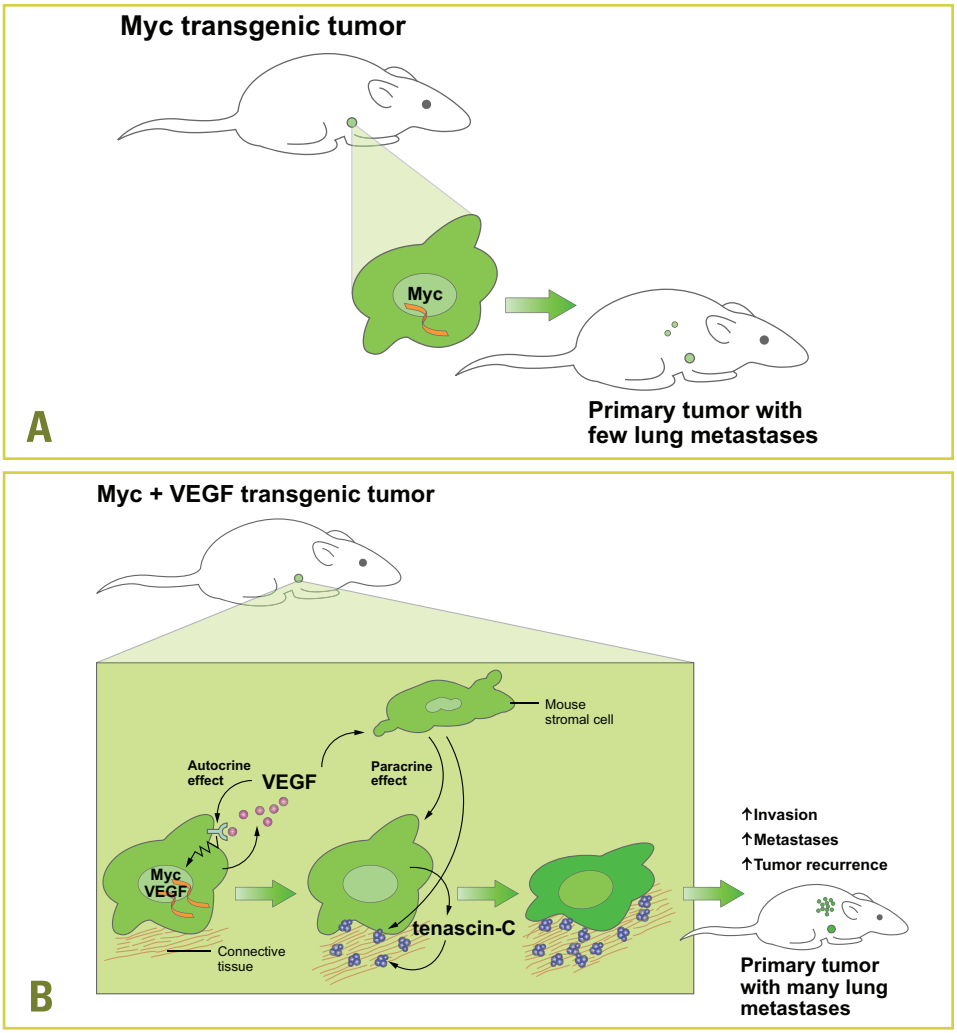
Exposing Cancer Cells' Secret Aides to Spread Disease to Distant Sites

Researchers are shedding new light on the way cancer spreads from the primary organ to distant sites in the body, a process called metastasis. The assault of metastatic tumors on vital organs too frequently results in death, and until recently, little was known about the molecular mechanisms governing this devastating phenomenon.

Metastasis is the primary cause of death in patients with breast cancer, resulting in more than 40,000 deaths in the United States each year. The most common regions of tumor spread in metastatic breast cancer include lung, liver, and bone. Treatment of metastatic disease normally focuses on the relief of symptoms and short-term survival, but there may now be cause for hope in inhibiting breast cancer lung metastasis.

A team of researchers, led by Jeffrey Green, M.D., of the NCI Laboratory of Cancer Biology and Genetics, and Michael Johnson, Ph.D., of the Lombardi Comprehensive Cancer Center at Georgetown University, has identified a potential target gene—*tenascin-C* (*TNC*)—for therapy against tumor metastasis to the lung. The team, whose findings were published online in the May 26, 2008, issue of the journal *Oncogene*, observed that overexpression of a cancer-related gene (oncogene) called *c-Myc* is



Graphic A shows that transgenic mice with increased expression of the oncogene *c-Myc* in the mammary gland have tumors with slight ability to spread to the lungs. Conversely, as shown in B, when both *c-Myc* and vascular endothelial growth factor (VEGF), a growth factor that promotes the formation of blood vessels within the tumor, are highly expressed in the mammary gland, dissemination of tumor cells to the lung dramatically increases. One reason for this increase is that VEGF acts through both an autocrine signaling loop (where signaling molecules made by the tumor leave and return to activate the tumor cell) and a paracrine signaling loop (where signaling molecules made by the tumor leave and activate nearby stromal cells). These signals change the connective tissue surrounding tumor cells, triggering it to produce tenascin-C, a protein that serves as a scaffold for the tumor cells to migrate from the tumor to the lungs, thus causing metastasis.

associated with high rates of metastasis in breast cancer patients but not in experimental (i.e., transgenic) mice expressing the *c-Myc* gene. The researchers surmised that another protein called vascular endothelial growth factor (VEGF), which is involved in tumor blood vessel formation and is found in high levels in metastatic breast cancer patients, might be involved in metastasis. To test this hypothesis, the team generated transgenic mice expressing both *c-Myc* and VEGF, resulting in a high rate of lung metastasis in these mice. A cross-species comparison of breast cancer lung metastasis–related genes was conducted between these mice and humans to detect common target genes associated with metastasis. *TNC* was one of five genes identified. Because of its prior implications in tumor cell invasion and tissue remodeling, the researchers decided to further investigate the role of *TNC* in metastasis.

A functional analysis of the *TNC* gene in mice revealed its role in regulating the migration of tumor cells through the body and the formation of new tumor tissue—two fundamental steps in the metastatic process. The researchers also found that reduced expression of *TNC* resulted in a decrease in tumor growth, tumor relapse after surgical removal, and lung metastasis. A potential *TNC*-targeted therapy would entail blocking *TNC*-dependent signaling pathways and, consequently, cutting off one of the chains of command responsible for the hostile actions of metastatic tumor cells.

TNC is just one gene involved in metastatic breast cancer. Thus, a more effective maneuver for countering metastasis would require targeting several gene pathways responsible for tumor invasion into other organs. Future research in the field of breast cancer metastasis will likely focus on further identification of metastatic genes and the development of a multi-target tactic for therapy. Such a treatment may be the weapon that metastatic breast cancer patients use to finally defeat this invasive disease.

Reference

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