Discovery of epigenetic memory during breast cancer

January 25 2010

Researchers from the Boston University School of Medicine (BUSM) have determined how the TGFβ-Smad signaling pathway, which is over activated in late-stage cancers, is responsible for the "epigenetic memory" that maintains unique patterns of regulatory DNA hypermethylation causing silencing of critical genes that facilitate breast cancer progression. The findings, which appear online in *Cancer Research*, may lead to the development of new therapeutic strategies for late stage breast and other cancers.

According to the researchers, it is becoming increasingly accepted that changes that do not affect the genetic blueprint or DNA sequence, known as the epigenetic landscape, play a major role in defining the properties of normal as well as the cancer cells. While specific epigenetic alterations have been associated with cancer progression, the molecular mediators that ensure transmission of these reversible alterations to successive tumor cells has been elusive.

The BUSM researchers found that the disruption of TGFβ signaling caused a corresponding decrease in the promoter DNA binding activity of DNA methyl transferase 1 leading to passive demethylation of the newly synthesized DNA resulting in expression of genes that are silenced during breast cancer progression.

"The re-expression of genes that promote cell adhesion in cancer cells upon inhibition of the Smad signaling pathway causes reversal of tumorigenic properties and puts the brakes on cancer progression," said

principal investigator, Sam Thiagalingam, PhD, an associate professor of medicine and pathology and a member of the Cancer Research Center at BUSM. "This study may pave the way to discovering other pathways and network of events that are responsible for sustaining epigenetic memory in cancer and cancer stem cells and could lead to the unraveling of effective targets for eradication of tumor cells as well as tumor initiating cells," he added.

"While targeting of TGFβ and TGFβ receptors have been actively pursued for cancer therapy, the current finding may introduce a new spin on the wheel and lead to the development of new therapeutic strategies for late stage breast and other cancers by the direct perturbation of the Smad signaling pathway," explained lead author Panos Papageorgis, PhD, a post-doctoral fellow in the genetics program at BUSM.

Provided by Boston University Medical Center