COMPUTATIONAL BIOLOGY WEBINAR @ IMSc

CELL-SPECIFIC RESPONSES TO THE CYTOKINE TGFβ ARE DETERMINED BY VARIABILITY IN PROTEIN LEVELS

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Information encoded in the dynamics of signaling pathways often elicit critical cell fate decisions. For instance, sustained dynamics of TGFβ pathway impart growth inhibition, a property abrogated in diseases like cancer.To understand how cells encode the extracellular input and transmit its information to elicit appropriate responses, we acquired quantitative time-resolved measurements of pathway activation at the single-cell level. We compared the signaling dynamics of thousands of individual cells and build mathematical models to understand the regulatory processes controlling the cell specific dynamics, both sustained and transient. Our combined experimental and theoretical study revealed that the response to a given dose of TGFβ is determined specifically by the levels of defined signaling proteins in individual cells. Heterogeneity in signaling protein expression led to decomposition of cells into classes with qualitatively distinct signaling dynamics and corresponding phenotypic outcome. Also, negative feedback regulators promote heterogeneous TGFβ signaling, as SMAD7 (a negative regulator of the pathway) knock-out specifically affected the signal duration in a subpopulation of genetically identical cells. Taken together, our study established a quantitative framework that allows predicting and testing sources of cellular signaling heterogeneity.

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