Computational Modeling and Bioinformatics of Cancer Angiogenesis at the Molecular, Cellular, Tissue, and Whole-Body Scales

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We report several computational approaches to study the complex phenomena associated with angiogenesis and tumor progression.
(a) Using bioinformatics methodologies we study the angiogenesis interactome to better understand the role of different classes of proteins in angiogenesis. Gene expression analysis of published datasets on *in vitro* capillary network formation in 3D scaffolds of type I collagen and other substrates allows us to study the dynamic nature of protein-protein interactions (PPI) that reveal the complexity of protein clustering and interactions during various stages of angiogenesis.
(b) Vascular endothelial growth factor (VEGF) receptor-2 (VEGFR2) is a key receptor responsible for transducing pro-angiogenic signals in the endothelial cells. During the signaling cascade, VEGFR2 undergoes a number of modifications: receptor phosphorylation and dephosphorylation, ubiquitination and deubiquitination, ligand-induced and constitutive internalization, receptor degradation, and receptor recycling. We constructed a model of these processes and conducted computer simulations. We also predicted the time course of surface receptor levels, phosphorylated receptor levels and total receptor levels are compared with experimental results.
(c) We also studied the signaling pathways downstream from VEGFR2 that include the early receptor activation events such as receptor-ligand binding and adaptor protein association; to give a sense of the complexity of this model, it describes approximately 60 biochemical reactions with over 50 unique parameters. VEGFR2-specific experimental data are used where possible to validate the model.
(d) Moving up with the level of multiscale modeling, we have constructed an object-oriented module-based computational framework that can integrate modules at different temporal and spatial scales, using a Java-based modeling controller that implements data exchange between the different modules and controls their execution. In its current implementation, we use this approach to integrate modules representing microvascular blood flow, oxygen transport, VEGF transport and vascular network formation based on endothelial cell sensing of VEGF concentration and gradient, as well as endothelial cell migration and proliferation. Modeling methodologies in these modules include algebraic equations, ordinary and partial differential equations and agent-based models with complex logical rules. This computational tool can effectively incorporate other important modules that have been built by our laboratory, such as biochemical pathways for the transcription factor HIF1α and the VEGF signaling pathways introduced above. It can also be used to incorporate modules built by others, as it is platform-independent.
(e) At the highest level of integration, we have constructed a whole-body molecular-detailed compartment model of tumor-bearing human, comprising three compartments: normal tissue, blood, and tumor. The model is specific to VEGF, but could be generalized to include other important angiogenic factors. Currently, we consider two major VEGF isoforms $VEGF_{121}$ and $VEGF_{165}$, receptors VEGFR1, VEGFR2 and co-receptors neuropilin-1 and neuropilin-2 that are expressed on endothelial and tumor cells. The model results in 67 non-linear ordinary differential equations describing detailed biochemical reactions and transport processes (e.g., transendothelial macromolecular transport, lymphatic transport, plasma clearance). We use the model to simulate the action of bevacizumab, a VEGF-neutralizing antibody, to better understand its mechanism of action. We also conducted extensive simulations aiming at optimizing the anti-VEGF drug for an individual breast cancer patient with her own tumor microenvironment and tissue-specific expression of VEGF receptors. These studies form a foundation for experiment-based modeling of tumor growth and therapeutic interventions. Acknowledgements: Supported by NIH grants R01 CA138264, F32 CA154213, T32 HL007581, FASEB Postdoctoral Professional Development Award and UNCF/Merck Postdoctoral Fellowships.