IBT researchers learn about tumor suppressor

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HOUSTON – Researchers at the Texas A&M Health Science Center Institute of Biosciences and Technology have discovered how a specialized membrane protein can turn a common signaling system that promotes cell growth and tumors into one that inhibits cell growth and suppresses tumors.

The study of the protein, called βklotho, was led by Wallace McKeehan, Ph.D., director of the HSC-Institute for Biosciences and Technology Center for Cancer and Stem Cell Biology, and Yongde Luo, Ph.D., center assistant professor. It is currently available in the Journal of Biological Chemistry.

The FGF (fibroblast growth factor) family of tyrosine kinases normally instructs specific cells to regenerate as needed in embryonic development or for replacement of damaged or worn out cells in adult organs. However, when this family is unrestrained, signaling from the receptor contributes to the excessive proliferation of cells observed in cancers.

In this study, Drs. McKeehan, Luo and their colleagues found when βklotho is present, it interacts directly with the transmembrane FGFR signaling complex and redirects which intracellular molecules are activated.

Abnormal growth of tissues, particularly in cancers, is due to too many cells dividing or not enough cells dying. FGFR signaling promotes tumors by sending signals that interfere with a regulated process of cell death called apoptosis. This interference allows too many cells to survive and grow.

However, the researchers found when βklotho is present, it interferes with the signals that allow cells to avoid death and survive, contributing to the cancer. This interference results in more apoptotic cell death, less total cells that populate the cancer and suppression of the cancer rather than its promotion when FGFR is left on its own.

“The ability of βklotho to switch a normally tumor-promoting signaling system to a tumor suppression system has exciting implications for limiting tumor growth driven by the FGFR signaling system in cancers in general as well as in hepatomas,” Dr. McKeehan said.

The researchers based their findings on previous studies in mice that showed animals with a specific form of the FGF receptor (FGFR4) missing in the liver had larger and more deadly hepatomas induced by carcinogens. They observed that βklotho that is highly expressed in normal liver cells was reduced in mouse and human hepatomas more often than FGFR4.

In a normal liver, the βklotho-FGFR4 partnership also participates in endocrine control of cholesterol, bile acid and lipid metabolism. But when the liver is insulted and damaged severely enough to cause compensatory growth of new liver cells, the partnership also serves to prevent unlimited growth and development of deadly hepatomas. This insures that a normal endocrine system working routinely to provide balance in lipid metabolism does not contribute to formation of tumors.

Other contributors to the Journal of Biological Chemistry study were doctoral student Chaofeng Yang and Drs. Chengliu Jin and Fen Wang of the Center for Cancer and Stem Cell Biology, along with Dr. Weiqin Lu and Peng Huang of Baylor College of Medicine. Research was supported by the U.S. Public Health Service, the Susan Komen Breast Cancer Foundation and the John S. Dunn Research Foundation.

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