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Critical parameters in a computational model of TGF-beta-induced epithelial mesenchymal transition.

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Epithelial to mesenchymal transition (EMT) is a fundamental biological process that plays a central role in embryonic development, tissue regeneration, and pathological conditions, such as cancer metastasis and cystic fibrosis. EMT is the transdifferentiation of an epithelial cell to a mesenchymal stem cell; losing the characteristic cell-cell adhesion of an epithelial cell and gaining the increased cell motility of a mesenchymal cell. Classically, EMT has been viewed as an all-or-none switch; however, recent work has demonstrated the existence of bistability in the system, with an intermediate or partial (pEMT) state that retains some characteristics of the primary epithelial state but also shows features of mesenchymal state. Prior work has demonstrated that transforming growth factor-beta (TGF-beta) is a major and potent inducer of this cellular transition. In our study, we used a mathematical model of the core regulatory network describing TGF-beta-induced EMT, which consists of coupled reversible and irreversible bistable switches. We performed simulations to determine critical parameters that govern two key features of the EMT process: (1) hysteresis in the TGF-beta-dependence of the transition from epithelial to the pEMT states and (2) the reversibility of the pEMT to mesenchymal state transition. We found that the presence of hysteresis depended on critical properties of the microRNA-34 signaling pathway. In contrast, we found that mesenchymal reversibility depended on properties of the endogenous TGF-beta production. Model predictions demonstrate that both the reversibility and sensitivity of TGF-beta-mediated EMT is governed by complex interactions between these coupled switches.