Multiscale Compartment Model of VEGF Distribution in the Body: Applications to Cancer Therapy

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Vascular endothelial growth factor (VEGF) is a potent regulator of angiogenesis, and its role in cancer biology has been widely studied. Our laboratory previously developed a whole-body model of VEGF-mediated angiogenesis under pathological conditions (in the presence of breast tumor). In the present study, we significantly extend the previous computational model to include receptors on parenchymal cells (muscle fibers and tumor cells); specifically, we consider two major VEGF isoforms $VEGF_{121}$ and $VEGF_{165}$, receptors VEGFR1, VEGFR2 and co-receptors Neuropilin-1 and Neuropilin-2. The model results in 67 non-linear ordinary differential equations describing detailed biochemical reactions and transport processes: 24 for the normal tissue compartment, 16 for the blood, and 27 for the tumor compartment. Our previous model was limited by a lack of accurate surface receptor densities. Therefore, using quantitative flow cytometry, we have determined the density of receptors on the endothelial, myocyte, and tumor cell plasma membrane, and incorporated these key parameters into the current model. This is the first human model to include experimental measurements of receptor densities as well as receptors on parenchymal cells, and thus represents a significant advance compared to previous models. By incorporating *in vivo* and *in vitro* quantifications of VEGF receptor expression on endothelial and parenchymal cells, we have created a predictive tool that reflects physiological elements of VEGF transport in the body.

We utilize the model to investigate the action of VEGF-neutralizing agents (called "anti-VEGF") in the treatment of cancer. A sensitivity study was performed to examine how systemic properties, drug characteristics, and the tumor microenvironment influence the response to VEGF-neutralizing drugs. Importantly, we predict the ranges of parameter values which elicit the undesired effect of increasing blood and/or tumor interstitial VEGF concentration beyond even their baseline levels. Our results are important in elucidating effects of drug design parameters that are difficult to predict *a priori*. We can predict the optimal drug and tumor properties for which an anti-VEGF agent may have a therapeutic effect, thus aiding in the optimization of VEGF-neutralizing drugs.

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