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Cardiac Actions of Fibroblast Growth Factor 23

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Abstract

Fibroblast growth factors (FGF) are mitogenic signal mediators that induce cell proliferation and survival. Although cardiac myocytes are post-mitotic, they have been shown to be able to respond to local and circulating FGFs. While precise molecular mechanisms are not well characterized, some FGF family members have been shown to induce cardiac remodeling under physiologic conditions by mediating hypertrophic growth in cardiac myocytes and by promoting angiogenesis, both events leading to increased cardiac function and output. This FGF-mediated physiologic scenario might transition into a pathologic situation involving cardiac cell death, fibrosis and inflammation, and eventually cardiac dysfunction and heart failure. As discussed here, cardiac actions of FGFs - with the majority of studies focusing on FGF2, FGF21 and FGF23 - and their specific FGF receptors (FGFR) and precise target cell types within the heart, are currently under experimental investigation. Especially cardiac effects of endocrine FGFs entered center stage over the past five years, as they might provide communication routes that couple metabolic mechanisms, such as bone-regulated phosphate homeostasis, or metabolic stress, such as hyperphosphatemia associated with kidney injury, with changes in cardiac structure and function. In this context, it has been shown that elevated serum FGF23 can directly tackle cardiac myocytes via FGFR4 thereby contributing to cardiac hypertrophy in models of chronic kidney disease, also called uremic cardiomyopathy. Precise characterization of FGFs and their origin and regulation of expression, and even more importantly, the identification of the FGFR isoforms that mediate their cardiac actions should help to develop novel pharmacological interventions for heart failure, such as FGFR4 inhibition to tackle uremic cardiomyopathy.

Keywords

Cardiac hypertrophy; Chronic kidney disease; Fibroblast growth factors; Receptor tyrosine kinases; Uremic cardiomyopathy

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The effects of growth factors on the heart

Myocardial hypertrophy is an essential adaptive process through which the heart responds to various mechano-physical and metabolic stresses resulting in tissue protection and increased cardiac output (1). Dependent on the type of stress and the duration of stimulation, cardiac hypertrophy can become pathologic resulting in cardiac myocyte apoptosis and myocardial fibrosis and the development of heart failure (2, 3). The precise molecular events and cell types that contribute to the induction of the hypertrophic growth of cardiac myocytes and the activation of cardiac fibroblasts and to the transition from cellular protection to cell death are only poorly understood. Clearly, the development of pathologic cardiac hypertrophy is a complex process that involves a miscommunication between cardiac myocytes and fibroblasts, decreased capillary density, and actions of infiltrating monocytes (4, 5).

Several growth factors have been shown to be involved in the regulation of cardiac remodeling (6). Since shortly after birth cardiac myocytes become post-mitotic, one would assume that mitogenic growth factors do not directly target cardiac myoyctes, but rather affect the heart by inducing proliferation of cardiac fibroblasts (7). However since by contributing to cell survival and increased tissue mass and function, cellular hypertrophy in post-mitotic cells is similar to the proliferative state of dividing cells, it is possible that growth factors have direct pro-hypertrophic actions on cardiac myocytes and thereby regulate cardiac plasticity (1).

Among the many growth factors that employ receptor tyrosine kinases, only a few have been studied in regards to potential effects on cardiac myocytes. Insulin-like growth factor 1 (IGF-1) and its tyrosine kinase receptor, IGF-1R, have been shown to induce hypertrophy and promote survival of cardiac myocytes (8), which serves as a major mechanism for the induction of physiologic cardiac hypertrophy that elevates cardiac output in response to situations of increased demand, such as pregnancy or physical work-out (9, 10). Furthermore, neuregulin-1, a member of the epidermal growth factor (EGF) family and its tyrosine kinase receptor, ErbB2 (also known as HER-2 or c-neu), promote cardio-protection, including anti-apoptotic and pro-hypertrophic effects, and increase contractility of cardiac myocytes (11–14). This mechanism serves as an explanation for the clinical observation that cancer therapy against ErbB2 with trastuzumab (Herceptin) is often associated with the induction of cardiac dysfunction (15, 16). Finally, several members of the family of fibroblast growth factors (FGF) have also been shown to be involved in the regulation of cardiac remodeling (17), as discussed in detail here.

An introduction to fibroblast growth factors

The protein family of fibroblast growth factors (FGF) consists of 22 members (18) with varied functions dependent on their target tissue (19). The name of the family seems to be misleading since not all of its members can induce proliferation and survival in fibroblasts. Some seem to not even target fibroblasts at all, but promote growth of other cell types. Other members seem to lack any mitogenic activity, and rather induce cell migration or differentiation or regulate other cell type-specific functions, thereby lacking the defining feature of growth factors. Being a member of the FGF family is not defined by similarities in

cellular actions, but is determined by the presence of an about 120 amino acid-long intrinsic protein domain that mediates FGF binding to a particular family of cell surface receptors, called fibroblast growth factor receptors (FGFR).

The biological effects of FGFs on target cells are mediated by their interaction with one of the four widely expressed FGFR isoforms (FGFR1–4) which belong to the superfamily of receptor tyrosine kinases (20). FGFRs consist of three external immunoglobulin (Ig)-like domains, a transmembrane domain and an intracellular tyrosine kinase domain. The four FGFRs are encoded by separate genes, and alternative splicing within the third Ig-like domain, which results in b and c variants, increases the variety within the FGFR family. The different FGFR isoforms and splice variants show different ligand binding specificities, and the presence of specific FGFRs determine if a cell can respond to a particular member of the FGF family.

