Endothelial cells, which form the inner lining of all blood vessels, are constantly exposed to the frictional force of flowing blood, which is known as shear stress. This force, which is exerted parallel to the surface of the endothelial cells, has the potential to damage cells and in extreme, rip endothelial cells away from their location in the vessel wall. Endothelial cells have developed numerous adaptive mechanisms that allow them to resist the damaging influence of shear stress. One such mechanism is the production of protease inhibitors that prevent the excessive degradation of the matrix proteins to which endothelial cells attach. While it is recognized that shear stress increases the production of protease inhibitors, the cellular signaling mechanisms that control this response are not known. In this study, we investigated the regulatory mechanisms the control the production of the protease inhibitor, tissue inhibitor of matrix metalloproteinase -1 (TIMP-1). Using cultured endothelial cells exposed to a defined level of shear stress for varying amounts of time, we observed a biphasic increase in TIMP-1 protein, at 2 and 24 h of shear stress exposure. We demonstrated that the early increase in TIMP-1 protein required the transcription factor Sp1. We also found that production of the growth factor transforming growth factor beta (TGFb) was increased by shear stress. We showed that inhibition of TGFb signaling, either by blocking the TGFb receptor, or by siRNA inhibition of the TGFb-specific transcription factors SMAD2,3, prevented the shear stress induced increase in TIMP-1 after long term (24 h) shear stress exposure. These results suggest that both acute and chronic elevations in shear stress stimulate signals to maintain blood vessel integrity through increasing TIMP-1 production, and that the TGFb signaling pathway is an essential component of this response. It is possible that disruptions in this normal signaling pathway may contribute to the development of vascular diseases.

Uchida C, **Haas TL**. Endothelial cell TIMP-1 is upregulated by shear stress via Sp-1 and the TGFb signaling pathways. Biochem Cell Biol. 92(1):77-83, 2014.

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