Key mechanism identified in tumor-cell proliferation in pediatric bone cancers

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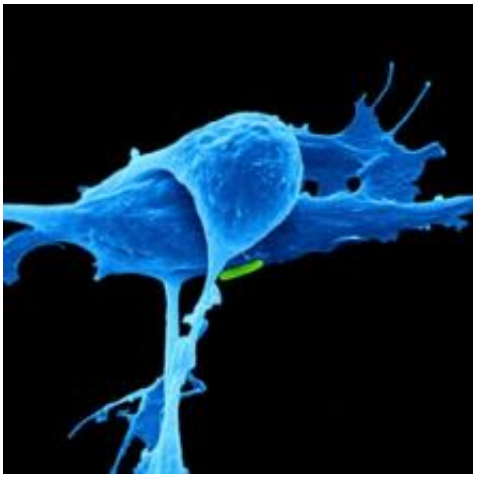

A particular molecular pathway permits stem cells in pediatric bone cancers to grow rapidly and aggressively, according to researchers at NYU Langone Medical Center and its Laura and Isaac Perlmutter Cancer Center.

In normal cell growth, the Hippo pathway, which controls organ size in animals, works as a dam, regulating cell proliferation. What the researchers found is that the transcription factor of a DNA binding protein called sex determining region Y box 2, or Sox2 for short, which normally maintains cell self-renewal, actually releases the floodgates in the Hippo pathway in osteosarcomas and other cancers, permitting the

growth of highly aggressive, tumor-forming stem cells.

Results from the study are to be published in the journal *Nature Communications* online April 2.

"This study is one of the first to identify the mechanisms that underlie how an osteosarcoma cancer stem cell maintains its tumor-initiating properties," says senior study investigator Claudio Basilico, MD, the Jan T. Vilcek Professor of Molecular Pathogenesis at NYU Langone and a member of its Perlmutter Cancer Center.

In the study, the investigators used human and mouse osteosarcomas to pinpoint the molecular mechanisms that inhibit the tumor-suppressive Hippo pathway. The researchers concluded that Sox2 represses the functioning of the Hippo pathway, which, in turn, leads to an increase of the potent growth stimulator Yes Associated Protein, known as YAP, permitting cancer cell proliferation.

"Our research is an important step forward in developing novel targeted therapies for these highly aggressive cancers," says study co-investigator Alka Mansukhani, PhD, an associate professor at NYU Langone and also a member of the Perlmutter Cancer Center. "One possibility is to develop a small molecule that could knock out the Sox2 transcription factor and free the Hippo pathway to re-exert tumor suppression."

Mansukhani adds that the research suggests that drugs such as verteporfin, which interfere with cancer-promoting YAP function, might prove useful in Sox2-dependent tumors.

The study expands on previous work in Basilico's and Mansukhani's molecular oncology laboratories at NYU Langone and on earlier work by Upal Basu Roy, PhD, MPH, the lead study investigator, who found that Sox2 was an essential transcription factor for the maintenance of

osteosarcoma stem cells.

The NYU group has shown that, in addition to playing a role in osteosarcoma, Sox2 operates in other tumors, such as glioblastomas, an aggressive type of brain cancer.

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