FGFs can have paracrine, endocrine or intracrine functions (21). Intracrine FGFs (i.e. FGF11, FGF12, FGF13 and FGF14) are not released from the producing cells and act as FGFR-independent intracellular signal mediators. Their main function is the regulation of voltage-gated sodium channels in neurons (22, 23). To activate FGFR-mediated signaling in cells, paracrine-acting FGFs, such as FGF2 (also called basic FGF or bFGF), must bind to heparin or heparan sulfate proteoglycans (HPG) that function as cofactors promoting the FGF:FGFR interaction (24–26). In contrast, endocrine FGFs, i.e. FGF19, FGF21 and FGF23, have reduced affinity for HPG due to topological differences in their heparin-binding region (27, 28). Therefore, these FGFs are not captured by extracellular matrices and they can function as circulating hormones. However, this feature also reduces the capacity of HPG to promote FGF binding to FGFRs (29). Instead, endocrine FGFs require klotho, a single-pass transmembrane protein, as a co-receptor on target cells for efficient binding to FGFRs (30, 31). While FGFRs are widely expressed, the restricted distribution of klotho defines only a few selected tissues as physiologic targets for endocrine FGFs (32, 33).

The complex formation of FGF:FGFR:co-factor in a 2:2:2 stoichiometry leads to the activation of specific signal transduction pathways that converge in the nucleus to induce changes in gene expression (20). Belonging to the superfamily of receptor tyrosine kinases (20, 34, 35), FGFR signaling is transduced by the cytoplasmic effectors, phospholipase Cγ (PLCγ) and FGF receptor substrate 2α (FRS2α) (20). Following ligand-induced auto-phosphorylation of FGFR, PLCγ binds directly to one specific phosphorylated tyrosine residue within a consensus YLDL sequence in the FGFR cytoplasmic tail (36, 37). Subsequent tyrosine phosphorylation on PLCγ results in full PLCγ activation by the receptor (38). Downstream signal transduction is mediated by PLCγ-catalyzed production of diacylglycerol and inositol 1,4,5-triphosphate (IP_3) that increases cytoplasmic Ca^{2+} levels and activates Ca^{2+}-regulated signaling such as the calcineurin/nuclear factor of activated T-cells (NFAT) pathway (20). FGFR signaling can also be transduced via activation of FRS2α by FGFR-mediated tyrosine phosphorylation. In contrast to PLCγ, FRS2α is constitutively bound to FGFR independently of the receptor's activation state (39). FRS2α-mediated signaling results in activation of Ras/mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3'-kinase (PI3K)/Akt signaling (20).

The role of fibroblast growth factor receptors in the heart

Several FGFR isoforms appear to be present in the heart. A global FGFR expression screen by quantitative real-time PCR (qPCR) has shown that FGFR1 seems to be the main isoform in the mouse heart, with no or very low expression of FGFR2, FGFR3 and FGFR4 (40). A qPCR analysis of cardiac myocytes that were isolated from adult mice showed a similar outcome (41). In the human heart, FGFR1 expression has been detected by qPCR and immunoblotting (42), and cardiac myocyte localization has been determined by immunohistochemistry (43). FGFR1 functions as the main receptor for FGF2 and isolated cardiac myocytes that overexpress FGFR1 can bind FGF2 (44). Studies using radio-labeled FGF2 indicated the presence of FGFR1 in the rat heart (45) and in isolated cardiac myocytes (46, 47). Interestingly, a transgenic mouse line with inducible cardiac-specific overexpression of a constitutively active FGFR1 mutant form develops cardiac hypertrophy (48). In this model, acute transgene expression rapidly increases cardiac contractility while chronic expression causes cardiac hypertrophy and fibrosis. Although the underlying signaling pathways in cardiac myocytes are not understood, this study showed for the first time that cell autonomous activation of FGFR signaling is sufficient to induce cardiac hypertrophy. Since isolated cardiac myocytes that overexpress FGFR1 produce and secret higher levels of FGF2 (44), it is possible that FGF2/FGFR1 signaling is part of a paracrine feed-forward mechanism that regulates cardiac function and remodeling under physiologic conditions, and might contribute to pathologic cardiac hypertrophy when out of balance and over-activated.

Although FGFR2 plays an essential role in proper cardiac development (49–51), it seems to be absent from the adult heart (40, 43). This is further supported by a qPCR analysis detecting FGFR2 in neonatal but not in adult cardiac myocytes isolated from mice (41). FGFR3 seems to be absent form the adult heart (40, 43), and from neonatal as well as adult cardiac myocytes (41). Although some Northern blot and qPCR analyses indicate the absence of cardiac FGFR4 expression in mice and humans (40, 52, 53), other studies could detect FGFR4 mRNA in the adult human heart (42). Furthermore, FGFR4 can be detected by immunohistochemistry in the adult human heart (41–43), and by Western blot analysis in the mouse and human heart (41, 42, 54). Although expression levels are low when compared to FGFR1, isolated cardiac myocytes from newborn as well as adult mice both express FGFR4 as revealed by qPCR (41). Furthermore, in the adult mouse heart FGFR4 is mainly expressed by myocytes, but not in non-myocytes including fibroblasts, as determined by flow cytometry analysis of isolated cardiac cell populations (41). Interestingly, a knockin mouse line that expresses a constitutively active FGFR4 mutant form at levels that are comparable to those of FGFR4 in wild-type mice (54), spontaneously develops cardiac hypertrophy (41). In these mice, cardiac calcineurin/NFAT signaling is elevated which might mediate the effect.

