MedicalXpress

Researchers find potential target for treating metastatic cancer

December 13 2011

Finding ways to counteract or disrupt the invasive nature of cancer cells, called "metastasis," has been a long-term goal of cancer researchers. Now, researchers at Moffitt Cancer Center in Tampa, Fla., have identified an interactive pathway that regulates metastases in some cancers that may be vulnerable to chemical targeting in order to prevent cancer cell proliferation and tumor growth.

Ongoing collaboration by researchers in Moffitt's Departments of Tumor Biology and Drug Discovery has revealed the potential for combating metastatic disease by disrupting the interaction between the retinoblastoma tumor suppressor protein (Rb) and Raf-1 (a gene with a potential to cause cancer) with RRD-251, a selective, chemical disrupter of Rb-Raf-1 interaction.

Their recent study, aimed at understanding the association between Rb-Raf-1 and genes known to be over-expressed in metastatic non-small lung cancer, was published in the recent issue of Cancer Research, a journal of the American Association for Cancer Research. This work, using a mouse model, was a continuation of the researchers' study of RRD-251's successful disruption of Rb-Raf-1 interaction in metastatic melanoma in test mice, a study published in Molecular Cancer Therapeutics in 2010.

"The Rb gene is mutated in a variety of cancers," said study corresponding author Srikumar P. Chellappan, Ph.D., chair of Moffitt's Department of Tumor Biology and scientific director of the National

Functional Genomics Center. "Our earlier studies have shown that Raf-1 interacts with Rb early in the cell cycle and facilitates its inactivation."

The ongoing work of Chellappan and his colleagues in Moffitt's Department of Tumor Biology focuses on understanding the mechanisms by which external signals regulate cell proliferation and how a loss of regulation may cause cancer. They work extensively with the Rb protein, the Raf-1 signaling molecule, and E2Fs, genes that affect cell proliferation, differentiation and cell death (apoptosis).

E2Fs, a family of genes that play a role in the mammalian cell cycle and can transform normal cells to have properties of cancer cells, interact with Rb. In addition, E2Fs are important for the development, differentiation and DNA damage repair programs in cells. Their previous studies have shown that RRD-251-mediated disruption of the Rb-Raf-1 interaction could inhibit the activity of E2F. They now show that E2Fs regulate matrix metalloproteinases (MMPs), which are involved in cancer metastasis, and RRD-251 can prevent the expression of MMPs.

"A considerable amount of research has been dedicated to identifying novel E2F- regulated genes, but a clear role for E2Fs in cancer progression and metastasis had not been established," explained Chellappan. "We find that the Rb-E2F pathway contributes to the expression of many genes involved in different aspects of cancer, and that targeting this pathway might fight metastatic disease."

Their study found that a mouse model of non small cell lung cancer metastasis being treated with RRD-251 had "significantly less metastasis to the lung and surrounding areas." They concluded that disrupting the Rb-Raf-1 interaction using RRD-251 could inhibit the regulatory function of E2Fs as an activator of gene promoters that are related to tumor growth and metastases.

"There is a possibility that E2F might indirectly regulate tumor metastasis as a consequence of its activating these genes," suggested Chellappan. "Taken together, our studies link the Rb-E2F cell cycle regulatory pathway to advanced stages of cancer development and metastasis."

Although further studies are underway, their work suggests that disrupting Rb-Raf-1 interaction can prevent cancer cell proliferation, cell vascular growth (angiogenesis), tumor growth, and the metastatic colonization of organs.

"This approach appears to be a fruitful avenue to combat metastatic disease," concluded Chellappan.

Provided by H. Lee Moffitt Cancer Center & Research Institute