

Mapping phenotypic heterogeneity in melanoma onto the epithelial-hybrid-mesenchymal axis

Maalavika Pillai^{1,2,†}, Gouri Rajaram^{3,†}, Pradipti Thakur³, Nilay Agarwal^{1,2}, Ankita Ray³, Mohit Kumar Jolly^{1,*}

1 Centre for BioSystems Science and Engineering, Indian Institute of Science, Bangalore, India

2 Undergraduate Programme, Indian Institute of Science, Bangalore, India

3 Department of Biotechnology, Indian Institute of Technology, Kharagpur

Presenting Author: M.P (maalavikap@iisc.ac.in)

**Authors to whom correspondence should be addressed: M.K.J. (mkjolly@iisc.ac.in)*

† Authors contributed equally: M.P. and. G.R.

Epithelial to mesenchymal transition (EMT) is a well-studied hallmark of epithelial cancers characterized by the loss of epithelial markers such as E-cadherin and the gain of mesenchymal markers such as Vimentin and N-cadherin. Interestingly, non-epithelial cancers like melanoma have also reported mesenchymal-like phenotypes under the influence of various micro-environmental cues. Our study connects EMT to the well-characterized phenomenon of de-differentiation (i.e., transition from proliferative to more invasive phenotypes) seen in melanoma cells during drug treatment. De-differentiation in melanoma is accompanied by the upregulation of mesenchymal genes. However, unlike epithelial cancers, there is no concomitant loss of epithelial program accompanying it. Moreover, samples lying in the hybrid regime for EMT (i.e., displaying epithelial and mesenchymal characteristics) also correspond to one of the intermediate phenotypes seen on the proliferative-invasive axis. Interestingly, as melanoma cells progress along the invasive axis, the changes in their EMT signatures are not monotonic. We observe a peak in mesenchymal scores followed by a decline, as samples become further de-differentiated. This recapitulates events during melanocyte development, suggesting close interactions among genes controlling the differentiation and mesenchymal programs in melanocytes. Overall, we explain how the EMT and de-differentiation axis interact and overlap with one another in a non-epithelial cancer like melanoma.