Lung Cancer Cells Activate Inflammation to Induce Metastasis

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A research team from the University of California, San Diego School of Medicine has identified a protein produced by cancerous lung epithelial cells that enhances metastasis by stimulating the activity of inflammatory cells. Their findings, to be published in the January 1 issue of the journal *Nature*, explain how advanced cancer cells usurp components of the host innate immune system to generate an inflammatory microenvironment hospitable for the metastatic spread of lung cancer. The discovery could lead to a therapy to limit metastasis of this most common lethal form of cancer.

The scientists - headed by Michael Karin, Ph.D., UC San Diego Distinguished Professor of Pharmacology and Pathology, who has been investigating the effects of inflammation on cancer development and progression - used a straightforward biochemical approach to identify proteins produced by metastatic cancer cells that are responsible for generation of an inflammatory microenvironment that supports the growth of metastases. Focusing on macrophages, white blood cells that are key players in the immune response to foreign invaders as well as in cancer growth and progression, they screened for factors produced by metastatic cancer cells in mice that could stimulate the activity of this inflammatory cell type.

Among the mouse cell lines screened, a highly metastatic cell line called Lewis lung carcinoma (LLC) showed particularly potent activation of macrophages. Furthermore, macrophage activation was mediated by a secreted protein. Biochemical purification of proteins secreted by LLC cells resulted in identification of an extracellular matrix protein called versican as the major macrophage activator and metastasis enhancing factor. Versican is also found in very low amounts in normal human lung epithelial cells, but is upregulated in human lung cancer, where a very large amount of this protein is found, especially in aggressive tumors.

The scientists found that versican strongly enhances LLC metastatic growth by activating receptors that lead to production of cytokines - signaling proteins that regulate the immune system. One of these receptors, TLR2, and a cytokine, TNF#, were found to be required for LLC metastasis. However, the normal function of TLR2 and TNFa is in host defense-innate immunity to microbial infections. According to Karin, these findings are relevant, not just to the mouse model, but also to human lung cancer - the most common cause of cancer-related deaths worldwide. The major cause of lung cancer is tobacco smoking.

"By usurping these elements of the host immune system, versican helps generate an inflammatory environment that spurs the growth and spread of metastatic cancer," said Karin. "If we can find a way to block the production of versican or its binding to TLR2, therapeutic intervention could be used to limit metastasis of lung cancer."

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