Prostaglandins (PGs), a group of key lipid mediators, are involved in numerous physiological and pathological processes including inflammation and cardiovascular homeostasis. Each PG acts on its specific and distinct cell surface G protein-coupled receptors (GPCRs) or peroxisome proliferator-activated receptors (PPARs). Prostaglandin F$_{2\alpha}$ receptor (FP) is required for female reproductive function such as luteolysis and parturition. It has recently been implicated in blood pressure regulation, atherosclerosis and other inflammation-related disorders. The emerging role of FP in cardiovascular diseases is highlighted and potential therapeutic translation is discussed in the current review.

**Keywords:** prostaglandin F$\alpha$, hypertension, atherosclerosis, FP receptor

**INTRODUCTION**

Prostanoids, including prostaglandin (PG) E$_2$, PGD$_2$, prostacyclin (PGI$_1$), thromboxane A$_2$ (TXA$_2$), and PGF$_{2\alpha}$ are generated through PGH synthase (PGHS) – known commonly as cyclooxygenase (COX), in response to a wide variety of stimuli acting as paracrine or autocrine manner. Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, inhibit COX isforms to achieve antipyretic, analgesic, and anti-inflammatory actions through blocking PGs biosynthesis (Funk, 2001). Accumulating evidences demonstrate COX-derived PGs play crucial role in mediating an array of cellular processes such as cell proliferation, differentiation, and apoptosis and in regulating female reproductive function and parturition, platelet aggregation, and vascular homeostasis (Smith et al., 2000; Yu et al., 2006; Funk and FitzGerald, 2007; Yu and Funk, 2007). In addition, PGs also are involved in pathogenesis of inflammation, cancer, and cardiovascular disorders (FitzGerald and Loll, 2001; Smyth et al., 2009). The biological functions of PGs could be modulated at multiple levels such as COX, PG synthases, and downstream receptors (Narumiya and FitzGerald, 2001). Elucidating the physiological roles of COX-derived PGs in cellular and whole body homeostasis and the mechanism underlying their action will no doubt offer opportunity for developing novel therapeutics for inflammatory disease, cancer, and hypertension. Here, we summarized the recent works focusing on PGF$_{2\alpha}$/FP receptor response in cardiovascular system and reviewed the recent development of potential therapeutic target of FP receptor.

**PGF$_{2\alpha}$ AND FP RECEPTOR**

Prostanoids are formed through COXs on arachidonic acid via a two-step enzymatic process. First the arachidonic acid is biotransformed to PGG$_2$ through COX catalytic activity and then PGH$_2$ through peroxidase activity (POX) of PGHS enzymes. Subsequently the PGH$_2$ is subject to metabolize to active prostanoids through individual PG synthases (Figure 1). Diversity in expression of downstream synthases results in the generation of one or two dominant PGs by individual cells. In general, PGF$_{2\alpha}$ is formed by reduction of PGH$_2$ by PG endoperoxide synthase or reductase. It also can be also formed from other PGs (Figure 1) such as PGE$_2$ through 9-keto reductases and PGD$_2$ through 11-keto reductases (Watanabe et al., 1985), although relatively rare. Endogenous primary PGF$_{2\alpha}$ is rapidly degraded enzymatically, half-life is less than 1 min in peripheral circulation, and its relatively stable metabolite is 15-keto-dihydro-PGF$_{2\alpha}$ (Basu et al., 1992).

