

Discovery of gene mechanism could bring about new ways to treat metastatic cancer

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Virginia Commonwealth University and VCU Massey Cancer Center researchers have uncovered how a gene, melanoma differentiation associated gene-7/interleukin-24 (mda-7/IL-24), induces a bystander effect that kills cancer cells not directly receiving mda-7/IL-24 without harming healthy ones, a discovery that could lead to new therapeutic strategies to fight metastatic disease.

The findings may provide a method to target metastatic disease – which is one of the primary challenges in cancer therapy. When cancer cells are localized in the body, specialists may be able to surgically remove the diseased area. However, when cancer metastasizes or spreads to sites remote from the primary tumor through the lymph system and blood vessels to new target sites, treatment becomes more difficult and in many instances ineffective.

In the study, published online in the June 30 issue of the *Proceedings of the National Academy of Sciences*, researchers report on the molecular and biochemical mechanisms by which the gene, mda-7/IL-24, is able to selectively kill cancer cells through apoptosis, or programmed cell death. The gene induces a potent bystander effect, meaning that it not only kills the original tumor, but distant ones as well, which has been observed but previously not mechanistically defined in animal models containing human cancers and in a Phase I Clinical Trial involving direct injection of an adenovirus expressing mda-7/IL-24 into advanced carcinomas and melanomas.

Further, the team determined that mda-7/IL-24 induces tumor-specific killing through a process known as endoplasmic reticulum stress. The endoplasmic reticulum, or ER, is a subcellular structure that plays a key role in cellular protein disposition. ER stress results from accumulation of extra proteins in the ER of a cancer cell and can activate pro-survival or pro-cell suicide pathways.

"Cancer cells cannot accommodate or recover from stress the way normal, healthy cells can. When the ER is stressed in this way, the result is an unfolded protein response which overloads the system and shorts out the cancer cell. This prevents tumor development, growth and invasion – and ultimately the cancer cell dies," said Paul B. Fisher, Ph.D., professor and interim chair of the Department of Human and Molecular Genetics, and director of the VCU Institute of Molecular Medicine, in the VCU School of Medicine.

Source: Virginia Commonwealth University

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