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Tumors Bring Their Own Support Cells When Forming Metastases; Noncancerous Cells from Primary Site Appear to Facilitate Tumor Growth

The process of metastasis requires that cancer cells traveling from a primary tumor find a hospitable environment in which to implant themselves and grow. A new study from Massachusetts General Hospital (MGH) Cancer Center researchers finds that circulating tumor cells prepare this environment by bringing along from their original site noncancerous cells that support tumor growth.

The report has been published online in Proceedings of the National Academy of Sciences Early Edition.

"It has been known for some time that noncancerous stromal cells -- which provide a support structure for tissues and organs -- contribute to the growth of primary tumors, providing the 'soil' in which tumors can grow," says Dan Duda, PhD, DMD, of the Steele Laboratory for Tumor Biology in the MGH Department of Radiation Oncology, lead author of the report. "Our study shows that this primary soil also helps the initial growth of tumor seeds in a 'foreign' soil. This new role for these noncancerous cells is both a conceptual advance and offers potential new targets for treating or preventing metastatic disease."

Several previous studies by members of the MGH team and others have found clumps containing both tumor cells and stromal cells in blood and lymphatic vessels of cancer patients and have shown that these "passenger" stromal cells will proliferate along with the tumor cells if implanted at a new site. The current investigation was designed to determine whether primary tumors release fragments containing tumor and stromal cells, whether those stromal cells survive and contribute to the development of metastases, and whether depletion of stromal cells could interfere with metastatic growth.

Several experiments in mice confirmed that implanted tumors shed both single tumor cells and clumps containing tumor and stromal cells and that tumor cells accompanied by stromal cells were more likely to survive. Not only did stromal cells from the original tumor proliferate at the site of metastasis, metastatic nodules that contained both tumor and stromal cells were more likely to survive and grow than were those containing tumor cells alone. Experiments using tumor cell lines known to be highly metastatic found that lung metastases that developed after a primary tumor was removed still contained stromal cells from the primary site and that reducing the number of stromal cells in lung metastases slowed tumor growth and increased the animals' survival.

To investigate whether stromal cells play a similar role in human metastatic tumors, the researchers examined brain tumor samples from patients with several different types of cancer for the presence of fibroblasts -- stromal cells not normally present in brain tissue. Fibroblasts were frequently found in brain metastases -- implying that stromal cells had traveled along with cancer cells from the primary tumor -- but not in either primary brain tumors or normal brain tissue.

"We used fibroblasts in our experiments because they are frequently found in metastatic nodules, but we expect that other types of passenger cells -- including immune cells and the endothelial cells that line blood vessels and other body cavities -- also will play an important role in supporting metastasis," says co-corresponding author Dai Fukumura, MD, PhD, of the Steele Lab. "Cancer researchers here at the MGH and at other institutions are focused on detecting and analyzing circulating tumor cells, and our findings demonstrate that characterizing these non-cancerous passenger cells should also be a priority."

Adds Rakesh Jain, PhD, Director of the Steele Lab and Senior Author of the PNAS Early Edition report, "Prevention of metastasis has been clinically difficult because these supportive nontumor cells arrive at the secondary site long before metastatic disease can be detected. Applying treatments that block participation of fibroblasts or other stromal cells in metastatic lesions at the time the primary tumor is removed could help prevent the spread of localized tumors."

Jain is the Cook Professor of Radiation Oncology (Tumor Biology) at Harvard Medical School, where Duda is an assistant professor and Fukumura an Associate Professor of Radiation Oncology. Additional co-authors are Annique Duyverman, Mitsutomo Kohno and Ernst Steller of the Steele Laboratory, and Matija Snuderl, MD, MGH Pathology. The study was supported by grants from the National Institutes of Health, the Department of Defense and the Japanese Ministry of Health and Welfare.