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Renal FGFR1 signaling and blood pressure regulation

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Abstract

FGF-23 is a bone-derived hormone that regulates phosphate and vitamin D homeostasis through activation of FGFR/α-Klotho binary receptor complexes in the kidney. The association between elevated circulating FGF-23 concentrations and increased cardiovascular mortality, particularly in chronic kidney disease (CKD), has brought new interest in understanding FGF-23's on-target and off-target cardiovascular actions. Preclinical data indicates that FGF-23 administration to mice elevates blood pressure and causes left ventricular hypertrophy (LVH), but the mechanisms mediating FGF-23's hemodynamic effects and cardiotoxicity are the subject of controversy and debate. In this mini review, the role of FGF-23 and FGFR1 signaling in regulation of hemodynamic is discussed.

Keywords: FGF-23; FGFR1 signaling; Blood pressure; LVH

Introduction

Fibroblast growth factor (FGF) ligands produced in the kidney have paracrine/autocrine functions to regulate kidney development through heparin sulfate proteoglycan co-factor dependent activation of FGF receptors [1-12]. The fibroblastic growth factor signaling consists of 22 distinct ligands (designated FGF1–18, 20–23 in mouse, and FGF1–14, 16–23 in humans, with FGF15 being the rodent orthologous of human FGF19). Seven FGF receptors tyrosine kinases, including FGFRs 1b, 1c, 2b, 2c, 3b, 3c, and 4 that are derived from alternative splicing and have different FGF ligand affinities [1-4]. FGF ligands can be further classified as having auto-crine/paracrine effects mediated by heparin/heparin sulfate proteoglycans acting as co-factors for activation of cell-surface FGFRs by FGFs (i.e., FGF-FGFR-HS complexes) [5]. Whereas, FGF ligands also have hormonal actions, which includes FGF-19 and FGF-21 activation of FGFRs complexed to β-Klotho, and FGF-23 activation of FGFR 1,3 or 4 complexed with α- Klotho in target tissues FGF signaling in the adult kidney may also lead to hypertension, as evidenced by genetic association studies linking FGF1, FGF2 and FGF5 to hypertension in humans [13-15].

Local production renal FGF ligands regulate renal natriuretic peptide catabolism, the renin-angiotensin cascade and sodium handling [16-18]. We have discovered that fibroblast growth factor receptor 1 (FGFR1) in the kidney plays an important role in regulating blood pressure and cardiovascular homeostasis. Our lab pioneered the study of FGFR1 in kidney and defined the separate functions of FGFR1 in the renal proximal (PT) and distal tubules (DT). Most recently, we show that conditional deletion of FGFR1 in renal distal tubule (DT) of mice (FGFR1DT-cKO) results in down regulation of α-Klotho (α-Kl), ACE2 angiotensin I converting enzyme 2 (Ace2), and upregulation of Na-K-Cl cotransporter 2 (NKCC2) associated with hypertension (HTN) and left ventricular hypertrophy (LVH). Furthermore, we show that activation of FGFR1 by a FGFR1 activating antibody (R1MAb1) rescues both hypertension and LVH in a Phosphate regulating neutral endopeptidase (PHXE) gene mutation mouse (Hyp mouse), while FGFR1DT-cKO mice were refractory to R1MAb1

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treatment. These findings suggest that renal FGFR1 signaling involves a novel renal-cardio axis, which mediates blood pressure and cardiovascular function possible through regulation of α-Kl, NKCC2, and Ace2 in the kidney.

Role of FGF/FGFR signaling in cardiovascular disease

FGF23-induced hypertension and LVH

A new schema for understanding FGF-23's cardiovascular effects proposes the presence of a bone-renal-cardiac axis (**Figure 1**). In this model, FGF-23 production by osteoblasts in bone is stimulated by the RAAS, SNS and 1, 25 (OH) 2D (1,25D). In this model, FGF-23 activates FGFR4 in the absence of α-Klotho (α-KI) in the heart or FGFR1 in the presence of α-Kl in the kidney to induce left ventricular hypertrophy (LVH).

Indeed, increased circulating concentrations of FGF-23 are associated with hypertension, cardiovascular disease and increased mortality in CKD and the general population [19-26]. FGF-23 induced cardiotoxicity may be mediated through activation of FGFRs in the renal tubules leading to stimulation of Na reabsorption, suppression of Ace2, and/or reductions in 1,25D production that cause hypertension and LVH [19-23]. FGF-23 suppression of the secreted form of α-Kl (s-Kl) from the kidney has also been proposed to lead to LVH by upregulating TRPC6 in the myocardium [27, 28]. Kidney specific deletion of α-Kl causes salt-sensitive hypertension in mice [29]. Autocrine/paracrine FGF signaling in the kidney can also lead to hypertension. In this regard, there are genetic association studies linking FGF1, FGF2 and FGF5 to hypertension in humans [13-15]. Local renal FGFs are reported to regulate renal natriuretic peptide catabolism, the renin-angiotensin cascade and sodium handling [16-18]. Surprisingly little is known about the specific role of FGFR1 in regulating renal processes linked to hypertension and LVH.

