Chromatin regulation of cancer metastasis

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Pancreatic ductal adenocarcinoma (PDA) is one of the most lethal human malignancies, owing in part to its propensity for metastasis. Here, we used an organoid culture system to investigate how transcription and the enhancer landscape become altered during discrete stages of disease progression in a PDA mouse model. This approach revealed that the metastatic transition is accompanied by massive and recurrent alterations in enhancer activity. We implicate the pioneer factor FOXA1 as a driver of enhancer activation in this system, a mechanism that renders PDA cells more invasive and less anchorage-dependent for growth *in vitro*, as well as more metastatic *in vivo*. In this context, FOXA1- dependent enhancer reprogramming activates a transcriptional program of embryonic foregut endoderm. Collectively, our study implicates enhancer reprogramming, FOXA1 upregulation, and a retrograde developmental transition in PDA metastasis.