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Causal Connections From Chronic Kidney Disease to Cardiac Fibrosis

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Summary: Cardiovascular disease and heart failure are the primary cause of morbidity and mortality in patients with chronic kidney disease. Because impairment of kidney function correlates with heart failure and cardiac fibrosis, a kidney−heart axis is suspected. Although our understanding of the underlying mechanisms still is evolving, the possibility that kidney−heart messengers could be intercepted offers ample reason to focus on this clinically highly relevant problem. Here, we review the current knowledge of how kidney injury causes heart failure and fibrosis.
Semin Nephrol 38:629−636 © 2018 Elsevier Inc. All rights reserved.
Keywords: Chronic kidney disease, cardiac fibrosis, endothelial-mesenchymal transition, fibroblasts, Klotho, phosphate

Patients with chronic kidney disease (CKD) are more likely to get heart disease, and in fact cardiovascular disease is the primary cause of morbidity and mortality in these patients, even by early stages of CKD.[1] Because approximately 35% of all individuals older than 70 years are affected by early stages of CKD, the health care burden is dramatic.[2] Although common comorbidities such as hypertension and diabetes undeniably contribute to both the progression of CKD and cardiovascular disease, the presence of CKD is an independent risk factor for cardiovascular morbidity and mortality, suggesting that mechanisms specific for CKD patients are at play. More specifically, CKD is linked to augmented atherosclerosis, arrhythmias, heart failure, and cardiac fibrosis. This review summarizes the current knowledge of CKD-associated heart failure and cardiac fibrosis.

CARDIAC FIBROSIS

Although all forms of chronic heart disease are associated with cardiac fibrosis, CKD patients are especially prone to cardiac fibrogenesis.[3] Several post-mortem studies have shown that the stage of CKD directly correlates to the extent of cardiac fibrosis.[4,5] Typically,

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Financial disclosure and conflict of interest statements: none.
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patients with CKD have significantly more fibrotic tissue in the heart as compared with subjects without CKD (Fig. 1).

Cardiac fibrosis in general is defined as a disproportional increment of the connective tissue compartment in the heart. Although all forms of chronic heart disease are associated with cardiac fibrosis, it may be of specific relevance in heart failure with preserved ejection fraction, contributing to increased stiffness and impaired diastolic filling of the heart.[6-8] Fibrosis is characterized by excessive accumulation of fibrillar extracellular matrix, rarefaction of microvessels, a sterile mononuclear infiltrate, and accumulation of fibroblasts, the main mediators of fibrosis.[5,6,8] As opposed to the essential process of scar formation after acute myocardial infarction, pathologic fibrosis is a continuous process affecting all areas of the heart, which also commonly is referred to as remodeling. Fibroblasts are the main source of extracellular matrix and thus mechanisms that induce extracellular matrix production by fibroblasts are of the highest interest.[8,9] Because not all fibroblasts proliferate, alternate sources contribute to accumulation of activated fibroblasts such as invasion of bone marrow−derived fibrocytes and conversion of endothelial cells into fibroblasts through a process termed *endothelial-mesenchymal transition* (EndMT). EndMT in the context of fibrosis first was identified in the heart.[10] In consecutive studies, EndMT also was found to contribute to fibrogenesis of other organs such as kidney, lung, and gut, and also to the tumor stroma.[11-14] Meanwhile, hundreds of studies have studied EndMT in different settings (and thus provided indisputable evidence for this process). However, controversy has arisen about when exactly EndMT happens and what the extent of EndMT (and its relevance) is in different models, which likely reflects the fact that EndMT is highly context-dependent and a process that is still only partially understood. Apart from the cellular source for fibroblasts, numerous mediators of cardiac fibrosis have been identified including growth factors (eg, transforming growth factor β1 [TGFβ1], connective tissue growth

factor [CTGF][15,16]), cytokines (eg, tumor necrosis factor-α [TNF-α], interleukin [IL]-1β[17,18]), and metabolic products (eg, the reduced form of nicotinamide adenine dinucleotide phosphate oxidases [NOXs], reactive oxygen species [ROS][19-21]). Because of the direct correlation of the degree of impaired kidney function and the severity of cardiac fibrosis, it is plausible that profibrotic mechanisms specific for chronic kidney disease exist, which are reviewed later.

