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Qualitative Modeling of Transforming Growth Factor Beta-Associated Biological Regulatory Network: Insight into Renal Fibrosis

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Abstract : Kidney fibrosis is an anticipated outcome of possibly all types of progressive chronic kidney disease (CKD). Epithelial-mesenchymal transition (EMT) signaling pathway is responsible for production of matrix-producing fibroblasts and myofibroblasts in diseased kidney. In this study, a discrete model of TGF-beta (transforming growth factor) and CTGF (connective tissue growth factor) was constructed using Rene Thomas formalism to investigate renal fibrosis turn over. The kinetic logic proposed by Rene Thomas is a renowned approach for modeling of Biological Regulatory Networks (BRNs). This modeling approach uses a set of constraints which represents the dynamics of the BRN thus analyzing the pathway and predicting critical trajectories that lead to a normal or diseased state. The molecular connection between TGF-beta, Smad 2/3 (transcription factor) phosphorylation and CTGF is modeled using GenoTech. The order of BRN is CTGF, TGF-B, and SMAD3 respectively. The predicted cycle depicts activation of TGF-B (TGF-β) via cleavage of its own pro-domain (0,1,0) and presentation to TGFR-II receptor phosphorylating SMAD3 (Smad2/3) in the state (0,1,1). Later TGF-B is turned off (0,0,1) thereby activating SMAD3 that further stimulates the expression of CTGF in the state (1,0,1) and itself turns off in (1,0,0). Elevated CTGF expression reactivates TGF-B (1,1,0) and the cycle continues. The predicted model has generated one cycle and two steady states. Cyclic behavior in this study represents the diseased state in which all three proteins contribute to renal fibrosis. The proposed model is in accordance with the experimental findings of the existing diseased state. Extended cycle results in enhanced CTGF expression through Smad2/3 and Smad4 translocation in the nucleus. The results suggest that the system converges towards organ fibrogenesis if CTGF remains constructively active along with Smad2/3 and Smad 4 that plays an important role in kidney fibrosis. Therefore, modeling regulatory pathways of kidney fibrosis will escort to the progress of therapeutic tools and real-world useful applications such as predictive and preventive medicine.

Keywords : CTGF, renal fibrosis signaling pathway, system biology, qualitative modeling
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