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Fibroblast growth factor 23: fueling the fire

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Abstract

In chronic kidney disease, systemic inflammation is common and associated with mortality. The present study demonstrates that fibroblast growth factor 23 (FGF23) contributes to uremic inflammation by increasing hepatic expression and secretion of inflammatory cytokines. FGF23 binds to hepatic FGFR4, inducing calcineurin/nuclear factor of activated T-cell signaling, resulting in increased expression of interleukin 6 and C-reactive protein. The proinflammatory effects of FGF23 are inhibited by an isoform-specific FGFR4 blocking antibody and by cyclosporine, a calcineurin inhibitor.

In chronic kidney disease (CKD), systemic inflammation is common, of multifactorial etiology, and associated with overall and cardiovascular mortality.[1] In the current issue of the journal, Singh *et al.* (2016)[2] implicates fibroblast growth factor 23 (FGF23) as an additional, novel factor contributing to uremic inflammation. Although higher FGF23 levels have been independently associated with higher levels of inflammatory markers in CKD patients,[3] in the current article, Singh *et al.*[2] demonstrate through a series of elegant *in vitro* and *in vivo* experiments that FGF23 directly induces hepatic expression and secretion of inflammatory cytokines.

First, primary mouse hepatocytes were isolated and characterized. These cells expressed only FGF receptor isoform 4 (FGFR4), and did not express α-klotho, the FGF23 coreceptor in the kidney. In this cultured hepatocyte model, FGF23 bound to and activated FGFR4, induced downstream calcineurin/nuclear factor of activated T-cell signaling, and increased expression and secretion of interleukin 6 and C-reactive protein (CRP). These effects were inhibited by administration of an isoform-specific FGFR4 blocking antibody (anti-FGFR4) or cyclosporine A, a calcineurin inhibitor, and were not observed in hepatocytes cultured from FGFR4 knockout mice (Figure 1).

These *in vitro* experiments were complemented by *in vivo* studies that included 4 different animal models, in which it was demonstrated that FGF23 increases hepatic and serum levels

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DISCLOSURE

All the authors declared no competing interests.

of inflammatory cytokines in an FGFR4-dependent manner. First, in wild-type mice, 5 days of recombinant FGF23 administration increased hepatic CRP expression, hepatic interleukin 6 expression, and serum CRP levels. Second, α-klotho null mice, which develop high FGF23 levels, were found to also have increased hepatic CRP expression, hepatic interleukin 6 expression, and serum CRP levels. Third, in wild-type mice, 12 weeks of a high phosphate diet induced elevated FGF23 levels and increased hepatic and serum CRP. However, FGFR4 knockout mice placed on the high phosphate diet did not display increased hepaticand serum CRP, despitea similar degree of serum FGF23 elevation, demonstrating the necessity of FGFR4 for FGF23-mediated induction of hepatic inflammatory cytokine expression.

Lastly, in the 5/6 nephrectomy rat model, Singh *et al.*[2] characterized the effects of pharmacologic blockade of FGF23-FGFR4 signaling. Compared with control animals, 5/6 nephrectomized rats had elevated FGF23 levels, increased hepatic CRP expression, and increased serum CRP. However, 5/6 nephrectomized rats treated with anti-FGFR4 did not have increased hepatic or serum CRP. Similarly, 5/6 nephrectomized rats treated with cyclosporine A did not have increased hepatic or serum CRP, despite a similar degree of serum FGF23 elevation as 5/6 nephrectomized rats treated with vehicle. These findings show that, in a well-established animal model of CKD, FGFR4 blockade or calcineurin inhibition decreases hepatic and serum CRP. The novel demonstration of FGF23-induced hepatic inflammation raises the intriguing question of whether FGF23 may be able to also induce the expression of inflammatory mediators in nonhepatic tissues.