EndMT AS A MODULATOR OF CARDIAC FIBROSIS AND VASCULAR LOSS

EndMT is a cellular transition process in which endothelial cells lose their endothelial characteristics and gain a myofibroblast-like phenotype. EndMT not only contributes to cardiac fibrosis,[10] but also plays a pivotal role in myocardial vascular loss owing to loss of microvascular density. EndMT is mediated by a set of master-transcription factors including Twist, Snail, and Slug.[22] Several stimuli have been identified to induce EndMT, including TGFβ1, which is abundantly present within the fibrotic microenvironment, and intrinsic mechanisms such as aberrant promoter methylation of Rasal1.[10,23] Because in patients with impaired kidney function the incidence of EndMT within the heart is 17% higher in comparison with healthy controls, it is tempting to speculate that a direct kidney−heart axis exists and that the chronically diseased kidney releases EndMT inducers.[5] In this regard, treatment of endothelial cells with serum derived from CKD patients resulted in a change toward a myofibroblast-like, spindle-shaped morphology and increased expression of EndMT transcription factors.[5] This indicates the presence of factors in the serum of patients with CKD that can induce EndMT.

Because TGFβ1 is an important profibrotic growth factor in heart and kidney, and because TGFβ1 is a well-established inducer of EndMT, it also is attractive to speculate that kidney-derived TGFβ1 is responsible for the EndMT observed in the heart of CKD patients. However, the literature is mixed with regard to increased TGFβ1 serum levels within CKD patients. Although in an African American study population TGFβ1 serum levels correlated with the incidence of CKD,[24] such correlation is not always observed.[25]

Nitric oxide (NO) is not only a modulator of vasodilatation but also of angiogenesis, the de novo development of new blood vessels, which has been linked to partial EndMT of the tip cells (the leading cells of vascular sprouts that mediate angiogenesis) and therefore NO could play a role in the EndMT phenotype induced by CKD. Indeed, in CKD the overall production of NO is decreased.[26] There are several factors such as the NO synthase inhibitor asymmetric dimethylarginine (ADMA) and the angiogenesis inhibitors

angiopoietin-2 (ANG-2), thrombospondin-2 (TSP-2), and endostatin, which are associated with lower NO levels and increased cardiovascular disease.[27-34] All of these factors are increased in the serum of CKD patients, and all could induce the expression of at least one of the EndMT transcription factors, indicating their involvement in EndMT.[5] The serum of patients with CKD also induced endothelial cell apoptosis in vitro, showing another mechanism that contributes to vascular loss.[5] Three of four factors that affect EndMT (ADMA, ANG-2, and TSP-2) also are responsible for increased endothelial cell apoptosis.[5] Altogether, this shows the interplay of NO and its regulators with EndMT, which contributes to both vascular loss and cardiac fibrosis in the context of CKD. Importantly, these results are in line with prior studies that showed that ADMA, ANG-2, and endostatin are increased in CKD and are associated with higher risks of cardiovascular and overall mortality.[29,34-37] High levels of circulating TSP-2 similarly are associated with a poor prognosis in patients with heart failure with preserved ejection fraction, a patient group in which CKD is common and cardiac fibrosis is an important pathomechanistic factor.[38-40] EndMT and fibrogenesis induced by these factors therefore at least may contribute to the observed increased overall mortality in patients with CKD.

