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Extracellular matrix roles in cardiorenal fibrosis: Potential therapeutic targets for CVD and CKD in the elderly

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Abstract

Whereas hypertension, diabetes, and dyslipidemia are age-related risk factors for cardiovascular disease (CVD) and chronic kidney disease (CKD), aging alone is an independent risk factor. With advancing age, the heart and kidney gradually but significantly undergo inflammation and subsequent fibrosis, which eventually results in an irreversible decline in organ physiology. Through cardiorenal network interactions, cardiac dysfunction leads to and responds to renal injury, and both facilitate aging effects. Thus, a comprehensive strategy is needed to evaluate the cardiorenal aging network. Common hallmarks shared across systems include extracellular matrix (ECM) accumulation, along with upregulation of matrix metalloproteinases (MMPs) including MMP-9. The wide range of MMP-9 substrates, including ECM components and inflammatory cytokines, implicates MMP-9 in a variety of pathological and age-related processes. In particular, there is strong evidence that inflammatory cell-derived MMP-9 exacerbates cardiorenal aging. This review explores the potential therapeutic targets against CVD and CKD in the elderly, focusing on ECM and MMP roles.

Keywords

Cardiorenal aging; Inflammaging; Fibrosis; Extracellular matrix; Matrix metalloproteinase-9

1. Introduction

Aging is an independent risk factor for cardiovascular disease (CVD) and chronic kidney disease (CKD), and elderly patients diagnosed with these diseases have poor clinical outcomes. CVD and CKD not only share many age-related risk factors including hypertension and diabetes but also interact in an interdependent and bidirectional manner

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Conflict of interest statement

The authors declare that there are no conflicts of interests.

(Abadir et al., 2011; Boudoulas, Triposkiadis, Parissis, Butler, & Boudoulas, 2017; Ebert et al., 2017). In elderly individuals, the immune response to new pathogens is often impaired, and this diminished immune response is termed immunosenescence (Oishi & Manabe, 2016). Immunosenescence is characterized by an elevated basal systemic in-flammatory state. Higher levels of circulating proinflammatory cytokines are observed in the elderly even in the absence of overt infection and chronic disease, a process termed inflammaging (Bruunsgaard & Pedersen, 2003).

Inflammation induces the production and release of fibrogenic cytokines and growth factors, leading to fibrosis (Wynn, 2008). The accumulation of fibrillar collagens leads to irreversible dysfunction and results in heart failure and end-stage renal failure (Biernacka & Frangogiannis, 2011; Wynn, 2008; Zhou et al., 2008). Although matrix metalloproteinases (MMPs) are traditionally believed to suppress fibrosis because of their proteolytic activity, MMPs, particularly MMP-9, play key roles in stimulating fibrillar extracellular matrix (ECM) collagen accumulation (Giannandrea & Parks, 2014; Horn et al., 2012; Horn & Trafford, 2016; Tan & Liu, 2012).

In this review, we summarize current findings regarding the mechanisms of cardiorenal aging and fibrosis, including recent reports showing common mechanisms that may provide comprehensive anti-aging strategies. This review focuses on the roles of ECM and MMPs as common underlying mediators. Assessment of age-related alterations in cardiac and renal ECM and MMPs may provide common and distinct therapeutic targets for CVD and CKD.

2. Cardiorenal interactions

Approximately 25% patients with chronic heart failure have renal dysfunction, and renal dysfunction is one of the most important predictors of mortality, prolonged hospitalization, and rehospitalization in patients with heart failure (Forman et al., 2004; Gottlieb et al., 2002; Hillege et al., 2000; Hillege et al., 2006). Conversely, a major cause of death in patients with primary renal disease is CVD, and reversal of renal function by renal transplantation results in normalization of cardiac physiology (Tonelli et al., 2006; Wali et al., 2005). Cardiorenal interactions include not only secondary effects of common risk factors, including aging, hypertension, diabetes mellitus, and atherosclerosis, but also a vicious bidirectional effect. In this section, by reviewing the mechanisms of cardiorenal interaction which are reported previously in the settings of CVD and CKD, we would like to strengthen the importance to protect both the heart and kidney in the elderly stage (Fig. 1).

2.1. Cardiac-renal interactions

Reduced renal perfusion, due to reduced cardiac output in heart failure, is likely to lead to the progressive decline in glomerular filtration rate (GFR). However, ESCAPE (Evaluation Study of Congestive Heart failure and Pulmonary Catherization Effectiveness) found no correlation between cardiac index (hemodynamic variables) and renal function (serum creatinine) (Bhatia et al., 2006; Nohria et al., 2008). Instead, venous congestion, rather than arterial blood flow, is likely to be an important mediator. Elevated central venous and intraabdominal pressure causes an insufficient pressure gradient across capillary networks,

including those in the renal circulation, resulting in reduced renal blood flow and GFR (Bock & Gottlieb, 2010; Mullens et al., 2008; Winton, 1931).

