Potentially targetable signaling pathway generates slowly proliferating, chemo-resistant cancer cells

January 12 2015

A signaling pathway responsible for the generation of slowly proliferating cancer cells, which are hard to eradicate with current treatments and thought to be a cause of subsequent disease relapse, has been reported in a Rapid Impact study published in *Molecular Cancer Research*, a journal of the American Association for Cancer Research.

"We have identified a new pathway in which well-studied signaling molecules string together to regulate cell proliferation," said Sridhar Ramaswamy, MD, an associate professor of medicine at Massachusetts General Hospital Cancer Center and Harvard Medical School in Boston. "Since a number of these molecules are under intensive study as therapeutic targets for various cancer types, we are currently designing strategies to target this pathway in animal models in order to better clarify the potential clinical implications of these findings.

"All cancers contain some cells that are rapidly proliferating and many that proliferate only very slowly," explained Ramaswamy, who is also an associate member of the Broad Institute and the Harvard Stem Cell Institute. "Most cancer treatments target rapidly dividing cancer cells but leave the slowly dividing ones unharmed and still capable of causing disease recurrence after the initial treatment. Our goal has been to understand how these slow proliferators are produced in order to devise ways to eliminate them."

When cancer cells growing in the laboratory divide, they usually produce two daughter cells that have the same rate of proliferation, but sometimes one daughter cell proliferates at a much slower pace than the other.

Ramaswamy and colleagues have been investigating why cancer cells undergo this type of asymmetric cell division for a number of years. In a previously published study, they found that if a cancer cell asymmetrically suppresses expression of a protein called AKT right before dividing, it produces two daughter cells: one that has normal levels of AKT protein and proliferates rapidly like the parent cell, and one that has low levels of AKT and proliferates slowly. They also detected these rare cancer cells with low levels of AKT in breast cancer patients and found that these cells were highly resistant to the combination chemotherapy being used to treat the patients.

In this new study, the researchers used a number of molecular biology techniques to investigate how cancer cells dividing in the laboratory produce daughter cells with different levels of AKT. They found that decreased signaling through beta1-integrin, a molecule found on the surface of most cancer cells, decreased the activity of the signaling molecule FAK. This, in turn, increased the activity of a complex of signaling molecules called mTORC2, which led to suppression of AKT1 protein levels by a molecule called TTC3 and the proteasome complex.

"Prior to these studies, we thought that asymmetric suppression of AKT might just relate to random fluctuations in protein levels during cell division," said Ramaswamy. "We discovered that this is not the case; it is actually regulated by a potentially targetable signaling pathway, which may offer new avenues for reducing the proliferative heterogeneity within tumors for therapeutic effect."