Potent metastasis inhibitor identified

June 22 2009

Researchers at Children's Hospital Boston have isolated a potent inhibitor of tumor metastasis made by tumor cells, one that could potentially be harnessed as a cancer treatment. Their findings were published in the online Early Edition of the *Proceedings of the National Academy of Sciences* during the week of June 22.

Metastasis—the migration of cancer cells to other parts of the body—is one of the leading causes of death from cancer, and there is no approved therapy for inhibiting or treating metastases. Randoph S. Watnick, PhD, an assistant professor in the Vascular Biology Program at Children's, has been finding that metastatic tumors prepare landing places in distant organs for their metastases, by secreting certain proteins that encourage tumor growth and attract feeder blood vessels. Now, he and his colleagues show that non-metastatic tumors secrete a protein called prosaposin -- which inhibits metastasis by causing production of factors that block the growth of blood vessels.

Cells from localized prostate and breast tumors, which didn't metastasize, secreted high levels of prosaposin, they found, while metastatic tumors secreted very little. When the researchers injected mice with tumor cells that were known to be highly metastatic, but to which they had added prosaposin, lung metastases were reduced by 80 percent and lymph node metastases were completely eliminated, and survival time was significantly increased. Conversely, when they suppressed prosaposin expression in tumor cells, they saw more metastases.

When prosaposin was directly injected into mice that had also received an injection of tumor cells, the tumor cells formed virtually no metastases in the lung, or, if they did, formed much smaller colonies. These mice lived at least 30 percent longer than mice not receiving prosaposin.

Watnick and colleagues also demonstrated that prosaposin stimulates activity of the well-known tumor suppressor p53 in the connective tissue (stroma) surrounding the tumor. This in turn stimulated production of thrombospondin-1, a natural inhibitor of blood vessel growth (angiogenesis), both in the tumor stroma and in cells at the distant location.

"Prosaposin, or derivatives that stimulate p53 activity in a similar manner in the tumor stroma, might be an effective way to inhibit the metastatic process in humans," says Watnick.

If this bears out, Watnick envisions treating cancer patients for their primary tumor, and concurrently giving them drugs to prevent metastases or slow their growth. "While we may not be able to keep patients from getting cancer, we can potentially keep them metastasis-free," he says.

Initially, Watnick's scientific interest was focused on metastatic cancer cells; he hoped to use proteomics techniques to isolate different proteins that steered metastases to different parts of the body (explaining, for example, why lung cancer often metastasizes to bone, or prostate cancer to liver). But the late Judah Folkman, MD, founder of the Vascular Biology program at Children's, encouraged him to focus on the metastasis inhibitor -- prosaposin. "You might have a drug right here," he told Watnick.

A patent has been filed by Children's Hospital Boston on the discovery. The hospital's Technology and Innovation Development Office is in

active discussions to license prosaposin for commercial development.

Source: Children's Hospital Boston (news : web)