Role of zinc-mediated CREB pathway activation in PASMC proliferation during PH

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Abstract

The transcription factor CREB plays an important role in the development of pulmonary hypertension (PH). However, both increased and decreased CREB expression have been proposed to mediate the proliferation of pulmonary artery smooth muscle cells (PASMCs). Additionally, the regulatory signaling of CREB activation in PASMCs proliferation has not been well characterized in PH. Researchers recently used various in vitro techniques to clarify CREB's role. CRE-containing genes were upregulated in PH PASMCs, and total and phosphorylated CREB protein levels were elevated in PASMCs from rats with monocrotaline (MCT)-induced PH. Prolonged upregulation of serum-induced CREB phosphorylation was also observed in hypoxia-pretreated PASMCs. These results may have been due to activation of multiple protein kinases and downregulation of numerous phosphatases targeting CREB. PASMC proliferation in experimental PH was dependent on CREB-mediated transcriptional activity, and increases in intracellular labile zinc mediated by ZIP12 upregulation may have been linked to the reductions in phosphatases and the increases in transcriptional activity and PASMC proliferation. Although further research is needed to investigate ZIP12-mediated zinc in regulating CREB transcriptional activity, the findings may help to elucidate the role and regulation of CREB pathway in pulmonary hypertension. In summary, CREB pathway was overactivated in the development of PH and contributed to PASMC proliferation, which was associated with multiple protein kinases and/or reduced CREB phosphatases and raised intracellular zinc. This study may reveal a critical role of zinc-mediated CREB pathway activation in PASMC proliferation, thus providing a novel insight into the CREB pathway in the pathogenesis of PH.