Prostaglandin E-EP4-Mediated Fibulin-1 Up-regulation Plays a Role in Intimal Thickening of the Ductus Arteriosus

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Keywords

Ductus arteriosus · Cell migration · Intimal thickening

The normal closure of the ductus arteriosus (DA) consists of two steps: vasoconstriction and intimal thickening (IT). We have revealed that prostaglandin E₂ (PGE₂)-EP4 signaling plays a critical role in IT formation via smooth muscle cell (SMC) migration through hyaluronic acid [1]. In this study, we found that fibulin-1 was the most significantly up-regulated gene by EP4 stimulation in DA smooth muscle cells (SMCs).

It has been reported that fibulin-1 has binding domains for ADAMTS-1 (a disintegrin and metalloprotease with thrombospondin motif type 1) and versican [2, 3], which participates in cell migration, and this fibulin-1-binding protease ADAMTS-1 promotes versican fragmentation [4, 5]. Furthermore, coupling of fragmented versican and hyaluronic acid promotes cell migration [6]. We speculated that fibulin-1 promotes DASM migration and induces IT of the DA with ADAMTS-1 and versican. We aimed to examine the role of PGE₂-EP4-signaling-mediated fibulin-1 in IT of the DA.

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Based on the microarray analysis showing that fibulin-1 was the most increased gene by EP4 stimulation in DASMCs, we performed RT-PCR and confirmed similar findings. EP4 stimulation did not increase fibulin-1 in aortic SMCs. Protein expression of fibulin-1 was markedly increased by EP4 stimulation in DASMCs. Immunohistochemistry of rat DA tissues showed that fibulin-1, ADAMTS-1, and fragmented versican were co-localized in the area of IT. VersicanV1 mRNA expression was significantly higher in endothelial cells than in DASMCs, and ADAMTS-1 was expressed in both endothelial cells and DASMCs. EP4 stimulation significantly increased binding of hyaluronic acid to fragmented versicanV1 protein in DASMCs. A Scratch assay showed that EP4 promoted DASMC migration, which was attenuated by fibulin-1-targeted siRNA and ADAMTS-1-targeted siRNA.

In conclusion, PGE₂-EP4-mediated fibulin-1 integrates extracellular matrices such as ADAMTS-1, versican V1, and hyaluronic acid to promote SMC migration of the DA.

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