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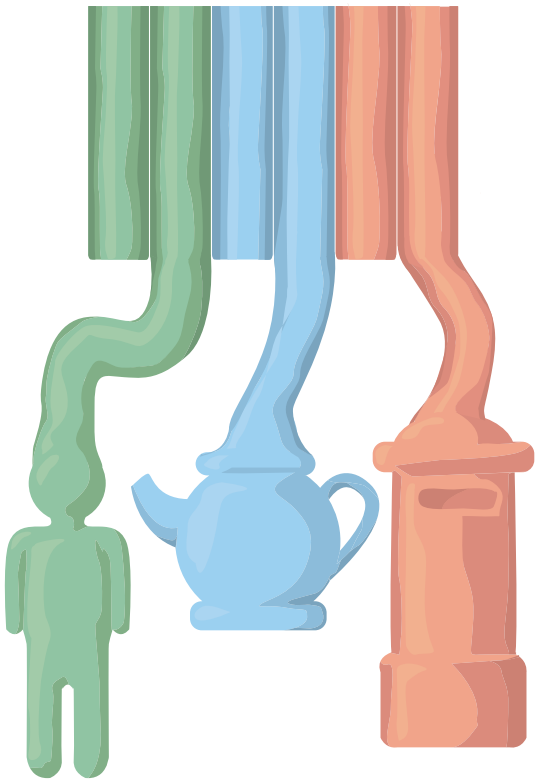

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METASTASIS

The plastic state

Partial epithelial–mesenchymal transition (EMT), whereby tumour cells gain migratory characteristics but at the same time maintain certain epithelial traits, was regarded as important in the promotion of metastasis. However, two studies in 2015 used mouse models of breast and pancreatic cancer to show that EMT is dispensable for metastasis. A new study by Krebs *et al.* is challenging these findings.

The KPC mouse model of pancreatic ductal adenocarcinoma (PDAC) driven by conditional expression of mutant *Kras* and mutant *Trp53* was previously used to show that deletion of either of the EMT activators *Snai1* or *Twist1* did not suppress metastasis. Krebs and colleagues used this same genetic background and conditionally deleted another EMT transcription factor *Zeb1* in the pancreas to generate KPC;$Zeb1^{fl/fl}$ mice (KPCZ). Ablation of ZEB1 did not affect primary tumour growth, but resulted in lower grade and less heterogeneous tumours compared with those in KPC mice. These primary KPCZ tumours also displayed decreased local invasion and, importantly, had reduced metastatic competence, suggesting that in contrast to depletion of SNAI1 or TWIST1, ZEB1 supports metastasis during PDAC tumour progression.

> “ZEB1 supports metastasis during PDAC tumour progression”

Tumour cell lines derived from KPC primary tumours showed a range of phenotypes from mesenchymal to mixed and epithelial, whereas KPCZ tumour cells were all epithelial, indicative of loss of cellular plasticity. Interestingly, intravenous tail vein injections of KPC and KPCZ tumour cells into syngeneic mice revealed that although KPCZ tumour cells were capable of disseminating to the lungs at a rate comparable to that of KPC tumour cells, they were incapable of colonizing the lung. In line with ZEB1 being important for distant colonization, KPCZ tumour cells had reduced tumorigenicity and stemness as assayed by subcutaneous tumour growth in mice and *in vitro* sphere formation, respectively. Of note, the authors also observed absence of the stem cell factor SOX2 in KPCZ tumours, likely due to the function of ZEB1 in stabilizing SOX2 expression through a feedback loop with miR-200c.

Given these effects on tumorigenicity, the authors questioned why primary tumour-free survival in KPCZ mice was unchanged. Reasoning that mutant p53 could cause mutations in other genes, generating fast-growing tumours that might mask the initial tumorigenic ability of ZEB1, Krebs *et al.* used KC mice with wild-type p53 to demonstrate that depletion of ZEB1 was necessary for KRAS-driven acinar-to-ductal metaplasia (ADM) and pancreatic intraepithelial neoplasia (PanIN) precursor lesions.

Focusing on the contribution of ZEB1 to cellular plasticity, Krebs *et al.* treated KPC tumour cells with the EMT inducer transforming growth factor β (TGFβ). This led to a switch in phenotype and gene expression from epithelial to mesenchymal. In contrast, KPCZ tumour cells retained an epithelial phenotype even after long-term exposure to TGFβ. Metabolic plasticity was also shown to be dependent on ZEB1 expression, as KPCZ tumour cells had a reduced oxidative phosphorylation and glycolytic reserve. The authors speculate that the plasticity of switching between basic energy pathways regulated by ZEB1 could be a feature required for adaptation of tumour cells to differing microenvironments at metastatic sites.

These data highlight that EMT can drive the transition to metastasis through ZEB1, and propose that the different EMT transcription factors are not redundant but likely to have complementary functions.

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ORIGINAL ARTICLE Krebs, A. M. *et al.* The EMT-activator Zeb1 is a key factor for cell plasticity and promotes metastasis in pancreatic cancer. *Nat. Cell Biol.* http://dx.doi.org/10.1038/ncb3513 (2017)
FURTHER READING Seton-Rogers, S. Epithelial–mesenchymal transition: untangling EMT's functions. *Nat. Rev. Cancer* **16**, 1 (2016)