Novel role: EZH2 boosts creation of ovarian cancer blood vessels

August 16 2010

A protein associated with cancer progression when abundant inside of tumors also unexpectedly regulates the creation of new blood vessels that feed the tumor outside, a research team led by scientists at The University of Texas MD Anderson Cancer Center reports in the August edition of *Cancer Cell*.

By using a nanoparticle-based gene-silencing system to block production of the protein, the researchers inhibited formation of new blood vessels (angiogenesis) to the tumor and caused a steep reduction in tumor burden in a mouse model of ovarian cancer.

"We've discovered that EZH2 promotes tumor growth by shutting down genes that block formation of new blood vessels," said study senior author Anil Sood, M.D., professor in UT MD Anderson's departments of Gynecologic Oncology and Cancer Biology. "Tumors treated with current anti-angiogenesis drugs eventually progress. This study presents a new mechanism for angiogenesis that opens the door for development of new treatment approaches."

EZH2 is a member of a group of proteins known to repress gene expression. It has been associated with the progression and spread of bladder, breast, prostate and gastric cancers and one type of cancer of the pharynx.

Increased EZH2 is tied to decreased survival for

patients

An examination of 180 ovarian cancer tumors found that the protein was overexpressed in the tumor in 66 percent of cases and in the endothelial cells of 67 percent of samples.

Endothelial cells line the inside of blood vessels and are crucial to angiogenesis.

Increased expression of the protein in either tumor or endothelial cells was associated with late-stage and high-grade disease and decreased median survival. Patients with increased EZH2 levels in their tumors had a median survival of 2.5 years compared to 7.33 years for those without. For overexpression in the endothelial cells, the difference was 2.33 years versus 8.33 years for those with normal levels.

In a series of lab experiments, the team found that vascular endothelial growth factor (VEGF), a known stimulator of angiogenesis, boosts the level of EZH2 in endothelial cells. EZH2 then silences the vasohibin1 (VASH1) gene, which normally inhibits blood-vessel-formation. Silencing the EZH2 gene in the tumor's endothelial cells reactivates VASH1, reducing angiogenesis and ovarian cancer growth in mice.

Silencing ezh2 reduces tumor weight

The ezh2 gene was targeted separately in tumor cells and in endothelial cells by delivery of small interfering RNA (siRNA) - short snippets of RNA that block gene expression - to mice with one of two strains of ovarian cancer.

Treating mice with siRNA that silenced ezh2 in the tumor-associated endothelial cells reduced average tumor weight by 62 percent and 40

percent in the two strains of cancer compared with control mice.
Hitting the gene only in the tumor had little significant effect on tumor burden.
Silencing in both tumor and endothelial cells reduced average tumor weight by 83 percent and 65 percent in the two cancer strains.
Additional tests showed that silencing ezh2 reduced both he number of blood vessels serving the tumors and ovarian cancer cell proliferation while increasing programmed death of tumor cells.

siRNA delivery system relies on crustacean shell component

Sood and co-author Gabriel Lopez-Berestein, M.D., professor in UT MD Anderson's Department of Experimental Therapeutics, have developed delivery systems that package siRNA with a fatty ball called a liposome to silence specific genes in cancer cells.

"Those systems are quite effective for delivery to tumors and tumor cells but not as effective for delivery to tumor vasculature," Sood said. They jointly developed a new delivery system that packages siRNA into chitosan nanoparticles. Chitosan is derived from a chitin, a structural component in the shells of crustaceans.

Chitosan nanoparticles carry a slight positive electrical charge, making them attractive to the mostly negatively charged endothelial cells. The nanoparticles penetrate the tumor by way of its vasculature, so the new system hits both targets.

The nanoparticles accumulate in the cancer cell and vasculature passively as they circulate in the blood stream. Chitosan nanoparticles are so small that they can flow through tiny holes in the tumor vasculature. They also accumulate in other organs, so the researchers are working to add a

targeting molecule that will limit nanoparticle uptake to tumors and their vasculature.

Provided by University of Texas M. D. Anderson Cancer Center

Citation: Novel role: EZH2 boosts creation of ovarian cancer blood vessels (2010, August 16) retrieved 6 May 2024 from https://medicalxpress.com/news/2010-08-role-ezh2-boosts-creation-ovarian.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.