Scientists report interplay between cancer and aging in mice

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Cancer risk increases with age, and scientists have long perceived a possible evolutionary tradeoff between longer lifespan and greater risk of cancer. Now, researchers at Fox Chase Cancer Center find direct evidence for that tradeoff in new data showing that expression of a key tumor suppressor protein induces premature aging in mice.

Greg H. Enders, MD, PhD, associate professor in the Epigenetics and Progenitor Cell Program at Fox Chase, will present the results at the AACR 102nd Annual Meeting 2011 on Tuesday, April 5.

"I didn't anticipate that increased production of the p16 tumor suppressor protein would so readily promote aging," says Enders, who led the study. "The p16 protein has been previously associated with aging, and we know its expression increases during late stages of aging. But the idea that its expression would be sufficient to generate features of aging was surprising."

Although scientists know that loss of p16 is associated with numerous human tumors, they know much less about the function of p16 in normal cells and tissues. To explore this, Enders' team engineered a strain of mice that enables them to control p16 expression in various tissues and at various times in an animal's lifespan. They quickly found that turning on p16 blocked cell proliferation in normal tissues.

The implications of blocked cell proliferation emerged when they expressed p16 in animals that were not yet fully mature. "They

developed features of premature aging," Enders says. "To my knowledge, this is the first model that induces striking characteristics of premature aging where there is no macromolecular damage. The premature aging appears to be the result of blocking cell proliferation."

Previous work showed that p16 accumulates in tissues as they age, but these new data suggest that p16 is not just associated with aging. Instead, the protein may be playing a more causal role. "What this suggests to us is that p16 may be an effector of aging — not just a marker of aging tissues."

Remarkably, the team also has preliminary evidence that they may be able to reverse the features of early aging in the immature mice by turning off p16.

The experiments also provide insight into how p16 suppresses tumor formation. Looking closely at the intestines of wild-type and engineered mice, the researchers saw that the p16 protein accumulates in the stem cells of the tissue and prevents them from dividing. Additionally, p16 expression reduced tumor formation in a mouse model of intestinal cancer. Putting those two observations together, Enders and colleagues think that p16 suppresses tumor formation by restraining proliferation of pre-cancerous stem cells, as well as tumor cells. They are currently testing that hypothesis.

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