A detailed rule-based computational model for the interaction of VEGF pathway with thrombospondin-1 integrating multiple signaling modules: Implications for pro-angiogenic therapeutic interventions

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The matricellular protein thrombospondin-1 (TSP1) is a potent inhibitor of angiogenesis. Binding of TSP1 to its major biological receptor CD47 contributes to its downstream anti-angiogenic effects including global inhibition of VEGF signaling through its receptor vascular endothelial growth factor receptor 2 (VEGFR2). TSP1 upregulation has been observed in peripheral arterial disease (PAD) characterized by the loss of vasculature in the lower extremities and disruption of angiogenesis. Some of these effects might be attributable to the loss of signaling through VEGFR2. To better understand the molecular mechanisms that contribute to the inhibition of VEGF signaling by TSP1 and to propose new therapeutic strategies for restoring VEGF signaling, computational models are necessary. The models must integrate different scales including detailed receptor-ligand and receptor-receptor interactions at the surface, signal transduction to downstream targets, and trafficking and signaling through subcellular compartments.

In this study we develop a detailed rule-based model to accurately capture receptor interactions at the cell membrane. We include major VEGF receptors VEGFR1, VEGFR2, and NRP1 and TSP1 receptor CD47. The receptor interaction model is then fed into a course grained signaling pathway model describing VEGF signaling to PI3K/AKT and eNOS activation. Three subcellular compartments are also included: two signaling endosomes and a recycling endosome. A separate calcium recycling compartment that includes calcium release from the sarcoplasmic reticulum and calcium release activated calcium channels are also incorporated into the system. By integrating these different modules within the BioNetGen programming environment, we then investigate mechanisms of inhibition of VEGF signaling to eNOS and AKT by TSP1. The model proposes that the acceleration of VEGFR2 degradation by TSP1 is sufficient to explain the inhibitory effects of TSP1 on VEGFR2 phosphorylation and eNOS activation. However, according to the model, abolishing AKT activation by TSP1 requires phosphatase recruitment to the receptor by TSP1-CD47.

The model is then utilized to test three different pro-angiogenic therapeutic strategies for rescuing VEGF signaling: 1) depletion of CD47, 2) depletion of external TSP1, 3) enhancing surface VEGFR2 levels by an integrin-binding peptide such as cilengitide. Our results indicate that depleting CD47 is a more advantageous strategy than inhibiting TSP1 in restoring VEGF signaling. The application of cilengitide may be considered as a strategy to rescue some of the signaling lost as a result of TSP1. The two strategies of CD47 depletion and cilengitide application may be used in combination for superior pro-angiogenic effects. Our detailed computational model may serve as a foundation for whole-body PK/PD models to investigate anti-CD47 therapies in peripheral arterial disease (PAD) and wound healing.
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