Hyperbaric oxygen activates discoidin domain receptor 2 via tumor necrosis factor-alpha and p38 pathway to increase vascular smooth muscle cells migration through matrix metalloproteinase 2

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摘要

Abstract

DDR2 (discoidin domain receptor 2) regulates collagen turnover mediated by SMCs (smooth muscle cells) in atherosclerosis. HBO (hyperbaric oxygen) has been used in medical practice; however, the molecular mechanism of the beneficial effects of HBO is poorly understood. Furthermore, the effect of HBO on DDR2 has not been reported previously. In the present study, we investigated the cellular and molecular mechanisms of DDR2 regulation by HBO in VSMCs (vascular SMCs). Cells were exposed to 2.5 ATA (atmosphere absolute) of oxygen in a hyperbaric chamber. DDR2 protein (3.63-fold) and mRNA (2.34-fold) expression were significantly increased after exposure to 2.5 ATA HBO for 1 h. Addition of SB203580 and p38 MAPK (mitogen-activated protein kinase) siRNA (small interfering RNA) 30 min before HBO inhibited the induction of DDR2 protein. HBO also significantly increased DNA-protein binding activity of Myc/Max. Addition of SB203580 and an anti-TNF-alpha (tumour necrosis factor-alpha) monoclonal antibody 30 min before HBO abolished the DNA-protein binding activity induced by HBO. HBO significantly increased the secretion of TNF-alpha from cultured VSMCs. Exogenous addition of TNF-alpha significantly increased DDR2 protein expression, whereas anti-TNF-alpha and anti-(TNF-alpha receptor) antibodies blocked the induction of DDR2 protein expression. HBO significantly increased VSMC migration and proliferation, whereas DDR2 siRNA inhibited the migration induced by HBO. HBO increased activated MMP2 (matrix metalloproteinase 2)

protein expression, and DDR2 siRNA abolished the induction of activated MMP2 expression induced by HBO. In conclusion, HBO activates DDR2 expression in cultured rat VSMCs. HBO-induced DDR2 is mediated by TNF-alpha and at least in part through the p38 MAPK and Myc pathways.