OXIDATIVE STRESS AS INDUCER OF CARDIAC FIBROSIS IN CKD

CKD is characterized by enhanced ROS production in the kidneys and enhanced ROS levels in the plasma.[41,42] The presence of ROS is beneficial under physiological conditions, but growing evidence supports that pathophysiological accumulation of ROS (such as H_2O_2, O_2^-, OH, and $ONOO^-$) influences fibrotic remodeling.[43-45] ROS is produced not only as a by-product during oxidative phosphorylation in mitochondria, but also from a variety of enzymatic and nonenzymatic process such as xanthine oxidase, NOXs, cytochrome P450; by auto-oxidation of catecholamines; and by uncoupling of NO synthase.[44,46,47] Among the variety of ROS sources, the one generated by NOXs has gained much attention in fibrotic remodeling.[48,49] Of the seven members of this family, NOX4 (highly expressed in the kidney) and NOX2 (also expressed in the kidney, but may be compensated by NOX4) are studied predominantly.[50] In cardiac fibroblasts, NOX2-induced ROS accumulation together with TGFβ drives fibrotic progression via up-regulation of collagen I and II.[19,49,51] Moreover, NOX4−Smad family member (Smad) 2/3 signaling also is involved in driving fibrotic progression of cardiac fibroblasts and NOX4 induces cardiac fibrosis via nuclear factor κ light-chain-enhancer of activated B cells signaling, a signaling pathway also important in inflammation.[52] In addition to
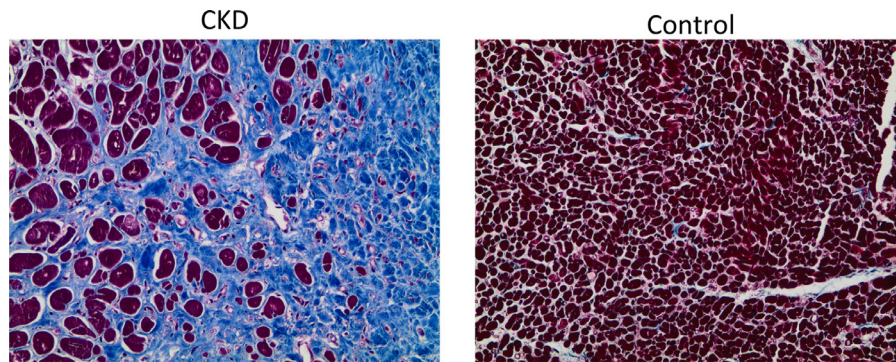
Figure 1. Representative light microscopy images from post-mortem heart tissue from a patient with CKD (left) and a control subject without CKD (right). Heart tissue was stained for collagen (in blue) by Masson trichrome staining. CKD patients show more fibrosis in the heart compared with non-CKD subjects.

cardiac fibroblasts, ROS also affects endothelial cells. Endothelial-specific overexpression of NOX2 in an angiotensin II−induced fibrotic mouse model results in enhanced EndMT, thereby exacerbating cardiac fibrosis.[53] Interestingly, NOX4 expression in endothelial cells mediates protection against fibrotic remodeling in transverse aortic constriction mouse models of cardiac fibrosis.[54] This indicates that NOX4 has a cell-specific role in mediating cardiac fibrosis: NOX4 drives fibrosis progression in cardiac fibroblasts whereas NOX4 expression in endothelial cells has a protective role. It is important to note that the ROS-induced changes in cardiac fibrosis have been studied only in mouse models of cardiac fibrosis to date and not in mouse models of chronic kidney disease. However, because there is increased ROS production in the kidney and increased ROS levels in the plasma of CKD patients, it is plausible to speculate that

the circulating ROS levels affect the endothelial cells and cardiac fibroblast activation in the heart.

