Protein in Embryonic Stem Cells Controls Malignant Tumor Cells

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CHICAGO --- A protein that governs development of human embryonic stem cells (hESCs) also inhibits the growth and spread of malignant melanoma, the deadliest skin cancer, Northwestern University researchers have discovered. Metastatic melanoma, which develops from the transformation of skin pigment cells or melanocytes, has a death rate of more than 80 percent and a median survival of less than 7.5 months.

The Northwestern scientists, led by researcher Mary J. C. Hendrix, additionally found that the protein, called Lefty, prevents aggressive breast cancer cells from metastasizing. Death from metastatic breast cancer exceeded 40,000 in 2007, with over 180,000 new cases diagnosed in the United States.

Importantly, Lefty is secreted only in hESCs, and not in any other stem cell type tested – including stem cells isolated from amniotic fluid, cord blood or adult bone marrow – or placental cells.

Results of the study, described in an article in the March 3rd online version of The Proceedings of the National Academy of Sciences, build on an elegant body of research by the Hendrix lab to identify the genes and cellular pathways involved in cancer metastasis.

Hendrix is president and scientific director of the Children's Memorial Research Center and professor in The Robert H. Lurie Comprehensive Cancer Center of Northwestern University and at Northwestern's Feinberg School of Medicine. Lynne-Marie Postovit, who was first author on the study and a post-doctoral trainee in the Hendrix lab, is currently an assistant professor at the University of Western Ontario, Canada.

Embryonic stem cells are pluripotent, meaning they can become any of 200-plus cell types in the adult body, depending on the signals they receive from their microenvironment (surrounding cells, tissues and vasculature). During cancer progression, malignant cells also receive and release signals from their microenvironment, cues that promote tumor growth and metastasis.

Groundbreaking work by Hendrix and colleagues is elucidating how, by becoming more like unspecialized stem cells, aggressive melanoma cells gain enhanced abilities to migrate, invade and metastasize while remaining virtually undetected by the immune system.

Hendrix and co-researchers previously demonstrated that a three-dimensional matrix conditioned by hESCs induced metastatic melanoma cells to revert to a normal, skin cell-like type with the ability to form colonies in the manner of hESCs (Postovit and Seftor et al, Stem Cells 24:501-505, 2006).

"This observation allowed us to appreciate the powerful influence of the hESC microenvironment on the reprogramming of metastatic melanoma cells," Hendrix said.

In subsequent experiments, Hendrix, Postovit and co-researchers found that aggressive melanoma and breast cancer produce a "morphogenic" protein called Nodal, which is essential for human embryonic

stem cell pluripotency (Topczewska et al, Nature Medicine 12:925-932, 2006). Other researchers have found that Nodal also is present in testicular cancer.

"Thus, Nodal may serve as a prognostic marker of aggressive behaviors in human cancers," Hendrix said.

As described in the PNAS study, the Lefty protein inhibits production of Nodal and therefore plays a major role in embryonic cell differentiation and development – under normal circumstances.

Hendrix and colleagues discovered that metastatic tumor cells do not express Lefty, allowing them to overproduce Nodal in an unregulated manner.

However, when the group exposed metastatic tumor cells to the microenvironment of hESCs containing Lefty, they witnessed dramatically reduced Nodal expression (production) in these cancer cells together with decreased tumor cell growth and invasiveness and an increase in apoptosis, or programmed cell suicide.

Although exposure to a hESC microenvironment inhibited Nodal expression and tumor growth in both metastatic melanoma and breast cancer cells, the breast cancer cells underwent more complex reprogramming. Melanoma cells responded to the hESC-derived factors within three days, but breast cancer cells required two additional days to achieve the most significant reduction in Nodal.

This discrepancy is likely due to differences in signaling mechanisms between the two cell types. Yet, despite the inherent differences between melanoma cells and breast cancer cells, these divergent tumor types both underwent cell suicide following exposure to the hESC microenvironment.

"The remarkable similarity of the responses of the two tumor types is likely attributable to the commonality of plasticity (for example, the aberrant and unregulated expression of Nodal) that indiscriminately unifies highly aggressive cancer cells, regardless of their tissue of origin," Hendrix said.

"Further, the tumor suppressive effects of the hECs microenvironment, by neutralizing the expression of Nodal in aggressive tumor cells, provide previously unexplored novel therapeutic modalities for cancer treatment," Hendrix said.

However, while findings from the study suggest that hESC-derived Lefty may have potential to prevent metastasis, it is not the only tumor suppressive factor within the embryonic microenvironment.

Observations from the study highlight the potential utility of isolating factors within the hESC microenvironment responsible for influencing tumor cell fate and reversing the cancerous properties of metastatic tumor cells, such as melanoma and breast cancer.

Additional contributing authors on the study include N. Margaryan; E. Seftor; D. Kirschmann; D. Abbott; W. Wheaton; A. Lipavsky; and R. Seftor.

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