

growth.

Source: Stanford University Medical Center (news : web)