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Oscillatory protein expression dynamics generates robust and irreversible differentiation of stem cells

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A systems-level understanding of cell differentiation is important for developmental biology. Some of the basic questions concerning such systems-level understanding include: What characteristics in a cellular state distinguish multi-potent stem cells from differentiated cells? How are developmental processes robust to molecular noise in spite of their complexity? Following the progress in the analysis of molecular mechanisms for cell differentiations, the time is ripe to answer the above questions to unveil nature of differentiation from stem cells.

In this study, using a dynamical system modeling, we performed simulations of the developmental process using small gene regulatory networks, and screened those that could generate cell type diversity through cell-cell interactions. We found that stem cells that both proliferated and differentiated always exhibited oscillatory expression dynamics, and the differentiation frequency of such stem cells was regulated, resulting in a robust number distribution. Based on the result of computer simulations, we propose a hypothesis for the mechanism of stem cell differentiation, in which the expression levels of some genes in multipotent stem cells exhibit temporal oscillation, and itinerate over several sub-states. As development progresses, each of these quasi-stable sub-states is modified and stabilized, leading to differentiated cell types.

Importantly, this hypothesis can explain the roles and mechanism of the recently observed dynamic heterogeneity and oscillatory behavior in cellular states of stem cells, and it can predict the regulatory motifs responsible for the dynamic differentiation process. These discussions promote a system-level understanding of multicellular development and provide a basis for clinical application of stem cells.

Biography

Chikara Furusawa has completed his PhD at the age of 28 years from University of Tokyo and postdoctoral studies from Center of Developmental Biology, RIKEN. He is a team reader at Quantitative Biology Center, RIKEN. He has published more than 60 papers in reputed journals

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