Cardiac fibrosis is a hallmark of cardiomyocyte death during heart disease progression and considered to be both a cause and a result of heart failure. It is characterized by excessive growth of interstitial fibroblasts and collagen deposition in the myocardium, which initially contributes to an increase of cardiac stiffness and subsequent diastolic dysfunction, but eventually leads to contractile dysfunction. The initiation of cardiac fibrosis is cardiomyocyte death or other stimuli such as cytokine production, followed by infiltration of inflammatory cells and subsequent replacement with proliferating fibroblasts and collagen fibers. Since the extent of fibrotic area is correlated with the degree of contractile dysfunction and frequency of premature death by heart failure or lethal arrhythmia, efforts have been focused on the attenuation of the fibrosis.

Prostaglandins (PGs) are physiologically active lipid compounds synthesized from arachidonic acids. The name prostaglandin derives from the prostate gland where it was first isolated by V. Euler in 1935 but it is produced by almost all nucleated cells. Until now, more than 10 types of prostaglandins have been discovered. Among them, prostaglandin E2 (PGE2) has been well studied, especially in inflammatory cells, and is also known to be the predominant type of PGs in solid tumors, skin, and left ventricular cardiomyocytes. PGE2 has versatile biological effects in many organs, which depend on the activation of its prostanooid EP receptors, of which there are 4 subtypes, EP1, EP2, EP3, and EP4. These are the 7-transmembrane G protein-coupled receptors expressed on vascular smooth muscle cells, vascular endothelial cells, cardiac fibroblasts, and cardiomyocytes in the context of the heart organ. Despite intensive investigation of PGE2 signaling in the heart, there still remains controversy as to whether the functional outcome of the PGE2-EPs axis is beneficial or maladaptive. The reasons behind this are that it shares variable downstream targets such as Gi- or Gs-type G-proteins, and the redundancy of each EP. Nevertheless, PGE2-EPs signaling plays important roles in the pathophysiological aspects of heart disease.

In the current issue of International Heart Journal, Wang, et al provided evidence supporting the beneficial effects of the PGE2-EP4 axis in the pressure-overloaded heart. They first subjected wild type mice to transverse aortic constriction (TAC) surgery to induce high blood pressure in the left ventricular chamber, an established model of left ventricular hypertrophy and heart failure. Three weeks after the TAC surgery, the estimated time frame during which the myocardium undergoes transition from hypertrophy to heart failure, they administered the novel selective EP4 agonist ONO-0210614 and demonstrated that the administration of ONO-0210614 for 2 weeks resulted in a reduced heart weight/tibia length ratio and preserved left ventricular systolic function as compared with vehicle treated heart. This cardioprotective effect was accompanied by significantly reduced cardiac fibrosis at 5 weeks after TAC, assessed with Masson’s trichrome staining, but did not affect the degree of cardiomyocyte hypertrophy as evidenced by echocardiography and the cross-sectional areas of histological sections. Quantitative real-time PCR revealed that the up-regulation of fibrosis-related gene expressions, Col Iα1 and Col 3α1, after TAC surgery, were both ameliorated with the administration of ONO-0210614. These results suggest that, in the setting of a pressure-overloaded murine heart failure model, ONO-0210614 acts as a potent anti-fibrotic signal. Since fibroblasts are representative cells that govern fibrotic signals and form the extracellular matrix via synthesis of collagen, the authors performed in vitro studies using neonatal rat cardiac fibroblasts to investigate the regulatory mechanisms by which ONO-0210614 acts. In the presence of TGF-β1, the expression levels of collagen type-I and type-III proteins were markedly increased, and these increases were significantly suppressed by the EP4 agonist, ONO-0210614. Next, the authors explored the downstream target of EP4 signals, that is, activation of PKA. After confirming the induction of PKA phosphorylation with ONO-0210614 in a time-dependent manner, a PKA agonist and inhibitor were employed to determine whether the anti-fibrotic effects of ONO-0210614 were PKA dependent or not. Indeed, while the PKA inhibitor, H89, successfully abolished the anti-fibrotic effects of ONO-0210614 on TGF-β1-induced collagen type-I up-regulation, the PKA agonist, forskolin, alone was sufficient to recapitulate the anti-fibrotic effects of ONO-0210614. These results collectively suggest that the attenuation of collagen deposition by ONO-0210614 is, at least in part, through the inhibition of TGF-β1 signals via PKA-dependent EP4 signals on murine cardiac fibroblasts.

Fibrosis is the pathological alteration and endpoint of various dysfunctional organs including kidney, liver, and heart.
It is considered as excessive deposition of extracellular matrix and serves as non-functional tissue, namely scar tissue, which obstructs the normal functions of intact cells. Understanding the mechanisms of how fibrosis develops could lead to the discovery of novel treatments for many dysfunctional organs in the body. Among the therapeutic targets being investigated as an anti-fibrotic therapy, PGE2 has been reported to be promising. In the context of kidney disease, Nakagawa, et al demonstrated that administration of a specific EP4 agonist, ONO-4819, attenuated unilateral ureteral obstruction-induced renal fibrosis through mechanisms in which macrophage infiltration and fibroblast activation were involved.11) Conversely, EP4 knockout resulted in augmented fibrotic change in the same model. Another PGE2 receptor, EP2, has been reported to be responsible for anti-fibrotic effects in a bleomycin-induced pulmonary fibrosis model. Kach, et al reported that noscapine, an antitussive drug, acts on lung fibroblasts and reduces fibrosis by inhibiting the TGF-β1 pathway via PKA activation.12)

With regard to cardiac disease, PGs have been mainly investigated in terms of their roles in inflammatory cell infiltration in the settings of myocardial ischemia, cardiac transplantation, and myocarditis,9) and the roles of PGs in cardiac fibrosis have been less investigated. Wang, et al shed light on the importance of EP4-mediated anti-fibrotic effects in a murine heart failure model and partially revealed the molecular mechanisms in which PKA plays a central role in inhibiting the TGF-β1 pathway to treat cardiac fibrosis (Figure). However, there are some issues remaining that need to be elucidated. One is that the authors only focused on fibroblasts and did not mention the involvement of EP4 in cardiomyocytes or infiltration of inflammatory cells, which have been previously reported.13,14) The elucidation of precise targets of PKA in the TGF-β1 pathway is also crucial. Nevertheless, further studies are required to uncover the full mechanisms of the EP4-PKA-mediated cardioprotective effects prior to putting EP4 agonists into clinical practice.

**REFERENCES**