Curcumin, special peptides boost cancer-blocking PIAS3 to neutralize STAT3 in mesothelioma

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A common Asian spice and cancer-hampering molecules show promise in slowing the progression of mesothelioma, a cancer of the lung's lining often linked to asbestos. Scientists from Case Western Reserve University and the Georg-Speyer-Haus in Frankfurt, Germany, demonstrate that application of curcumin, a derivative of the spice turmeric, and cancer-inhibiting peptides increase levels of a protein inhibitor known to combat the progression of this cancer. Their findings appeared in the Aug. 14 online edition *Clinical Cancer Research*; the print version of the article will appear Oct. 1.

Malignant mesothelioma has received widespread notoriety because it occurs frequently in the lung linings of people exposed to asbestos. However, asbestos does not always cause this particular cancer that kills 43,000 people worldwide each year. Many mesothelioma patients were never exposed to asbestos.

"Mesothelioma is a disease that continues to have a significant burden worldwide, and the treatment option is really suboptimal. We must find better ways to treat it," said senior author Afshin Dowlati, MD, Professor of Medicine – Hematology/Oncology, Case Western Reserve University School of Medicine, and member of the Case Comprehensive Cancer Center. "We now understand the mechanisms that drive cell proliferation and growth in malignant mesothelioma."

The culprit in sparking many cancers, particularly mesothelioma, is the intracellular protein and transcription factor STAT3 (signal transducer and activator of transcription 3). A signal transducer and activator is a pathway for instructing the growth and survival of cells, and a transcription factor is a protein that controls genetic information directing cells how to perform. STAT3 is notorious for sending signals to trigger the onset of human cancers and to fuel their continued growth. The great neutralizer of STAT3 is PIAS3 (protein inhibitor of activated STAT3). PIAS3 possesses the strength to inhibit and block STAT3's ability to cause cancer.

In this study, investigators assessed PIAS3 expression in tissue samples of mesothelioma solid tumors and the protein inhibitor's subsequent effects on STAT3 activity. Tissue samples came from three different locations in the country, and information logged for each specimen detailed how long the patient lived and the types of mesothelioma they had. Investigators then linked the levels of PIAS3 with STAT3 activity in each sample. Additionally, investigators examined the effects of curcumin and peptides extracted from PIAS3 segments on malignant mesothelioma cells in vitro.

"In those mesothelioma patients where PIAS3 is low, indeed STAT3 is activated," said Dowlati, Director of the Center for Cancer Drug Development at University Hospitals Seidman Cancer Center. "Mesothelioma patients who have low PIAS3 and high STAT3 have a greater chance of dying early. On the flip side, those patients with a high PIAS3 levels have a 44 percent decreased chance of dying in one year, which is substantial."

Investigators also found that curcumin and PIAS3 peptides raised PIAS3 levels, which brought down STAT3 activity and caused mesothelioma cells to die. Their study served as proof of principle about the effectiveness of these two compounds in treating malignant

mesothelioma, a first step in moving a treatment toward clinical trials. Additionally, their findings demonstrated that PIAS3 could serve as a predictive marker for managing mesothelioma because the disease's tumors do not always progress in a consistent, predictable manner, even when tumor stages, grades and clinical presentations appear similar.

"Our findings suggest that PIAS3 expression positively affects survival in mesothelioma patients and that PIAS3 activation could become a therapeutic strategy," Dowlati said. "Our interest for the future is that we want to find better, more simple ways to increase intracellular levels of PIAS3 for malignant mesothelioma through the use of synthetic PIAS3 peptide or curcumin analogs. We must develop a curcumin analog that is absorbable by the human body. Currently, curcumin ingested as the spice turmeric has practically no absorption within the gut."

Their investigation also contributes to the overall body of scientific knowledge for all cancer.

"Our findings beg the question of what role PIAS3 could play in limiting STAT3 activation in other cancers as well," Dowlati said. "There is an opportunity to extend this discovery because a number of cancers are STAT3-activated."

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