Multiscale molecular-detailed pharmacokinetic and pharmacodynamic model predicts response to anti-VEGF therapies in cancer

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Vascular endothelial growth factor (VEGF) is a potent regulator of angiogenesis, the formation of new blood vessels from pre-existing vasculature. Due to its role in tumor growth and development, several cancer therapies aim to inhibit VEGF signaling. Computational modeling of angiogenesis can aid in the development and optimization of these therapies. Our laboratory has developed a whole-body molecular-detailed model of VEGF kinetics and transport in the presence of a solid tumor. We consider three compartments: normal tissue (represented by skeletal muscle), blood, and tumor. The model includes two VEGF isoforms $VEGF_{121}$ and $VEGF_{165}$, receptors VEGFR1 and VEGFR2, and co-receptors, called neuropilins, NRP1 and NRP2. Additionally, we have expanded the model to include soluble factors α-2-macroglobulin (α2M), which is confined to the plasma, and soluble VEGF receptor-1 (sVEGFR1), present in the plasma and interstitial fluid. Model parameters are based on experimental data, where available. The model is parameterized for both human patient and tumor-bearing mouse, thus allowing translation from mouse experiments to human applications. The model is defined by 154 ordinary differential equations for human and 248 for mouse (in this case, both mouse and xenograft-secreted human isoforms are present) that describe chemical kinetic reactions and biological transport mechanisms.

We have applied the model to predict the dynamics of VEGF distribution in the body in response to VEGF-targeting cancer therapeutics. Following neutralization of VEGF with an antibody such as bevacizumab, plasma free VEGF and total circulating VEGF, which includes VEGF bound to α2M or sVEGFR1, increase several fold. The increase in plasma free VEGF has been observed clinically. Interestingly, the model predicts that, paradoxically, VEGF in the tumor interstitium can increase or decrease following administration of the VEGF antibody, depending on properties of the tumor microenvironment, including the relative rate at which the VEGF isoforms are secreted by the tumor and the expression level of the VEGF receptors on tumor cells. In contrast, all VEGF in the body is depleted when the neutralizing agent is VEGF Trap, a soluble decoy receptor. The implications of these findings are analyzed within the framework of available clinical data.

Thus, we have developed a computational framework for investigating the systemic effects of anti-angiogenic drugs that inhibit VEGF signaling, which are predicted to depend on tumor-specific properties. The model can be applied to develop personalized cancer treatment strategies that target the VEGF pathway. Our work will be used to design and analyze pre-clinical and clinical studies of the levels of VEGF in the body following VEGF neutralization.

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