MicroRNA and protein cell fate determinants synergize in asymmetric division as safeguard against stem cell proliferation

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***Short Abstract* — The microRNA miR-34a regulates the decision of colon cancer stem cells to undergo either symmetric or asymmetric division. However, how does miR-34a manage to achieve this seemingly complex task reliably? Here we report that miR-34a employs several mechanisms for robust spatiotemporal regulation. First, miR-34a forms an incoherent feedforward loop with a canonical cell fate determinant to enhance bimodality and adaptivity. Second, this spatial microRNA switch is enforced by an epigenetic mechanism. Third, miR-34a selectively form bimodal switches with cell fate decision genes. Collectively, microRNA-mediated cell fate decisions involve multiple layers of regulatory strategies in a context-dependent manner for decision-making.**

***Keywords* — microRNA, cancer stem cell, asymmetric division, feedforward loop, robustness.**

I. Purpose

Many stem cells can perform asymmetric division to accomplish self-renewal and differentiation simultaneously [1,2]. There have also been reports that cancer stem cells of various cancer types undergo both symmetric and asymmetric division [3-5]. Altering the ratio between symmetric and asymmetric division can change the balance between self-renewal and differentiation, which impact tumor growth.

Asymmetric cell division usually relies on imbalance of cell fate determinant proteins in the two cellular compartments to break symmetry, resulting in daughter cells with distinct cell fates. Recently, emerging evidence suggests that asymmetric distribution of microRNAs can also give rise to asymmetric cell fates [6,7]. For example, we have reported that miR-34a directly targets Notch to form a cell fate determination switch in colon cancer stem cells (CCSCs) [6]. These CCSCs then form xenograft tumors with the heterogeneous histopathology observed in human cancer [8].

However, this raises the question as to whether microRNA and protein cell fate determinants act independently or coordinate with each other to determine cell fate. The relationship between miR-34a and Numb is intriguing, because both target Notch in CCSCs.

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II. Results

Here we show that miR-34a directly suppresses the canonical cell fate determinant protein Numb in early-stage colon cancer stem cell (CCSC), although both target Notch to promote differentiation. Computational modeling and quantitative analysis revealed that this incoherent feedforward loop (IFFL) synergizes the two cell fate determinants to produce a sharper and more robust switch. This switch enforces strict bifurcation of cell fates and generates a well-separated bimodal distribution in the population. Perturbation to the IFFL leads to a new population of cells with more plastic and ambiguous identity between stem and differentiated cells. The IFFL is also active in normal intestinal stem cells (ISCs). Knockout of miR-34 in ISCs does not generate any phenotype in mice, but causes excessive proliferation of ISCs in organoids to form CCSC-like spheres upon TNF-a treatment.

III. Conclusion

Collectively, our data indicate that microRNA and protein cell fate determinants form regulatory motif to enhance robustness of cell fate decision, and they provide a safeguard mechanism against stem cell proliferation under stress conditions. This mechanism is still active in early-stage tumors but eventually subverted by progression of cancer.

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