ACTIVATION OF THE RENIN-ANGIOTENSIN SYSTEM IN CKD

Hyperactivity of the renin-angiotensin system is associated with CKD.[55] In short, angiotensinogen is produced by the liver and is converted into angiotensin I by renin, and further converted into angiotensin II by angiotensin-converting enzyme. Angiotensin II is responsible for systemic arterial vasoconstriction and the release of aldosterone, resulting in increased systemic blood pressure. Chronic activation of the renin-angiotensin system is known to result in both myocardial fibrosis and inflammation, and therefore is very likely involved in CKD-associated cardiovascular
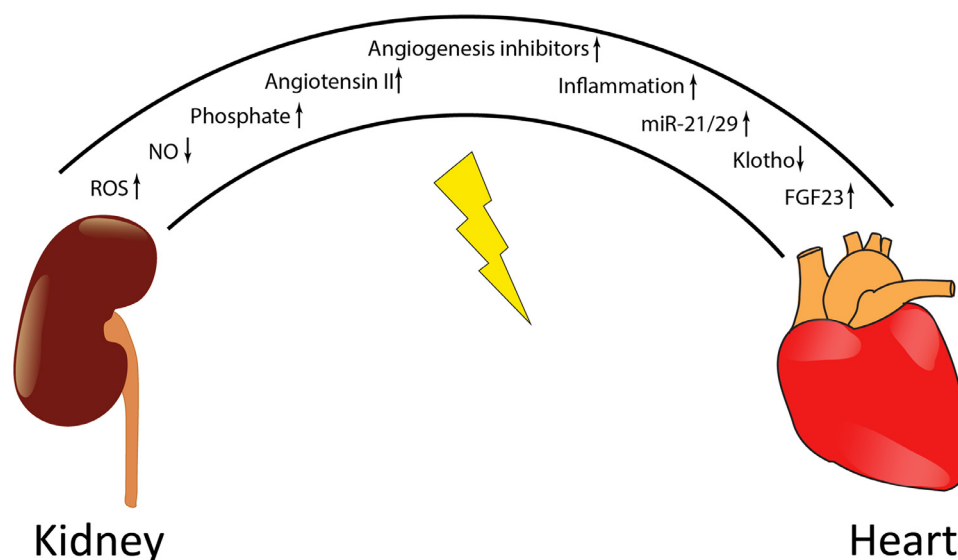
Figure 2. Mediators of CKD-associated cardiac fibrosis. The mediators of CKD-associated cardiac fibrosis include increased levels of ROS, phosphate, angiotensin II, angiogenesis inhibitors, inflammation, FGF23, microRNA-21 (miR-21) and microRNA-29 (miR-29), and decreased levels of NO and Klotho. The lightning bolt indicates damage.

disease and angiotensin II−releasing pumps are used to induce both kidney and heart fibrosis in mice.[49] Although hyperactivity of the renin-angiotensin-aldosterone system (RAAS) typically is associated with increased blood pressure, local blood pressure−independent mechanisms contribute to the profibrotic activity of RAAS. One of the underlying mechanisms of angiotensin II−induced cardiac fibrosis is NOX2-mediated perivascular fibrosis via the production of ROS.[53] NOX2 also is important in the angiotensin II−induced expression of adhesion molecules on endothelial cells, which are responsible for leukocyte attachment to the endothelium and subsequent perivascular infiltration.[56] Knockout of NOX2 attenuated angiotensin II−induced myocardial fibrosis in mice, indicating its importance in facilitating myocardial fibrosis.[57] Whether angiotensin II and NOX2 induce cardiac fibrosis in the context of CKD has yet to be established. Nevertheless, this indicates the synergistic effect of angiotensin II and NOX2 in mediating cardiac fibrosis, and underlines the possible link of both mediators with inflammation.

INFLAMMATION AS A MODULATOR OF CARDIOVASCULAR DISEASE

Inflammation is an important mediator of both CKD and cardiovascular disease, and therefore could represent a mechanism by which CKD induces cardiovascular disease. In CKD, a spectrum of proinflammatory and anti-inflammatory cytokines are secreted into the circulation and thereby influence pathologic remodeling in the heart. One example is NACHT, LRR, and PYD domain-containing protein 3 (NLRP3), a cytokine that is more abundant in the circulation during CKD and that, together with other molecules, can activate the proinflammatory cytokines IL-1β and IL-18.[58] Oral administration of theracurmin, a novel formulation of curcumin (a naturally occurring chemical compound that is found in the spice turmeric with antioxidant and anti-inflammatory properties), in a rat model of subtotal nephrectomy (which induces cardiac fibrosis and diastolic dysfunction) decreases NLRP3 expression and thereby reduces proinflammatory IL-1β levels in the heart.[58] In addition, theracurmin-induced inhibition of NLRP3 resulted in decreased expression of collagen type 1 (an extracellular matrix protein involved in fibrosis) and decreased phosphorylation of Smad2 (a protein involved in canonical TGFβ1 signaling) in the heart.[58] Together, this results in decreased cardiac fibrosis and decreased expression of TGFβ1, an important modulator of fibroblast activation and EndMT.[58] This indicates that individual components of inflammation can contribute to cardiovascular disease in the context of CKD. What should be noted is that additional but as yet unknown mechanisms of theracurmin also could be responsible for the antifibrotic effect

