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COMMENTARY

# Transition to resistance: An unexpected role of the EMT in cancer chemoresistance

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Breast cancer;
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EMT;
Pancreatic cancer;
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**Abstract** Two recent studies provide intriguing evidence that challenges the role of the epithelial–mesenchymal transition (EMT) as a critical mediator of cancer metastasis, while revealing an unexpected role in cancer drug resistance.[1,2] While these findings may not settle the EMT's role in metastasis, these studies suggest that targeting the EMT may inhibit both cancer metastasis and chemoresistance.


The phenomenon whereby epithelial cells can lose their epithelial characteristics and acquire mesenchymal characteristics was first described in the early 1980s.[3] This dramatic cell transposition process, known as the epithelial–mesenchymal transition (EMT), not only plays critical roles in governing embryonic development and maintaining adult tissue hemostasis (e.g., via regulating wound healing and stem cell behavior), but also contributes to many pathological conditions, such as fibrosis and cancer progression.[4–7] The EMT process is regulated by several key transcription factors, such as SNAIL, zinc-finger E-box-binding (ZEB) and basic helix–loop–helix transcription factors, which are further controlled by multiple signaling pathways, such as the TGFβ and WNT pathways, in response to extracellular cues.[5–9]

It is well accepted that the EMT plays an important role in cancer metastasis. It has been considered that the non-motile epithelial cancer cells at the primary site first acquire the migratory characteristics of mesenchymal cells and then undergo a reverse mesenchymal-to-epithelial transition (MET) when they seed at a secondary site.[5,8,10] The metastatic tumors formed at the secondary site display the same epithelial cell phenotype as the cancer cells at the primary site, leaving little evidence of their transient mesenchymal state. This notion of an EMT-induced early stage of metastasis has been supported by numerous *in vitro* studies and mouse models of metastatic human cancers, but the clinical evidence supporting the occurrence of EMT in tumor specimens has been limited. However, two recent studies presented data that highlighted an unexpected role of the EMT in cancer drug resistance, while challenging the role of the EMT as a critical process for cancer metastasis.[1,2]

In one study, Fischer et al created two mouse models of mammary tumors that develop spontaneous metastases, which were traced by Cre-mediated switching of fluorescent markers.[1] The transgenic mice expressing either *PyMT* or the *Neu* oncogene in the mammary gland harbored a Cre-switchable fluorescent marker in the cells expressing fibroblast-specific protein 1 (*Fsp1*; indicating early EMT) which changed from red fluorescent protein (RFP) to green

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fluorescent protein (GFP). Thus, GPF-positive cells were indicative of the EMT, and persisted in the progeny of these cells after they reverted to an epithelial fate because their GFP expression was not reversible. They found that the development of primary tumors and spontaneous lung metastases in these tri-*PyMT* and tri-*Neu* mouse models was indistinguishable from that in controls. However, the tumor cells in the lung metastases were RFP-positive, indicating that they had never undergone the EMT or expressed *Fsp1*. Using the tri-*PyMT* mouse model that switched from RFP-positive to GFP-positive when vimentin (*Vim*, another EMT marker) was expressed, the authors found that the lung metastases in the tri-*PyMT*/*Vim* mice were also RFP-positive. Furthermore, the authors orthotopically injected tri-*PyMT* or tri-*PyMT*/*Vim* tumor cells into wild-type mice and showed that inhibiting the EMT by expressing miR-200, which targets transcription factors required for the EMT (*Zeb1* and *Zeb2)*, failed to inhibit metastasis following orthotopic injection. Surprisingly, while the treatment of mice bearing orthotopic tri-*PyMT* tumors with cyclophosphamide reduced primary tumor size, many metastatic tumors in the treated mice contained a significant number of GFP-positive cells, which expressed many factors implicated in proliferation and the resistance to chemotherapy, suggesting that these metastatic cells may become more resistant to cyclophosphamide in an EMT-dependent manner.

In a companion study, Zheng et al reported similar findings using tissue-specific deletion of the EMT-inducing transcription factors Snail or Twist to assess the consequences of the EMT in a mouse model of pancreatic ductal adenocarcinoma (PDAC), in which mice develop metastatic tumors due to the expression of mutant p53 and KRAS-G12D in pancreatic cells.[2] When these mice were crossed with mice lacking the EMT transcription factor *Snail1* or *Twist1*, there were similar numbers of metastases in the liver, lungs and spleen in these EMT-deficient mice and the EMT-competent mice. Moreover, the authors showed that suppressing the EMT had no effect on the number of circulating tumor cells, the ability of tumor cells to form tumor spheres or colonize the lung following intravenous injection, or the overall frequency of metastasis. However, suppressing the EMT in these PDAC mice reduced the tumor progression and increased the survival of mice when they were treated with gemcitabine. Using another PDAC model which expressed mutant KRAS and lacked TGF-β receptor 2 (TGFβR2), the authors also found that knocking out *Snai1* did not prevent the development of metastatic PDAC, while it enhanced the sensitivity of their tumors to gemcitabine, suggesting a role for the EMT in cancer drug resistance.

Both of these reports provide convincing evidence linking the EMT to cancer drug resistance, which may be caused by an enhancement of cancer cell survival, cell fate transition, and/or up-regulation of drug resistance-related genes. At the same time, both studies challenge the current prevailing view of the EMT's role in cancer metastasis. However, the EMT is a highly complex cellular process that is regulated by multiple signaling molecules and transcription factors. In fact, the precise mechanism(s) underlying the EMT are still not fully understood. Thus, the possible limitations of the tumor models used by Fischer et al and Zheng et al need to be considered before EMT's role in cancer metastasis and tumor invasion can be dismissed outright.

First, tracing the EMT switch phenotype on the basis of the expression of a single gene may not fully represent the complicated nature of the process. Second, an effective suppression of the EMT may not be accomplished by simply inactivating either Snail or Twist, because both are known to function redundantly in many contexts. Third, the acute nature of the transgenic tumor models used in these studies may over-exaggerate the tumorigenic and metastatic processes that occur in the clinical setting, as the EMT may provide a metastatic advantage to slower-growing tumors. Fourth, the transgenic tumors used in these studies may have lacked intra-tumoral heterogeneity because they were driven by the expression of a few cancer-initiating genes, which may further affect the impact of the EMT on the tumors' invasiveness and metastatic potential. Fifth, without fully understanding the molecular mechanisms governing the EMT, it may not be possible to recapitulate the full process of the EMT that may occur spontaneously in cancer cells using highly simplified mouse tumor models. Lastly, it is worth noting that cancer metastasis and cancer drug resistance are two complex and poorly understood processes, which often co-exist clinically. Thus, there are tremendous challenges ahead to overcome these hurdles in order to achieve effective cancer treatment. Nonetheless, the good news coming from these studies is that targeting the EMT may be able to "kill two birds with one stone", providing a better therapeutic outcome.

## Conflicts of interest

The authors declare no conflicts of interest.

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