Modeling the Association between Epithelial-Mesenchymal Transition (EMT) and Stemness

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Short Abstract — Two mutually inhibiting chimeric feedback loops, miR-200/ZEB and LIN28/let-7, determine cell fate during metastasis and tumor relapse. miR-200/ZEB, a three-way switch, regulates EMT, the initial step of metastasis, by allowing three different phenotypes – epithelial, mesenchymal and hybrid epithelial/ mesenchymal (E/M). LIN28/let-7 regulates Cancer Stem Cells (CSCs) population that cause tumor relapse. Here, using a novel theoretical framework, we show that LIN28/let-7 circuit is also a three-way switch, and that hybrid E/M cells are more likely to be stem-like than mesenchymal cells. Our results corroborate with recent experiments, thereby offering novel insights into how tumor relapse and metastasis are intertwined.

***Keywords* — Epithelial Mesenchymal Transition, Cancer Stem Cells, Multistability, Toggle switch, microRNA**

Introduction

Cell fate decisions during tumorigenesis and tumor progression pose a major research challenge in modern cancer biology. For instance, metastasis and tumor relapse, two deadliest aspects of cancer, remain clinically insuperable [1]. Metastasis starts when some epithelial cells from primary tumor undergo Epithelial to Mesenchymal Transition (EMT) to lose cell-cell adhesion and gain migratory and invasive traits; whereas tumor relapse is caused by therapy resistant Cancer Stem Cells (CSCs). Two chimera toggle switches regulate cell fate determination in both these processes – miR-200/ZEB for EMT [2], and LIN28/let-7 for CSC population [3].

Using a novel theoretical framework for microRNA-mediated translational repression [4], we earlier showed that miR-200/ZEB acts as a three-way switch, allowing for three phenotypes – epithelial (E), mesenchymal (M) and hybrid epithelial/ mesenchymal (E/M) [2]. Here we extend the theoretical framework to include LIN28/let-7 circuit and learn how cells undergoing EMT also gain stemness.

I. Results

From modeling perspective, the challenge posed by the combined system is due to novel modes of regulation involved – miRNA mediated translational repression, translational self-activation and the processing of miRNA. We extend our previous model to incorporate the novel modes of regulation in LIN28/let-7 circuit – inhibition and activation of microRNA processing, and translational self-activation. We found that for biologically relevant circuit parameters, LIN28/let-7 can act as a three-way or ternary switch that allows for the co-existence of three states – (i) (high LIN28, low let-7) or (1, 0); (ii) (low LIN28, high let-7) or (0, 1); and (iii) (medium LIN28, medium let-7) or (½, ½), which we connect with M, E and E/M phenotypes respectively due to the coupling between LIN28/let-7 and miR-200/ ZEB loops. We also included OCT4 in this coupling to show that cells in hybrid E/M state are more likely to stem-like as compared to mesenchymal cells.

Our results corroborate with experiments indicating that in addition to many cells that belong to (1, 0) or (0, 1) state, many cells are in (½, ½) state or have simultaneous intermediate expression of both LIN28 and let-7 [5]. Recent experiments also indicate that the hybrid E/M state is more stem-like as compared to the M state.

II. Conclusion

We devised a special theoretical framework to study the dynamics of the LIN28/let-7 stemness regulatory circuit. We show this circuit can act as a three-way switch. Based on its coupling to miR-200/ZEB and OCT4, we show that cells in hybrid E/M phenotype are more stem-like as compared to those in a mesenchymal phenotype. Our results explain how a cluster of circulating tumor cells (CTCs) in the bloodstream hinge on this association between epithelial plasticity and stemness to successfully complete metastasis, the cause of 90% of all cancer deaths.

References

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