Report

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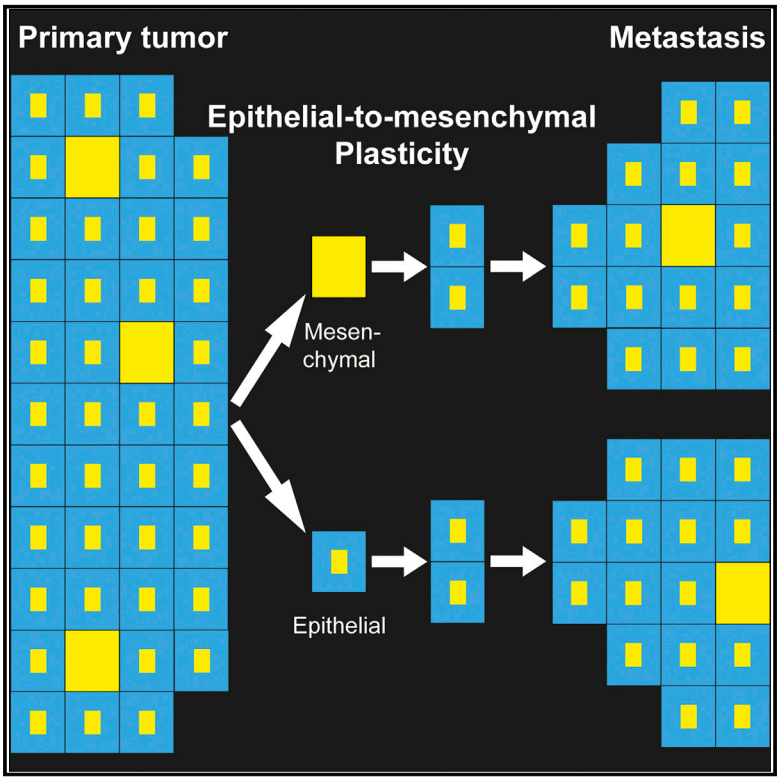
Plasticity between Epithelial and Mesenchymal States Unlinks EMT from Metastasis-Enhancing Stem Cell Capacity

Graphical Abstract



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In Brief

Beerling et al. identified a previously undetectable pool of cells in epithelial breast tumors that have undergone EMT without experimental induction. These cells are motile when disseminating and revert back to the epithelial state upon metastatic outgrowth. This epithelial-mesenchymal plasticity equalizes metastatic outgrowth potential between epithelial and mesenchymal tumor cells.

Highlights

- Direct evidence of EMT obtained in unperturbed breast tumors by real-time visualization
- EMT exists in breast tumors without experimentally altering EMT inducers
- Tumor cells that underwent EMT are the migratory cells within a tumor
- Outgrowth potential differences between states are irrelevant due to plasticity

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Plasticity between Epithelial and Mesenchymal States Unlinks EMT from Metastasis-Enhancing Stem Cell Capacity

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SUMMARY

Forced overexpression and/or downregulation of proteins regulating epithelial-to-mesenchymal transition (EMT) has been reported to alter metastasis by changing migration and stem cell capacity of tumor cells. However, these manipulations artificially keep cells in fixed states, while in vivo cells may adapt transient and reversible states. Here, we have tested the existence and role of epithelial-mesenchymal plasticity in metastasis of mammary tumors without artificially modifying EMT regulators. In these tumors, we found by intravital microscopy that the motile tumor cells have undergone EMT, while their epithelial counterparts were not migratory. Moreover, we found that epithelial-mesenchymal plasticity renders any EMT-induced stemness differences, as reported previously, irrelevant for metastatic outgrowth, because mesenchymal cells that arrive at secondary sites convert to the epithelial state within one or two divisions, thereby obtaining the same stem cell potential as their arrived epithelial counterparts. We conclude that epithelial-mesenchymal plasticity supports migration but additionally eliminates stemness-enhanced metastatic outgrowth differences.

INTRODUCTION

Metastatic growth is the major cause of cancer-associated mortality. To successfully grow metastases, epithelial tumor cells need to acquire invasive properties to disseminate and stem cell properties to grow new tumors at distant sites (Hanahan and Weinberg, 2011). Metastasizing cancer cells have been suggested to hijack a developmental program named epithelial-to-mesenchymal transition (EMT) (Bill and Christofori, 2015; Kalluri and Weinberg, 2009; Lim and Thiery, 2012). During developmental EMT, cells lose cell-cell contacts and concomitantly decrease the expression of the epithelial adherens junction molecule E-cadherin (E-cad) and gain expression of proteins involved in, e.g., invasion and stemness (Kalluri and Weinberg, 2009; Lim and Thiery, 2012; Thiery and Sleeman, 2006).

The effect of EMT on stemness, as well as the role and even the very existence of EMT during metastasis, are heavily debated (Del Pozo Martin et al., 2015; Fischer et al., 2015; Zheng et al., 2015). For example, contradicting findings were published on the stem cell potential of tumor cells with an epithelial or mesenchymal state. Some studies found that EMT-inducing transcription factors, such as Twist, coincide with the acquisition of stem cell properties, thereby supporting metastatic growth (Mani et al., 2008; Morel et al., 2008; Wellner et al., 2009; Yang et al., 2004). Other studies found that a forced reversion to an epithelial state through Twist knockdown leads to metastasis-initiating abilities (Ocaña et al., 2012; Tsai et al., 2012). Importantly, both experimental approaches may not represent the true in vivo status of cells because they require gene manipulations that artificially force cells into fixed states, while in vivo cells may be able to transiently and reversibly switch between states, a process that from here on is referred to as epithelial-mesenchymal plasticity. Moreover, the non-physiological overexpression or complete loss of EMT-regulators, such as Twist1, may induce expression profiles and subsequently stem cell phenotypes that do not exist under physiological conditions. Finally, EMT regulators can have oncogenic functions independently of their ability to induce EMT, thus observed phenotypes that result from gene manipulation may not be exclusively due to EMT induction (Beck et al., 2015). These data and concerns illustrate the importance of studying EMT in non-manipulated in vivo settings.

Although EMT would best be studied in the physiological in vivo settings, non-experimentally induced EMT during metastasis has yet to be observed. For example, extensive histological examination of human invasive ductal mammary carcinomas

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