

Primary tumors can drive the growth of distant cancers

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Primary tumors can encourage the growth of stray cancer cells lurking elsewhere in the body that otherwise may not have amounted to much, according to a new study in the June 13 issue of the journal *Cell*. As people age, most may have such indolent cancer cells given the sheer number of cells in the body, although their rarity makes them impossible to detect, the researchers said.

The primary tumors under study, which were derived from human breast cancers, seem to "instigate" the growth of other cancers by mobilizing bone marrow cells, which then feed the secondary tumors' growth, they report.

One key to the process is the secretion of a substance known as osteopontin by the instigating tumor, a finding that may have therapeutic implications. Indeed, the researchers noted that osteopontin is present at elevated levels in women with metastatic breast cancer, supporting the notion that the new findings may hold clinical significance.

"If metastases depend on stimulation by primary tumors, interception of the signal through neutralizing antibodies" might block cancer spread, said Robert Weinberg of the Massachusetts Institute of Technology. "That's still speculative, but it's an interesting idea to ponder," he added, noting that treatments today don't specifically target metastases, which are responsible for the vast majority of cancer deaths.

The researchers noted that while the effects of the tumor

microenvironment has been much studied, much less was known about how the systemic environment in the body contributes to tumor growth. Several earlier reports had shown that assorted bone marrow-derived cells can be incorporated to various extents into the supportive framework, or stroma, of tumors. However, it wasn't clear whether tumors actively recruit stromal cells by directly perturbing other cell reservoirs, such as the bone marrow, or whether tumors are just passive recipients of stromal cell precursors that normally circulate throughout the body.

In the new study, the researchers injected "instigating" human tumor cells into mice along with indolent "responding" cancer cells also derived from humans. Those indolent cells formed vigorously growing tumors only in the presence of the instigating tumor cells, they reported. They found further evidence that the instigating tumor somehow perturbs the makeup of the bone marrow, although Weinberg said they don't really know how that happens. They also show that osteopontin is necessary to the process, but that it does not act alone.

Finally, they showed that the same instigation process can encourage the growth of disseminated metastatic cancer cells. Instigating breast tumors in the mice also drove the growth of implanted fragments of human colon tumors, a finding that they said shows the generality of the physiologic signaling.

Nonetheless, the researchers said they don't yet know how universal this systemic instigation of tumor growth might be. Still, the findings challenge the "prevailing view that primary tumors suppress the growth of derived metastases," Weinberg said. "We argue they can foster cancer's spread by activating bone marrow that is then recruited by distant metastases."

The findings also have important implications for the preclinical study of

human cancers, Weinberg emphasized.

" The ability of instigating tumors to foster the growth of a human colon tumor surgical specimen underscores the powers of systemic instigation," the researchers wrote. "Indeed, to our knowledge, methods to expedite the growth of human tumor surgical specimens in vivo have not been previously described. These results suggest that the presently described procedure can be used to study aspects of human tumor biology that would otherwise be difficult if not impossible to study.

" In the longer term, identification of additional tumor-derived factors that perturb the host systemic environment in one way or another may allow one to predict the effects that a given primary tumor type has on the outgrowth of indolent cancer cells that have disseminated to distant sites."

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