Deconstructing transcriptional mechanisms of cancer progression

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Cancers arise through sequential acquisition of specific driver mutations, but how this leads to the establishment of tissue-specific oncogenic programmes remains largely unknown. With a focus on clear cell renal cell carcinoma (ccRCC), a tumour type characterised by initiating mutations in the VHL tumour suppressor, we are investigating the functional consequences of VHL loss, how they result in renal tumorigenesis, and how tissue-specific epigenetic programmes contribute to the oncogenic process. We find that VHL loss and the consequent activation of hypoxia inducible factor 2A (HIF2A)-dependent transcriptional programmes support canonical oncogenic signalling through interaction with renal lineage factors, suggesting an underlying mechanism for the tissue-specific oncogenic effects of the VHL-HIF2A pathway. Furthermore, the functional output of the tumour-initiating VHL-HIF2A pathway is not static but it evolves through cross-lineage co-option of physiological enhancer states in support of cancer progression and metastasis. Our results support a model whereby the phenotypic consequences of cancer driver mutations are dependent on tissue-defining physiological programmes that facilitate tumour initiation and progression, thus providing clues to the principles of tissue-specific carcinogenesis and origins of metastatic traits.