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Gene dose affects tumor growth

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Researchers at Johns Hopkins and Ohio State University have found that the number of copies of a particular gene can affect the severity of colon cancer in a mouse model. Publishing in the Jan. 3 issue of *Nature*, the research team describes how trisomy 21, or Down syndrome in humans, can repress tumor growth.

“We took a new approach to a 50-year-old debate about whether people with Down syndrome develop cancer less often than other people,” says Roger H. Reeves, Ph.D., professor of physiology in the McKusick-Nathans Institute of Genetic Medicine at Hopkins. “Studying the genetic differences associated with Down syndrome has revealed a new way of thinking about repressing cancer growth in everyone.”

The research team started with a mouse model that carries, rather than a whole extra copy of chromosome 21 as is seen in trisomy 21, or Down syndrome, a partial copy containing 108 genes. They then mated those trisomic mice to mice that carry a mutation that causes intestinal tumors, similar to those seen in colon cancer in humans. The trisomic, colon cancer mice had 44 percent fewer intestinal tumors compared to the colon cancer mice without the extra 108 genes.

The team then used another mouse model of Down syndrome, one that carries extra copies of only 33 of the genes on chromosome 21, and repeated their genetic crosses. Mice with three copies of the 33 genes developed half the number of tumors as mice with the standard two copies. Mice carrying a deletion that left them with only one copy of these 33 genes developed twice the number of tumors as usual.

“Not only does having an extra copy of one or more of these genes repress tumor formation, it turns out that missing a copy enhances tumor growth-this was really surprising,” says Reeves.

Taking a closer look at the 33 genes to identify a likely culprit for the dose-specific relationship with tumor growth, the researchers focused on one gene, Ets2, which previously has been implicated as a cause of cancer. However, some research suggested that Ets2 activity might be involved in pathways that cause cells to die.

They then repeated their genetic crosses, this time with mice that had three, two or one copy of the Ets2 gene only. Once again, mice that were trisomic for 33 genes (including Ets2) had fewer tumors, but mice that were trisomic for 32 of these genes but had the normal two copies of Ets2 had a tumor number similar to control (non-trisomic) mice. Mice with just one copy of Ets2 developed more tumors.

“These results support studies concluding that people with Down syndrome get fewer cancers of many types. While we’ve only shown this effect with Ets2 and a particular type of colon tumor in mice, we think that the human Ets2 gene might contribute to resistance toward other types of cancer, based on what happens in Down syndrome,” says Reeves.

“Our findings are significant because they broaden the definition of an ‘oncogene’ or ‘tumor suppressor gene’ to include the effect of gene dosage,” says Michael Ostrowski, an Ohio State cancer researcher and Ets2 expert who developed the mouse models used in this study. “They also suggest that finding ways to increase the expression of genes such as Ets2 might lead to a new strategy for treating or controlling cancer,” he says.

Source: Johns Hopkins Medical Institutions