Jianhua Xing, J Tissue Sci Eng 2014, 5:3
http://dx.doi.org/10.4172/2157-7552.S1.014

OMICS Group Conferences
Accelerating Scientific Discovery

3rd International Conference on
Tissue Science & Regenerative Medicine
September 24-26, 2014 Valencia Convention Centre, Spain

A cascade of bistable switches controls TGF-β-induced epithelial to mesenchymal transition

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Epithelial to mesenchymal transition (EMT) is essential for cell plasticity during development and plays important roles in cancer progression. Two mathematical models proposed different mechanisms on the regulation of TGF-β1 induced EMT. One model predicted that two bistable switches, governed by SNAIL1/miR-34 and ZEB/miR-200 double-negative feedback loops respectively, lead to epithelial, partial EMT, and mesenchymal phenotypes. Another model argued that the three phenotypes came from a tertiary switch formed by the ZEB/miR-200 loop. In this work we quantitatively measured the dynamics of TGF-β1 induced MCF10A EMT. We identified three cell subpopulations during EMT using flow cytometry. Our measurements at RNA and protein levels verified that the temporal and steady state dynamics show a two-step behavior, and can be well represented by sequential Markovian transition among the three phenotypes, reversible transition between epithetial and partial EMT phenotypes, and irreversible transition between partial EMT and mesenchymal phenotypes. Furthermore, SNAIL1 shows both unimodal and bimodal distributions under different TGF-β1 concentration, indicating the bistable behavior of SNAIL1. These experimental results quantitatively confirmed that a cascade of two binary switches governs TGF-β1 induced MCF10A EMT.

Biography

Jianhua Xing has completed his PhD in theoretical chemistry from UC Berkeley, and did postdoctoral studies also at UC Berkeley. After a short period stay at Lawrence Livermore National Laboratory. He joined Virginia Tech in the department of Biological Sciences, and is affiliated to the physics department as well. The current research in Xing's lab focuses on combined computational and experimental quantitative biology studies of regulation mechanisms of cell phenotypic transitions, especially the epithelial-to-mesenchymal transition, at transcription, translational, and epigenetic levels.

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