Georgia Institute of Technology

SCHOOL OF CHEMICAL & BIOMOLECULAR ENGINEERING
SPRING 2011 SEMINAR SERIES
MARCH 16

DR. BABATUNDE A. OGUNNAIKE

Deputy Dean and William L. Friend Chaired Professor
Chemical Engineering Department
Professor, Center for Systems Biology, Delaware Biotechnology Institute
University of Delaware

"Computational Approaches to Resolving the TGF-β Paradox in Cancer"

Transforming growth factor β (TGF-β) signaling regulates a wide range of cellular and physiologic processes including proliferation, apoptosis, differentiation, migration, angiogenesis, and immune surveillance. During the early stages of epithelial tumorigenesis, TGF-β functions as a potent tumor suppressor primarily by inhibiting cell proliferation and by inducing apoptosis. However, the level of this cytokine, TGF-β, is often significantly elevated in malignant tissues and blood from cancer patients with poor prognosis. Accordingly, in the late phases of tumor progression, the role of TGF-β appears to become one of tumor promotion, apparently supporting growth, subverting the immune system, and also facilitating epithelial to mesenchymal transition (EMT), invasion and angiogenesis. This has created the widely held perception that TGF-β is simultaneously a tumor suppressor under one condition and a tumor promoter under another. But how does a single stimulus produce multiple contradictory results? This long-standing enigma of TGF-β biology remains poorly understood because the role of TGF-β on cancer is too complex for qualitative description.

As a first step toward a quantitative explanation of such paradoxical roles of TGF-β in cancer, we have developed a dynamic model of the canonical TGF-β pathway via Smad transcription factors, the major intracellular mediators of the signaling cascades, based on reported experimental observations in the literature. By describing how an extracellular signal of the TGF-β ligand is sensed by receptors and transmitted into the nucleus through intracellular Smad proteins, the model yields quantitative insight into how TGF-β-induced responses can be modulated and regulated. The model also allows us to predict possible dynamic behavior of the Smad-mediated pathway in abnormal cells, and provides clues regarding possible mechanisms for explaining the seemingly contradictory roles of TGF-β during cancer progression. Based on

the reported observations that TGF-β receptors are abnormally altered in a variety of human cancers, simulations of cancerous signaling using our model indicate that reduction in the levels of functional receptors may lead to altered TGF-β signaling behavior where tumor suppression characteristics are lost as a result of attenuated and nearly transient Smad retention in the nucleus. In particular, our dose-response results provide a potentially important characteristic of cancer, that is, cancer cells may require higher than normal levels of TGF-β in order to elicit nuclear Smad-mediated activity. These results have motivated the development of a macroscopic computational model of TGF-β regulation of prostate cell population from a control theory perspective to explain the paradoxical clinical observation that unusually high levels of TGF-β correlate with poor prognosis in prostate cancer. Our macroscopic model indicates that the observed elevated level of TGF-β is a consequence of acquired TGF-β resistance exhibited by the cancer cell, not the cause, because a putative TGF-β control system must secrete more TGF-β in a futile attempt to achieve the level of tumor suppression attainable with normal, responsive cells. If this hypothesis is validated, its most significant implication will be that the current approach of targeting TGF-β ligand therapeutically may have to be abandoned in favor of re-sensitizing the cells to the tumor suppressive effect of the TGF-β.