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Conference Abstract

P.31 Von Willebrand Factor Induces Vascular Smooth Muscle Cell Proliferation and Migration Through Low Density Lipoprotein-Related Receptor Protein 4 and αvβ3 Integrin

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ABSTRACT

Background and Objectives: Von Willebrand factor (VWF) is a plasma glycoprotein involved in primary hemostasis but recent data suggest additional roles beyond hemostasis in angiogenesis and potentially in vascular smooth muscle cell (VSMC) proliferation. Our aim was to investigate how VWF can modulate VSMC proliferation and identified the underlying mechanisms and the *in vivo* pathophysiological relevance.

Methods and Results: Cultured aortic VSMCs proliferation and migration were increased in the presence of VWF. VSMCs treatment with a siRNA targeting α_v integrin or the RGT-peptide blocking $\alpha_v\beta_3$ signaling completely inhibited proliferation. VWF did not bind directly to $\alpha_v\beta_3$ on VSMCs. We identified that VWF A2 domain was able to bind VSMCs. Since the low-density lipoprotein-related receptor protein (LRP) family are known to act as co-receptors we hypothesized the involvement of a member in the signaling pathway. Using the universal LRP-inhibitor (RAP), we confirmed LRP-mediated VSMC proliferation. siRNA experiments and proximity ligation assay staining identified LRP4 as the VWF-counterreceptor on VSMCs and showed co-localization between $\alpha_v\beta_3$ and LRP4. Carotid ligations were applied to VWF +/+ and -/- mice and intimal hyperplasia (IH) was measured. Less VWF-/- mice developed IH compared to VWF +/+ mice. Finally, the proliferative effect of VWF was confirmed in human atherosclerotic lesions from different vessels (aortas, carotids) showing a proximity between VWF and a-SM actin positive cells.

Conclusions: VWF mediates VSMC proliferation through its A2 domain binding to the LRP4 receptor and integrin $\alpha_v\beta_3$ signaling. The decreased IH following vascular injury suggests that targeting VWF-LRP4 interactions may contribute to limit remodeling.

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