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Sp1, acetylated histone-3 and p300 regulate TRAIL transcription: Mechanisms of PDGF-BB-mediated VSMC proliferation and migration

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Abstract

We recently reported that TNF-related apoptosis-inducing ligand (TRAIL) is important in atherogenesis, since it can induce vascular smooth muscle cell (VSMC) proliferation and arterial thickening following injury. Here we show the first demonstrate that TRAIL siRNA reduces platelet-derived growth factor-BB (PDGF-BB)-stimulated VSMC proliferation and migration . PDGF-BB-inducible VSMC proliferation was completely inhibited in VSMCs isolated from aortas of TRAIL $^{-/-}$ mice; whereas inducible migration was blocked compared to control VSMCs. TRAIL transcriptional control mediating this response is not established. TRAIL mRNA, protein and promoter activity was increased by PDGF-BB and subsequently inhibited by dominant-negative Sp1 , suggesting that the transcription factor Sp1 plays a role. Sp1 bound multiple Sp1 sites on the TRAIL promoter, including two established (Sp1-1 and -2) and two novel Sp1-5/6 and -7 sites. PDGF-BB-inducible TRAIL promoter activity by Sp1 was mediated through these sites, since transverse mutations to each abolished inducible activity. PDGF-BB stimulation increased acetylation of histone-3 (ac-H3) and expression of the transcriptional co-activator p300 , implicating chromatin remodelling. p300 overexpression increased TRAIL promoter activity, which was blocked by dominant-negative Sp1 . Furthermore, PDGF-BB treatment increased the physical interaction of Sp1 , p300 and ac-H3, while chromatin immunoprecipitation studies revealed Sp1 , p300 and ac-H3 enrichment on the TRAIL promoter. Taken together, our studies demonstrate for the first time that PDGF-BB-induced TRAIL transcriptional activity requires the cooperation of Sp1 , ac-H3 and p300 , mediating increased expression of TRAIL which is important for VSMC proliferation and migration . Our findings have the promising potential for targeting TRAIL as a new therapeutic for vascular proliferative disorders. © 2012 Wiley Periodicals, Inc.

Author keywords

Proliferation and migration ; Trail ; Transcription ; VSMC

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