Overall it appears that in the adult heart FGFR1 is the predominant FGFR isoform that is expressed by different cell types, including high expression levels in cardiac myocytes. FGFR2 and FGFR3 seem to be absent while FGFR4 might be only present in cardiac myocytes and expressed at relatively low levels. Since activation of FGFR1 and FGFR4 per se appears to be sufficient to trigger pro-hypertrophic signaling and induce cardiac

remodeling, it might be operative in different forms of pathologic cardiac hypertrophy and heart failure. Furthermore, since FGF/FGFR signaling seems to play an important role in cardiac remolding, it is not surprising that the FGFR expression pattern is altered in response to cardiac stress and injury. This has been shown in rats where after myocardial infarct FGFR1 levels increase in the area of injury (45). Since in this model delivery of an FGF2-mutant with diminished affinity for FGFR1 is not cardio-protective (55), and administration of a pan-FGFR inhibitor prevents the cardio-protective effects of FGF2 (56), FGF2/FGFR1 signaling seems to play an important role in cardiac regeneration following infarction. Furthermore, in a Zebrafish model of cardiac regeneration following myocardial ablation, expression levels of FGFR2 and FGFR4 are increased (57). Finally, in cardiac hypertrophy associated with kidney injury (also called uremic cardiomyopathy and discussed in more detail below), cardiac FGFR4 and FGFR1 levels are significantly elevated in patients (42) and rat models (58), respectively. In this scenario, FGFR4 activation and subsequent PLCγ/calcineurin/NFAT signaling seems to promote cardiac hypertrophy (41, 59).

FGFRs are potent drug targets, and based on mitogenic effects of FGF/FGFR signaling pharmacologic FGFR inhibitors are used in cancer therapy (35). However, since pan-FGFR inhibition is toxic in humans (60, 61) and induces cardiovascular dysfunction in rats (62), the development of more targeted approaches to block the specific culprit FGFR isoform is necessary. To do so, it is inevitable to experimentally determine activation rather than expression of specific FGFR isoforms in the heart, since the receptor's activity state and expression level do not necessarily correlate with each other. This could be done by immunoprecipitation-immunoblot analysis of cardiac protein extracts to determine the degree of tyrosine-phosphorylation of specific FGFR isoforms. However, compared to qPCR expression analyses such protein-based assays are experimentally challenging and expensive. Cardio-protective effects of isoform-specific FGFR blockade have been shown for the first time in a rat model of uremic cardiomyopathy, where administration of an FGFR4-specific blocking antibody prevented the development of cardiac hypertrophy and fibrosis (41).

The effects of paracrine fibroblast growth factors on the heart

Among the paracrine-acting FGF family members, FGF2 seems to play an important role in the regulation of cardiac remodeling (63–65). Several studies have reported that FGF2 induces hypertrophic growth of cultured cardiac myocytes (66–70). Since FGF2 induces a switch in expression of β-myosin heavy chain from the adult to fetal isoform (66), it seems that FGF2-mediated hypertrophy is pathologic. However, since FGF2 treatment of cardiac myocytes increases intracellular calcium levels and contraction (71), it is likely that FGF2 can also induce transient physiologic hypertrophy. In addition, FGF2 has protective and anti-apoptotic effects in cultured cardiac myocytes (72). As reported in other cell types, FGF2 activates MAPK signaling in cardiac myocytes (69, 73–76), which has been shown to contribute to cardiac hypertrophy in a variety of animal models (77). Furthermore, in cardiac myocytes and isolated hearts FGF2 induces calcium-mediated signal transduction, including activation of PLCγ, IP_3, calcineurin and protein kinase C (71, 72, 74, 75, 78–80), which are also major inducers of cardiac hypertrophy (3).

Although FGF2 has clear hypertrophic effects in cardiac myocyte cultures, transgenic mice with global or cardiac-specific overexpression of FGF2 (75, 76, 81) and rats that received systemic infusions of recombinant FGF2 (82) do not develop cardiac hypertrophy, indicating that FGF2 per se cannot induce cardiac hypertrophy in vivo. Instead, FGF2 seems to modify cardiac remodeling in response to other stress or injury stimuli. Several stimuli that induce pathology cardiac hypertrophy have been shown to elevate FGF2 expression in cardiac myocytes, including angiotensin II (AngII) (69), aldosterone (83), as well as α1- and β-adrenergic agonists (84, 85). Overexpression of FGF2 in transgenic mice exacerbates hypertrophy due to β-adrenergic stimulation (76, 86), while FGF2 knockout mice are protected (76). Furthermore, FGF2 knockout mice are protected from pathologic cardiac hypertrophy induced by pressure overload (87) or hypertension (69). These in vivo studies indicate that cardiac FGF2, although not a potent inducer of cardiac remodeling by itself, mediates the development and progression of pathologic cardiac hypertrophy in the presence of other stress stimuli.

As a potent inducer of fibroblasts proliferation and survival, FGF2 might also contribute to pathologic cardiac remodeling by promoting cardiac fibrosis. Indeed, it has been shown that compared to wild-type mice, FGF2 deficient mice develop less fibrosis when challenged by coronary ligation (88). Furthermore in response to AngII, cardiac fibroblasts release FGF2 that in an autocrine manner induces fibroblast activation and in a paracrine manner causes hypertrophic growth of cardiac myocytes (70). Since transgenic mice with FGF2 overexpression have more infiltrated leukocytes in the heart (86, 89), and in the hypertrophic heart FGF2 expression correlates with levels of inflammatory cytokines (83), FGF2 might contribute to cardiac injury by inducing local inflammation. Finally, FGF2 might harm the heart via systemic effects. Global FGF2 knockout mice are hypotensive (90, 91) indicating that FGF2 might elevate blood pressure and thereby contribute to cardiac remodeling.

