Medical Xpress

Targeted virus compels cancer cells to eat themselves

May 2 2006

An engineered virus tracks down and infects the most common and deadly form of brain cancer and then kills tumor cells by forcing them to devour themselves, researchers at The University of Texas M. D. Anderson Cancer Center report this week in the Journal of the National Cancer Institute.

The modified adenovirus homed in on malignant glioma cells in mice and induced enough self-cannibalization among the cancer cells -- a process called autophagy -- to reduce tumor size and extend survival, says senior author Seiji Kondo, M.D., Ph.D., associate professor in the Department of Neurosurgery at M. D. Anderson.

"This virus uses telomerase, an enzyme found in 80 percent of brain tumors, as a target," Kondo says. "Once the virus enters the cell, it needs telomerase to replicate. Normal brain tissue does not have telomerase, so this virus replicates only in cancer cells."

Other cancers are telomerase-positive, and the researchers showed in lab experiments that the virus kills human prostate and human cervical cancer cells while sparing normal tissue.

In addition to demonstrating the therapeutic potential of the virus, called hTERT-Ad, Kondo says the international research team also clarified the mechanism by which such conditionally replicating adenoviruses (CRAs) infect and kill cancer cells.

Autophagy is a protective process that cells employ to consume part of themselves when nutrients are scarce or to destroy some of their organelles to recycle their components. A double membrane forms around the material to be consumed, then everything inside is digested.

Kondo and colleagues showed that hTERT-Ad (short for human telomerase reverse transcriptase promoter regulated adenovirus) infected the glioma cells and induced autophagy by inactivating a molecular pathway -- the mammalian target of rapamycin (mTOR) pathway -- that is known to prevent cellular self-cannibalization.

The result was a huge difference in tumor volume among mice with subcutaneous malignant glioma that got hTERT-Ad and those that received a different, non-replicating virus. Average tumor size in the hTERT-Ad group was 39 cubic millimeters, while those receiving the other virus had an average tumor volume of 200 cubic millimeters.

Among mice with malignant gliomas in the brain, those treated with three injections of hTERT-Ad on average lived 53 days. Those receiving the control adenoviruses lived on average 29 days. Two of the hTERT-Ad mice survived 60 days and had no detectable brain tumors.

Analyses of dead cancer cells showed telltale signs of autophagy: bits of virus in the cell nucleus and autophagic vacuoles -- cavities with residual digested material.

The cells showed no sign of having been killed by apoptosis -- a much better known process of programmed cell death. A normal biological defense mechanism that systematically kills defective cells, apoptosis is suppressed or dysfunctional in cancer cells. Many cancer therapies focus on restoring or enhancing apoptosis to combat the disease.

"We believe that autophagy, but not apoptosis, mediates the principal

anti-tumor effect of conditionally replicating adenoviruses," Kondo says.

Cells killed by apoptosis show specific damage to the cell nucleus and DNA, with other cellular organelles preserved, Kondo explains. Cells killed by autophagy have little damage to the nucleus but heavy degradation of the cells' organelles.

Apoptosis and autophagy should be viewed as type 1 and type 2 versions of programmed cell death, Kondo says. In a Nature Reviews Cancer paper last September, Kondo and colleagues reviewed therapies and molecules that cause or inhibit the self-cannibalization process and compared autophagy and apoptosis, which has been more heavily studied.

To improve cancer therapeutics, Kondo and colleagues concluded that it is vital to identify molecules that regulate autophagy in cancer cells and to understand how autophagy is associated with cell death, a relatively new field in cancer research.

The research group is following up the malignant glioma findings by studying ways to improve the efficiency of viral infection of cancer cells.

Source: University of Texas