Decline in cardiac output and consequent renal and pressure-sensing baroreceptor blood flow reduction cause renal ischemia and stimulate sympathetic nerves and the renin-angiotensin-aldosterone system, which causes sodium and volume retention and left ventricular remodeling. Renal sympathetic denervation shows significant improvements in resistant hypertension, left ventricular hypertrophy, and diastolic function without significant relation to blood pressure and heart rate, suggesting that renal sympathetic activation affects both vascular and cardiac function (Schirmer et al., 2014). As described below, angiotensin II and aldosterone induce oxidative stress and inflammation, resulting in excessive fibrosis in both organs.

Natriuretic peptides, such as atrial natriuretic peptide, brain natriuretic peptide, C-type natriuretic peptide, and N-terminal prohormone of brain natriuretic peptide, are neurohormones released from the heart, brain, and other organs to compensate cardiovascular derangement (Federico, 2010). Natriuretic peptides exert opposite effects to activate the sympathetic nerves and the renin-angiotensin-aldosterone system, because they decrease central venous pressure, sodium retention, and systemic and intrarenal vascular resistance and improve myocardial contractility and GFR. Maintaining and activating the natriuretic peptides could put a brake on adverse cardiorenal interactions.

2.2. Renal-cardiac interaction

Renal dysfunction causes sodium and water retention and hyper-tension, resulting in increased cardiac afterload and reduced catecholamine clearance to further activate sympathetic nerves (Laederach & Weidmann, 1987). Protein-bound uremic toxins, such as indoxyl sulfate and p-cresyl sulfate, cause cardiovascular and renal injury by inducing oxidative stress (Lekawanvijit, Kompa, Wang, Kelly, & Krum, 2012).

While erythropoietin increases in response to anemia, insensitivity to erythropoietin in heart failure causes inflammation and advanced kidney diseases result in anemia by the absolute deficiency of erythropoietin (Bock & Gottlieb, 2010). Since erythropoietin can protect cardiac, vascular, and renal cells by its anti-apoptotic, anti-oxidative, and anti-inflammatory effects, erythropoietin deficiency may exacerbate cardiorenal interactions by not only inducing ischemia but also taking away cell protective actions (Toba et al., 2009; Toba et al., 2010; Toba et al., 2011; Toba et al., 2012; Wang et al., 2013).

2.3. Vascular-cardiac interactions

Age-related arterial alterations include endothelial dysfunction, wall thickening, and narrowing diameter. The presence of endothelial dys-function is an independent risk factor for both progression to and adverse outcomes after heart failure development (Fischer et al., 2005; Heitzer, Baldus, von Kodolitsch, Rudolph, & Meinertz, 2005; Meyer et al., 2005). Cushioning effects of the elastic arteries are needed for their expansion during systole and delivery of blood to the coronary arteries during diastole. Arterial stiffness of the coronary artery impairs coronary blood flow, because the coronary arteries are perfused during

diastole (O'Rourke & Hashimoto, 2007; Zieman, Melenovsky, & Kass, 2005). Increased stiffness of larger arteries increases afterload (Tomiyama & Yamashina, 2015).

Arterial-ventricular coupling (E_A/E_{LV}) is maintained within a narrow range to provide optimal energetic efficiency at the expense of mechanical efficacy. Whereas this coupling at rest is optically maintained during healthy aging, the coupling during acute maximal exercise is impaired with age. Arterial stiffness, in particular the larger arteries, contributes to increases in resting E_A, leading to abnormal coupling (Tomiyama & Yamashina, 2015).

2.4. Vascular-renal interactions

Increased blood pressure is a critical risk factor for renal damage, and arterial stiffening results in a decrease of the pressure gradient in the arterial tree, where the pressure at more distal sites is higher than more central sites (O'Rourke & Hashimoto, 2007; Tomiyama & Yamashina, 2010).

Increased aortic stiffness attenuates its shock absorbing effects against cardiac constriction, resulting in increases in the transmission of the heart-generated pulsatile energy to the peripheral circulation, including renal circulation. This phenomena lead to pulsatile nephropathy, which results in decline of renal function (O'Rourke & Hashimoto, 2007; O'Rourke, Safar, & Dzau, 2010; Tomiyama & Yamashina, 2010).

