New epigenetic mechanisms for improved cancer therapy

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A review article by researchers at Boston University School of Medicine (BUSM) proposes a new epigenetic hypothesis linked to tumor production and novel ideas about what causes progenitor cells to develop into cancer cells. Published in the February 2013 issue of *Epigenomics*, the article provides examples of how epigenetic drug treatments could be beneficial in treating cancers while also decreasing the likelihood of cancer relapse.

The article was written by researchers at the Boston University Cancer Center. Sibaji Sarkar, PhD, adjunct instructor of medicine at BUSM, is the article's corresponding author.

Cancer is a complex disease characterized by uncontrolled cell growth, division and invasion into other tissues. A 2004 review article published in Nature Medicine suggests that epigenetics, which is the phenomena whereby genetically identical cells express their genes differently resulting in different phenotypes and other factors play an important role in the formation of cancer originating from cancer stem cells.

Sarkar and colleagues propose that epigenetic processes, specifically DNA methylation, may trigger cancer progenitor cell formation from somatic cells in coordination with other cellular and environmental events. DNA methylation is a process that changes the DNA and causes genes to be silenced. In the absence of definitive proof of the existence of cancer stem cells, this hypothesis discusses a possible explanation for the formation and existence of cells that may develop into cancer. The

researchers also explore why only some individuals develop cancer, despite identical genetic predispositions.

In cancer cells, the enzyme that maintains high levels of methylation in tumor suppressor genes is highly expressed, allowing uncontrolled growth. At the same time, many oncogenes, or genes with the potential to cause cancer, are activated and have lower levels of methylation. The apparent anomaly of the existence of both low and high rates of methylation could be explained with either the compartmentalization of these two processes and/or by the existence of both a methylation and demethylation system operating simultaneously at specific locations with the help of various accessory proteins.

The authors hypothesize the existence of both DNA methylating and demethylating enzymes in cells that regulate the methylation and demethylation process. Accessory proteins and/or small RNA factors could lead these enzymes to their sites of actions, resulting in some genes remaining methylated and others not methylated simultaneously within the same cellular environment. DNA sequences around the regions that are methylated and demethylated may also play role in these events. During drug treatments, the demethylating system dominates while the methylating enzyme is down-regulated, resulting in re-expression of silenced genes.

Recent studies have shown that epigenetic drug treatments prior to and with standard chemotherapy reduce the chance of cancer relapse.

"Progenitors are known to cause cancer relapse, and because epigenetic drugs can help destroy progenitor cells, these drugs could help reduce the chance of cancer relapse and improve the long-term outcomes of people with cancer," said Sarkar. "While our hypotheses are based on current knowledge, we are proposing important and exciting areas to be explored in the future."