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Hypoxia induces connexin 43 dysregulation by modulating matrix metalloproteinases via MAPK signaling

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Abstract Connexin 43 (Cx43) is a major structural protein found in the gap junctions of the ventricular myocardium and a major determinant of its electrical properties. The effects of matrix metalloproteinases (MMPs), the mitogen-activated protein kinase (MAPK) signaling pathway, transcription factor NF-kB, and activator protein-1 (AP-1)/c-Jun on the regulation of Cx43 gene expression in H9c2 cardiomyocytes were assessed. The MAPK signaling pathway (MEK/ERK1/2 and PI3K) and transcription factors NF-kB and AP-1/c-Jun were inhibited, then Cx43 expression was assessed using Western blot analysis, and MMP-9 activity was assessed using gelatin zymography. Hypoxia decreased the Cx43 protein level by approximately 30–50 %. Doxycycline (10 μg/mL), an inhibitor of MMP, markedly attenuated the hypoxia-induced downregulation of Cx43 protein expression at 6 h. The hypoxia-induced decrease in Cx43 protein expression was significantly reversed by U0126 (10 μM), a MEK/ERK1/2 inhibitor, at 6 and 12 h; LY294002 (30 μM), a PI3K inhibitor, downregulated Cx43 expression. Hypoxia-induced MMP-9 activation was inhibited by treatment with LY294002, U0126, and, most especially, U0126. JSH-23 (30 μM), an NF-kB inhibitor, and SP600125 (10 μM), an AP-1/c-Jun inhibitor, attenuated the loss of Cx43. These results suggest that MAPK signaling and the activities NF-kB and MMPs play an important roles in the regulation of Cx43 expression.

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Abbreviations

Cx43	Connexin 43
MMPs	Matrix metalloproteinases
MAPK	Mitogen-activated protein kinases
AP-1	Activator protein-1
ECM	Extracellular matrix
PI3K	Phosphoinositide-3 kinase
NF-κB	Kappa-light-chain enhancer of activated B cells
LPS	Lipopolysaccharide

Introduction

Gap junctions, which are composed of channel-forming integral membrane proteins known as connexins, mediate cell–cell communication in almost all tissues [1]. Connexin 43 (Cx43) is a major structural protein found in the gap junctions of the ventricular myocardium and a major determinant of myocardial electrical properties [2]. Cx43 dysfunction in cardiomyocytes may contribute to the pathogenesis of ventricular arrhythmias. Transferring the Cx43 gene to pigs with anterior infarction reduces ventricular tachycardia in the border zone of the healed scar [3].

Matrix metalloproteinases (MMPs) reportedly play an important role in the degradation of the extracellular matrix (ECM) [4]. The degradation of the ECM by MMPs is involved in the pathogenesis of cardiovascular diseases, including atherosclerosis and myocardial infarction [5, 6]. MMP expression is regulated at the transcription level by the activation of various transcription factors, such as