Short chromosomes put cancer cells in forced rest

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A Johns Hopkins team has stopped in its tracks a form of blood cancer in mice by engineering and inactivating an enzyme, telomerase, thereby shortening the ends of chromosomes, called telomeres.

"Normally, when telomeres get critically short, the cell commits suicide as a means of protecting the body," says Carol Greider, Ph.D., the Daniel Nathans chair of molecular biology and genetics at Johns Hopkins. Her study, appearing online this month at *Cancer Cell*, uncovers an alternate response where cells simply - and permanently - stop growing, a process known as senescence.

In an unusual set of experiments, the research team first mated mice with nonoperating telomerase to mice carrying a mutation that predisposed them to Burkitt's lymphoma, a rare but aggressive cancer of white blood cells. Telomerase helps maintain the caps or ends of chromosomes called telomeres, which shrink each time a cell divides and eventually - when the chromosomes get too short - force the cell to essentially commit suicide. Such cell death is natural, and when it fails to happen, the result may be unbridled cell growth, or cancer.

The first generation pups born to these mice contained no telomerase and very long telomeres. These mice all developed lymphomas by the time they were 7 months old. The researchers then continued breeding the mice to see what would happen in later generations. By the fifth generation, the researchers discovered that the mice had short telomeres and stopped developing lymphomas.

When the researchers blocked the suicide machinery in these fifth-generation mice, they were very surprised to find that the mice still remained cancer free.

"We were confused as to what was going on; we thought for sure that blocking the cells' ability to commit suicide would lead to the cancer's returning," says Greider. A closer look showed microtumors in the mice's lymph nodes that had begun the road to cancer, but stopped, falling instead into a state of senescence.

"They don't die, they don't divide, they just sit there in permanent rest," says Greider.
Greider, who won the Lasker Award in 2006 for her discovery of telomerase, says further study of the road to senescence should suggest new ways of preventing or treating cancer by interfering safely with telomerase and the cell-suicide system.

Source: Johns Hopkins Medical Institutions