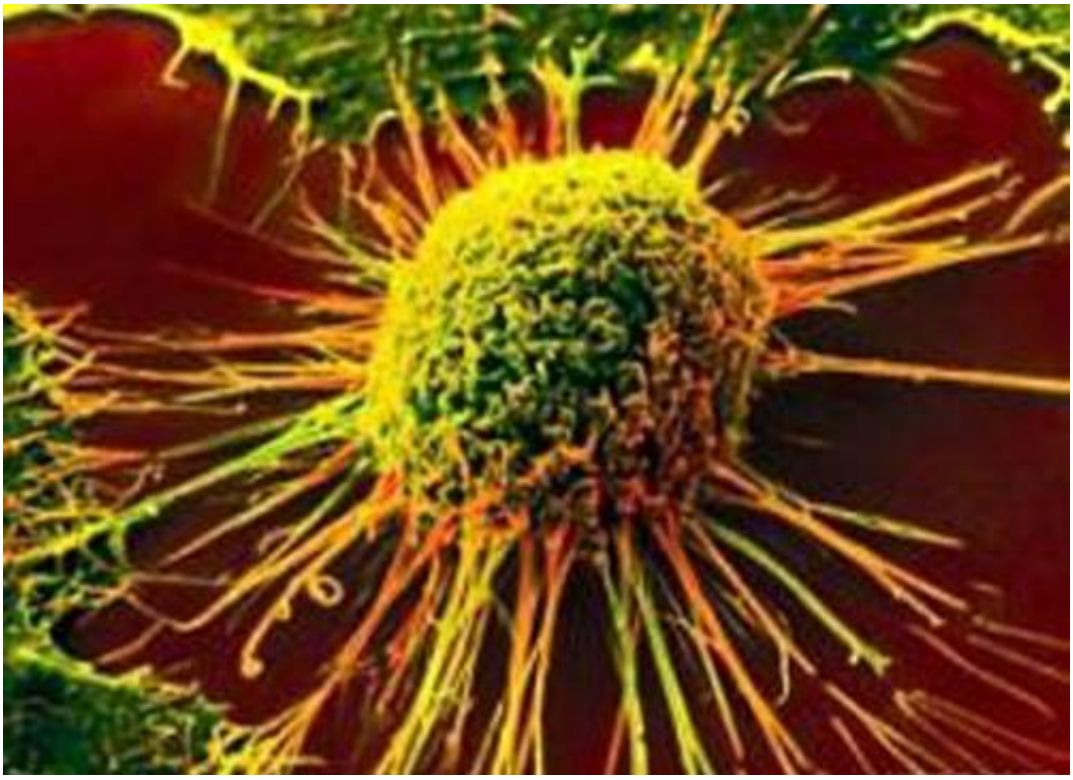
Review article provides new insights on how tumors metastasize

March 6 2015



In a review article recently published in the journal *Clinical and Translational Medicine*, researchers from Boston University School of Medicine (BUSM) shed new light on the underlying processes of tumor metastasis and highlight the role of epigenetics in this process. By comparing embryogenesis with cancer metastasis they hypothesize that

reversible epigenetic events regulate the development of different types of metastatic cancers. They also describe that the surrounding cells of the tumors (stromal cells) play a significant role in this process.

The BUSM researchers support the hypothesis that metastasis is more of a gradual process, leading to a heterogenic tumor population with cells of various epigenetic and differentiation statuses. They propose that cancer progenitor cells slow their growth while differentiating into more metastatic forms and then resume rapid division once the cells have metastasized to certain state or grade. Similar processes again take place when that grade of metastatic cancer changes to another grade.

As this process is not a one-time event during tumor metastasis, the slowing of growth and increase in differentiation must happen many times. Once the desired grade is achieved, the reverse process needs to take place. Epigenetics is what allows the cells to transform reversibly. In accordance with this hypothesis, metastasized tumors of various types and prognoses demonstrate known epigenetic markers.

Localization and growth of the metastatic tumor cells in distant location is another important event in tumor metastasis. For the tumor cells to take hold and form a new tumor at a secondary location, the more motile mesenchymal cells need to convert to an epithelial state to enable them to attach to the distant organ (MET). The reversible epigenetic changes can now turn on the reverse differentiation genes and turn off on the genes for rapid growth; this occurs once the cells are settled in the distance location.

Embryogenesis is a physiological process that involves growth and differentiation and is regulated primarily by epigenetic events. Opportunistic cancer cells and cancer progenitor cells use this process to their advantage to achieve metastasis. According to corresponding author and principal investigator Sibaji Sarkar, PhD, instructor of medicine at

BUSM, the embryonic differentiation epigenetic mechanisms can be hijacked to produce disease conditions including cancer. "Permanent mutations and alterations in the genome certainly do play a role in cancer progression, but in order for the cancer to initiate, differentiate, metastasize and adapt to new locations in the body, reversible epigenetic processes are necessary."

As an example, Sarkar presents two patients that have the same predisposition for cancer. "Though they may have the same genetic mutations that put them at an increased risk of developing cancer, they will not develop cancer at the exact same time, in the same way or in the same location, if they both develop cancer at all. Epigenetics can, in this case, be seen as the cancer kick-starter, turning on or off the genes necessary for a precancerous cell to become cancer progenitor cell," he said.

Future studies will determine how epigenetic changes perform this "gene turn on and gene turn off" process to both initiate cancer from cancer progenitor cells and also enable them to differentiate into metastatic tumors. Understanding, and targeting, the ways in which epigenetic changes contribute to cancer progenitor cells undergoing differentiation will be crucial in developing anti-cancer drugs, anti-metastatic drugs and preventing cancer relapse.

Provided by Boston University Medical Center