observed in the heart. Interestingly, theracurmin does not influence kidney fibrosis, indicating that NLRP3 specifically targets the heart.[58]

It also has been reported that circulating proinflammatory TNF-α receptors are associated with cardiovascular disease in the context of CKD.[59] Interestingly, TNF-α has been described to be involved in ROS, mitogen-activated protein kinase (MAPK) cascade, and the renin-angiotensin system, underlining the link between oxidative stress, inflammation, and the renin-angiotensin system.[60-62] This indicates that TNF-α and its receptors could have pleiotropic functions in facilitating cardiovascular disease in the context of CKD. Interestingly, both proinflammatory IL-1β and TNF-α can induce the expression of another proinflammatory cytokine: IL-33. IL-33 is expressed in both cardiac endothelial cells and cardiac fibroblasts, suggesting an essential role of IL-33 in modulating cardiovascular disease in the context of CKD.[63] IL-33 activates the MAPK signaling pathways, which in turn activates the proinflammatory nuclear factor κ light-chain−enhancer of activated B cells signaling.[64] Interestingly, IL-33 has been shown to induce endothelial dysfunction by promoting inflammatory infiltration (via increased intracellular adhesion molecule expression) and increased endothelial permeability (via decreased vascular endothelial cadherin [VE-cadherin] expression), resulting in adverse myocardial remodeling.[65] Decreased VE-cadherin expression is also a sign of EndMT, suggesting IL-33 can influence EndMT directly. This shows that besides NLRP3 and TNF-α receptors, IL-33 also has pleiotropic functions in the heart, suggesting that inflammation is an important component of CKD-induced cardiovascular disease. Other examples of up-regulated proinflammatory cytokines are C-reactive protein, pentraxin 3, and IL-6, whereas the anti-inflammatory cytokine IL-10 also is up-regulated in the context of CKD.[66-68] These cytokines all are associated with the risk of cardiovascular events in CKD patients and therefore are likely to impact the heart.[67,68] In mice, C-reactive protein and IL-6 both have been described to promote cardiac fibrosis,[69,70] whereas IL-10 has been described to inhibit cardiac fibrosis, suggesting that not all factors increased in CKD are detrimental to the heart.[71] The specific role of pentraxin 3 on affecting the heart also has yet to be described. Importantly, the exact impact of these cytokines on the heart in the clinical setting of CKD has yet to be defined. Interestingly, the proinflammatory cytokines IL-1β, IL-6, and TNF-α stimulate angiotensin II−mediated ROS production, again showing the interplay of different factors in stimulating cardiovascular disease in the context of CKD.[72,73] To conclude, inflammation seems to be tightly connected to oxidative stress and RAAS, which together induce pathologic cardiac remodeling in the context of CKD. In addition, the MAPK signaling pathway seems pivotal in exerting the

inflammation-mediated effects on cardiovascular disease during CKD.