In contrast, several other studies indicate that FGF2 does not promote pathologic cardiac remodeling but is rather cardio-protective. Mechanical activity can induces the release of FGF2 from cardiac myocytes evoking a paracrine hypertrophic response (67, 85), indicating that FGF2 might be part of a paracrine mechanism that increases cardiac function. One study reported that transgenic FGF2 mice are actually protected from pathologic cardiac hypertrophy following isoproterenol injections for continuous β-adrenergic activation (89). Furthermore, many studies in different animal models as well as ex vivo models for ischemia-reperfusion injury and cardiac infarct have shown that elevating FGF2 is cardio-protective and increases resistance to injury as well as the healing process (56, 75, 81, 92–96). In this context, FGF2 might induce hypertrophy in the non-infarcted myocardium and actually prevents from cardiac fibrosis (95, 97, 98). Since cardiac FGF2 expression is elevated following ischemia-reperfusion injury (45, 95), FGF2 might be part of a paracrine mechanism that protects from ischemic heart damage. Interestingly, FGF2 seems to also promote the differentiation of cardiac precursor cells into functional cardiac myocytes in the adult heart thereby potentially contributing to cardiac repair (99). Besides directly targeting myocytes, beneficial cardiac effects of FGF2 might also involve FGF2's function as a potent stimulator of neovascularization. FGF2 transgenic mice show increased capillary density in the myocardium (75), and FGF2-mediated reduction in infarct size in animal models

involves increased cardiac angiogenesis and improved coronary flow (45, 79, 93–95, 100, 101).

Several, if not all cell types in the heart, including cardiac myocytes and endothelial cells, express FGF2 under normal conditions (65, 102–104). Surprisingly, global FGF2 knockout mice are viable and fertile and exhibit no baseline alterations in cardiac function and structure (76, 81, 87, 91). Therefore, FGF2 seems to be dispensable for proper development and regulation of the heart. Alternative, upregulation of other FGF members could compensate for the loss of FGF2 expression, but experimental evidence is missing. Instead cardiac FGF2 seems to come into action in the presence of other primary stimuli, and then contributes to protective or pathologic effects. If FGF2's action are beneficial or harmful might depend on the inducing stimulus as well as the precise levels and duration of FGF2 expression. Furthermore, the precise cell type(s) of FGF2 origin as well as the target cell type(s) for FGF2 actions within the heart have not been determined. Clearly, animal models with cell-type specific deletion of FGF2 as well as its receptor(s) are necessary to better understand the precise order and nature of cardiac events.

FGF1, also called acidic FGF or aFGF, and like FGF2 a prototypical paracrine FGF with mitogenic effects on fibroblasts, is also expressed and released by cardiac myocytes (65, 85, 102, 103). Although FGF1 activates MAPK and PLCγ signaling in cultured cardiac myocytes (41, 73), it seems that it cannot induce hypertrophic myocyte growth in vitro (66). It is not known if FGF1 has hypertrophic effects in vivo and/or affects cardiac remodeling that is induced by other stimuli. As shown for FGF2, cardiac expression levels of FGF1 are also elevated in animal models of myocardial infarct that is associated with angiogenesis and repair (45, 105). Experimental elevation of cardiac FGF1 in animal models for myocardial infarct seems to reduced infarct size, suggesting cardio-protective actions of FGF1 (45), but precise underlying mechanisms are not understood.

Similarly, myocardial elevation of FGF5 expression induces cardiac hypertrophy and improves cardiac function in an animal with hibernating myocardium (106). Interestingly, hypertrophic growth of cardiac myocytes rather than angiogenesis appears to be responsible for beneficial effects. FGF9 seems to be another paracrine FGF family member that promotes myocardial vascularization and remodeling. Conditional overexpression of FGF9 in adult mice induces cardiac hypertrophy, and following infarct transgenic mice show cardio-protection including increased microvessel density, reduced fibrosis and increased survival (107). Interestingly, FGF9 per se cannot directly induce hypertrophy in isolated cardiac myocytes, but rather promotes hypertrophic myocyte growth by target endothelial cells. Since the normal and infarct heart expresses FGF9 only at low levels (108), it is thought that FGF9 release by infiltrating bone marrow cells mediates adaptive cardiac hypertrophy following myocardial infarct (107). Finally, FGF16 seems to be predominantly expressed in the adult heart (109) where it has cardio-protective effects (110). Similar to FGF2 knockout mice, AngII-induced cardiac hypertrophy and fibrosis is increased in mice lacking FGF16 (111).

Besides its essential role in proper cardiac development (112), the family of FGFs seems to have important regulatory functions in the adult heart. However, if FGFs regulate cardiac

remodeling under physiologic conditions or modulate cardiac remodeling in the context of cardiac stress contributing or protecting from injury is not entirely clear. Underlying molecular mechanisms of FGF actions are not well understood. Precise origin of FGF production and release within the heart or from infiltrating cells as well as the precise target cell types for FGFs are not well described. If FGFs can directly induce hypertrophic growth of cardiac myocytes and/or can target fibroblast and promote fibrosis or alter the communication between fibroblasts and myocytes is unclear. Since many FGFs promote angiogenesis some of the family's cardiac effects might be caused by increased vessel density.

The role of endocrine fibroblast growth factors as metabolic regulators

The three endocrine FGFs, termed FGF19, FGF21 and FGF23, have important and distinct metabolic functions that are mediated by FGFRs as well as klotho co-receptors on their specific target organs (113, 114). α-klotho serves as the co-receptor for FGF23 (32), and β-klotho as co-receptor for FGF19 and FGF21 (115). Whereas FGFRs are broadly expressed across tissues, klotho co-receptors have a more restricted expression pattern thereby conferring tissue-specificity to the action of endocrine FGFs resulting in specific physiologic effects (116).