PGF$_{2\alpha}$ exits in almost all the tissues (Basu, 2007) with more abundant in the female reproductive system (Hao and Breyer, 2008); its cellular and physiological effects are mediated by a G protein-coupled receptor-the F prostanoid receptor (the FP; Narumiya et al., 1999). Two splice forms of FP (FP$_{2\alpha}$ and FP$_{1\alpha}$) exist in human. Initially, the FP receptor was characterized as coupling to Gq protein which lead to inositol triphosphate (IP3)/diacylglycerol (DAG) generation and mobilization of intracellular calcium (Abramovitz et al., 1994; Sugimoto et al., 1994; Watanabe et al., 1994), which is linked to the proliferation of cells (Watanabe et al., 1994). Stimulation of FP also led to activation of the small G protein Rho, resulting in phosphorylation of the p125 focal adhesion kinase, cytoskeleton rearrangement and cell morphology change (Pierce et al., 1999), and phospholipase C-mediated phosphorylation of the epidermal growth factor receptor (EGFR) and mitogen-activated protein kinase (MAPK) signaling pathways in endometrial adenocarcinoma cells (Sales et al., 2004). Recently, the coupling of Gi of FP receptor has been reported, which is response for water reabsorption in renal collecting ducts in rabbit (Hebert et al., 2005).
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In the heart, PGF$_2\alpha$ derives mainly from cardiac fibroblasts and its formation is increased in endocardium by ischemia (Rabinowitz et al., 1992), where it depresses contractile recovery through a mechanism associated with altered cellular energy metabolism and increased calcium accumulation (Karmazyn et al., 1993). Through FP receptor, PGF$_2\alpha$ promotes expression of c-fos, atrial natriuretic factor (ANF), and alpha-skeletal actin in cardiomyocytes and induces cardiac myocyte hypertrophy in vitro and cardiac growth in rat (Lai et al., 1996), but does not affect myocyte proliferation in culture (Adams et al., 1996). Mechanistic studies showed PGF$_2\alpha$ inhibits expression Ca$^{2+}$-ATPase (SERCA2) via induction of Early Growth Response Protein 1 (Egr-1) in cultured neonatal cardiac myocytes (Hara et al., 2008). We have recently found that selective deletion of cardiomyocyte COX-2 releases a restraint on expression of fibroblast COX-2, thereby augmenting PGF$_2\alpha$ formation. This, in turn, coincides with an increase in myocardial fibrosis and a predisposition to arrhythmogenesis (Wang et al., 2009). COX-2 derived PGF$_2\alpha$ can further promote fibroblast PGF$_2\alpha$ formation in a feed forward manner (Yoshida et al., 2002) and progressively promote fibrosis (Almirza et al., 2008). PGF$_2\alpha$ promotes arrhythmias in cultured neonatal rat cardiac myocytes (Kunapuli et al., 1997; Li et al., 1997) and FP deletion protects against inflammatory tachycardia in mice in vivo (Takayama et al., 2005). Thus, PGF$_2\alpha$/FP response is involved in

Expression of FP receptor and its corresponding function are summarized in Table 1. FP is highly expressed in the genitourinary tract (Sugimoto et al., 1997; Saito et al., 2003). Gene manipulation studies showed that, parturition is disrupted in mice lacking either cytosolic phospholipase A$_2$ (cPLA$_2$; Bonventre et al., 1997), that mobilizes arachidonic acid release for COX metabolism, COX-2, the more regulated form of that enzyme (Dinchuk et al., 1995; Morham et al., 1995) or the FP receptor (Sugimoto et al., 1997). Likewise, the onset of parturition is delayed in COX-1 knock out (KO) mice (Langenbach et al., 1995) but not COX-1 knockdown (KD; Yu et al., 2005). This results in high neonatal mortality that can be rescued by PGF$_2\alpha$ replacement (Gross et al., 1998). In the eye, the FP is expressed in the vasculature, the iris sphincter and in the anterior circular muscles, all relevant to the increased uveoscleral outflow of aqueous humor provoked by PGF$_2\alpha$ (Mukhopadhyay et al., 2001). FP agonists are approved for local application in the treatment of glaucoma (Ishida et al., 2006). Recently, abundant FP expression has also been detected in the distal convoluted tubules (DCT) and cortical collecting ducts (CCD) of the kidney (Saito et al., 2003), implicating its role in water and electrolyte homeostasis (Hebert et al., 2005). FP is observed in lung tissue and lung fibroblasts, which facilitates bleomycin-induced pulmonary fibrosis independently of transforming growth factor $\beta$ (TGF$\beta$; Oga et al., 2009). No FP receptor seems been detected in immune system organs such as spleen and thymus ( Tilley et al., 2001).

