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Team identifies new cancer stem cell driving metastatic tumors

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The molecular profile of cancer stem cells that initiate metastatic colon tumors is significantly different from those responsible for primary tumors, according to new research from a team at Weill Cornell Medical College.

Cancer researchers have long believed that a protein called CD133 identifies a population of cancer stem cells (so-called CD133+ cells), the only subset of cells that are responsible for tumor initiation. But in the experiment, in which immunocompromised mice were injected with human metastatic colon cancer, the Weill Cornell team discovered that cancer cells that do not express CD133 can also spur metastatic disease.

"In fact, metastatic tumors originating with these CD133- cells are more aggressive than those spurred by CD133+ cells," says study senior author Dr. Shahin Rafii, the Arthur B. Belfer Professor in Genetic Medicine and director of the Ansary Center for Stem Cell Therapeutics at Weill Cornell. Dr. Rafii is also a noted investigator at the Howard Hughes Medical Institute. "Our discovery shows that metastatic and primary cancer may not initiate in the same way. This could have significant implications for research going forward -- we believe the discovery opens up new avenues of investigation in cancer stem cell biology."

The findings were released as a special "highlighted" article in the May 22 online edition of the Journal of Clinical Investigation.

Cancer stem cells are a small, discrete class of cells that scientists believe

give rise to malignancy and are solely responsible for tumor maintenance. For years, experts have tracked expression of the CD133 protein as a means of identifying a population of tumor-initiating cells.

To understand the biology of CD133+ cells in a healthy state and during tumor formation the researchers generated a transgenic mouse in which the CD133 gene is replaced with a reporter gene called lacZ. "We relied on the expression of lacZ to detect the spatial and temporal location of CD133+ cells in vivo," explains co-researcher Andrea T. Hooper, a graduate student in Dr. Rafii's lab.

Studying the expression of CD133 in this genetic model, the researchers, for the first time, were able to visualize a real pattern of CD133 expression in a living organism. "It came as a big surprise that CD133 expression is not restricted to stem cells, but rather defines mature epithelial cells. This finding directed us to explore the actual contribution of CD133+ cells in tumorigenesis," notes the paper's lead author Dr. Sergey Shmelkov, an instructor in genetic medicine at Weill Cornell. "We examined human primary colon tumors, and we also induced colon cancer in CD133 transgenic mice, and discovered that all cancerous epithelial cells in the tumor express CD133, explaining why tumor-initiating cells in primary colon cancer are CD133+."

But was the scenario the same in metastatic disease" To find out, the researchers transferred fresh human metastatic colon cancer cells into immunocompromised mice. They then tracked the tumor formation ability of CD133+ and CD133- cells during metastases in these mice.

The investigators encountered yet another surprise. "We found that not all human colon cancer cells that form metastases were CD133+, as occurs in primary tumors," says co-lead author and postdoctoral fellow Dr. Jason Butler. "CD133- cells -- probably derived from CD133+ cells from the primary tumor -- were also capable of tumor initiation and

appeared to play a major role in the formation of metastases. In fact, tumors generated by CD133- cancer stem cells tended to be more aggressive than those originating from CD133+ cells."

The bottom line, according to the Weill Cornell–led team, is that origins of metastatic disease appear to be much more complex than that seen with primary cancer.

"There is a subpopulation of cancer stem cells that appears to lose CD133 expression during tumor progression, but then is able to move to the site of metastasis and form new tumors there," says co-senior author Dr. David Lyden, the Stavros C. Niarchos Associate Professor in Pediatric Cardiology, and an associate professor of cell and developmental biology at Weill Cornell.

The results of this study could change the direction of research into cancer stem cell biology and stimulate the search for new authentic cancer stem cell markers, the researchers say.

"The origins of primary and metastatic tumors are decidedly not the same, and we must broaden our thinking beyond CD133+ cells when it comes to the investigation of metastatic disease," Dr. Rafii says. "We expect this paper will have a tremendous impact in cancer stem cell biology, aiding research into the causes of cancer in laboratories worldwide."

Source: New York- Presbyterian Hospital