2.5. Senescence-associated secretory phenotype (SASP)

Senescent cells produce a complex mixture of secreted factors that include proinflammatory cytokines, chemokines, growth factors, and proteases (Coppe, Desprez, Krtolica, & Campisi, 2010; Kuilman & Peeper, 2009). The SASP secretion pattern is stimulated by various mechanisms, including sustained DNA damage, oxidative stress, and NF-κB (McHugh & Gil, 2018). One important function of SASP is recruiting immune cells to eliminate antigens and senescent cells and to activate cell proliferation and differentiation of progenitor and stem cells to repair tissues. However, senescent cells that are not repaired successfully secrete more SASP, further promoting cell senescence (Wang, Cai, & Chen, 2017). The SASP can accelerate both autocrine and paracrine senescent responses, suggesting important roles as a mediator of cardiorenal interaction and inflammaging (Acosta et al., 2013; McHugh & Gil, 2018).

3. Characterization of aging effects on heart and kidney

The heart and kidney undergo progressive and inevitable senescence, characterized by a gradual decline in cell structure and physiology that are independent of changes due to concomitant hypertension or diabetes (Table 1) (Lakatta, 2015). Normal aging is gradual, with small individual effect size, such that values are often still within the physiological range. The superimposition of age-related diseases on aging amplifies and accelerates functional decline to result in pathology (Lakatta, 2015).

3.1. Heart

3.1.1. Physiology—Early diastolic filling begins to slow beginning around 20 years of age in humans, with a reduction of about 50% by the age of 80 (Cannata, Camparini, Sinagra, Giacca, & Loffredo, 2016). This reduction in diastolic filling is attributed to ECM accumulation within the myocardium, decreased elasticity of the left ventricle (LV), and a delay in active relaxation due to residual myofilament Ca^{2+} activation (Horn & Trafford, 2016; Lakatta, 2003).

The decrease in early to late (E/A) relaxation ratio in the elderly is termed diastolic dysfunction and is a hallmark of cardiac aging (Dai, Chen, Johnson, Szeto, & Rabinovitch, 2012; Ferrari, Radaelli, & Centola, 2003; Steenman & Lande, 2017). Diastolic dysfunction predisposes an individual to develop heart failure with preserved ejection fraction. More than half of heart failure cases in the elderly (>75 years old) are diagnosed as diastolic heart failure (de Freitas, Batlouni, & Gamarsky, 2012). Decreased activity and protein levels of sarcoplasmic reticulum Ca^{2+} ATPase pump (SERCA), which causes relaxation of the cardiac muscle following the excitatory effects of high cytosolic Ca^{2+}, in the aged heart may account for prolongation of relaxation and thus diastolic dysfunction (Lakatta, 2003).

To maintain LV filling in late diastole, atrial contraction gradually increases with age, which induces atrial hypertrophy and increases the risk for atrial fibrillation (Steenman & Lande, 2017). Despite a decline of diastolic function with age, LV ejection fraction, a most commonly used clinical parameter for LV systolic function, and stroke volume are relatively preserved at rest (Lakatta & Levy, 2003).

Cardiac reserve shows age-related reduction, which is involved in a decrease in maximum heart rate due to a dropout of pacemaker cells and a decreased responsiveness to β-adrenergic receptor and a deficit in the ability to reduce end-systolic volume achieved during exercise (Lakatta, 2015; Roh, Rhee, Chaudhari, & Rosenzweig, 2016; Steenman & Lande, 2017; Sun et al., 2017). The additional LV filling time causes the aged LV to expand to a larger size during diastole, which allows the aged LV to pump out about as much blood as the young LV despite the larger systolic chamber.

3.1.2. Structure—Age-related structural change is characterized by LV concentric hypertrophy (Chiao & Rabinovitch, 2015; Ferrari et al., 2003; Horn & Trafford, 2016; Lakatta & Levy, 2003). The increase in LV wall thickness is seen as a compensatory response after cardiomyocyte loss due to increased apoptosis and necrosis (Dai & Rabinovitch, 2009; Zamilpa, Navarro, Flores, & Griffey, 2014). This compensation contributes to the enlargement of residual cardiomyocytes (Horn & Trafford, 2016). The loss of cardiomyocytes with age stimulates the accumulation of fibrillar ECM components within the interstitial space (Horn & Trafford, 2016). Age-related increases in LV afterload, due to arterial stiffening and subsequent hypertension, also exacerbate LV hypertrophy and prolonged LV relaxation in diastole (Lakatta, 2003, 2015; North & Sinclair, 2012).