**FP IN CARDIOVASCULAR DISEASES**

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multiple aspects of ischemia heart disease (Figure 2), blockage of the FP may facilitate recovery from cardiac ischemia-reperfusion induced injury.

Vascular endothelial cells secrete surprisingly large amounts of PGF$_{2\alpha}$ in response to shear stress in vitro (Di Francesco et al., 2009). The relevance of this phenomenon is poorly understood.

Table 1 | FP expression and its physiological/pathological function.

| Tissue/cell distribution         | Physiological/pathological process                          | References                                      |
|----------------------------------|-------------------------------------------------------------|-------------------------------------------------|
| Ovary                            | Luteolysis, parturition                                     | Sugimoto et al. (1997), Gross et al. (1998), Saito et al. (2003) |
| Myometrium                       | Uterine contraction                                         | Brodt-Eppley and Myatt (1999), Fischer et al. (2008) |
| Ocular vasculature; iris sphincter; ocular circular muscles | Aqueous humor homeostasis                                   | Mukhopadhyay et al. (2001)                      |
| Renal distal convoluted tubule, cortical collecting duct | Water and electrolyte reabsorption                          | Saito et al. (2003), Hebert et al. (2005), Hao and Breyer (2008) |
| Juxtaglomerular apparatus        | Renin secretion; blood pressure regulation                  | Yu et al. (2009)                                |
| Lung fibroblast                   | Pulmonary fibrosis                                          | Oga et al. (2009)                               |
| Cardiac fibroblast; cardiomyocyte | Myocardial fibrosis; arrhythmias; myocyte hypertrophy       | Lai et al. (1996), Kunapuli et al. (1997), Li et al. (1997), Yoshida et al. (2002), Takayama et al. (2005), Almirza et al. (2008), Wang et al. (2009) |
| Vascular smooth muscle cell (VSMC) | VSMC hypertrophy; vasoconstriction                         | Whittle et al. (1985b), Rice et al. (2008), Yu et al. (2009) |

FIGURE 2 | Scheme of PGF$_{2\alpha}$/FP pathway involved in pathogenesis of cardiovascular disease. Cardiac fibroblasts derived PGF$_{2\alpha}$ induce cardiac hypertrophy, fibrosis and arrhythmia through FP receptor in adjacent cardiomyocytes (CMs); PGF$_{2\alpha}$ stimulates renin release from juxtaglomerular granular cells (JGCs) by FP receptor in an autocrine fashion, and activate renin–angiotensin–aldosterone system (RAAS) to elevate blood pressure through enhancing salt/water reabsorption in kidney and constricting blood vessels directly via Angiotensin II (Ang II); PGF$_{2\alpha}$ promotes resistance artery constriction through FP in smooth muscle cells (SMCs), which eventually increases blood pressure and contributes to atherosclerosis; Activated RAAS also accelerates atherosclerosis. JGA, juxtaglomerular apparatus; AGT, angiotensinogen; ACE, angiotensin-converting enzyme; ALD, aldosterone.
but in sufficient quantities. PGF\(_{2\alpha}\) may act as an incidental ligand at the TXA\(_2\), receptor-the TP (Wong et al., 2009). Furthermore, the expression of FP receptors in the medial layer of resistance vessels was observed (Yu et al., 2009), which is involved in vasoconstriction (Whittle et al., 1985a). Thus it might prove relevant to the regulation of systemic blood pressure (BP) as PGF\(_{2\alpha}\) direct infusion causes dose-dependent elevation of BP in anesthetized mice (Yu et al., 2009). Moreover, PGF\(_{2\alpha}\) increases reactive oxygen species (ROS) and induces vascular smooth muscle cells (VSMCs) hypertrophy through translocation of mammalian target of rapamycin (mTOR) from nucleus to cytoplasm and activation of phosphatidylinositol 3-kinase (PI3K) pathway (Rice et al., 2008). In mice, FP deletion reduces significantly BP in mice, both when they are placed on a regular chow diet and after manipulation of dietary fat or sodium intake. This coincides with decreased activation of renin–angiotensin–aldosterone system (RAAS; Yu et al., 2009). FP receptor expression is marked in afferent arterioles of the juxtaglomerular apparatus (JGA) and renin-containing granular cells are decreased in the FP deficient mice (FP\(_{-/-}\)). Indeed, activation of the FP appears to regulate juxtaglomerular (JG) cell differentiation and consequent renin expression, explaining depressed activation of the RAAS in FP\(_{-/-}\) mice. Although FP expression was not detected in the aorta or even when it was complicated by atherosclerotic lesions, FP deletion attenuates atherosclerosis in hyperlipidemic mice [low-density lipoprotein (LDL) receptor was not detected in the aorta or even when it was complicated activation of the RAAS in FP\(_{-/-}\)]. Similar to PGE\(_2\), PGF\(_{2\alpha}\) and is subject to inhibition by NSAIDs such as low dose aspirin (Helmersson et al., 2005b). Perhaps restraint of atherogenesis in LDLr\(^{-/-}\) mice merely results from disruption of renal RAAS activation with a consequent impact on systemic BP (Figure 2). Taken together, antagonism of the FP receptor may afford a strategy for the control of hypertension and its attendant vascular diseases such as atherosclerosis (Yu et al., 2009).

