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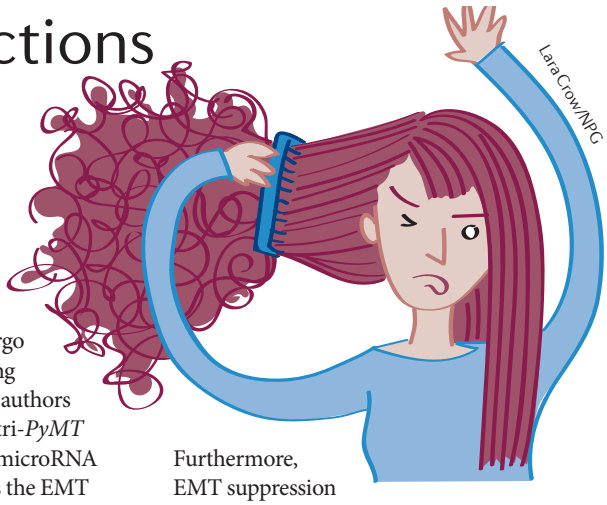
EPITHELIAL–MESENCHYMAL TRANSITION

Untangling EMT's functions



Although epithelial–mesenchymal transition (EMT) is commonly believed to contribute to metastasis, definitive *in vivo* evidence to support this theory is lacking. Two studies in *Nature* report that EMT is not required for metastasis in mouse tumour models; however, EMT can contribute to resistance to chemotherapy.

Fischer *et al.* generated mouse models of breast cancer that undergo spontaneous metastasis, and in which EMT can be traced. Mice expressing either polyomavirus middle T antigen (*PyMT*) or *Neu* (also known as *Erbb2*) in the mammary gland were engineered to also express a Cre-switchable fluorescent marker such that cells expressing fibroblast-specific protein 1 (*Fsp1;* which is activated early during EMT) would switch from expressing red fluorescent protein (RFP) to express green fluorescent protein (GFP). Therefore, cells that had undergone EMT were labelled with GFP (this was confirmed *in vitro*); importantly, this GFP expression is irreversible, so any cells subsequently undergoing mesenchymal–epithelial transition (MET) remain GFP$^+$. The development of primary tumours and spontaneous lung metastases in these tri-*PyMT* and tri-*Neu* mouse models was indistinguishable from controls. Unexpectedly, the tumour cells in the metastatic lesions in these mice were RFP$^+$, indicating that they had never expressed *Fsp1*.

As EMT could potentially occur without *Fsp1* expression, the authors also generated tri-*PyMT* mice that switched from RFP$^+$ to GFP$^+$ when vimentin (*Vim*, another common EMT marker) was expressed. Metastases in these tri-*PyMT*/*Vim* mice were also RFP$^+$. These data were confirmed using orthotopic injection of tri-*PyMT* or tri-*PyMT*/*Vim* cells into wild-type mice to ensure that only tumour cells that had undergone EMT would be GFP$^+$. As it remained possible that some cells might undergo EMT without expressing either *Fsp1* or *Vim*, the authors also inhibited EMT in tri-*PyMT* cells by expressing the microRNA miR-200, which targets the EMT transcription factors *Zeb1* and *Zeb2*. Although EMT was blocked in these cells, metastasis was not inhibited following orthotopic injection.

EMT also has a reported role in resistance to chemotherapy. Treatment of mice bearing orthotopic tri-*PyMT* tumours with cyclophosphamide reduced primary tumour size. In contrast to untreated mice, many metastatic lesions in the treated mice contained a substantial number of GFP$^+$ cells, and several lines of evidence showed these metastatic cells to be more resistant to cyclophosphamide in a manner that depended on induction of EMT. These GFP$^+$ cells expressed many factors implicated in proliferation and chemotherapy resistance, although the specific mechanisms underlying resistance were not determined.

Zheng, Carstens *et al.* reported similar data in the KPC mouse model of pancreatic ductal adenocarcinoma (PDAC), in which mice develop metastatic tumours owing to expression of mutant p53 and KRAS-G12D in pancreatic cells. KPC mice were crossed to mice lacking one of two EMT transcription factors: SNAI1 or TWIST1. Although EMT was suppressed in these mice, they had a similar tumour burden and no change in overall survival compared with KPC mice. Furthermore, EMT suppression did not affect the number of circulating tumour cells, the ability of tumour cells to form tumour spheres *in vitro* or colonize the lung following intravenous injection, or the overall frequency of metastasis. These authors also found that suppression of EMT in KPC mice reduced PDAC progression and increased survival following treatment with the nucleoside analogue gemcitabine, an effect shown to correlate with the upregulation of nucleoside transporters. KTC mice, which express mutant KRAS and lack transforming growth factor-β receptor 2 (TGFβR2), also develop metastatic PDAC, and as in KPC mice, knockout of *Snai1* did not prevent metastasis but did enhance sensitivity to gemcitabine.

These two studies provide intriguing evidence that although therapeutic inhibition of EMT might not prevent metastasis, combining chemotherapy with EMT inhibition might help to prevent the emergence of resistance.

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> “EMT is not required for metastasis in mouse tumour models; however, EMT can contribute to resistance to chemotherapy”

ORIGINAL ARTICLES Fischer, K. R. *et al.* Epithelial-to-mesenchymal transition is not required for lung metastasis but contributes to chemoresistance. *Nature* http://dx.doi.org/10.1038/nature15748 (2015) | Zheng, X., Carstens, J. L. *et al.* Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer. *Nature* http://dx.doi.org/10.1038/nature16064 (2015)