Systems Modeling and Analysis of TGF - β Induced Epithelial to Mesenchymal Transition in Cancer Metastasis

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ABSTRACT

Epithelial to Mesenchymal transition (EMT) is a process of a cell attaining mesenchymal phenotype in response to external stimuli. EMT plays an important role in tissue regeneration, embryonic development and cancer metastasis. Several signaling pathways are known to regulate EMT, among which the modulation of TGF-β induced EMT is crucial in several cancer types. Extensive Mathematical models describing various phenomenon associated with TGF-β signaling pathway are available. These models explore the role of receptor activation, nucleocytoplasmic shuttling of SMADs, their nuclear accumulation, SMAD dependent gene expression, regulation of downstream molecules and their feedback effects. Various emergent behavior including tristability, irreversible switches, existence of hybrid EMT states were enumerated. Presence of feedback loops were observed to result in these interesting dynamic behaviors. Major hallmark of TGF-β induced EMT involves the suppression of epithelial markers miR-200, miR-34a, and E-Cadherin by upregulating the expression of mesenchymal markers SNAIL, ZEB and N-Cadherin. Double negative feedback loops between ZEB/miR-200&SNAIL/miR-34a were shown to be responsible for the regulation of TGF-β induced EMT that controls the expression of E-Cadherin and N-Cadherin which is vital for cancer metastasis. Present study developed a mathematical model for TGF-β induced p53 dependent Epithelial Mesenchymal Transition (EMT). Inclusion of p53 acts as a mechanistic means in exploring the EM transition with respect to available multiple experimental observations. This formulated core regulatory network displays interesting dynamic behavior, systems response to various inputs, providing us with better understanding on TGF-β induced p53 dependent Epithelial to Mesenchymal Transition.

Keywords: Epithelial to Mesenchymal transition, TGF-β, feedback loops, mathematical modelling, cancer metastasis.

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