**PGF\(_{2\alpha}\) IN HUMAN INFLAMMATORY DISEASE**

In human studies, PGF\(_{2\alpha}\) is one of the more abundant PGs formed at sites of inflammation (Scher and Pillinger, 2009), and is subject to inhibition by NSAIDs such as low dose aspirin (Helmersson et al., 2005b). Similar to PGE\(_2\), PGF\(_{2\alpha}\) is present in joint fluid collected from rheumatoid arthritis, psoriatic arthritis, osteoarthritis patients (Trang et al., 1977; Basu et al., 2001), and the levels of these PGs could also be effectively retarded by NSAIDs treatment. In addition, the synovial cells from rheumatoid arthritis patient are able to secrete PGF\(_{2\alpha}\) in vitro (Seppala, 1987). Along with 8-iso-PGF\(_{2\alpha}\)-oxidative stress marker, PGF\(_{2\alpha}\) was elevated during the first hour in acute myocardial infarction (AMI) patient treated with percutaneous coronary intervention (PCI; Berg et al., 2005) and 24 h after post-surgery in elective PCI patients probably due to aspirin treatment before operation (Berg et al., 2004).

Atherosclerosis is a chronic vascular inflammation diseases characterized by the thickening of the arterial wall (Rader and Daugherty, 2008). Vascular endothelial dysfunction is believed as initial step during atherogenesis, high plasma LDL, free oxygen radicals caused by cigarette smoking, hypertension, and diabetes mellitus, and other genetic defects could cause endothelial dysfunction leading to atherosclerosis (Ross, 1999). As the major metabolite of PGF\(_{2\alpha}\) 15-keto-dihydro-PGF\(_{2\alpha}\) is elevated in the conditions associated with those increased cardiovascular risk, such as smoking (Helmersson et al., 2005a), obese (Sinaiko et al., 2005), rheumatic disease (Basu et al., 2001), type I (Basu et al., 2005) and type II (Helmersson et al., 2004) diabetes mellitus; increased PGF\(_{2\alpha}\) was found in urine from population with hypercholesterolemia and smoking – the conditions associated with oxidative stress (Yin et al., 2007). Moreover, plasma PGF\(_{2\alpha}\) level in the elder man is positively related with common carotid artery intima-media thickness (CCA-IMT) (Wohlin et al., 2007) – a valid index of atherosclerosis. Moreover, a polymorphism in COX-1 gene (rs10306135) identified recently is associated with significantly decreased PGF\(_{2\alpha}\) and further lower susceptibility for cardiovascular disease (Helmersson et al., 2009). Hence, PGF\(_{2\alpha}\) may be involved in initiation and progression of chronic cardiovascular diseases, such as atherosclerosis and hypertension.

