Population Dynamics of Epithelial-Mesenchymal Heterogeneity in Cancer Cells

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A population containing epithelial (E), mesenchymal (M), and hybrid (E/M) cells show varying degrees of stability and plasticity in vitro and in vivo across cancers and their subtypes. While H1975 lung cancer cells can maintain their hybrid E/M phenotype over two months[1]; hybrid E/M phenotype in CPKV prostate cells relatively quickly switches to other phenotypes[2]. These rates of cell-state transition can be influenced by the interplay between various stabilizing and perturbing mechanisms. While the expression of phenotypic stability factors (PSFs), such as GRHL2 and Np63α, and mechanisms such as chromatin remodeling increase stability of a phenotype[3-5]; asymmetric distribution of biomolecules at cell division, and stochastic gene expression perturb and can cause spontaneous state switching[6-7]. Here, we build upon the framework developed to study phenotypic switching among E, E/M, and M states at cell division due to the asymmetric distribution of biomolecules[6]. We propose proportional fluctuations in daughter cells' SNAIL levels w.r.t. the parent cells' SNAIL levels and observe its effects on the population distribution of E, E/M, and M phenotypes over time. Our model captures experimental observation of high EpCAM+ to low EpCAM- subpopulations ratio in PMC42-LA cell line[8]. Moreover, it also explains the heterogeneity observed in the EpCAM distribution of single-cell clones after the initial two passages. Further, we found that the skew in the ratio of E to E/M and M fractions enhances due to increasing heterogeneity in doubling times among phenotypes and the degree of asymmetric partitioning of SNAIL levels at cell division. We analyzed the switching probability and transition rates for each phenotype. They are the function of cell position along the E-M axis and the degree of asymmetric partitioning at cell division. Overall, we show how the nature of fluctuations at cell division can affect the population distribution and help explain different experimental observations.

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