Coordinated co-expression of PDGF-BB accelerates stabilization of VEGF_{164}-induced angiogenesis.

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VEGF induces normal or aberrant angiogenesis depending on its expression level in the microenvironment around each transduced cell. Further, four weeks of sustained expression are required to achieve vascular stabilization. We previously found that co-expression of PDGF-BB from a bicistronic construct induced only normal angiogenesis despite high and heterogeneous VEGF levels. Here we rigorously determined how PDGF-BB modulates VEGF dose-dependent angiogenesis.

We expressed mVEGF_{164}, hPDGF-BB or both in muscle implanting retrovirally transduced myoblasts. VEGF signaling was abrogated at defined time-points by VEGF-Trap treatment.

Two weeks after implantation, VEGF-induced vessels all regressed, whereas 50% of induced vessels already stabilized with PDGF-BB co-expression.

To investigate the role of factor dose, we implanted clonal populations homogeneously producing specific levels of VEGF, with or without PDGF-BB.

Interestingly, 35% and the 50% of normal vessels induced by low VEGF levels stabilize respectively at two and three weeks, while increasing levels of VEGF negatively correlated with stabilization. In particular, aberrant vessels caused by high VEGF levels never stabilized. PDGF-BB did not accelerate stabilization at low VEGF levels, whereas at high levels induced normal capillaries of which 50% and 80% were already VEGF-independent after two and three weeks. Therefore, we concluded that PDGF-BB co-expression accelerated vascular stabilization only at high VEGF levels.

By gene expression screening we identified Sema3A as a potential player in VEGF dose dependent stabilization and we are currently investigating the underlying mechanism.