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Road to perdition: Zeb1-dependent and –independent ways to metastasis

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One of the most important questions in cancer research and therapy is how tumor cells form metastases in distant organs. One concept is based on the hijacking of an embryonic program by individual cancer cells at the invasive front. The transient activation of the so-called epithelial-mesenchymal transition (EMT) program enables cell delamination and spreading of individual tumor cells via the blood stream. It is suggested that in these cells transient or partial EMT is induced by upregulation of a handful of EMT transcription factors (EMT-TFs) that include Snail, Slug, Twist and Zeb1.[1,2] Since following the cascade of metastasis *in vivo* is challenging, the concept of EMT is still debated, reflected by 2 recent publications that highly question this process and convincingly show that Snail and Twist are dispensable for metastasis in 2 mouse models of pancreatic and breast cancer.[3,4] In contrast, our lab has accumulated compelling evidence that in pancreatic cancer Zeb1 is a major driver of metastasis. Our data indicate that Zeb1 provides cellular plasticity, a prerequisite to escape the primary tumor mass and to adapt to the novel and hostile environment on the way to metastatic colony formation.[5] Isolated and cultured tumor cell lines specifically lost their colonization capacity in the absence of Zeb1. However, the effect of Zeb1 on tumor cell dissemination and survival in the blood stream still has to be analyzed thoroughly during disease progression in the genetic mouse tumor model. Interestingly, we also observed that, in a minority of mice, metastases still form even in the absence of Zeb1, suggesting that there are alternative paths to achieve the spread of tumor cells.

What are the potential mechanisms acting here? We have strong indications that in the absence of Zeb1 EMT is blocked, cell plasticity is impaired in multiple ways and colonization capacities are largely reduced,[5] however, it cannot be excluded that alternative mechanisms exist *in vivo* to induce EMT. Zeb1-deficient tumor cells may have found a loophole for metastasis formation via the remaining EMT-TFs expressed at low levels. They could still become malignant via collective cell migration, a process that shares some features of EMT but does not require substantial cell reprogramming and loss of epithelial properties, like the expression of E-cadherin and apical-basal cell polarity.[2,6] Examples can be found for normal cells, e.g. during development and wound healing, as well as for cancer cells. Several findings support the notion that a subset of tumor cells are able to leave the bulk tumor mass as a collective and stay grouped together during the whole metastatic cascade. During the *bona fide* process of collective cell migration a small subset of cells are instructed to become the leader cells at the tip. These leader cells form the invasion front, whereas follower cells tag along and migrate more passively by adhering to leader and other follower cells. Leader cells gain some mesenchymal properties without losing cell adhesion and epithelial characteristics completely.[2,6] Presumably, the same mechanisms that induce single cell migration are activated moderately, resulting in a low-level partial EMT. To allow directed cell migration through the stroma, release of proteases by leader cells for digestion of ECM components is necessary, as well as dynamic regulation of cell-cell (cadherins) and cell-matrix adhesion (integrins) and acquisition of a front-rear polarity. These processes are very well demonstrated in physiological conditions, e.g., by the formation of the lateral line organ during zebrafish development, when a cluster of proliferating epithelial cells migrates in a defined path from rostral to caudal, releasing groups of cells at defined positions.[6]

However, other mechanisms of metastasis, which are completely independent of the expression of EMT-TFs within the tumor cells, are also possible. Recently published data nicely showed that tumor-stroma crosstalk can instruct fibroblasts to act as leader cells and pull on tumor cells to induce and lead invasion without the need of cell plasticity and EMT-TFs. Interestingly, these activated cancer-associated fibroblasts use heterophilic cell-cell adhesion, via N-cadherin on stromal cells and E-cadherin on epithelial tumor cells, for this mode of invasion.[7] Although these findings are awaiting confirmation by mouse models, this scenario expands the view of how tumor cells gain invasive and metastatic properties.

In summary, EMT and collective cell migration may be very similar as they share several features. However, collective cell migration does not require global cell reprogramming and full cell plasticity compared with Zeb1-induced EMT which is impaired upon Zeb1-loss.[5] Accordingly, Zeb1-deficient tumor cells may well be still able to follow the route of collective cell

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migration as a lesser tread path. Additionally, metastatic mechanisms, which are completely independent of EMT-TFs, are likely also to exist. However, several lines of evidence strongly suggest that during malignant transformation, Zeb1-mediated EMT is the major and most important driving force for metastasis in pancreatic cancer.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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