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The interplay between TGF- β and VEGF signalling in endothelial cell function

Zhen Liu

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The Interplay between TGF- β and VEGF signalling in endothelial cell function

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The interplay between TGF- β and VEGF signalling in endothelial cell function

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To my Love

Nils Visser

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Scope of the investigation

Endothelial cell sprouting is a multi-step process, tightly regulated by diverse signalling pathways. Vascular endothelial growth factor (VEGF) is an essential inducer for angiogenesis as evidenced by *in vivo* and *in vitro* studies. Transforming growth factor (TGF)- β remodels the vascular morphogenesis *in vivo* and regulates the expression of VEGF and VEGF receptors *in vitro*. However, little is known about how these two factors orchestrate the modulation of endothelial cell function. The scope of the research presented in this thesis is to study the interplay between TGF- β and VEGF signalling on endothelial cell function, with the focus on the effect of TGF- β signalling on VEGF- induced endothelial cell function.

TGF- β transduces its effect by binding to two distinct TGF- β type I receptors, ALK1 and ALK5 on endothelial cells. In addition, the concentration of TGF- β affects the degree of activation of these two receptors. In Part I, to investigate the influence of ALK5 activity in response to VEGF stimulation, a selective inhibitor of ALK5 (SB-431542) was applied to investigate the role of ALK5 in VEGF-induced vascular network formation; to address the role of ALK1 in VEGF-induced endothelial cell behavior, BMP9 as a potent ALK1 ligand was used in the presence of VEGF.

Endoglin is a co-receptor for TGF- β and functions as a modulator for ALK1 and ALK5 in endothelial cells. The involvement of endoglin in VEGF-induced endothelial cell function remains unclear. In Part II, the studies were designed to elaborate the role of endoglin and its soluble form on VEGF-stimulated endothelial cell sprouting. Of note, Chapter 6 discusses the pathological contribution of elevated soluble endoglin levels to pre-eclampsia.

In conclusion, TGF- β and VEGF signalling intimately intertwine and crosstalk with each other to affect endothelial cell function accordingly. Since the aim of the thesis was to elucidate the underlying mechanism of vascular pathologies that are associated with perturbed TGF- β and VEGF signalling, the work of this thesis may open new opportunities for future development of new treatment modalities.

Thesis Outline

The studies presented in this thesis have focused on the crosstalk between the TGF- β , BMP9 and VEGF signalling pathways and their roles on EC function, and how endoglin, a co-receptor of TGF- β signalling influences VEGF-induced endothelial sprouting.

Chapter 1 provides a general overview of the role of TGF- β family signalling in vascular development concerning its role in endothelial cell and mural cells as well as the impact of TGF- β signalling in pathological conditions.

Part I: The effect TGF- β signalling in endothelial cell function in response to VEGF

Chapter 2 demonstrates that inhibition of the TGF- β signalling pathway using the TGF- β receptor I inhibitor SB-431542 enhances VEGF-induced endothelial cell function. Sub-optimal doses of VEGF and SB-431542 synergistically induce endothelial cell migration and sprouting.

Chapter 3 reports the new ligand BMP9 for ALK1 signalling and its inhibitory role in endothelial cell function.

Part II: The role of endoglin in endothelial cell function in response to VEGF

Chapter 4 describes the new observation that endoglin is required for efficient VEGF-induced endothelial cell sprouting.

Chapter 5 demonstrates that endoglin is cleaved by MMP14, and that the derived soluble form of endoglin exerts inhibitory effect on VEGF-induced endothelial cell sprouting

Chapter 6 gives an overview of the role of soluble endoglin and soluble Flt1 in pre-eclampsia.

Part III: General Discussion

Chapter 7 discusses the perspectives of the main focuses of this thesis reflected towards the current literature.