Identifying intercellular phenotypic stability factors for a hybrid epithelial/mesenchymal phenotype

Federico Bocci[1], Mohit Kumar Jolly[1], Satyendra C Tripathi[2], Jason George[1], Mitzi Aguilar[2], Samir M Hanash[2], Herbert Levine[1], Jose N Onuchic[1]

[1]Center for Theoretical Biological Physics, Rice University, Houston, TX, USA
[2] Department of Clinical Cancer Prevention, UT MD Anderson Cancer Center, Houston, TX, USA

Epithelial-mesenchymal transition (EMT) and its reverse Mesenchymal-epithelial transition (MET) are crucial for embryonic development, wound healing and cancer metastasis. Cells need not to undergo a full EMT or MET, rather they can maintain stably a hybrid epithelial/mesenchymal (E/M) phenotype and thus exhibit collective cell migration, forming clusters of circulating tumor cells - the primary drivers of metastasis. Mechanisms enabling cells to exhibit a hybrid E/M phenotype stably remain elusive. Here, using an integrated experimental-computational approach, we identify 'phenotypic stability factors' (PSFs) that can stabilize a hybrid E/M phenotype by mediating cell-cell communication through Notch signaling pathway. Our mathematical model predicts that Numb or Numb-like (Numbl) can inhibit a full EMT and stabilize a hybrid E/M phenotype. This prediction is validated by the observation that knockdown of Numb in stably hybrid E/M cells H1975 results in a full EMT, thereby indicating that Numb behaves as a PSF. Generalizing the mathematical model to a multi-cell level, Numb is predicted to alter the balance of hybrid E/M versus mesenchymal cells in clusters, potentially resulting in a higher tumor-initiation ability. Our model also suggests another PSF – Nrf2 (nuclear factor E2-related factor 2) – that couples both to EMT and Notch signaling, and stabilizes a hybrid E/M phenotype too. Intriguingly, Nrf2 levels are maximally observed in a hybrid E/M phenotype as compared to purely epithelial or mesenchymal phenotypes. Finally, high levels of Numb or Nrf2 also correlate with a worse survival in multiple independent cancer datasets, strengthening the association of a hybrid E/M phenotype with increased cancer aggressiveness.