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Contact: Ferdie De Vega
Ferdinand.DeVega@moffitt.org
813-745-7858
[H. Lee Moffitt Cancer Center & Research Institute](#)

Fibroblasts contribute to melanoma tumor growth, say Moffitt Cancer Center researchers

Fibroblasts also contribute to drug resistance and 'flare' response

TAMPA, Fla. -- Fibroblasts, cells that play a role in the structural framework of tissues, play an apparent role in melanoma tumor growth. Fibroblasts also contribute to melanoma drug resistance and may also facilitate the "flare" response when a tumor's metabolism is enhanced following a patient being removed from a targeted therapy, said researchers at Moffitt Cancer Center in Tampa, Fla.

Alexander R. Anderson, Ph.D., co-director of Integrative Mathematical Oncology at Moffitt, and Moffitt Comprehensive Melanoma Research Center member Keiran S. Smalley, Ph.D., along with colleagues from the Wistar Institute in Philadelphia, investigated the role of fibroblasts in melanoma progression and published their findings in a recent issue of *Molecular Pharmaceutics*.

"A role for fibroblasts in cancer progression has long been suspected," explained Anderson, who works with mathematical models of cancer to investigate tumor cell- microenvironment interactions. "In this study, we used an integrated mathematical and experimental approach to investigate whether melanoma cells recruit, activate and stimulate fibroblasts to deposit certain proteins known to be pro-survival for melanoma cells."

Fibroblasts are the most common of connective tissues, and they function to synthesize the "extra cellular matrix" of cells and collagen, the structural framework – also called "stroma" – for tissues.

The researchers knew that fibroblasts were drawn to cancer cells and that they became activated by cancer cells. They also knew that different cancer cell lines have varying capabilities for recruiting and stimulating fibroblasts. An expectation has been that aggressive cancers stimulate fibroblasts more than do less aggressive cancers.

When they investigated the relationship between fibroblasts and tumors using mathematical models, the research team came up with some unexpected findings.

Anderson and Smalley expected the fibroblast-derived "extra cellular matrix" that supports the tumor structure to have "direct effects on tumor behavior." However, once they ran their theoretical models they came up with a number of unexpected conclusions with potentially far-reaching implications about drug resistance and tumor growth.

"Our finding that the fibroblast population might facilitate the "flare response" – a period during which a tumor has enhanced metabolism and increases its progression trajectory after patients are removed from targeted therapy – was a surprise," said Smalley, whose research aims at developing new therapies for melanoma and getting them into clinical practice.

The researchers knew that a targeted therapy would kill only the tumor population, not the fibroblasts in the tumor structure. However, the finding that fibroblasts contribute to melanoma drug resistance was unexpected.

"Targeted therapies may actually hasten tumor progression when they are stopped due to resistance to the targeted drug," said Smalley. "We found in our models that fibroblasts appear to facilitate the flare response after targeted therapy ends."

Their conclusions about the relationship between fibroblasts and cancer tumors were not predicted or expected, but revealed through the use of mathematical models.

"If these conclusions are confirmed experimentally, we may gain important new insights into how drug resistance can be managed clinically," concluded Anderson.

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Located in Tampa, Florida, Moffitt Cancer Center is an NCI Comprehensive Cancer Center – a designation that recognizes Moffitt's excellence in research and contributions to clinical trials, prevention and cancer control. Moffitt currently has 14 affiliates in Florida, one in Georgia, one in Pennsylvania and two in Puerto Rico. Additionally, Moffitt is a member of the National Comprehensive Cancer Network, a prestigious alliance of the country's leading cancer centers, and is listed in *U.S. News & World Report* as one of "America's Best Hospitals" for cancer. Moffitt marks a very important anniversary in 2011 – 25 years committed to one mission: to contribute to the prevention and cure of cancer.

Media release by Florida Science Communications

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