FGF19 is a hormone that regulates diverse aspects of the postprandial response (117). Expressed in enterocytes of the small intestine, FGF19 acts on the liver to repress bile acid synthesis and gluconeogenesis. FGF19 directly targets hepatocytes via FGFR4 and β-klotho resulting in the activation of MAPK signaling (116, 118–120). In addition to its beneficial effects on liver metabolism, FGF19 also stimulates hepatocyte proliferation, and chronic exposure of mice to FGF19 results in hepatocellular carcinomas (121, 122).

FGF21 is an adipokine that is mainly produced by hepatocytes (123). FGF21 binds β-klotho in complex with FGFR1, 2 and 3, but not with FGFR4, and thereby activates the Ras/MAPK signaling cascade (116, 124, 125). Knockout studies in mice suggest that the FGFR1 isoform is particularly important for the in vivo actions of FGF21 (126, 127). Furthermore, studies with global β-klotho knockout mice showed that β-klotho is essential for the physiological functions of FGF21 (124, 125). FGFR1/β-klotho in adipocytes and in neurons of the hypothalamus serves as the main target receptor for FGF21 (117).

FGF21 regulates important aspects of metabolism and energy homeostasis in response to nutritional stress by primarily acting on white and brown adipose tissue (117). Hepatic and serum FGF21 levels rise in response to starvation that results in an increase in insulin sensitivity and increased glucose uptake and fatty acid storage in adipocytes (117). Furthermore, FGF21 induces browning of white adipose tissue and thermogenesis (128). FGF21 has also dramatic effects on liver metabolism including the induction of fatty acid oxidation, ketogenesis and gluconeogenesis, as well as the suppression of lipopgenesis (129–131). However, since the liver only expresses FGFR4 (132, 133), whereas FGFR1 in concert with β-klotho function as the FGF21 receptor (116), hepatic effects of FGF21 appear to be indirect (117). Overall, FGF21 has beneficial metabolic actions. FGF21 lowers circulating and hepatic triglyceride and cholesterol concentrations, reduces blood glucose

levels, causes weight loss and increases life span (117). Serum FGF21 levels are elevated in diabetic animal models and in patients with type-2 diabetes (134–139) as well as in obese rodents and humans (137, 140, 141). Since FGF21 has beneficial metabolic effects by increasing insulin sensitivity and reducing serum glucose levels (117), FGF21 elevations in these scenarios most likely have compensatory effects. However, diabetes and obesity may reflect an induced state of FGF21 resistance where expression levels of β-klotho are reduced and the organism cannot longer respond to circulating FGF21 (142).

FGF23 is a bone-secreted hormone that lowers serum phosphate levels (143). In the kidney and parathyroids, the classic target organs for FGF23, the hormone binds FGFR/α-klotho co-receptor complexes (30, 32). Knockout studies have shown that FGFR1 is the main FGFR isoform that mediates physiologic effects of FGF23 (144, 145), but FGFR3 and FGFR4 seem to be also involved (146–148). As shown in mice lacking α-klotho, renal α-klotho is required for FGF23's phosphaturic actions (149, 150).

FGF23 is primarily secreted from osteocytes in response to dietary phosphorus loading or high serum phosphate and vitamin D levels (151). FGF23's endocrine effects on phosphate metabolism include: (i) Decreasing the activity of sodium-phosphate cotransporters, NaPi-2a and NaPi-2c, in the kidney proximal tubule leading to increased urinary phosphate excretion (152). (ii) Down-regulating the expression of 1α-hydroxylase, the enzyme responsible for synthesizing 1,25-dihydroxyvitamin D_3 (calcitriol) from its precursor and concurrently up-regulating the expression of 24-hydroxylase, the enzyme that inactivates calcitriol, in the proximal tubule (152). (iii) Inhibiting the secretion of parathyroid hormone (PTH) from the parathyroid gland (33). Taken together, FGF23 induces a negative phosphate balance by functioning as a phosphaturic hormone and inhibitor of vitamin D, which leads to decreased absorption of phosphorus in the gut (153–155). As an overall physiological effect, FGF23 reduces phosphate absorption from the intestine and increases phosphate excretion by the kidney. These FGF23-mediated processes also help to prevent overt hyperphosphatemia early in the course of diminished renal function.

The effects of endocrine fibroblast growth factors on the heart

By targeting the heart, endocrine FGFs could couple metabolic regulation with cardiac remodeling and thereby provide a signaling mechanism that induces adaptive alterations in cardiac structure and function in response to metabolic stress. However, since α-klotho and β-klotho, the established co-receptors for FGF23 and FGF19/21, respectively, are not expressed in the heart (40, 115), direct cardiac effects of endocrine FGFs are not expected. Nevertheless, recent translational studies have indicated that FGF21 and FGF23 can regulate cardiac remodeling, which might be at least partially due to their direct actions on the myocardium. Cardiac effects of FGF19 have not been reported to date.

It has been shown that short-term elevation of circulating FGF21 has cardio-protective effects in animal and ex vivo models of myocardial infarct, ischemia/reperfusion injury and β-adrenergic activation (156–160). In scenarios of cardiac injury, FGF21 enhances capillary density (158), inhibits inflammation (156, 158, 159, 161), promotes fatty acid oxidation (156, 161) and blocks lipid accumulation (162). In cardiac myocytes, FGF21 seems to

suppress oxidative stress (159) and apoptosis (157, 158, 161). Furthermore, cardiac myocytes secret FGF21 as an autocrine factor to protect themselves against oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress and hypertrophic stimuli and the heart from adverse cardiac remodeling (156, 159–161, 163). Although it has been originally reported that β-klotho is not expressed in the heart (40, 115), more recent studies showed expression of β-klotho and activation of Ras/MAPK and PI3K/Akt signaling following FGF21 stimulation in cardiac myocytes (156, 157, 160, 164). It seems that as in other established FGF21 target cell types, FGFR1/β-klotho mediates effects of FGF21 in cardiac myocytes. Future studies involving animal models with cardiac myocyte-specific deletion of FGF21 and the FGF21 receptor are needed to distinguish between cardiac effects that are mediated by FGF21's systemic metabolic versus direct cardiac actions and between the role of liver-derived, circulating FGF21 versus FGF21 that is produced in the myocardium.

