ASHBi SEMINAR

Dissecting cell identity via network inference and in silico gene perturbation

Lecturer: Samantha A Morris Ph.D.

Associate Professor of Developmental Biology and Genetics, Washington University in St. Louis

Date Wednesday, 29 June 2022

Time 16:00 – 17:00 [JST] *New!*

Venue Zoom Online Meeting*

*Register via the right QR code

Abstract

Cell identity is governed by the complex regulation of gene expression, represented as Gene Regulatory Networks (GRNs). Here, we leverage GRNs inferred from single-cell multi-omics data to perform in silico transcription factor (TF) perturbations, simulating the consequent changes in cell identity without requiring experimental perturbation data. We apply this machine learning-based approach, CellOracle, to two well-established paradigms: mouse hematopoiesis and zebrafish embryogenesis, correctly simulating reported phenotypic changes due to TF perturbation. Via systematic in silico TF perturbation in the developing zebrafish, we simulate and experimentally validate a previously unreported phenotype upon loss of noto, an established notochord regulator. Further, we reveal a novel axial mesoderm regulator, lhx1a. Following validation of our approach in these well-characterized systems, we integrate CellOracle analysis with lineage tracing of fibroblast to induced endoderm progenitor (iEP) conversion, a prototypical direct lineage reprogramming paradigm. By linking early network state to reprogramming success or failure, we reveal distinct network configurations underlying different reprogramming outcomes. Using these network analyses and in silico simulation of TF perturbation, we identify new factors to coax cells into successfully converting cell identity, uncovering a central role for the AP-1 subunit Fos with the Hippo signaling effector, Yap1. Together, these results showcase CellOracle's ability to dissect TF-regulation of cell identity, enabling new mechanistic insights into development, differentiation, and reprogramming.

Organizer：Graduate School of Medicine
Institute for the Advanced Study of Human Biology (WPI-ASHBi)

Contact: Associate Prof. Ryo Yamamoto
[E-mail] yamamoto.ryo.2c@kyoto-u.ac.jp