Researchers hope newly discovered gene interaction could lead to novel cancer therapies

December 13 2013

This is Paul Fisher, M.Ph., Ph.D., Thelma Newmeyer Corman Endowed Chair in Cancer Research and co-leader of the Cancer Molecular Genetics research program at VCU Massey Cancer Center, and chairman of the Department of Human and Molecular Genetics and director of the VCU Institute of Molecular Medicine at VCU School of Medicine. Credit: VCU Massey Cancer Center

Scientists from Virginia Commonwealth University Massey Cancer

Center have revealed how two genes interact to kill a wide range of cancer cells. Originally discovered by the study's lead investigator Paul B. Fisher, M.Ph., Ph.D., the genes known as mda-7/IL-24 and SARI could potentially be harnessed to treat both primary and metastatic forms of brain, breast, colon, lung, ovary, prostate, skin and other cancers.

In the study, recently published in the online version of the journal *Cancer Research*, Fisher's team found that forced expression of MDA-7/IL-24 (melanoma differentiation associated gene-7/interlukin-24) stimulates SARI (suppressor of AP-1, induced by interferon) expression in what is known as an autocrine/paracrine loop, which ultimately causes cancer cells to undergo a form of cell suicide known as apoptosis. Autocrine/paracrine loops occur when the expression of a particular gene or its encoded protein causes cells to secrete molecules that bind to surface receptors and force the expression of more of the same protein in an ongoing cycle.

"Many previous studies show that MDA-7/IL-24 can selectively kill diverse cancer cells through multiple mechanisms, but what was unclear was how exactly MDA-7/IL-24 interacted with other genes to promote cancer toxicity," says Fisher, Thelma Newmeyer Corman Endowed Chair in Cancer Research and co-leader of the Cancer Molecular Genetics research program at VCU Massey Cancer Center, and chairman of the Department of Human and Molecular Genetics and director of the VCU Institute of Molecular Medicine (VIMM) at VCU School of Medicine. "Our study uncovered multiple signaling pathways used by MDA-7/IL-24 that facilitate cancer cell death through the induction of SARI."

Fisher and his team identified an existing combination of receptors, IL-20R1 and IL-20R2, and a discovered new combination of receptors, IL-22R1 and IL-20R1, through which signaling occurs to induce the MDA-7/IL-24 autocrine/paracrine loop. Once activated by the

MDA-7/IL-24 protein, these receptors cause both normal and cancer cells to produce and secrete the MDA-7/IL-24 protein, which, in turn, activates SARI. The process was shown to culminate in apoptosis in cancer cells. Normal, healthy cells were not affected in the experiments.

The researchers are now focusing on developing small molecule drugs that induce MDA-7/IL-24 and/or SARI in cancer cells. They have also been experimenting with cancer-selective replicating viruses that seek out cancer cells and infect them with the toxic genes—an approach that has already been successfully employed in a phase 1 clinical trial using engineered viruses that deliver MDA-7/IL-24.

"This study helped us better understand how MDA-7/IL-24 works to kill a broad range of cancer cells through the induction of SARI," says Fisher. "In addition to giving us another target for the development of new therapies, our research also suggests that we may be able to monitor the expression of SARI in order to determine the effectiveness of future therapies under development that target MDA-7/IL-24."

More information: cancerres.aacrjournals.org/con … 3-1062.full.pdf+html

Provided by Virginia Commonwealth University