Researchers identify unusual molecular switch for common form of advanced breast cancer

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New evidence demonstrates that a novel molecular switch is involved in the development of a common form of advanced breast cancer, known as locally advanced breast cancer. The research, published by Cell Press in the November 9, 2007 issue of *Molecular Cell*, provides an exciting paradigm shift in the understanding of a key event in breast cancer development and presents new therapeutic opportunities for this deadly disease.

Locally advanced breast cancers are typically large tumors that, remarkably, have rarely spread to form additional tumors in distant sites in the body when they are discovered. However, locally advanced breast cancer patients often have a high level of treatment failure as the disease is often detected at an advanced stage. Previous work has shown that for large tumors to progress they must develop their own blood supply through a process known as tumor angiogenesis. Angiogenesis is often triggered as the expanding tumor cells move away from the existing blood supply and are deprived of oxygen, a condition known as hypoxia.

The ability of tumors to develop their own vasculature limits their growth and is regulated at different levels of genetic control. Now, a research study led by Drs. Robert J. Schneider and Silvia C. Formenti of New York University School of Medicine presents new evidence demonstrating how an unorthodox second pathway in protein synthesis plays a key role in controlling the translation of genetic messages

(mRNAs) for factors that orchestrate angiogenesis, the tumor response to hypoxia and progression of tumors to form large locally advanced breast cancers.

“Our study shows that an unusual molecular switch occurs in the machinery that carries out synthesis of proteins that are essential for angiogenesis and tumor progression,” explains Dr. Schneider.

Drs. Schneider, Formenti and colleagues demonstrate that two factors involved in protein synthesis, 4E-BP1 and eIF4G, are strongly over-expressed in the majority of human large advanced breast tumors. Using breast cancer cells and animal tumor models, the researchers observed that elevated levels of 4E-BP1 trigger hypoxia inhibition of conventional protein synthesis in tumor cells, and with eIF4G, then increases the selective translation of specific mRNAs that promote tumor survival and angiogenesis, thereby functioning as a hypoxia controlled switch for tumor growth and survival.

These results present a entirely new understanding of the control of breast cancer angiogenesis that places the regulation of protein synthesis as a key event in malignant breast cancer. “This research opens new avenues for the development of targeted approaches in the treatment of one of the most common lethal forms of breast cancer worldwide”, says Dr. Formenti. The work was funded by the Breast Cancer Research Foundation and the Department of Defense Breast Cancer Research Program.

Source: Cell Press