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Gene therapy technique thwarts cancer by cutting off tumor blood supply

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University of Florida researchers have come up with a new gene therapy method to disrupt cancer growth by using a synthetic protein to induce blood clotting that cuts off a tumor's blood and nutrient supply.

In mice implanted with human colorectal cancer cells, tumor volume decreased 53 percent and cancer cell growth slowed by 49 percent in those treated with a gene that encodes for the artificial protein, compared with those that were untreated.

The research team, led by Dr. Bradley S. Fletcher, an assistant professor of pharmacology and therapeutics in the College of Medicine, created the so-called fusion protein to target another protein called tumor endothelial marker 8, or TEM8, which was recently found to be preferentially expressed in the inner lining of tumor vessels. Such differences in protein expression enable delivery of drug molecules to the cells that harbor these proteins.

"The protein we created did a very good job of homing to the tumor and binding," said Stephen Fernando, who recently completed his doctoral studies. "By targeting TEM8, we can potentially create a therapy against cancer."

The Fletcher group is the first to target cancer cells through protein binding to TEM8. The findings, now available online, are featured on the cover of the June 15 edition of *Cancer Research*.

"If you can cut off the blood supply, then you can inhibit the tumor from growing -- there have been many attempts," said Brad St. Croix, director of the National Cancer Institute's Tumor Angiogenesis Section, whose group first identified the TEM genes that over-express in tumor endothelial cells. "The concept of targeting tumor blood vessels has been around for many years, but it's good that we're finally getting around to the stage where we can see the vessels being targeted therapeutically -- it's pretty exciting, I think."

St. Croix was not part of the current research team, but donated some experimental materials.

The UF group created a "fusion protein" -- part of which binds to TEM8, and the other which promotes thrombosis, or blood clotting -- and delivered genes that encode for it to the lungs of mice. The delivery vehicle was a transposon called Sleeping Beauty, a piece of DNA that can insert new genes stably and efficiently into a cell's genome.

The lungs then functioned as a factory to produce the protein that later found its way to the target cells in the tumor vessels.

"We felt that TEM8 was an ideal target because it was inside the vessel, preferentially expressed there and unique," Fletcher said.

In addition to promoting blood clots, the strategy also resulted in reduced tumor vessel density, possibly by interfering with TEM8 function.

Fletcher's group previously applied the Sleeping Beauty transposon gene delivery method to the treatment of hemophilia and pulmonary hypertension and the prevention of lung transplant rejection in animal studies. After developing those three successful models, they looked for disease applications in which poor outcomes would be worth the risk associated with gene therapy.

"We felt that cancer was potentially a target," Fletcher said. "Gene therapy has a lot of risk associated with it, so you don't want to do it for diseases that are not life-threatening."

The group plans to come up with a method to increase the amounts of the thrombosis-inducing protein produced in the body, and test whether higher dosing leads to unintended blood clots.

They are also looking into ways to deliver the protein directly to the sites of interest, rather than through genes that later produce the protein, and apply the method in other areas such as prostate cancer. Other work will include the use of coated nanoparticles to detect tumors and deliver drugs or radiate heat to destroy cancer cells when bombarded by radio waves.

Source: University of Florida (news : web)