Renal FGFR1 signaling and blood pressure regulation

A cardio-renal axis is an established physiological and pathological network where by the heart regulates kidney functions to maintain cardiovascular homeostasis [30]. In a recent study, we have first shown that FGFR1 loss of function in renal distal tubule causes hypertension and LVH through mechanisms, at least in part, including downregulation of renal Klohto, Ace 2 and upregulation of NKCC2in FGFR1DT-cKO mice [31].

Mice with global knockout of FGFR1 are embryonic lethality and conditional knockout of FGFR1 causes organ (tissue) specific developmental defects accordingly [9,32-38]. In contrast, selectively deletion of FGFR1 in the specific renal tubule segments mainly results in changes of physiological function in the kidney [39]. The data presented in our study further provide compelling evidence indicating that loss of FGFR1 signaling in the distal tubule of kidney shares common phenotypic disorders observed in the Klotho-deficient mice, including altered expression of ion transporter in kidney and development of LVH in heart [39-42].

FGFR inhibitors have been studied for FGFR-related cancer therapies. Inhibition of FGFR1 often causes high blood pressure and cardiovascular dysfunction [43]. We found that systemic blood pressure was significantly elevated in FGFR1DT cKO mice, accompanied by decrease in NCC and ACE2 expression, and increase in NKCC2 expression in the kidney, respectively. NCC is mainly expressed in distal tubule and FGF23 up-regulates NCC expression via FGFR1/αKlotho signaling [27]. Reduced renal NCC expression found in FGFR1DT cKO mice was likely due to the loss of FGFR1 in distal tubule. Decrease in renal ACE2 expression seen in FGFR1DT cKO mice may contribute to higher systemic blood pressure by elevating tissue and circulating levels of angiotensin II [44]. Marked increasing in tAL NKCC2 expression was likely an adaptive response to the loss of NCC in the distal tubule of kidney to maintain the sodium hemostasis. Elevated level of angiotensin II also stimulates NKCC2 activity in the kidney [45].

Kidney is the principal organ producing Klotho [42,46]. Klotho gene encodes membrane (α-KI) or secreted (s-Kl) protein through alternative transcriptional termination [47,48]. α-KIothois a single-pass type 1 trans-membrane protein consisting of two extracellular domains (KL1 and KL2) subunits. Membrane-bound αKlotho can be cleaved by a disintegrin and metalloproteinase (ADAM)10 and ADAM17. Cleavage of Klotho occurs at a site directly above the plasma membrane (α-cut) or between the KL1 and KL2 domain (β-cut), resulting in soluble full-length klotho (KI1 and KI2), and KL1, or KL2 fragments, respectively [49]. αKIotho is an essential co-receptor, which couples with FGFR1 for fibroblast growth factor-23 (FGF23) signaling [50]. Soluble full-length Klotho is also able to function as a FGFR1 co-receptor for FGF23 signaling [51].

Soluble Klotho present in the systemic circulation has been found to have a cardioprotection effect through inhibiting Transient receptor potential cation channel, subfamily C, member 6 (TRPC6) currents in cardiomyocytes by blocking phosphoinositide-3-kinase-dependent exocytosis of TRPC6 channels [52]. Kuwahara and colleagues have shown that expression of TRPC6 is increased in mouse hearts in response to activated calcineurin and pressure overload. TRPC6 also provide a positive regulatory circuit for calcineurin-NFAT signaling during pathologic cardiac remodeling and activation of β-MHC gene expression [53]. They further demonstrated that Cardiac-specific over expression of TRPC6 in Tg mice resulted in fatal cardiomyopathy coupled to a pronounced increase in expression of β-MHC, a sensitive marker for pathologic hypertrophy [53]. Consistently, we found that FGFR1DT-cKO mice had a decreased Klotho production in the kidney, an elevated expression of TRPC6 and constantly activated PLCγ signaling in the heart. However, the cause of increased cardiac PLCγ signaling in FGFR1DT-cKO miceremains to be determined.

It is also interesting to note that expression of FGFR2-4 is differentially regulated between the kidney and the heart of FGFR1DT-cKO mice (unpublished data). Deletion of FGFR1 in the distal tubule has no impact on FGFR2-4 expression in the kidney. However, expression of FGFR2-4 was significantly increased in the heart, in which we found no change in the expression of cardiac FGFR1. FGF23 has been found to promote LVH by activating FGFR4/PLCγ signaling, and expression of a constitutively active FGFR4 is sufficient to induce LVH in mice independently of FGF23 levels [54]. A recent study showed thatchronic induction of cardiac FGFR1 expression also resulted in a pathologic state with molecular and histologic characteristics of hypertrophic car-diomyopathy [55]. Whether elevated expression of FGFR2 and 3 play a role in LVH is unknown.

