Title	An EP4 receptor agonist inhibits cardiac fibrosis through activation of PKA signaling in hypertrophied heart
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論　文　内　容　の　要　旨
Synopsis of Thesis

氏　名 Name	王 琦
論文題名 Title	An EP4 receptor agonist inhibits cardiac fibrosis through activation of PKA signaling in hypertrophied heart （EP4作動薬は肥大心において心臓線維芽細胞のPKAシグナル伝達系を活性化することで心筋線維化を抑制する）

論文内容の要旨

〔目　的(Purpose)〕

Cardiac fibrosis is a pathological feature of myocardium of failing heart and plays causative roles in arrhythmia and cardiac dysfunction, but its regulatory mechanisms remain largely elusive. In this study, we investigated the effects of a novel EP4 receptor agonist ONO-0260164 on cardiac fibrosis in hypertrophied heart and explored the regulatory mechanisms in cardiac fibroblasts

〔方法ならびに成績(Methods/Results)〕

In a mouse model of cardiac hypertrophy generated by transverse aortic constriction (TAC), ONO-0260164 treatment significantly prevented systolic dysfunction and progression of myocardial fibrosis at 5 weeks after TAC. In cultured cardiac fibroblasts of neonatal rats, transforming growth factor-β1 (TGF-β1) induced upregulation of collagen 1α1 and 3α1, which was inhibited by ONO-0260164 treatment. ONO-0260164 activated protein kinase A (PKA) in the presence of TGF-β1 in the cardiac fibroblasts. PKA activation suppressed an increase in collagen expression induced by TGF-β1, indicating the important inhibitory roles of PKA activation in TGF-β1-mediated collagen induction.

〔総　括(Conclusion)〕

We demonstrated for the first time the antifibrotic effects of the novel EP4 agonist ONO-0260164 in vivo and in vitro, and the important role of PKA activation in the effects.

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論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

Cardiac fibrosis is a pathological feature of myocardium of failing heart and plays causative roles in arrhythmia and cardiac dysfunction, but its regulatory mechanisms remain largely elusive. In this study, we investigated the effects of a novel EP4 receptor agonist ONO-0260164 on cardiac fibrosis in hypertrophied heart and explored the regulatory mechanisms in cardiac fibroblasts. In a mouse model of cardiac hypertrophy generated by transverse aortic constriction (TAC), ONO-0260164 treatment significantly prevented systolic dysfunction and progression of myocardial fibrosis at 5 weeks after TAC. In cultured cardiac fibroblasts of neonatal rats, transforming growth factor- 1 (TGF- 1) induced upregulation of collagen 1 1 and 3 1, which was inhibited by ONO-0260164 treatment. ONO-0260164 activated protein kinase A (PKA) in the presence of TGF- 1 in the cardiac fibroblasts. PKA activation suppressed an increase in collagen expression induced by TGF- 1, indicating the important inhibitory roles of PKA

activation in TGF- 1-mediated collagen induction. We demonstrated for the first time the antifibrotic effects of the novel EP4 agonist ONO-0260164 in vivo and in vitro, and the important role of PKA activation in the effects.