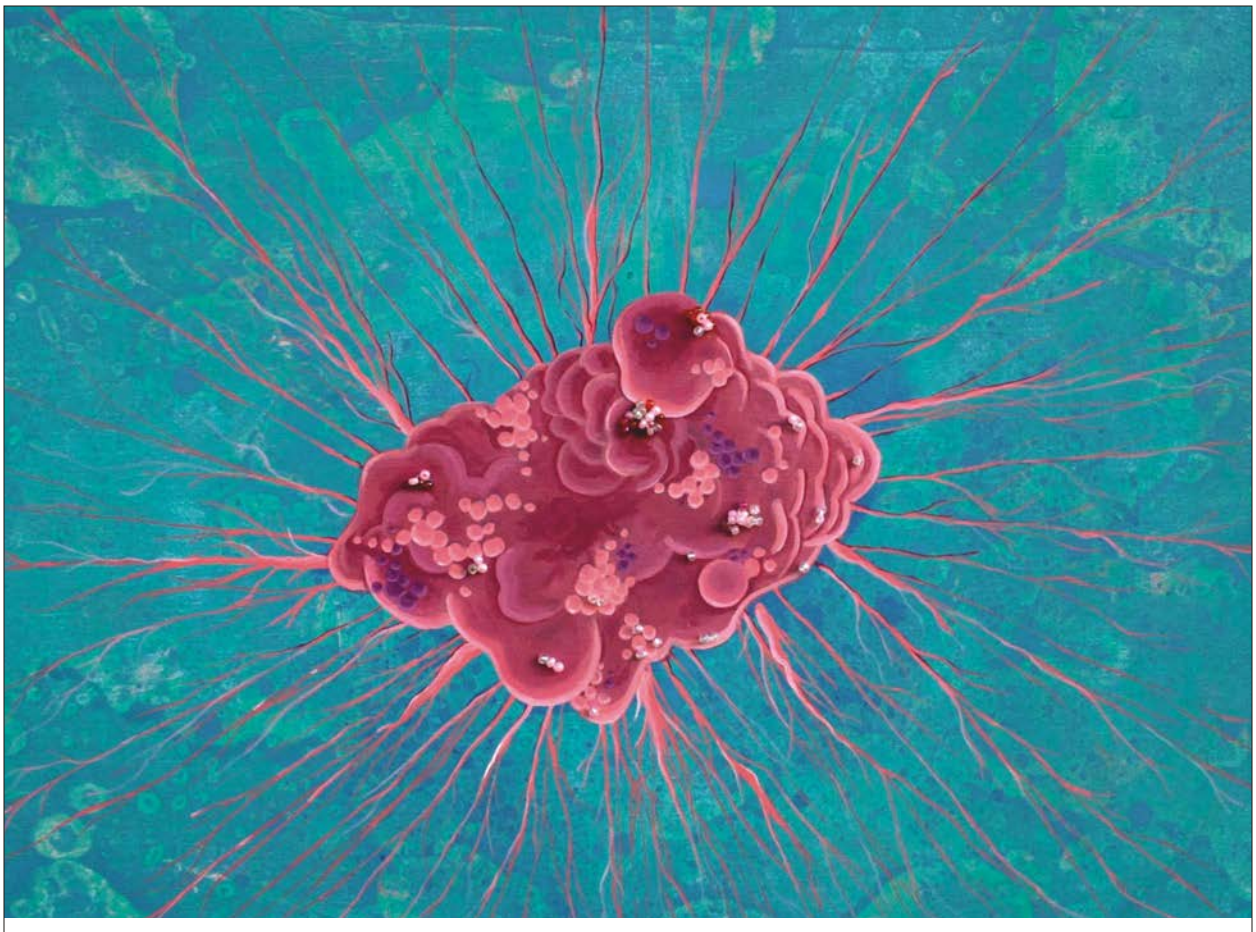

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Discovery Could Lead to Breakthrough for Non-Small Cell Lung Cancer

Research at Virginia Commonwealth University Massey Cancer Center led by Charles E. Chalfant, Ph.D., Associate Professor of Biochemistry and Molecular Biology, discovered a previously unknown mechanism in Non-small Cell Lung Cancer (NSCLC) cells that contributes to their ability to maintain and grow tumors. Narrowing in on this mechanism could provide a breakthrough for the development of effective therapies for NSCLC and other cancers.

The findings, recently published in Journal of Clinical Investigation, provide the first example of a protein factor regulating the expression of the protein caspase-9, a main player in apoptosis, or programmed cell death. Scientists have known that healthy cells favor caspase-9a, a form of the caspase-9 protein that promotes natural apoptosis. What Chalfant and his research team found is that NSCLC cells favor caspase-9b, which is the anti-apoptotic form of caspase-9 that promotes tumor formation, growth and maintenance. Their further investigation discovered that a protein known as hnRNP L functions as an RNA splicing factor by promoting the expression of caspase-9b through a process known as RNA splicing. While hnRNP L was previously known to have a role in protein expression, its function in relation to cancer biology was unclear until Chalfant's study.

"We're researching an unexplored area of RNA splicing factors in relation to cancer," says Chalfant. "Before this study, there had been very little evidence of an RNA splicing event that results in cancerous tumor development. This study points to caspase-9b as being a very important target in the development of a durable therapy for non-small cell lung cancer."

In mouse models, the researchers used a virus-based targeted gene therapy to reduce the amount of hnRNP L in NSCLC cells. They then observed a lower ratio of caspase-9b to caspase-9a. The result completely stopped the growth of the tumors and had no negative effects on healthy cells. This decrease in the cancer cells' capacity to maintain tumors could make them more susceptible to chemotherapy drugs that typically have little effect on NSCLC.

"Unfortunately, many current therapies for lung cancer are less effective and more toxic than we'd like," says Chalfant. "Lung cancer kills more people than any other cancer, and there is a real need for new cellular targets that are cancer-specific and show results in large numbers of patients regardless of the mutations found in individual tumors. Since caspase-9b is mainly expressed in malignant cells, these findings may provide innovative treatments for non-small cell lung cancer with little to no toxic side effects."

Chalfant collaborated on this work with Davis Massey, M.D., D.D.S., Ph.D., at VCU School of Medicine's Department of Pathology and with researchers at VCU School of Medicine's Department of Biochemistry and Molecular Biology and Department of Physiology, as well as with the University of Colorado Cancer Center; the University of Texas Southwestern Medical Center; and the Hunter Holmes McGuire Veterans Administration Medical Center.

The study was supported by grants from the Veteran's Administration, National Institutes of Health, National Cancer Institute, National Aeronautics and Space Agency and International Association for the Study of Lung Cancer as a Young Investigator Award.

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