Double negative leads to big positive against bladder cancer metastasis

September 9 2016, by Garth Sundem

Dan Theodorescu, M.D., Ph.D., director of the University of Colorado Cancer Center and colleagues detail a new link in the chain that leads to bladder cancer metastasis. Credit: University of Colorado Cancer Center

The popular kids' card game "Exploding Kittens" teaches a concept critical to cancer science: When a player plays a "Nope" card, the subsequent player may lay another "Nope", thus creating a double-negative that becomes a positive, allowing the initial action to proceed. A paper, stemming from a longstanding collaboration between investigators at the University of Colorado Cancer Center and Yale, published in the journal *Cancer Cell*, demonstrates a similar strategy that bladder cancer

uses to proliferate. By "Noping" the cancer-suppressing gene RhoDGI2, the disease evades a mechanism designed to stop its ability to metastasize. Now new understanding of this mechanism may allow doctors and researchers to Nope this Nope - stopping bladder cancer's ability to stop the tumor-suppressing gene RhoDGI2, thus allowing its initial action to proceed.

Here is how it works:

Circulating cancer cells recruit elements of the body's immune system to prime the tissue environment for the development of new tumors. The current study demonstrates a promising strategy to block the immune system's mistaken collaboration with cancer cells, resulting in the inability of circulating cells to seed new sites of metastasis.

"Working with bladder cancer cells, we were able to show not only how immune system macrophages recognize and aid circulating cancer cells, but also how we might intercede to block this mechanism," says Dan Theodorescu, MD, PhD, director of the University of Colorado Cancer Center and the paper's co-senior author.

The finding takes place in the context of the well-known tumor-suppressor gene RhoDGI2. Activity of this gene and the protein it encodes restricts the ability of bladder cancer cells, and potentially other circulating cancer cells, to grow at new sites of attachment. In fact, it is these sites of metastasis, specifically in the lung that can make bladder cancer fatal. Previous work in the Theodorescu lab published in the Journal of Clinical Investigation in 2011 and 2012 has shown one side of how loss of RhoDGI2 affects cancer growth: loss of RhoGDI2 allows a cancer cell to increase production of proteins called Endothelin and Versican, which signal immune system macrophages to the site of the cancer cells. These macrophages promote the development of new tumors by producing various cancer growth-promoting substances.

The current paper shows that one of these substances is the protein osteopontin. Basically, loss of RhoDGI2 leads to increased Endothelin and Versican, which brings macrophages, which secrete osteopontin, which signals tumor cells to reinitiate stem-cell-like programs that promote growth and survival. Osteopontin does this by binding to CD44 receptors on the surface of newly-attached bladder cancer cells, jumpstarting their ability to act as seeds of a new tumor site. CD44 is a cell surface glycoprotein that is overexpressed to some extent by almost all tumors of epithelial origin and plays an important role in tumor initiation and metastasis. CD44 is a compelling marker for cancer stem cells of many solid malignancies.

When the investigators blocked this osteopontin signaling pathway in animal models, bladder cancer cells were not able form metastases in the lungs and lymph nodes. Likewise, expression of osteopontin was associated with poor outcomes in human bladder cancer patients.

"Interestingly, blocking CD44 did nothing against the local tumor growth. The effect was very robust, but was limited to stopping the initial formation of metastasis," says Martin Schwartz, the Robert W. Berliner Professor of Medicine at Yale and the paper's co-senior author. Again, it is the ability of bladder cancer to invade the lung (and the brain) that makes the disease potentially fatal, and not the activity of the primary tumor itself. Thus treatment strategies targeting metastasis, potentially by blocking osteopontin binding to CD44, offer a compelling way to decrease mortality from the disease.

"What this paper shows is that targeting macrophages and/orCD44 are potential clinical therapeutic options," Theodorescu says. "Also, this demonstrates that when you lose RhoDGI2, it causes the cancer to attract macrophages that in turn secrete osteopontin, which stimulates cancer aggressiveness," he says.

Several years ago, Theodorescu discovered RhoDGI2 as a suppressor of tumor growth at metastatic sites and has worked on it since then. Now there is another step in this understanding. And each step presents another opportunity for doctors and researchers to insert a misstep. RhoDGI2, CD44, versican and osteopontin represent nodes in a signaling web that allows cancer metastasis. "Noping" cancer's "nope" in this web at any point may save lives.

More information: Mansoor Ahmed et al, An Osteopontin/CD44 Axis in RhoGDI2-Mediated Metastasis Suppression, *Cancer Cell* (2016). DOI: 10.1016/j.ccell.2016.08.002

Provided by CU Anschutz Medical Campus