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Zoom

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New perspectives on angiogenic signaling through VEGFRs

Angiogenesis is a key pathogenic component of obesity and at least 70 other diseases. It is primarily driven by the vascular endothelial growth factor receptor (VEGFR) and its family of VEGF ligands. However, targeting VEGF alone has not achieved the promise of stable vascular control. Angiogenesis involves several signaling axes in addition to VEGF, representing a complexity that cannot be captured by targeting one growth factor alone. Indeed, several non-VEGF growth factors are upregulated after anti-VEGF treatment for cancer therapy, including platelet-derived growth factors (PDGFs). Furthermore, dual growth factor therapy resulted in synergistic effects when used to promote vascularization in animal ischemia models. These combined findings present a compelling need to shift our pedagogy away from a uni-axis understanding of vascularization (e.g., VEGF alone) toward a multi-axis understanding (e.g., VEGF + PDGF). We recently discovered non-canonical, high-affinity binding of platelet derived growth factors (PDGFs) to the primary angiogenic receptor, vascular endothelial growth factor receptor-2 (VEGFR2). Delineating this currently undefined PDGF role in VEGFR2 signaling will provide new tactics for controlling angiogenesis in health and disease. Towards this aim, we computationally model binding and trafficking; experimentally measure signaling and angiogenic function; and molecular interactions. Our mass-action kinetics models predict significant PDGF:VEGFR2 binding when VEGFR2 is overexpressed and during anti-VEGF therapy. Our signaling assays reveal selective activation of VEGFR2 and activation of the common angiogenic signaling molecules: Src kinase (Src), focal adhesion kinase (FAK), phospholipase-Cγ (PLCγ), and phosphoinositide 3-kinase (PI3K). Furthermore, PDGF treatment induces cell proliferation, an angiogenic hallmark, and select PDGFs mediate cell migration. Finally, stable PDGF:VEGFR2 binding conformations are observed via molecular dynamics (MD) simulations. Our modeling, signaling, and functional analyses define the importance of PDGF:VEGFR2 signaling. Further exploration of this non-canonical signaling should drive the development of new treatments for angiogenesis-related diseases.

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