Why do people with Down syndrome have less cancer?

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Most cancers are rare in people with Down syndrome, whose overall cancer mortality is below 10 percent of that in the general population. Since they have an extra copy of chromosome 21, it's been proposed that people with Down syndrome may be getting an extra dose of one or more cancer-protective genes. The late cancer researcher Judah Folkman, MD, founder of the Vascular Biology Program at Children's Hospital Boston, popularized the notion that they might be benefiting from a gene that blocks angiogenesis, the development of blood vessels essential for cancer's growth, since their incidence of other angiogenesis-related diseases like macular degeneration is also lower. A study from Children's confirms this idea in mice and human cells and identifies specific new therapeutic targets for treating cancer.

Publishing online May 20 in the journal *Nature*, cancer researcher Sandra Ryeom, PhD, and colleagues from Children's Vascular Biology Program show that a single extra copy of Dscr1 (one of the 231 genes on chromosome 21 affected by trisomy, with three copies rather than two) is sufficient to significantly suppress angiogenesis and tumor growth in mice, as well as angiogenesis in human cells. The team also found its protein, DSCR1, to be elevated in tissues from people with Down syndrome and in a mouse model of the disease.

Further study confirmed that DSCR1 acts by suppressing signaling by the angiogenesis-promoting protein vascular endothelial growth factor (VEGF). In a mouse model of Down syndrome, endothelial cells (which make up blood vessel walls) showed a decreased growth response to

VEGF when they had an extra copy of Dscr1. An extra copy of another chromosome 21 gene, Dyrk1A, also appeared to decrease cells' response to VEGF.

Finally, Ryeom and colleagues showed that these extra genes suppress VEGF signaling via a specific signaling pathway inside endothelial cells -- the calcineurin pathway. Until now, Ryeom says, little has been known about the internal pathways VEGF activates once it binds to cellular receptors; most existing anti-VEGF drugs work by simply binding to VEGF (like Avastin) or blocking its ability to bind to its cellular receptors.

"We're now moving further downstream by going inside the cell," Ryeom says. "When we targeted calcineurin, we suppressed the ability of endothelial cells to grow and form vessels. While it's likely not the only pathway that's involved, if you take it out, VEGF is only half as effective."

Ryeom and her group next validated the mouse findings in human cells. In collaboration with George Daley, MD, PhD, and colleagues in the Stem Cell program at Children's, she worked with induced pluripotent stem cells (iPS cells) created from skin cells from a patient with Down syndrome -- one of 10 disease-specific lines recently developed in Daley's lab.

Knowing that iPS cells tend to induce tumors known as teratomas when inserted into mice, Ryeom guessed that teratomas grown from iPS cells with an extra chromosome 21 would have far fewer blood vessels than teratomas from iPS cells with the normal number of chromosomes. She was right: blood vessels budded in the Down teratomas, but never fully formed.

"The studies in the iPS cells helped validate and confirm that the

suppression of angiogenesis that we saw in mouse models also holds true in humans," says Ryeom. "It suggests that these two genes might point to a viable cancer therapy."

Ryeom's group has identified which part of the DSCR1 protein blocks calcineurin and is testing to see whether that fragment can be delivered specifically to endothelial cells, to prevent them from forming new blood vessels, without affecting calcineurin pathways in other cells and causing side effects. "Immunosuppressive drugs also target calcineurin in T-cells," Ryeom notes. "We think that Dscr1 blocks calcineurin specifically in endothelial cells, without affecting T-cells, but we need to check."

Folkman's interest in why patients with Down syndrome have such a reduced risk for cancer focused on endostatin, an anti-angiogenic compound made by the body. Discovered in the Folkman lab, endostatin is a fragment of collagen 18 -- whose gene is also on chromosome 21. People with Down syndrome reportedly have almost doubled levels of endostatin because of the extra copy of the gene.

"I think there may be four or five genes on chromosome 21 that are necessary for angiogenesis suppression," says Ryeom. "In huge databases of cancer patients with solid tumors, there are very few with Down syndrome. This suggests that protection from chromosome 21 genes is pretty complete."

Source: Children's Hospital Boston (news : web)