Microenvironment provides growth factor for metastasis

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Healthy bone is continuously involved in a dynamic process that includes bone deposition and bone resorption. However, when a person has cancer that spreads to the bone and bone marrow, the tissue becomes increasingly fragile, and this process is disrupted, usually leading to increased bone resorption.

In an early online edition in advance of publication in the *International Journal of Cancer*, investigators at Children's Hospital Los Angeles reported a surprising discovery - when neuroblastoma (NB) cells metastasize to the bone, there initially occurs an increase in bone deposition, not resorption. They also determined that this process is driven by a chemical messenger called VEGFA.

Neuroblastoma is the most common extra-cranial solid tumor occurring during childhood and frequently metastasizes to the bone and bone marrow, making the disease more difficult for doctors to treat and conferring a worse prognosis for patients. Teams of scientists have been working to determine what causes a tumor to metastasize, knowing it is an interaction between tumor cells and the metastatic site, called the microenvironment.

"Metastasis results from a vicious cycle: tumor cells accelerate bone deposition, which releases physiological factors that feed tumor cells," said Josephine H. HaDuong, MD, of Children's Hospital Los Angeles, who is first author on the study. She is also an assistant professor at the Keck School of Medicine of the University of Southern California.

HaDuong explains that the microenvironment includes the connective tissue, or stromal cells in the bone marrow, the cells that form and resorb bone along with other cells and growth factors.

Stroma includes a population of pluripotent progenitor cells that are able to become bone, muscle, fat or cartilage. A growth factor called bone morphogenetic protein, or BMP, drives the progenitor cells on the path to form bone. When BMP was added to progenitor and NB cells, the investigators expected bone deposition but they found more of it than anticipated. Using microarray analysis, they determined this increase to be mediated by VEGFA. In other experiments they specifically blocked VEGFA and found an increase in bone-resorbing cells and areas of severe bone loss.

"For years we have known that the microenvironment was key to understanding metastatic neuroblastoma," said principal investigator Yves DeClerck, MD, of the Center for Childhood Cancer and Blood Disorders at CHLA. "Now we have identified a new role for VEGFA, laying the groundwork for the development of therapeutics to target it." DeClerck holds the Richard Call Family Endowed Chair in Pediatric Research Innovation at CHLA, and is a professor at the Keck School of Medicine of the University of Southern California (USC).

More information:
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