# Cancer metastasis: Tumor plasticity counts

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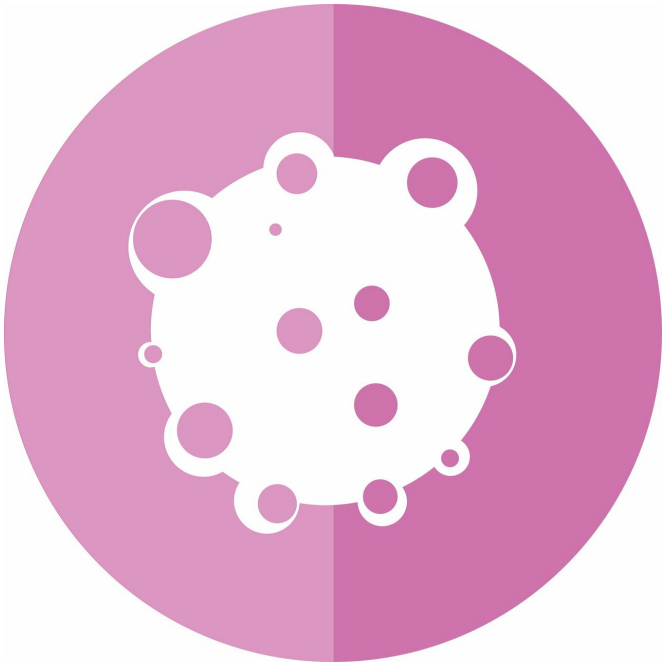

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Cancer metastasis, which is the propagation of tumor cells into distant organs, is the leading cause of cancer patient mortality. To undergo metastasis, cells must leave the primary tumor, invade the microenvironment, circulate into the blood or lymphatic circulation, reach distant organs, and establish a secondary tumor. The precise cellular and molecular events responsible for the different steps of the metastatic cascade are still incompletely understood.

It has been proposed that epithelial to mesenchymal transition (EMT), a process in which epithelial cells detach from their neighboring cells, lose their adhesion features and acquire mesenchymal migrating properties, is important to initiate the metastatic cascade allowing the cancer cells to leave the primary tumor. However, recent studies had challenged this notion. Consequently, the importance of EMT for metastasis is still unclear. Does the EMT requirement depend on the tumor type? Does EMT occur in the circulating tumor cells? Does EMT revert to an epithelial phenotype at the metastatic sites?

In a study published in *Cell Reports*, researchers lead by Pr. Cédric Blanpain, MD/Ph.D., WELBIO investigator and Professor at the Université Libre de Bruxelles, Belgium had now provided evidence that the tumor cells that initiate the metastatic process undergo EMT and that the reverse transition called MET is occurring at the metastatic site, underscoring the importance of tumor cell state transitions and tumor cell plasticity during the metastatic process.

To resolve whether EMT is required for metastasis, they used two distinct models of skin squamous cell carcinoma (SCC) undergoing or not spontaneous EMT during tumorigenesis. The mouse model in which the tumors displayed EMT presented high metastatic incidence. In sharp contrast the SCC model without EMT presents very low incidence of metastasis, supporting the notion that EMT is important for metastasis.

Circulating tumor cells (CTCs) is one of the first steps in metastatic cascade. Up to now CTCs are detected based on the expression of epithelial markers such as Epcam, the gold standard and is used in clinic to evaluate the number of CTCs to predict metastasis and response to therapy. Our genetic model tracking the cancer cells based on the expression of fluorescent protein allowed the researcher to determine the presence of CTCs, regardless the expression of known markers. They found that CTCs were always associated with metastases. However, the vast majority of CTCs were Epcam-negative. This finding suggests that CTC needs to undergo EMT to form metastasis and that the use of Epcam marker to track CTCs is not optimal. "Clearly new methods using novel markers that recognize CTC that underwent EMT would be required to better monitor CTCs in the blood of cancer patients," comments Tatiana Revenco, the first author of this study.

Importantly, the researchers observed that the majority of metastases present little signs of EMT, supporting the notion that the reversion of EMT, called MET is important for the metastatic outgrowth. "This finding is very important to take into consideration when applying anti-EMT treatment, as it can prevent the metastatic dissemination from primary tumor but can favor the metastatic growth in distant organs" comments Pr Blanpain, the last and corresponding author of the study.

**More information:** Tatiana Revenco et al, Context Dependency of Epithelial-to-Mesenchymal Transition for Metastasis, *Cell Reports* (2019). DOI: 10.1016/j.celrep.2019.09.081

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