Recent clinical studies have reported correlations between serum FGF21 levels and cardiovascular disease, such as hypertension (165), coronary artery disease (166, 167), acute myocardial infarction (168), atrial fibrillation (169) and atrial fibrosis (170). In patients with end-stage heart failure, serum and cardiac levels of FGF21 are significantly elevated (159), and circulating FGF21 concentrations correlate with cardiac hypertrophy and diastolic dysfunction (171). Combined these clinical observations suggest that FGF21 might be involved in pathological myocardial remodeling. This finding appears to be paradox to FGF21's cardio-protective effects in the described experimental studies and to its established beneficial functions in other tissues. Clearly, animal studies that describe the precise cardiac effects of FGF21 elevation in a time- and concentration-dependent manner as well as the identification and deletion of the putative FGF21 receptor(s) in cardiac myocytes are needed in order to determine if FGF21 effects on the heart are beneficial and/or pathological and occur in a direct and/or indirect manner.

Since serum levels of FGF21 are significantly elevated in diabetes, the potential role of FGF21 in associated cardiac pathologies, also termed diabetic cardiomyopathy, is of particular interest. In patients with type 2-diabets, serum FGF21 levels are associated with cardiovascular events and mortality (172, 173), indicating that FGF21 might contribute to cardiac injury. In contrast, in animal models of hyperglycemia, deletion of FGF21 exacerbates cardiac remodeling and dysfunction and cardiac myocyte apoptosis (162, 164), and elevation of FGF21 expression in the heart prevents cardiac fibrosis and inflammation (174). It is possible that as in other organs diabetes reflects an induced state of FGF21 resistance and that not direct pathological effects of FGF21 but rather the absence of its protective actions contribute cardiac injury. This is supported by a recent experimental study in an animal model for obesity with insulin-resistance, showing that long-term administration of FGF21 improves FGF21 sensitivity and attenuates cardiac dysfunction (161).

It has been recently shown that in the absence of α-klotho, FGF23 can elevate intracellular calcium levels in isolated cardiac myocytes as well as increase contractility in primary cardiac myocytes and ventricular muscle strips from mice (175). Whereas α-klotho-expressing cells respond to FGF23 by activating the Ras/MAPK cascade (30), FGF23 activates the PLCγ/calcineurin/NFAT signaling axis in myocytes thereby promoting cardiac

hypertrophy (41, 176). These in vitro findings have been supported by data derived from different rodent models with elevated serum FGF23 levels, such as injections of recombinant FGF23 in wild-type mice, renal ablation in rats, α-klotho deficiency in mice, and application of a high phosphate or adenine diet in mice, showing the development of cardiac hypertrophy (41, 176–178). This is the first example of a α-klotho-independent biological effect of FGF23 and suggests that the presence of α-klotho is not a prerequisite for FGF23-responsivness. It also indicates that the heart might be capable of directly responding to circulating FGF23 (179).

In vitro screens to identify FGFR isoforms that could mediate FGF23's α-klotho-independent signaling revealed FGFR4 as the mediating receptor (41). Deletion or blockade of FGFR4 protects cultured cardiac myocytes from FGF23-induced hypertrophy and mice with elevated serum FGF23 from developing cardiac hypertrophy (41). The finding that rodent models with elevated serum FGF23 as well as knockin mice with a constitutively active FGFR4 mutation and normal serum FGF23 (as described earlier) show increased cardiac PLCγ/calcineurin/NFAT signaling and develop cardiac hypertrophy (41), suggests that FGF23/FGFR4 signaling acts as a potent pro-hypertrophic signaling pathway in the heart.

Based on previous biochemical binding studies, the finding that in the absence of α-klotho FGFR4 but none of the other FGFR isoforms is activated by FGF23 is somewhat surprising. Surface plasmon resonance spectroscopy has revealed that FGF23 can bind FGFR4 with similar affinity as FGFR2c and with only slightly higher affinity than FGFR1c and FGFR3c (180). The low affinity of FGF23 for FGFR1c is increased by the presence of α-klotho by about 20 fold (181). The effect of α-klotho on FGF23's binding affinity for other FGFR isoforms has not been reported so far. Furthermore a functional in vitro screen has shown that at high treatment concentrations, FGF23 can induce cell proliferation to a similar degree in cells exclusively overexpressing FGFR1c, FGFR2c, FGFR3c or FGFR4 (180). Combined, these studies indicate that FGF23 can bind different FGFR isoforms, including FGFR4, with low affinity. However it remains unclear why within the FGFR family, FGFR4 would have the highest affinity for FGF23. It is possible that cells that lack α-klotho but can respond to FGF23 under pathophysiologic conditions, such as cardiac myocytes, express other co-receptor(s) for FGF23 binding that might specifically interact with FGFR4. However, to date such factors have not been identified.

The role of FGF23 in uremic cardiomyopathy

Chronic kidney disease (CKD) is a public health epidemic that affects approximately 26 million Americans and many more individuals worldwide (182). The presence of CKD increases risk of premature death, and cardiovascular disease is the leading cause at all stages of CKD (183). Although there is a high prevalence of conventional cardiovascular risk factors in the CKD population, the relationship between these factors and outcome is less clear than in the general population (184, 185). Hypertension is common in CKD, and it has been hypothesized that cardiac hypertrophy develops as a result of pressure overload (186). However, correction of hypertension in animal models with renal injury does not always prevent hypertrophy (187–189). Complications in mineral metabolism, including

elevated serum levels of phosphate and FGF23, are common in CKD and associate with cardiovascular disease, especially with cardiac hypertrophy, also termed uremic cardiomyopathy, and with mortality (176, 190–197). Based on the observed FGF23 effects on cultured cardiac myocytes, it is possible that elevated FGF23 might act as a causal factor in the pathogenesis of uremic cardiomyopathy thereby repositioning FGF23 from biomarker of risk to mechanism of disease.

