Medical Xpress

Engineered virus targets and kills apparent cancer stem cells in neuroblastoma

January 21 2009

After identifying an apparent population of cancer stem cells for neuroblastoma, researchers successfully used a reprogrammed herpes virus to block tumor formation in mice by targeting and killing the cells.

Published online Jan. 21 by *PLoS (Public Library of Science) One*, the study led by Cincinnati Children's Hospital Medical Center adds to a growing body of evidence suggesting early stage cancer precursor cells with stem-cell-like properties may explain how some cancers form, are treatment resistant and prone to relapse. The study also underscores the increasing potential of targeted biological therapies to help people with stubborn cancers like neuroblastoma, which often recur and metastasize, said Timothy Cripe, M.D., Ph.D., senior investigator and a physician/researcher in the division of Hematology/Oncology at Cincinnati Children's.

"The main finding of our study is that pediatric neuroblastomas seem to have a population of cells with stem-cell characteristics that we may need to target for therapy," Dr. Cripe said. "We also show that one promising approach for targeted treatment is biological therapy, such as an engineered oncolytic virus that seeks out and kills progenitor cells that could be the seeds of cancers."

Neuroblastoma's solid tumors usually attack the sympathetic nervous system, part of the body's autopilot mechanism that controls vital organ function and instinctive responses, like "fight or flight." The disease can be thrown into remission by chemotherapy, radiation or surgery, but it's

also known for treatment resistance and a high rate of relapse and death. In patients with high-risk forms of the disease, long-term survival rates are less than 50 percent. The reasons for neuroblastoma's tendency to relapse and spread still need to be proven, said Dr. Cripe, also professor of Pediatrics at the University of Cincinnati College of Medicine.

To further explore the cancer stem cell theory, the research team took human neuroblastoma cells and grew them in laboratory cultures. The cultures contained cells exhibiting biological properties of neural stem cells - which are specific to the nervous system and grow to form a variety of nerve tissue. The cultures generated cell colonies that acted like stem cells in the way they divided, grew and were capable of diverse, or multi-lineage, differentiation. Analysis showed the cells also carried known biological markers for nerve stem cells, such as the proteins CD133 and nestin.

The cells advanced into tumor-like cell spheres and were tumorigenic, meaning they had the potential to form tumors. Cells derived from these tumorspheres were relatively resistant to the chemotherapy agent doxorubicin, similar to that seen with some treatment-resistant neuroblastomas. Researchers also noted cells from the tumorspheres carried a gene (MYCN) that is found at amplified levels in aggressive forms of neuroblastoma.

Because neural stem cells and neuroblastoma cells both carry the protein nestin, Dr. Cripe and his colleagues tested the effect of an oncolytic herpes simplex virus called rQNestin34.5 on cells. Developed by cancer researchers Ohio State University, rQNestin34.5 carries a molecular promoter for nestin, which causes it to seek out the protein and cancerous, or precancerous, cells where nestin resides. The virus is genetically programmed to grow inside and be toxic to cancer cells, while leaving healthy tissues alone.

The tumorigenic cells were infected with rQNestin34.5 and then injected into mice to see if neuroblastoma tumors would form. Tumors did not form in any of the mice over a 60-day observation period, leading the researchers to report that rQNestin34.5 "abolished tumor growth" by attacking apparent tumor-initiating cells.

In comparison experiments for control, researchers also infected tumorigenic cells with another oncolytic herpes virus called rQLuc, which does not target cells that contain the nestin protein. Next to rQNestin34.5, rQLuc showed only moderate success, with all treated mice having tumor formation within 40 days. In mice where cells were treated only with saline, all animals had tumors form within 30 days.

Although a promising step forward, Dr. Cripe said the study's main limitation is that precancerous cells were infected with the oncolytic virus in a laboratory culture before being injected into mice.

"Targeting and hitting the cells after they are already in the mice will be another matter," he said.

The research team also nurtured the stem-cell like tumorigenic cultures over an extended period of time in the laboratory. In the next research phase, the team will try to verify results in the current study by seeing if they can detect the presence of cancer stem cells in primary neuroblastoma tumor cells from patients.

Dr. Cripe cautioned much more research is needed before determining whether rQNestin34.5 would be efficacious in treating neuroblastoma patients in a clinical setting.

Source: Cincinnati Children's Hospital Medical Center