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Evolutionary Dynamics of Feedback Escape and the Development of Stem-Cell-Driven Cancers

Cancers are thought to arise in tissue stem cells, and similar to healthy tissue, are thought to be maintained by a small population of tumor stem or initiating cells, whereas the majority of tumor cells are more differentiated with limited replicative potential. Healthy tissue homeostasis is achieved by feedback loops, and particular importance has been attached to signals secreted from differentiated cells that inhibit stem-cell division and stem-cell self-renewal, as documented in the olfactory epithelium and other tissues. Therefore, a key event in carcinogenesis must be escape from these feedback loops. In this talk we present an evolutionary computational model of feedback escape in cancer. We find that out of all potential evolutionary pathways, only one unique sequence of phenotypic transitions can lead to complete escape in stem-cell-driven tumors, even though the required mutations for these transitions are certainly tissue specific. This insight, supported by data, facilitates the search for driver mutations and for therapeutic targets. Different growth patterns can result from feedback escape, which we call “inhibited”, “uninhibited”, and “sigmoidal”, and which are found in published data. The finding of inhibited growth patterns in data indicates that besides architecture, the regulatory mechanisms of healthy tissue continue to operate to a degree in tumors.