Pravastatin Induces Thrombomodulin Expression in TNF- -treated Human Aortic Endothelial Cells by Inhibiting Rac1 and Cdc42 Translocation and Activity.

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摘要

Abstract

Expression of functionally active thrombomodulin (TM) on the luminal surface of endothelial cells is critical for vascular thromboresistance. The 3-hydroxyl-3-methyl coenzyme A reductase inhibitor, pravastatin, can protect the vasculature in a manner that is independent of its lipid- lowering activity. We examined the effect of pravastatin on TM expression by human aortic endothelial cells (HAECs) with subsequent tumor necrosis factor alpha (TNF alpha) stimulation and investigated the signaling pathways involved . TNFa treatment attenuated TM expression in HAECs in a time -dependent manner. Pravastatin upregulated TM levels in TNF alpha- treated HAECs. Specific inhibition of geranylgeranyltransferase-1 or the Rho family by GGTI-286 or TcdB, respectively, enhanced TM expression in TNF alpha- treated HAECs, whereas MAP kinase inhibitors, inactivation of Rho by Clostridium botulinum C3 exoenzyme, or the Rho kinase inhibitor, Y- 27632, had no effect. In TNF alpha- treated HAECs, pravastatin inhibited Rac1 and Cdc42 activation and their translocation to the cell membrane. Blocking the transcriptional activation of NF-kappa B prevented the TNF alpha-induced downregulation of TM. The pravastatin-induced increase in TM expression in TNF alpha- treated HAECs was mediated through inhibition of NF-kappa B activation. Pravastatin regulates TM expression by inhibiting the activation of the Rho family proteins, Rac1 and Cdc42, and the transcription factor, NF-kappa B. The increase in endothelial TM activity in response to pravastatin constitutes a novel pleiotropic (nonlipid- related) effect of this commonly used compound and may be of clinical significance in disorders in which

deficient endothelial TM plays a pathophysiological role.