Indeed, the liver is not the only organ in which FGF23 induces “off-target” effects. In groundbreaking work, Faul *et al.*[4] and Grabner *et al.*[5] have previously shown that, in the heart, FGF23 binds to FGFR4 independent of klotho, activating the calcineurin/nuclear factor of activated T-cell signaling pathway, resulting in cardiac myocyte hypertrophy. In the large Chronic Renal Insufficiency Cohort (CRIC), higher FGF23 levels are associated with increased left ventricular mass index and are independently associated with overall mortality.[4,6] As cardiovascular disease is the leading cause of death in CKD patients, the importance of FGF23-mediated pathologic effects cannot be overstated.

As FGF23-induced adverse effects in the liver and heart depend on FGFR4, the therapeutic promise of anti-FGFR4 is intriguing. Anti-FGFR4 inhibits FGF23-induced expression of hepatic inflammatory cytokines in cultured hepatocytes and decreases hepatic and serum CRP in rats with CKD.[2] Similarly, anti-FGFR4 reduces FGF23-induced hypertrophy of isolated cardiac myocytes and attenuates left ventricular hypertrophy in rats with CKD.[5] Certainly, it could be hypothesized that anti-FGFR4 treatment in CKD patients may result in less inflammation, less left ventricular hypertrophy, and improved cardiovascular outcomes.

Notably, the relationship between FGF23 and inflammation seems to be bidirectional, as it has been shown that acute and chronic inflammation increases bone FGF23 production.[7] Mechanistically, inflammatory stimuli both directly and indirectly increase FGF23 production via increased activity of hypoxia-inducible factor 1a. Inflammation directly increases transcription of hypoxia-inducible factor 1a, and also induces “functional” iron deficiency, which stabilizes hypoxia-inducible factor 1a.[7] Singh *et al.*[2] suggest that FGF23 and inflammatory cytokines may constitute a positive feedback loop in which FGF23-

induced inflammation in turn increases bone FGF23 expression, engendering a pathologic upward spiral resulting in massively elevated FGF23 levels. As such, it may be hypothesized that decreased FGF23-mediated hepatic inflammation may result in decreased osteocytic FGF23 production, lowering circulating FGF23 levels. However, in the CKD rat model used in the current study, although anti-FGFR4 and cyclosporine A reduced hepatic and serum CRP, circulating FGF23 concentrations did not significantly decrease. Yet, as noted by Singh *et al.*,[2] many factors affect FGF23 production in CKD, and inflammation-induced increases in bone FGF23 production may be dependent on different types of cytokines, varying degrees and durations of cytokine elevation, or a combination of these.

Demonstration that FGF23 directly induces inflammation in CKD only adds to the list of adverse effects and outcomes associated with elevated FGF23 levels in CKD, which includes mortality,[6] left ventricular hypertrophy,[4] CKD progression,[6] and, most recently, impaired neutrophil activation.[8] The growing body of literature linking elevated FGF23 levels in CKD with hard clinical endpoints underscores the critical need to develop and conduct well-designed clinical trials aimed at reducing FGF23-associated morbidity in CKD. Theoretically, this outcome may be accomplished by lowering or preventing pathologically high FGF23 levels, by blocking FGF23-FGFR4 signaling, or both. One such study that is currently underway is the CKD Optimal Management with BInders and NicotinamidE (COMBINE) study.[9] This randomized clinical trial will assess, in predialysis CKD patients, whether the early use of phosphate binders, with or without concurrent blockade of the intestinal sodium-phosphate cotransporter NPT2b, decreases serum phosphate and FGF23 concentrations and improves surrogate measures of cardiovascular disease, CKD progression, and inflammation. If the hypotheses of the COMBINE study are confirmed—that early phosphate binder therapy with or without NPT2b blockade improves the outcome measures—then the results may provide the basis for future clinical trials assessing the effects of such novel CKD–mineral and bone disorder treatment paradigms on hard clinical endpoints.