FIBROBLAST GROWTH FACTOR 23 AS A POTENTIAL MODULATOR OF CARDIAC FIBROSIS

Fibroblast growth factor 23 (FGF23) is an endocrine hormone that regulates phosphate excretion and vitamin D metabolism under physiological conditions.[74] FGF23 binds to the FGF receptor and the co-receptor Klotho, to exert its effects in both the kidney and parathyroid glands.[74-76] Under pathophysiological conditions, a decrease of renal function and loss of klotho expression results in increased serum levels of FGF23, which has been associated with greater risks of cardiovascular events and mortality.[77-80] Indeed, increased serum levels of FGF23 are associated independently with left ventricle hypertrophy, one of the underlying characteristics of chronic heart failure in CKD patients.[81] It has been shown in vitro that, in the heart, FGF23 is expressed the most highly in cardiac fibroblasts in comparison with cardiomyocytes, suggesting a role of FGF23 in cardiac fibrosis.[82] In this respect, FGF23 induces the proliferation of adult mouse cardiac fibroblasts and increases the expression of collagens.[82] In vivo myocardial injection of FGF23 together with myocardial infarction or ischemia/reperfusion surgery exacerbated left ventricular diastolic dysfunction and cardiac fibrosis via increased TGFβ and collagen levels.[82] Interestingly, this effect was mediated partially by β-catenin, indicating that as yet to be defined other regulators also are involved in FGF23-induced cardiac dysfunction.[82] A possible regulator is angiotensin II, which is a well-known inducer of cardiac fibrosis and stimulates FGF23 expression.[82] Another possible regulator would be parathyroid hormone, because FGF23 directly affects the parathyroid glands. However, there was no difference observed in parathyroid hormone serum levels, indicating that FGF23 and parathyroid hormone work independently of each other. Another possible regulator is inflammation, because it has been reported that FGF23 expression in cardiac fibroblasts can be up-regulated by systemic inflammation.[83] Because MAPK signaling is involved in the FGF23-mediated effect on cardiac hypertrophy, and MAPK signaling also is pivotal in inflammation associated with CKD-induced cardiovascular disease, MAPK signaling might represent an important modulator with pleiotropic functions in facilitating CKD-induced cardiovascular disease. Although numerous studies have shown an association of FGF23 with cardiovascular disease in CKD, the direct effect of FGF23 on the heart in the context of CKD still is unclear. However, because FGF23 levels are increased in CKD patients, and FGF23 induces cardiac fibrosis at least in the context of myocardial infarction, it is reasonable to postulate that FGF23 induces cardiac fibrosis in the context of kidney disease.

KLOTHO DEFICIENCY INDUCES CARDIAC FIBROSIS

Besides functioning as a co-receptor for FGF23, the extracellular domain of Klotho also can be cleaved, resulting in circulating Klotho. CKD patients show decreased expression of Klotho in the kidney and decreased serum levels.[84] Klotho deficiency (kl/+) in mice results in cardiac hypertrophy and decreased cardiac function, indicating its role in cardiovascular disease.[84] Moreover, complete knock-out of klotho results in both cardiac fibrosis and hypertrophy.[84] This is associated with increased phosphorylation of Smad2/3, modulators of the canonical TGFβ pathway, which is important for fibrosis and suggestive of EndMT, and extracellular signal-regulated kinase, which is pivotal in MAPK signaling, again underlining the interplay of different mediators in facilitating CKD-mediated cardiovascular disease. Interestingly, administration of phosphate to non-CKD mice resulted in decreased Klotho serum levels and decreased Klotho expression in the kidney, indicating the role of phosphate in regulating Klotho and Klotho-induced cardiovascular disease.[84] Klotho in turn attenuated TGFβ1-, angiotensin II−, and phosphate-induced collagen expression and extracellular signal-regulated kinase phosphorylation in cardiac fibroblasts in vitro.[84] This suggests that Klotho interferes at different levels to mediate a cardioprotective effect in the context of CKD. In this respect, indoxyl sulfate is an important uremic solute that induces cardiac hypertrophy, and Klotho inhibits indoxyl sulfate−induced cardiac hypertrophy by counteracting oxidative stress via reduced NOX2 and NOX4 expression and by counteracting MAPK signaling.[85] Although in these studies the contribution of FGF23 to Klotho-mediated cardiac dysfunction is not addressed, they underline the importance of FGF23/Klotho/phosphate-mediated cardiovascular disease in the context of CKD. Extensive research is necessary to identify the interplay between FGF23, Klotho, and phosphate to be able to specifically target these mediators of cardiovascular disease.

