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Cancer metastasis: Cell polarity matters

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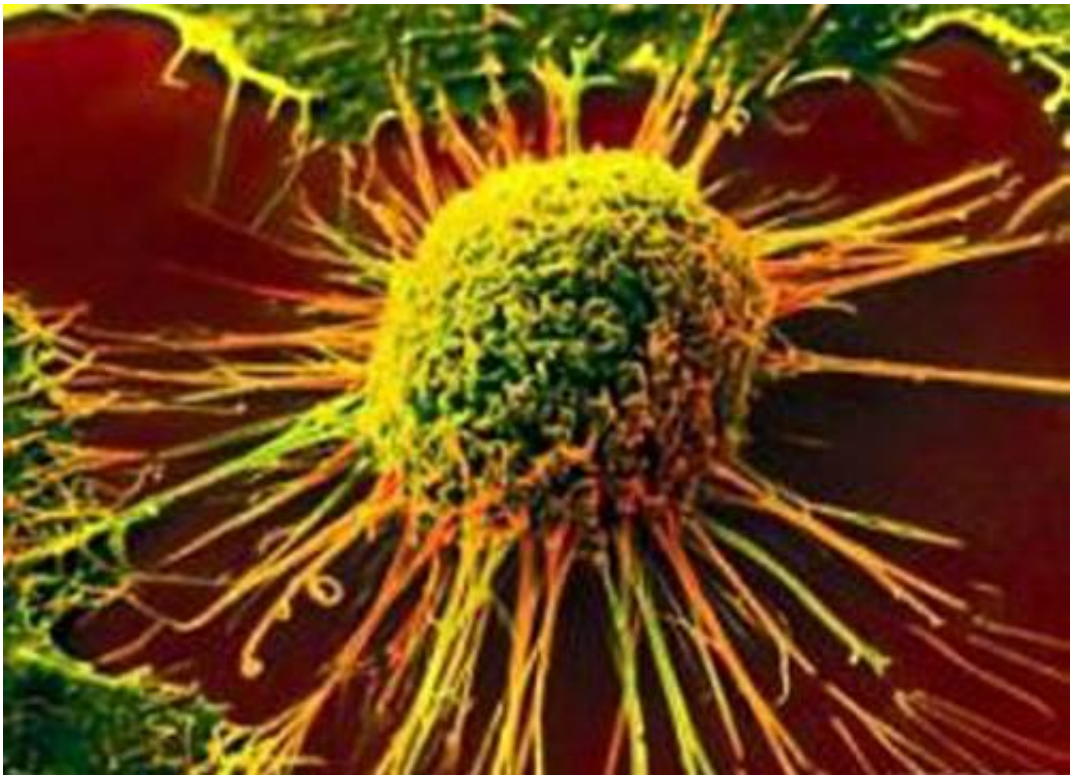

It's not only the number of migrating cancer cells that determines the risk for metastasis, but also their characteristics, scientists from the German Cancer Research Center (DKFZ) report in *Nature Communications*. For circulating cancer cells to invade tissues and settle at other sites in the body, they have to exhibit a specific polarity. This discovery might contribute to better predicting individual risk for metastasis and find appropriate therapies that can reduce it.

Metastatic tumors form when cancer cells break away from a tumor and migrate via the lymph system and the bloodstream to distant sites in the body. However, the quantity of circulating cancer cells in the body is not the only factor that determines a patient's risk of developing metastatic sites. "Some patients display high quantities of circulating tumor cells and have no or only a few metastatic sites, while in others who suffer from many metastases, hardly any migrating tumor cells can be found," said Mathias Heikenwälder from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) in Heidelberg.

The team led by Heikenwälder has therefore taken a closer look at the properties of migrating cancer cells. In human cancer cells as well as in patients with different types of cancer, and also in mice, they observed that a portion of the circulating cancer cells exhibit a specific polarity. "Under the microscope, this looks as if the cells had a kind of nose," Heikenwälder described. Two cytoskeletal proteins called ezrin and merlin play a key role in the formation of this structure. Furthermore, the scientists also found that the number of freely circulating tumor cells exhibiting this special polarity correlates with the risk of developing metastasis, both in human tumor cell lines and in mice.

"This polarity seems to help the free cancer cells return from the blood vessels into body tissue," explains Anna Lorentzen, who is the first author of the publication. With the polarized end, i.e., the "nose," the cells attach to the endothelial layer lining the interior of the vessels. Subsequently, the pole is shifted to the side facing the attachment site and the tumor cell migrates through the endothelial layer into the tissue.

As a cross-check, the researchers used a cell-biological trick to block polarization of the circulating cells. Both in culture and in mice, the manipulated cells were no longer able to attach efficiently to endothelial cells. With this discovery, the DKFZ researchers have not only found a new mechanism promoting the formation of metastatic sites—"we have

also found a link that might in future be used to better predict and even reduce the risk for metastasis in cancer patients," Heikenwälder said.

More information: Anna Lorentzen et al, Single cell polarity in liquid phase facilitates tumour metastasis, *Nature Communications* (2018). DOI: 10.1038/s41467-018-03139-6

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