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Research findings reveal that tumors promote myeloid-derived suppressor cell accumulation through IRF-8 loss

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(Medical Xpress)—Researchers at Roswell Park Cancer Institute (RPCI) have uncovered a new pathway by which cancer cells, such as in breast cancer, stimulate the expansion of myeloid-derived suppressor cells (MDSCs), a blood cell population known to interfere with the body's anti-tumor response. The findings, published online today in *The Journal of Clinical Investigation*, shed new light on the pathological events that fuel tumor growth and could lead to the development of new therapies to hinder it.

"Tumors are often described as 'wounds that do not heal," says Scott I. Abrams, Ph.D., Associate Professor of Oncology at RPCI and senior author of this study. "With any type of tissue injury, the immune system is engaged to repair the damage. But that response is typically ineffective in cancer because the myeloid arm of the immune system which participates in tissue repair paradoxically supports rather than blocks tumor growth."

The MDSC is now thought to represent a key perpetrator in this scenario, in part through the secretion of substances, which do not discriminate normal from cancerous cells that promote new vessel formation.

Although much is known about how MDSCs act, little is known about how they develop. Abrams and colleagues hypothesized that tumors

disrupt normal myelopoiesis, the process by which myeloid cells ordinarily develop, through inhibition of a critical myeloid-related protein called interferon regulatory factor-8 (IRF-8). Decreasing IRF-8 levels facilitated MDSC expansion; whereas, increasing IRF-8 levels reduced MDSC burden and improved tumor growth control. So, what caused IRF-8 levels to decline?

"Certain products released by cancer cells initiated the drop in IRF-8 levels, and they did so by activating either one of two other proteins, known as STAT3 or STAT5 [signal transducers and activators of transcription], which then repressed IRF-8," Abrams says.

These findings were confirmed using blood samples obtained from 30 RPCI breast cancer patients taken at diagnosis. Patients with lower MDSC levels had higher IRF-8 levels than patients with higher MDSC levels. In addition, patients with higher MDSC levels had a significantly poorer prognosis than patients with lower MDSC levels, in terms of progression-free and overall survival. The researchers are now designing novel approaches to modulate IRF-8 levels with the goal of improving the anti-cancer immune response.

Provided by Roswell Park Cancer Institute