**PHARMACOLOGY OF FP MODULATION**

Given the accumulating evidence pleading for the involvement of PGF\(_{2\alpha}\)/FP receptor response pathway in regulating ocular uveoscleral outflow and normal parturition as well as pathogenesis of hypertension and atherosclerosis, the exploration of novel compounds able to specifically stimulate or inhibit FP receptor will constitute promising therapeutic avenues.

Human FP receptors are expressed in the human ocular trabecular meshwork (Anthony et al., 1998) and topical exogenous PGF\(_{2\alpha}\) and FP agonists reduce intraocular pressure (IOP) in monkeys and humans without causing inflammation (Weinreb et al., 2002). Thus, FP agonists, latanoprost, bimatoprost, and travoprost, are used in the treatment of glaucoma and ocular hypertension (Ishida et al., 2006), although the precise mechanism by which they work is poorly understood. More directly relevant has been the suggestion that FP antagonism may delay luteolysis and uterine contraction during parturition (Bernal, 2001), with the potential to delay preterm birth (Olson, 2005). Until recently, AL-8810, reported 10 years ago, is the first described FP antagonist, albeit that it is a partial agonist (Griffin et al., 1999) with which there is much experience in model systems (Sharif et al., 2000; Hirst et al., 2005). Theratechnologies compound THG 113 tested as FP receptor blocker, inhibits the contractile activity of smooth muscle cells from mouse (Peri et al., 2002), sheep (Hirst et al., 2005), and human myometrium (Friel et al., 2005) in response to exogenous PGF\(_{2\alpha}\) in vitro probably through activating Ca\(^{2+}\)-activated K\(^+\) channel (BKCa; Doheny et al., 2007), and delays lipopolysaccharide (LPS)-induced preterm birth in mice (Peri et al., 2002), and lowers uterine electromyographic activity and delays RU486 (a progesterone receptor blocker)-induced preterm birth in sheep (Hirst et al., 2005). More recently, AS604872, another patented FP antagonist, was shown to be effective to delay preterm parturition in rodents (Chollet et al., 2007; Girillo et al., 2007). Thus, FP receptor could be a potential target for the pharmacological management of preterm labor. Given that renin is elevated in pregnancy-induced hypertension with decreased PGI\(_2\) biosynthesis (Fitzgerald et al., 1987), FP antagonist seems more suitable theoretically for management of pregnancy-induced hypertension with broad gestational benefits. However, further clinical investigation is required regarding therapeutic efficacy of FP antagonist in clinic.
CONCLUSION
In summary, PGFαα, an early focus of prostaglandin research has been quite neglected outside the field of reproductive biology in recent decades. However, emerging evidence, particularly from mice lacking its FP receptor, hint at its importance in BP regulation and atherosclerosis. PG1, a potent renin secretagogue, antagonism or deletion of its receptor (the IP) protects against high-renin hypertension in renoprival models of in rodents (Fujino et al., 2004), while accelerates atherosclerosis (Kobayashi et al., 2004). Thus, blockade of the FP may represent a novel therapeutic strategy in syndromes of renin dependent hypertension with a more cardioprotective profile than suppressing synthesis or disrupting activation of the PGI2 receptor (IP).

Given the use of FP agonists in the treatment of glaucoma, the synthesis of antagonists seems readily tractable. Such pharmacological probes will facilitate our determination of whether FP antagonists might have utility in a wide variety of cardiovascular disorders in the future.

ACKNOWLEDGMENTS
This work was supported by grants from Chinese Academy of Sciences (Knowledge Innovation Program O914X41281 and Talent 100 Program 2010OHPT10), Clinic Research Center at Institute for Nutritional Sciences, Shanghai Institutes for Biological Sciences (CRC20100007) and the Ministry of Science and Technology of China (2011CB503906).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.