Co-designed experiments and multi-physics modeling of the VEGFR2 relocation on endothelial cells.

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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 mainly by the interaction between vascular endothelial growth factor receptors-2 (VEGFR2), expressed by endothelial cells (ECs), and specific extracellular ligands, produced by tumor cells. This interaction triggers the activation of intracellular signaling cascades and kinetic processes, which eventually cause cell division and proliferation. Ligand stimulation induces the polarization of ECs and the relocation of VEGFR2 in cell protrusions or in the basal aspect in cells laid on ligands-enriched extracellular matrix (ECM) [1]. EC response to angiogenic growth factors is regulated by distinct sets of inputs conveyed by receptors and different co-receptors including integrins (membrane proteins that are responsible of stress fibers formation, adhesion, and cell deformation and contractility).

A chemo-transport-mechanical model [2] has recently been proposed. It aims at simulating the dynamics of recruitment of VEGFR2 in EC and at co-designing experimental and numerical investigations to characterize the lateral mobility (diffusion) of VEGFR2 on the plasma membrane as well as their interactions (reaction) with immobilized ligands. The model stems from continuity equations (for mass, energy, and entropy), standard chemical kinetics, thermodynamic restrictions, and constitutive specifications. This sequence provides the governing equations in a strong form, stated for dimensionless unknown fields and converted in a weak form prior to the numerical approximation via the Finite Element Method. The model reproduces the experimental data well and allows identifying three phases of the receptor dynamics, which are controlled respectively by the high chemical reaction rate, by the mechanical deformation rate, and by the diffusion of free receptors on the membrane. The identification of the laws that regulate receptor polarization opens new perspectives towards developing innovative anti-angiogenic strategies through the modulation of ECs activation.

References

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