MedicalXpress

Cancer cells' evasive action revealed

March 2 2016, by Mike Williams

Researchers at Rice University and the University of Texas MD Anderson Cancer Center have uncovered a trick used by lung cancer cells to hide from the body's immune system.

The researchers have found links between subtle actions and reactions that allow cancerous cells to spread with little to stand in their way. The team led by Dr. Edwin Ostrin, an assistant professor of pulmonary medicine at MD Anderson, and theoretical biological physicist Herbert Levine at Rice, details its findings in study in this week's Proceedings of the National Academy of Sciences.

The study shows for the first time that some aggressive lung cancer cells display significantly reduced expression of proteins known as immunoproteasomes, a key player in the process that signals the immune system's T-cells to attack diseased cells. The researchers suggest it may be possible to enhance the production of these proteins to override the cells' escape mechanism.

Immunoproteasomes are produced inside cells, where they degrade unneeded or damaged proteins, including those produced by invading pathogens. The degraded pieces are secreted by the cell and bond to its surface and create beacons that inform nearby T-cells of the cell's diseased nature.

If T-cells don't sense these surface beacons, called antigens, a cancer is more likely to evade detection and destruction. Data gathered over the years by MD Anderson researchers shows patients with early stage non-

small-cell lung cancer—the most common type—who have low expression of immunoproteasomes are more likely to see their cancers return after treatment and metastasize.

The researchers led by Dr. Satyendra Tripathi, a postdoctoral fellow at MD Anderson and lead author of the paper, set out to discover why immunoproteasomes are reduced in lung cells transitioning from epithelial-type cells, which bind to each other to form skin and organ linings, to free-floating mesenchymal-type cells. Tripathi had observed the expression of a cluster of genes that encode immunoproteasomes and their association with epithelial to mesenchymal transition.

"Cancers containing cells that express mesenchymal markers tend to be later-stage, more aggressive and more metastatic," Ostrin said. "Identifying this new mechanism opens a potential pathway for exposing these cells to immune attack."

Researchers at MD Anderson and Rice combined efforts to view the cause and effect of the expression levels of dozens of genes representing proteins from 42 non-small-cell lung cancer lines.

"One of the main new ideas in therapy is to somehow get the immune system to fight against the cancer," Levine said. "What we want to understand is how the characteristics of the cancer cells either enhance that possibility or preclude it."

Levine, co-director of Rice's Center for Theoretical Biological Physics, said it's been known for some time that motile mesenchymal-type cells are relatively resistant to chemotherapy. "Now, what seems to also be true is that the cells are relatively more resistant to immunotherapy." Immunotherapy aims to boost the body's own immune system to fight cancer.

MD Anderson researchers led by Ostrin and Dr. Samir Hanash, director of the McCombs Institute for the Early Detection and Treatment of Cancer, profiled protein expression in the target cell lines and correlated the data to patient outcomes; meanwhile, the Rice researchers built computer models that allowed them to rapidly combine and evaluate protein-signaling pathways over time.

"The idea was to leave no stone unturned," Levine said. "We modeled the changes in gene expression that can be readily measured, how they might be caused and how these are correlated to all the other changes going on in the cells.

"We want to go from the basic biology of defining the circuits and how they change the expression of these key proteins to showing that they really do have a consequence in terms of recognition by the immune system," he said.

What emerged was that the suppression of immunoproteasomes appears to be a consequence of feedback loops activated by the transition to mesenchymal-type cells. The next step, the researchers said, is to consider whether inducing immunoproteasome production in target cancer cells will counteract their evasion tactics. This might be tested in animal models.

"We would hope that reversal of this downregulation through treatment with IFN-gamma, rapamycin or 5-aza-dC may work symbiotically with immune checkpoint inhibition that is currently proving so promising in many cancers," Ostrin said.

"From the lofty goal of saying how one should modify treatment of cancer, any purely modeling effort is going to be incremental," Levine said of his team's contribution. "But in this study, because it has real data from real patients saying this is a real problem, modeling helps point us

in a treatment direction we might actually begin to try."

More information: Satyendra C. Tripathi et al. Immunoproteasome deficiency is a feature of non-small cell lung cancer with a mesenchymal phenotype and is associated with a poor outcome, *Proceedings of the National Academy of Sciences* (2016). DOI: 10.1073/pnas.1521812113

Provided by Rice University