Current knowledge about the de novo mechanisms of causing LVH during CKD and solutions to the problem are limited. CKD is accompanied by an inevitable progressive derangement of mineral homeostasis, an imbalance between blood and tissue concentrations of phosphate and calcium, and changes in circulating levels of phosphotropic hormones [56]. The decrease in Klotho protein in the blood is an early event in CKD and is progressively reduced along with the decline of renal function. Low Klotho partially induces FGF23 resistance, causing an initial compensatory increase in blood FGF23 to maintain phosphate homeostasis. The increase in FGF23 decreases active vitamin D levels and is followed by elevation of PTH [57]. Interestingly, FGF23 null mice and Klotho null mice exhibit almost identical phenotypes [58,59]. Klotho is an anti-inflammatory modulator [60], while FGF23 has pro-inflammatory properties by stimulating macrophages TNFα production and impairing neutrophils recruitment through FGFR2-mediated signaling [51,61]. In vivo, FGF23 and Klotho ap-pear to act as “Yin and Yang” via interactions with FGFRs, by which to drive the actions of FGF23 signaling and mediates its physiological functions including maintaining phosphate and calcium hemostasis, or promoting excessive FGF23-induced pathophysiological events, such as cardiomyocytes hypertrophy and pro-inflammatory activities. Hence, completely dissecting the mechanisms of FGF23/FGFRs/Klotho axis in both physiological and pathophysiological conditions in vivo might provide insight for CKD treatments.

In summary, our studies have identified previously unknown, α-Klotho-independent functions of FGFR1 in the kidney distal tubule to regulate blood pressure and cardiac function. This suggest the presence of a novel renal-cardiac axis controlled by paracrine release of FGF ligands by the kidney. In contrast, our data and prior publications suggest that hormonal activation of FGFRs/α-Klotho binary complexes in the kidney by FGF-23 have effects opposite to activation of FGFR1 by locally derived FGF intrarenal ligands. α-Klotho independent functions of FGFR1 inhibition in the DT to cause hypertension in mice, may explain how pharmacological inhibition of FGFRs to treat cancer may cause hypertension in humans. Finally, drugs that activate FGFR1 in the DT might provide a novel mechanism to lower blood pressure.

Outlook

Critical barriers to further progress include: 1) gaps in our understanding of how renal FGFR1 signaling regulates blood pressure; 2) the need to determine the role of Klotho in FGFR1 mediated renal-cardio axis; 3) the necessity of defining the FGFs legend that directly mediates renal FGFR1 signaling and regulates hemodynamics in health and disease.

Approaches to answer these questionsare: 1) apply genetic modified mouse models and tubule specific anti-hypertension drugs to pinpoint the action site(s) for FGFR1 signaling regulation of blood pressure; 2) examine precise mechanism proposed to explain the role of renal FGFR1 signaling in Klotho’s cardiac effects, and 3) identify FGF legend that mediates FGFR1 hemodynamic effect.

Figures

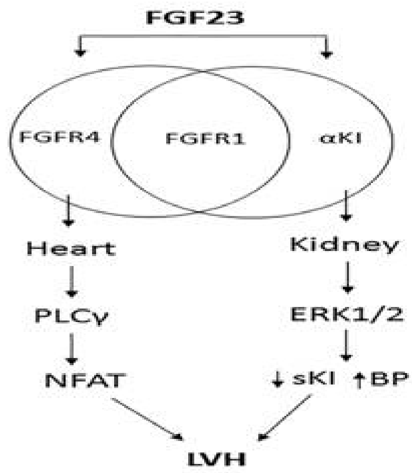

Figure 1: Schematic showing effects on hemodynamic response induced by paracrine FGF-23 activation of FGFR1 and FGFR4 in the kidney and heart leading to LVH, respectively.

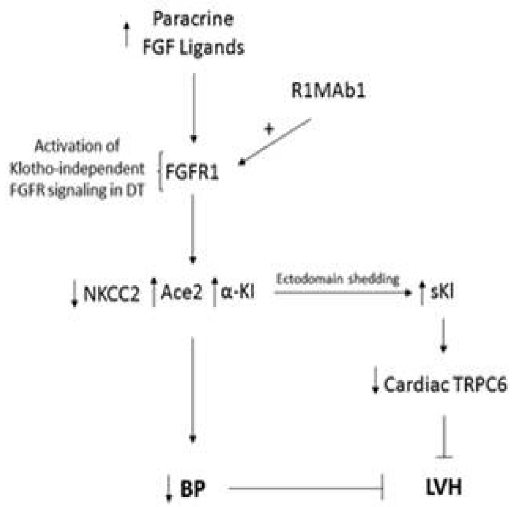

Figure 2: Schematic showing effects on hemodynamic response induced by paracrine FGF ligands activation of FGFR1 in the kidney leading to lowering blood pressure and blocking LVH, respectively.

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