A study on the VEGFR2-ligand multi-physics interactions in Angiogenesis.

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Tumor growth is sustained by angiogenesis, i.e. the formation of new blood vessels from pre-existing ones. Angiogenesis is modulated by the interaction between tyrosine kinase receptors (TKRs), expressed by endothelial cells (ECs), and extracellular ligands, produced by tumor cells. This interaction triggers the activation of intracellular signaling cascades and kinetic processes, including cell deformation and adhesion, which eventually cause cell division and proliferation. Vascular Endothelial Growth Factor Receptor-2 (VEGFR2) is a pro-angiogenic receptor expressed on ECs. Ligand stimulation induces the polarization of ECs and the relocation of VEGFR2 in cell protrusion or in the basal aspect in cells plated on ligand enriched extracellular matrix (ECM) [1]. EC response to angiogenic growth factors is regulated by distinct sets of inputs conveyed by TRKs and different co-receptors including integrins, membrane proteins that are responsible of stress fibers formation and cell contractility [2]. Although biochemical pathways following VEGFR2 activation are well established, knowledge about the receptor dynamics on the plasma membrane remains limited.

A multi-physics model has been developed [3] to describe: i) the diffusion of VEGFR2 on the cellular membrane; ii) the chemical kinetics of the ligand-receptor binding reaction; iii) the mechanical adhesion and spreading of the cell onto a ligand-rich extracellular substrate, in finite strain. The identification of the multi-physics interactions that regulate receptor polarization could open new perspectives to develop innovative anti-angiogenic strategies through the modulation of EC activation.

References

[1] Ravelli, C., Grillo, E., Corsini, M., Coltrini, D., Presta, M., Mitola, S., "Beta3 integrins drive lipid raft-localized endothelial VEGFR2 polarization by extracellular matrix-associated ligand." in *Arteriosclerosis, Thrombosis, and Vascular Biology*, (2015).

[2] Ravelli, C., Mitola S., Corsini M., Presta M., "Involvement of $\alpha_v\beta_3$ integrin in gremlin-induced angiogenesis " in *Angiogenesis*, (2013).

[3] Damioli, V., Salvadori, A., Beretta, G.P., Ravelli, C., Mitola S., " Multi-physics interactions drive VEGFR2 relocation on endothelial cells. " submitted to *eLife*, (2017).