

Uprooting breast tumor heterogeneity

A decade ago, J. Visvader hypothesized that the cell that undergoes malignant transformation, the so-called cell-of-origin, is intimately linked to the molecular identity of the resulting tumor. Following this concept, we demonstrated that the differentiation status of the cell-of-origin is associated with a unique susceptibility to malignant transformation when subjected to oncogenic insult. In addition, disruption of tissue homeostasis may increase the susceptibility of specific cell populations to be transformed, ultimately fueling tumor heterogeneity. Hence, the next step was to identify early oncogenic events that increase the level of pliancy of certain cancer cell precursors. In this context, we explored the consequences of XIST loss, a phenomenon observed in 30% of breast cancers, on tumor initiation. We demonstrated that XIST deficiency triggers epigenetic changes and activation of the Mediator subunit MED14. MED14 overexpression results in hyperactivation of the mammary stem cell (MaSC) enhancers. A direct consequence of these epigenetic changes is an impairment of MaSC differentiation, suggesting that XIST acts as a gatekeeper of mammary epithelial homeostasis. Interestingly, upon oncogenic activation, XIST-depleted MaSCs increasingly give rise to highly metastatic breast tumors. These results suggest that lineage plasticity may modulate oncogene addiction, supporting the link between tumor heterogeneity and therapeutic resistance.