As FGFR4 expression levels and NFAT activity are increased in cardiac tissue from individuals with CKD that had developed cardiac hypertrophy, when compared to CKD patients without cardiac hypertrophy (42), FGF23/FGFR4 signaling has emerged as a novel therapeutic target in CKD (41, 198). However, recent clinical and animal studies have shown that FGF23 reduction by phosphate binders and systemic FGF23 inhibitors lack sufficient safety and effectiveness (199, 200). Complete abrogation of FGF23 function causes severe hyperphosphatemia resulting in aggressive vascular calcification and increased mortality (200). In contrast, FGFR4 blockade might serve as a novel and safe pharmacological intervention for cardiac hypertrophy in patients with CKD (41). It is possible that FGFR4 blockade can selectively interfere with FGF23's pathological cardiac effects, while retaining the desirable physiological functions of FGF23 that are primarily dependent on FGFR1 (30, 31). In line with this hypothesis, constitutive FGFR4 knockout mice do not exhibit a severe phenotype (201, 202).

Recent research has revealed that several different cell types can respond to FGF23 (203, 204). Therefore, the generation of conditional knockout mouse lines for cardiac myocyte-specific deletion of FGFR4 and cardiac analysis following FGF23 elevation as well as co-culture studies using isolated cardiac myocytes in combination with non-myocytes, such as fibroblasts, will be necessary to determine if indeed cardiac myocytes serve as direct target for FGF23 and/or if other cardiac cell types receive the initial FGF23 hit and hypertrophic myocyte growth occurs secondarily in response to other events, such as fibrosis or angiogenesis. To date, it is not clear if FGF23 can target fibroblasts, in the heart or elsewhere, and if it has pro-fibrotic effects as some of the other FGF family members. It is also not established if FGF23 can directly target endothelial cells or vascular smooth muscle cells and contribute to cardio-angiogenesis, as shown for other FGF isoforms. Based on the cardiac actions of paracrine FGFs (as described above) it would be not surprising if FGF23 could also promote cardiac fibrosis and/or angiogenesis that could then contribute to FGF23-mediated cardiac remodeling. Furthermore, a genome-wide analysis of FGF23-regulated genes in mouse models with elevated FGF23 suggests inflammatory cytokine genes as FGF23 targets (205), and experimental studies have shown that FGF23 stimulates expression of inflammatory cytokines in macrophages (206, 207), spleen (208) and hepatocytes (204). Therefore, FGF23 might have general pro-inflammatory features that might contribute to cardiac inflammation associated with pathologic hypertrophy. If FGF23 can induce expression and secretion of inflammatory cytokines in cardiac cells such as myocytes and/or contributes to the infiltration and activation of inflammatory cells in the heart needs to be established.

Hypertension is a common feature of CKD and by itself a potent inducer of cardiac hypertrophy. Although some treatment studies in animal models of CKD show a reduction

of cardiac hypertrophy without lowering blood pressure (41, 59, 176, 198, 209–211), thereby uncoupling cardiac injury from hypertension in the context of kidney injury, it is most likely that in CKD increases in blood pressure together with a variety of other factors, such as serum elevations of FGF23 and uremic toxins (212), synergistically contribute to cardiac injury. In fact, FGF23 might directly contribute to hypertension by targeting the renal renin-angiotensin system (205) and by regulating renal sodium handling via targeting the distal tubules (213). Interestingly, a recent study indicates that FGF23's hypertensive effects might be required for the development of cardiac hypertrophy in mice (213).

Serum FGF23 levels do not only associate with cardiac hypertrophy in the CKD population, but also in cardiovascular cohorts with no or only slightly impaired renal function (214–219). Furthermore, elevated serum FGF23 levels associate with primary cardiac injury in a mouse model for myocardial infarct (220). These studies suggest that elevated serum FGF23 might contribute to primary cardiac injury in the absence of kidney injury. It this scenario an unknown endocrine heart-bone feedback mechanism might elevate FGF23 synthesis and secretion in bone following cardiac injury (219, 220). Since the injured heart releases pro-inflammatory cytokines, and inflammatory cytokines can directly increase production of FGF23 in bone (221–223), it is possible that such cytokines together with FGF23 serve as a bidirectional communication route between bone and heart that might provide the bone with the capability to regulate cardiac remodeling and vice versa enable the heart to control phosphate homeostasis. An alternative explanation for the source of FGF23 in the context of primary cardiac injury would be the existence of a paracrine mechanism in the heart. In fact, it has been shown that cardiac myocytes can produce FGF23, and that myocardial FGF23 levels are elevated in patients with dilated cardiomyopathy and ischemic heart disease as well as in mice with inflammatory heart failure (224, 225). Furthermore, systemic inflammation elevates FGF23 expression in cardiac fibroblasts (226, 227). Myocardial FGF23 expression has been also reported in patients with CKD, where levels positively correlate with the development of cardiac hypertrophy (42).

