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Activation of proMMP-2 by U46619 occurs via involvement of p^{38}MAPK-NFκB-MT1MMP signaling pathway in pulmonary artery smooth muscle cells

Animesh Chowdhury · Soumitra Roy · Tapati Chakraborti · Kuntal Dey · Sajal Chakraborti

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Abstract We investigated the mechanism by which TxA_2 mimetic, U46619, activates proMMP-2 in bovine pulmonary artery smooth muscle cells. Our study showed that treatment of the cells with U46619 caused an increase in the expression and subsequently activation of proMMP-2 in the cells. Pretreatment with p^{38}MAPK inhibitor, SB203580; and NF-κB inhibitor, Bay11-7082 inhibited the expression and activation of proMMP-2 induced by U46619. U46619 also induced increase in MT1-MMP expression, which was inhibited upon pretreatment with SB203580 and Bay11-7082. U46619 treatment to the cells stimulated p^{38}MAPK activity as well as NF-κB activation by IκB-α phosphorylation, translocation of NF-κBp65 subunit from cytosol to nucleus and subsequently, by increasing its DNA-binding activity. Induction of NF-κB activation seems to be mediated through IKK, as transfection of cells with either IKKα or IKKβ siRNA prevented U46619-induced phosphorylation of IκB-α and NF-κBp65 DNA-binding activity. U46619 treatment to the cells also downregulated the TIMP-2 level. Pretreatment of the cells with SB203580 and Bay11-7082 did not show any discernible change in TIMP-2 level by U46619. Overall, U46619-induced activation of proMMP-2 is mediated via involvement of p^{38}MAPK-NFκB-MT1MMP signaling pathway with concomitant downregulation of TIMP-2 expression in bovine pulmonary artery smooth muscle cells.

Keywords proMMP-2 · MT1-MMP · p^{38}MAPK · NF-κB · TIMP-2

Abbreviation

SMC	Smooth muscle cell
proMMP-2	pro matrix metalloprotease 2
MT1-MMP	Membrane type 1 matrix metalloprotease
TIMP-2	Tissue inhibitor of matrix metalloprotease 2
IKK	Inhibitory κB kinase
NF-κB	Nuclear factor κB, IκB-α, inhibitory κBα

Introduction

Thromboxane A_2 (TxA_2), a potent vasoconstrictor that mediates a broad range of cellular responses, has been implicated in the progression of many pulmonary vascular diseases including pulmonary hypertension and right ventricular hypertrophy [1–3]. Remodeling of extra cellular matrix (ECM)—its synthesis and degradation—is a major feature of many pulmonary vascular diseases [4, 5]. Excessive ECM degradation may favor pathophysiology of diseases [6]. Degradation of ECM could be orchestrated by several types of proteases, among which matrix metalloproteinases (MMPs) are of prime importance [7, 8]. MMPs are zinc-dependent endopeptidases, produced as an inactive proenzyme, which are activated by a variety of stimuli under normal as well as different pathophysiological conditions. Role of MMPs have been implicated in a variety of pulmonary vascular diseases through remodeling of ECM. Among the MMPs, MMP-2 is one of most studied

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A. Chowdhury · S. Roy · T. Chakraborti · K. Dey · S. Chakraborti (✉)
Department of Biochemistry and Biophysics, University of Kalyani, Kalyani 741235, West Bengal, India
e-mail: sajal_chakraborti@yahoo.com