CONTRIBUTION OF INCREASED PHOSPHATE CONCENTRATIONS TO CARDIAC FIBROSIS

Both FGF23 and Klotho are phospho-regulatory hormones, and, as discussed in detail earlier, although numerous studies corroborated their relevance on cardiovascular morbidity, high phosphate levels still decreased lifespan when FGF23 and Klotho were absent in *FGF23*$^{-/-}$ and *Klotho*$^{-/-}$ knockout mice, suggesting an independent role of phosphate in heart failure and cardiac fibrosis. In this regard, hyperphosphatemia is a hallmark of chronically impaired excretory kidney function.[86] Plasma phosphate levels, ranging typically between 0.8 and 1.5 mmol/L, are a reflection of the

body's phosphate balance and in advanced CKD insufficient renal phosphate excretion causes phosphate overload, as reflected by hyperphosphatemia (and altered levels of phospho-regulatory hormones).[87] Although in absence of known phosphate-sensitive receptors phosphate had been long considered biologically inert, exposure of cultured fibroblasts to media supplemented with high phosphate recapitulated all features of fibroblast activation and EndMT when endothelial cells were cultured within high phosphate media.[88,89] This was dependent on increased phosphate uptake and subsequently increased phosphorylation of the DNA methyltransferase Dnmt1, resulting in its increased activity. Although the underlying cause of observed aberrant Dnmt1 phosphorylation remained unclear in these studies, it is tempting to speculate that excessively increased intracellular phosphate concentrations within CKD patients could serve as a nonspecific phosphate donor, bringing inorganic phosphate to life. Phosphate is an essential constituent of critical cellular functions, including energy metabolism, nucleic acid synthesis, and phosphorylation-dependent cell signaling. Increased plasma phosphate levels are an independent risk factor for decreased life expectancy as well as for heart and kidney failure.[89,90] In summary, insights into the mechanisms underlying the detrimental effect of high phosphate on cardiovascular morbidity in the context of CKD still are emerging and may provide an important novel therapeutic target.

MicroRNAs AS PROFIBROTIC KIDNEY−HEART MESSENGERS

MicroRNAs are small endogenously transcribed regulatory RNAs that modulate gene expression by binding to untranslated regions of messenger RNA or to promoter sequences. MicroRNAs have been reported to regulate various pathogenic processes in the heart and kidney.[91,92] There is considerable overlap of profibrotic microRNAs in heart and kidney, and microRNA-21 and microRNA-29 are among the most abundantly expressed microRNAs in the heart and kidney and both are known to regulate fibrosis by their action on messenger RNA of extracellular matrix proteins and TGFβ1.[91,92] In a mouse model of cardiorenal syndrome, both microRNA-21 and microRNA-29 were shown to be increased in the heart after myocardial infarction associated with an increase of uremic toxins.[93] Because microRNAs are present in the circulation,[94] this conceptually offers the possibility that microRNAs are released by the injured kidney and directly induce fibrosis in the heart, possibly via exosome-mediated RNA transfer.[95,96] Another possible explanation for the synchronized increase of microRNA-21 and microRNA-29 in the heart and kidney is an increase of common inducing factors such as uremic toxins. In this regard, it was shown in the earlier-mentioned

mouse model of myocardial infarction that treatment with uremic toxin−adsorbent AST-120 inhibited the increase of microRNA-21 and microRNA-29 levels in the heart.[93]

SUMMARY

The progression of chronic heart failure and cardiac fibrosis is a complex process, which involves numerous cell types, soluble factors, and novel mechanisms that still are evolving (Fig. 2). Augmented heart disease through kidney failure via a kidney−heart axis adds further complexity to this process. Although our understanding of the underlying mechanisms still is evolving, the possibility that kidney−heart messengers could be intercepted offers ample reason to focus on this clinically highly relevant problem.

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