Overall, it seems that myocardial and circulating levels of FGF23 associate with cardiac hypertrophy in CKD and non-CKD. Future animal studies should aim to determine if paracrine and endocrine FGF23 differ in their ability to target the heart and to contribute to cardiac hypertrophy and heart failure. Furthermore, it appears that inflammatory cytokines and FGF23 together are part of positive regulatory cycle where FGF23 increases cytokine release in cardiac cells and macrophages and cytokines contribute to increased FGF23 production in bone and heart. The precise characterization of molecular and cellular events in relation to time and concentrations of FGF23 exposure will be necessary to determine if FGF23's cardiac effects are purely pathologic, or originally beneficial and eventually transition into maladaptive events. It would be interesting to determine if FGF23 can aggravate cardiac hypertrophy induced by other pathologic stimuli, or convey cardio-protection in the presence of cardiac stress stimuli, as shown for other FGFs and discussed above. Since in CKD serum and cardiac FGF23 levels correlate with serum phosphate (42), it is possible that hyperphosphatemia might serve as such a cardiac stressor, but precise actions of high phosphate levels on the myocardium are not well described.

Of note, since knockin mice with constitutive FGFR4 activation develop cardiac hypertrophy (41), it is possible that FGFR4 might serve as a novel drug target for the pathological hypertrophy associate with non-renal etiologies. If future studies can confirm that FGFR4 activation per se is sufficient to induce pathological cardiac hypertrophy and that cardiac FGFR4 activation is a feature in animal models of heart failure, it is possible that FGFR4 serves as a component of a novel hypertrophic signaling pathway that is generally activated in patients with heart disease marked by aberrant cardiac remodeling. In the United States, heart failure affects 5.1 million people, and each year 825,000 new cases are diagnosed (228). The prevalence and incidence of heart failure are increasing, because of increasing life span, the increased prevalence of risk factors (hypertension, diabetes, dyslipidemia, and obesity) and the improved survival rates from other types of cardiovascular disease such as myocardial infarction and arrhythmias. However despite current therapies, the 5-year mortality for heart failure remains 50%, making it necessary to derive new therapies for the treatment of cardiac diseases. FGFR4 blockade might serve as such a novel pharmacological approach.

A potential role of other FGF family members in uremic cardiomyopathy

Besides FGF23, also some of the other FGF family members have been linked to CKD. Cardiac expression of FGF2 is significantly elevated in a rat model of CKD, and treatment with the antioxidant apocynin reduces FGF2 expression as well as cardiac hypertrophy and fibrosis (229). Mice with global FGF2 deletion are protected from developing compensatory cardiac hypertrophy following surgically induced reno-vascular hypertension (69). Therefore, it is likely that cardiac FGF2 might directly contribute to uremic cardiomyopathy. Furthermore, it is possible that the two other members of the endocrine FGF subfamily, i.e. FGF19 and FGF21, can tackle the heart in the context of kidney injury. While experimental data to support such a hypothesis are still missing, clinical studies have shown that serum levels of FGF19 (230) and FGF21 (231–234) are elevated in CKD patients. One study also reported that serum FGF21 levels are higher in CKD patients with than without cardiac hypertrophy (235). It will be interesting to determine serum levels of FGF19 and FGF21 and associations with cardiac alterations in larger CKD populations and to experimentally determine their potentially direct actions on the heart as well as causality between serum levels and cardiac injury.

Conclusion

A variety of in vitro and in vivo studies have indicated that FGF/FGFR signaling provides an important base for the paracrine and endocrine regulation of cardiac remodeling. However, if these effects stem from direct activation the signaling system in cardiac myocytes is not fully understood. Since several FGF family members activate fibroblasts and induce angiogenesis and might also elevate blood pressure, FGFs have the potential to indirectly contribute to cardiac remodeling. If FGF/FGFR signaling per se can initiate changes in cardiac function and structure, or only modulates cardiac remodeling in concert with other cardio-toxic factors remains unclear. Furthermore, whether FGF/FGFR signaling fulfills physiologic functions in the heart or purely mediates pathologic effects leading to cardiac injury is not known. The precise characterization of cardiac events driven by FGF/FGFR activity is

necessary, in order to determine whether the development of pharmacologic agonists or antagonists for FGF/FGFR signaling is desirable. Most likely, the cardiac scenario depends on the nature of the underlying primary injury and the associated secondary pathologies. In recent years, this scenario has become clearer in uremic cardiomyopathy. Based on the strong associations between elevated serum FGF23 levels and cardiac injury in CKD and mechanistic studies showing that FGF23 can activate FGFR4 in the heart, FGF23 appears to be a major driver of uremic cardiomyopathy. Studies in uremic rodent models have indicated that pharmacological inhibition of all FGFR isoforms as well as specifically of FGFR4 protects the heart and even prevents or reverses cardiac injury. Therefore, FGFR4 blockade might appear as a novel cardio-protective therapy in patients with CKD. It will be worthwhile to experimentally determine the causative involvement of FGF signaling events in other cardiac pathologies, such as FGF21/FGFR1/β-klotho in diabetic cardiomyopathy, and FGF2/FGFR1 in the progression of pathologic cardiac hypertrophy to heart failure.

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ABBREVIATIONS

AngII	angiotensin II
CKD	chronic kidney disease
EGF	epidermal growth factor
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FRS2α	FGF receptor substrate 2α
HPG	heparan sulfate proteoglycans
IGF-1	insulin-like growth factor 1
IP_3	inositol 1,4,5-triphosphate
MAPK	mitogen-activated protein kinase
NFAT	nuclear factor of activated T-cells
PI3K	phosphatidylinositol 3'-kinase
PLCγ	phospholipase Cγ
PTH	parathyroid hormone
qPCR	quantitative real-time PCR

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Highlights

- FGFs functions as paracrine and endocrine modulators of cardiac structure and function.
- FGFs affect cardiac remodeling by activating fibroblasts and inducing angiogenesis.
- FGFs can also directly target cardiac myocytes and induce cardiac hypertrophy.
- By activating FGFR4, FGF23 contributes to uremic cardiomyopathy.