Transcription factor KLF6 upregulates gene expression of metaloprotease MMP-14 and soluble endoglin release upon vascular injury

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It has been postulated that an impaired vascular remodelling in an endoglin haploinsufficient setting is at the pathogenic basis of hereditary hemorrhagic telangiectasia. After endothelial injury, the transcription factor Kru¨ppel-like factor 6 (KLF6) translocates into the cell nucleus to regulate a variety of target genes involved in vascular repair and remodelling, including components of the membrane TGFbeta receptor complex such as endoglin and ALK1. While most of endoglin studies have focused on the membrane form, the regulation and role of soluble endoglin are poorly understood. The membrane metalloproteinase 14 (MMP14) targets membrane endoglin to release soluble endoglin and is involved in vascular inflammation and endothelial tube formation, but little is known about the regulation of MMP14 expression during vascular wounding. In vitro denudation of monolayers of human endothelial cells (ECs) leads to an increase in the KLF6 gene transcriptional rate, followed by an upregulation of MMP14 and soluble endoglin. Concomitant with this process, MMP14 co-localizes with endoglin in the sprouting endothelial cells surrounding the wound border. Moreover, after wire-induced endothelial denudation, Klf6+/- mice show lower levels of MMP14 in their vasculature compared with their wild-type siblings. Overexpression of KLF6 results in an increased transcription rate of MMP14, and chromatin immunoprecipitation assays show that KLF6 interacts with MMP14 promoter in ECs, this interaction being enhanced during wound healing. Furthermore, KLF6 markedly increased the transcriptional activity of different luciferase reporter constructs of MMP14 gene promoter. These results suggest that KLF6 regulates MMP14 transcription and is a critical player of the complex gene expression network triggered during endothelial repair.