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Epithelial-mesenchymal plasticity orchestrates the functional and spatial heterogeneity of cancer hallmarks in breast cancer

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EMT plays a pivotal role in embryonic development, adult tissue repair and significantly contributes to pathological plasticity in fibrosis and cancer. Despite recent progress in understanding EMT implications in cancer progression towards metastasis, how EMT orchestrates phenotypic plasticity in other cancer hallmarks remains poorly understood.

In this study, we employed a combination of lineage tracing and single-cell transcriptomics to unveil the simultaneous activation of two distinct EMT programmes in breast cancer. These two programmes were organized into different molecular and transcriptional regulated trajectories reminiscent of embryonic-like or adult injury-like EMTs to, respectively, drive dissemination or inflammation. Cancer cells acquiring the identified EMT programmes occupy distinct spatial niches within individual tumours in mouse and human cancers. Interestingly, we found that the genetic manipulation leading to truncation of the disseminating trajectory not only decreases invasion and metastatic burden, but also expands the inflammatory trajectory suggesting the cross-regulation and interdependence of the two EMT programmes.

Altogether, we uncover a new role for epithelial plasticity in orchestrating an additional layer of intratumor heterogeneity, driving the spatial distribution of functions associated with cancer progression. Our findings hold implications for potential therapeutic interventions to modulate tumor plasticity and progression and underscore the role of epithelial-mesenchymal plasticity as a regulator of the interplay between functional cancer modalities, namely invasiveness, and inflammation.