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Exploring the potential of antiangiogenic strategies targeting the TGF-β family in the tumor microenvironment

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ABSTRACT

Members of the transforming growth factor (TGF)-β family exert their effect on virtually all cell types in the body, producing diverse and complex cellular responses. Additionally, TGF-β signaling is deregulated and hyperactive in many malignant conditions, making it an appealing target in the combat of cancer disease. The predominantly endothelial TGF-β receptors, ALK1 and endoglin, which are activated during neoangiogenesis both during development and pathological conditions, pose attractive modulating opportunities to impair tumor vessel formation and cancer progression. However, the precise function of TGF-β family signaling in endothelial cells is difficult to predict, as it appears highly context dependent due to a myriad of ligands and receptors influencing the final outcome. Furthermore, TGF-β is involved in autocrine and intricate dynamic paracrine signaling events in the context of the tumor microenvironment. Pharmacological inhibitors for ALK1 and endoglin have been developed and will facilitate more comprehensive studies on the exact function of the TGF-β family in the tumor-associated endothelium. Here, we summarize the current knowledge on TGF-β signaling in the regulation of the vascular network as alternative targets to VEGF and incorporate our novel and promising findings in the field. Our two studies aiming at dissecting the independent role of ALK1 and endoglin resulted in very distinctive outcomes. While ALK1 suppression results in sustained tumor growth by affecting the tumor neovasculature, endoglin impairment generates a weakened and increasingly lenient vasculature to the passage of malignant cells to and from the bloodstream. Our both seemingly contradictory studies challenge the current view of a strong interconnection between ALK1 and endoglin in the vasculature.

The ongoing clinical trials of inhibitors affecting ALK1 and endoglin involvement in vascular formation during malignant progression will further clarify the valuable potential of targeting alternative pathways to VEGF.