

**PPAR{delta}-mediated p21/p27 induction via
increased CBP nuclear translocation in
beraprost-induced antiproliferation of murine
aortic smooth muscle cells.**

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摘要

Abstract

We previously showed that an increase in the peroxisome proliferator-activated receptor-delta (PPAR), together with subsequent induction of inducible nitric oxide synthase (iNOS) by beraprost (BPS), inhibits aortic smooth muscle cell proliferation. Herein, we delineated the mechanisms of the antiproliferative effects of BPS through the induction of p21/p27. BPS concentration-dependently induced the p21/p27 promoter- and consensus c-AMP responsive element (CRE)-driven luciferase activities, which were significantly suppressed by blocking PPAR activation. Surprisingly, other than altering the CRE-binding protein (CREB), BPS-mediated PPAR activation increased nuclear localization of the CREB-binding protein (CBP), a co-activator, which was further confirmed by chromatin immunoprecipitation. Furthermore, novel functional PPAR responsive elements (PPREs) next to CREs in the rat p21/p27 promoter regions were identified, where PPAR interacted with CREB through CBP recruitment. BPS-mediated suppression of restenosis in mice with angioplasty was associated with p21/p27 induction. Herein, we demonstrate for the first time that BPS-mediated PPAR activation enhances transcriptional activation of p21/p27 by increasing CBP nuclear translocation, which contributes to the vasoprotective action of BPS.