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Pioneering study looks at p53's role in tumor-stroma interactions

Atlanta, GA-Researchers at Emory University's Winship Cancer Institute have conducted the first comprehensive study of the role an important tumor suppressor gene plays in cancer development.

P53 is known as a major tumor suppressor that is frequently mutated in human cancer. In this study, researchers used novel proteomic techniques to identify the proteins secreted by cells specifically in response to p53. The findings suggest a newfound role for wt-p53 in the control of the tumor's ability to communicate with the normal stromal cells surrounding it. The results of the study, "Proteomic identification of the wt-p53-regulated tumor cell secretome," are found in the October 9 advance online print of Oncogene.

"Cancer formation is traditionally thought of as a cell-autonomous process driven by mutations in genes that increase cell proliferation and survival, where a tumor is composed primarily of transformed cells," says Erwin G. Van Meir, PhD, Professor of Neurosurgery and Hematology/Oncology and lead-author of the study. "But increasing evidence suggests that the tumor microenvironment also contributes to neoplasm and that tumor-stroma interactions play a major role in tumor development, maintenance, and progression. A tumor is more like a casserole of chili than a bowl of white rice, where all the components in the mix interact. We need to better understand these tumor-stroma interactions to develop more effective cancer therapies."

But little is know about how the genetic changes that underlie cell transformation elicit extrinsic changes that modulate cell interactions. So, the researchers examined whether those events involve a modification in the cell's secreted proteins, which then act as mediators of intercellular communication.

Focusing on p53 as a proof-of-principle was a natural starting point as p53 is a transcription factor that directly controls the synthesis of numerous proteins. p53 is best known for its role in maintaining genomic integrity and cell survival in response to DNA damage. Yet some prior studies suggested that p53 could influence the tumor microenvironment by suppressing angiogenesis and tumor invasion.

To identify p53-regulated secreted proteins involved in intercellular communication, the researchers used a cell line derived from a malignant human glioma. The researchers found a total of 111 secreted proteins, 39 that showed enhanced secretion and 21 that showed inhibited secretion in response to wt-p53 expression. However, none of the proteins were found to be transcriptional targets, which suggests that wt-p53 may have an indirect role in intracellular protein trafficking and secreted-protein stability, says Dr. Van Meir. "These secreted targets will be helpful in better understanding how wt-p53 may modulate interactions of tumor cells with their environment and establishes p53 loss in tumors as a major trigger of changes in tumor-stroma interactions. A better understanding of these phenomena will improve our ability to devise new therapies for cancer."

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