Major study stops bladder cancer from metastasizing to lungs

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The diagnosis of localized bladder cancer carries an 80 percent five-year survival rate, but once the cancer spreads, the survival rate at even three years is only 20 percent. A major study published today in the *Journal of Clinical Investigation* not only shows how bladder cancer metastasizes to the lungs but pinpoints a method for stopping this spread.

Specifically, the study shows that versican, a protein involved in cancer cell migration, is a driver of lung metastasis and that high levels of versican are associated with poor prognosis in bladder cancer patients. The study is the first to show how that when a cancer cell makes the protein RhoGDI2, it reduces the cell's production of versican, thus blocking the ability of the cancer cell to grow in the lungs.

"For a decade, we've known that the major challenge of treating bladder cancer is treating or preventing the metastatic form of the disease. This study represents an advance in the latter – by preventing the spread of bladder cancer to the lungs, we could improve patient survival," says Dan Theodorescu, MD, PhD, director of the University of Colorado Cancer Center, the paper's senior author.

When a cancer metastasizes from its birth location to another, it's not necessarily that cells suddenly become mobile and thus able to float through the blood or lymph to new homes. In fact, these cancer cells may have been floating through a patient's blood for quite some time, and metastasis occurs only when one of these intrepid cells is finally able to grow in the place where it is attached, such as the lungs.

When the first cancer cells to attach to, say, the lung, they have a tough time – they become distressed. Cancer cells express this distress in the form of versican. And the more versican they express, the more help they get, which arrives in the form of macrophages, a part of the body's immune response that eat pathogens and other debris.

In most cases, the fact that macrophages benefit distressed cells is good, but in addition to helping healthy cells survive, these arriving macrophages also promote the growth of cancer cells that have landed in distant sites such as the lung, thus promoting metastasis of the disease.

More versican made by the cancer cells calls more macrophages, which aid cancer cells' survival and increase the likelihood that a cancer cell's toehold will develop into a clinically significant tumor in the lung.

Theodorescu and colleagues showed that the protein RhoGDI2 reduces the expression of versican. Cancer cells that make more RhoDI2 produce less versican and thus call fewer macrophages, making it difficult for these high-RhoGDI2 cancer cells to survive.

Sure enough, when Theodorescu and colleagues added RhoGDI2 to tumors, versican went down and with it so did metastasis.

"We believe this study provides an important contribution to the scientific literature by delineating for the first time a new mechanism of metastasis suppression, namely that suppression of metastasis is possible by altering the tumor microenvironment, including reducing the presence macrophages," Theodorescu says.

In fact, this paper also shows for the first time one more step: versican's ability to attract macrophages to the tumor depends on a protein called CCL2. This step is important because drugs that inhibit CCL2 are already in clinical trials for other conditions.

If the effect in humans is the same as the effect in the laboratory – namely that inhibiting CCL2 reduces versican's ability to attract the macrophages that promote tumor growth at distant sites – one of these CCL2 inhibitors could soon become part of the treatment regimen for bladder cancer patients with tumors that make low levels of RhoGDI2 and high versican. This approach has the potential to lower the chance of bladder cancer metastasis and thus a significantly improved outcome for patients with high risk bladder cancer.

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