Scientists reveal how white blood cell promotes growth and spread of cancer

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Scientists at The Scripps Research Institute have shown that a particular white blood cell plays a direct role in the development and spread of cancerous tumors. Their work sheds new light on the development of the disease and points toward novel strategies for treating early-stage cancers.

The study was published in September 2011 print issue of the American Journal of Pathology.

Scripps Research Professor James Quigley, Staff Scientist Elena Deryugina, and colleagues had previously demonstrated that white blood cells known as neutrophils—bone marrow-derived cells that function as "first responders" at sites of acute inflammation—promote the growth of new blood vessels in normal, healthy tissue.

The team has now tied these cells to the induction and growth of new blood vessels in malignant tumors and to the spread of tumor cells through those newly formed vessels. The scientists have also uncovered some of the mechanisms underpinning this process—which could be interrupted by properly targeted drugs.

Potent and Uninhibited

The Scripps Research team has been particularly interested in neutrophils, in part because several studies have demonstrated a link

between elevated neutrophil levels and high rates of tumor invasion among cancer patients. Mounting evidence has also indicated that neutrophils play a particularly important role during the early stages of tumor development.

"During tumor development, neutrophils appear to be one of the first inflammatory cell types on the scene," said Deryugina, who spearheaded the new study.

The researchers have been especially interested in the blood vessel-forming or "angiogenic," powers of neutrophils, which stem from a special enzyme they produce known as MMP-9 (matrix metalloproteinase type 9). The enzyme is, in fact, synthesized by a number of different types of white blood cells and has long been linked to tumor development. But the particular form synthesized by neutrophils is especially potent, in part because it does not come bound up with the natural inhibitory regulating agents that other cells supply.

Whereas other types of white blood cells only manufacture the enzyme later and invariably deliver it in combination with one of its natural inhibitors, neutrophils come loaded with pre-synthesized MMP-9 in a form that is unencumbered.

Making the Case

In a series of cleverly designed experiments, Quigley, Deryugina, and colleagues established a link between neutrophils, their MMP-9, and the growth and spread of tumors.

The scientists alternately raised and lowered the quantity of neutrophils allowed to flow into two different kinds of early-stage tumors, which had been transplanted into chicken embryos and mice. They also introduced several different versions of the enzyme, sometimes

combining it with dampening agents, sometimes not.

By observing the subsequent decrease and increase in the formation of new blood vessels, the Scripps Research team was able to establish that the unique form of the enzyme delivered by neutrophils was directly responsible for heightening the growth of new blood vessels in the tumors. Just as importantly, they were able to determine that the newly formed blood vessels served as "escape routes" or conduits for the spread of tumor cells beyond their initial location.

First, the scientists established that the most aggressive tumors—that is, the ones that were able to most quickly penetrate the surrounding blood vessels and spread to different areas—depended on their ability to attract large numbers of neutrophils.

The researchers then proceeded to spur the growth of new blood vessels in even relatively nonaggressive tumors by supplying additional quantities of neutrophil-derived enzyme. They also blocked the formation of new vessels with the anti-inflammatory drug ibuprofen and then restored, or "rescued," angiogenesis by pumping in additional enzyme.

Quigley and Deryugina also drastically reduced the influx of neutrophils by neutralizing IL-8 (interleukin 8), the chemical attractant that draws neutrophils to sites of inflammation. Blood vessel formation declined correspondingly, as did the penetration of vessels by tumor cells, clearly linking neutrophils to the development and spread of two different, but highly aggressive, forms of cancer. To further strengthen that link, the researchers again reversed the decline with an infusion of neutrophil-derived enzyme.

"By dampening neutrophil influx into tumors, we dampen angiogenesis, but we also dampen metastasis," Quigley said. "And when we rescue

angiogenesis, we also rescue the high metastatic rate of the tumors."

Significantly, only the unregulated, uninhibited version of the enzyme provided by neutrophils reversed the dampening effect caused by reducing inflammation or cutting off the flow of neutrophils. No such rescue occurred when the enzyme was combined with its natural inhibiting agents—the same molecules that accompany the enzyme when it is delivered by other kinds of white blood cells.

Intriguing Possibilities

The scientists note that the study suggests tumors that engender a strong inflammatory response may be particularly amenable to early-stage treatment by drugs that specifically target neutrophils, whether that means inhibiting the enzyme they deliver or simply preventing them from showing up in the first place.

"It might be best to combat tumor angiogenesis earlier rather than later," Quigley said, adding that "more specifically directed anti-neutrophil agents might be better suited than a general anti-inflammatory."

The Quigley lab continues to investigate.

More information: "Neutrophil MMP-9 in Tumor Progression" doi:10.1016/j.ajpath.2011.05.031

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