The central role FGF23 plays in various pathologic processes mediating CKD-associated morbidity and mortality is becoming more well defined. As such, FGF23 is clearly a very important factor in CKD–mineral and bone disorder—a syndrome encompassing and linking CKD-associated bone disease, hormonal alterations, and cardiovascular abnormalities—and a target worthy of therapeutic intervention. We eagerly anticipate the results of future basic science and translational studies of FGF23 in CKD, as well as clinical trials focused on strategies for reducing or preventing high FGF23 levels in CKD, all of which may help to improve clinical outcomes and quality of life for CKD patients.

Acknowledgments

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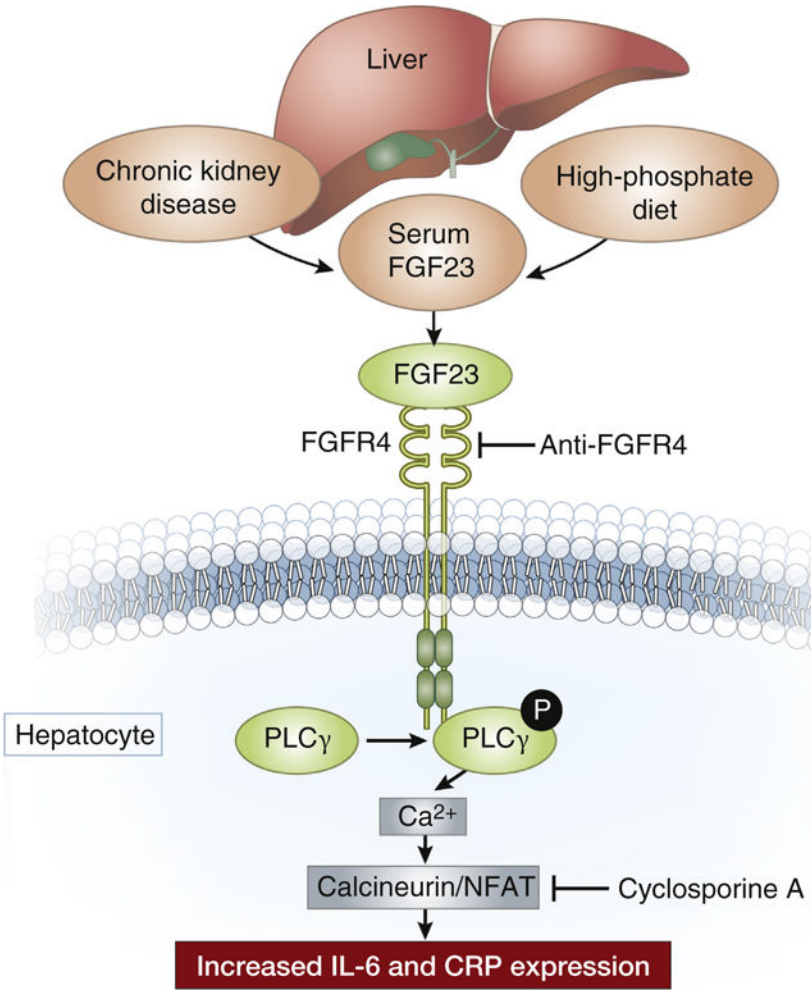

Figure 1. In hepatocytes, fibroblast growth factor 23 (FGF23) binds to and activates FGF receptor isoform 4 (FGFR4), inducing calcineurin/nuclear factor of activated T-cell (NFAT) signaling, resulting in increased expression of interleukin 6 (IL-6) and C-reactive protein (CRP)

These effects are blocked by anti-FGFR4 antibody and cyclosporine A, a calcineurin inhibitor. P, phosphate; PLC, phospholipase C. Figure adapted with permission from Grabner A, Amaral AP, Schramm K, et al. Activation of cardiac fibroblast growth factor receptor 4 causes left ventricular hypertrophy. *Cell Metab.* 2015;22:1020–1032. Copyright © 2015, with permission from Elsevier.[5]