Amyloid and lipofuscin accumulate in aged cardiomyocytes (Shioi & Inuzuka, 2012). The presence of amyloid strongly correlates with the age at time of death in the >85 year old population (Tanskanen et al., 2008). Lipofuscin is an autofluorescent substance composed

primarily of crosslinked protein and lipid residues that accumulates over time in lysosomal of cardiomyocytes due to an imbalance between protein damage and clearance of the damaged proteins (Terman & Brunk, 1998). Lipofuscin induces cell death and inhibits mitochondrial function, suggesting deleterious cardiomyocyte roles for lipofuscin in age-related cardiac dysfunction (Han, Li, & Liu, 2013).

3.1.3. Cardiac inflammaging and fibrosis—Age-related LV wall thickening and myocyte hypertrophy results in an additional oxygen demand (Fig. 2). Higher plasma concentrations of von Willebrand factor and LV expression of vascular endothelial cell growth factor (VEGF) are observed in aged mice and are indicative of an increased stimulation for angiogenesis (Yabluchanskiy et al., 2014). Despite an increase in proangiogenic stimuli, the number of vessels in the aged LV was not increased (Yabluchanskiy et al., 2014).

Insufficient vascularization leads to an imbalance of oxygen supply and consequently a hypoxic environment. In addition to vessel rarefaction, nitric oxide (NO) deficiency in coronary artery and arterioles, due to endothelial cell senescence, endothelial NO synthase (eNOS) inactivation, reactive oxygen species (ROS)-induced decline in NO bioavail-ability, and vasoconstriction, exacerbates ischemic statement in the aged heart (North & Sinclair, 2012). Hypoxic state triggers an inflammatory response in the myocardium. LV vascular permeability, the excessive leakage of fluid and proteins from vessels to the interstitial space, increases with age, which is associated with endothelial cell apoptosis, oxidative stress, and inflammation (Yabluchanskiy et al., 2014). High susceptibility to ischemia/reperfusion injury in aged hearts may be due to the potentially high vascular permeability (Oakley & Oakley & Tharakan, 2014).

Vascular cell adhesion molecule 1 and integrin αE mRNAs, both of which are involved in adhesion of inflammatory cells, increase with age in mouse LV (1.9-fold for both) (Toba et al., 2016). Indeed, macrophage numbers are approximately 4-fold age-related increased in the LVs of N18 month old mice compared to 3–5 month old mice. Age-related cardiac inflammation is a milder response than what is observed after pathological conditions, in which peak macrophage infiltration increases by approximately 100-fold with myocardial infarction and 10-fold with hypertensive heart failure (Halade, Jin, & Lindsey, 2013; Xia et al., 2009). Changes in vascular cell adhesion molecule 1 and integrin αE mRNAs in the myocardial setting (infarct area of day 5 after myocar-dial infarction in mice) are more drastic than normal aging and show 5.3- and 4.0-fold increases, respectively (Zamilpa et al., 2012). Since neutrophil numbers do not show such dramatic age-related changes, macrophages are the prominent player in cardiac inflammaging (Chiao et al., 2012; Toba et al., 2015).

In murine LV, the mRNA levels of pro-inflammatory cytokines and their receptors such as chemokine (C-C motif) ligand (Ccl)5, chemokine (C-X3-C motif) ligand 1, CC chemokine receptor (Ccr)2, Ccxr3, and macrophage migration inhibitory factor (Mif) are increased in an age-dependent manner with 2.3-fold, 1.6-fold, 2.0-fold, and 3.6-fold increases (young vs. old mice), respectively (Toba et al., 2015). In infarct area of day5 post-myocardial infarction, Cx3cl1 and Ccr2 mRNA levels show 1.8-fold and 4.4-fold increases (Zamilpa et al., 2012).

Ccl5, chemokine (C-X3-C motif) ligand 1, Ccr2, and Cxcr3 play roles in inducing migration and recruitment of inflammatory cells (Altin & Schulze, 2011; Dawson, Miltz, Mir, & Wiessner, 2003; Ferrandi et al., 2007; Houard et al., 2009). Mif, which regulates the release of pro-inflammatory mediators, is released in response to a brief hypoxia in the heart (Koga et al., 2011). In old healthy subjects, plasma monocyte chemoattractant protein (MCP)-1, Ccl5, and Mif levels are higher than young controls (Mansfield et al., 2012; Rammos et al., 2014).

Macrophages are classified into pro-inflammatory (classically activated) M1 and anti-inflammatory (alternatively activated) M2 macrophages *in vitro*, a naming system that overly simplifies the *in vivo* scenario but is used here for simplicity. Cardiac tissue resident macrophages express a number of anti-inflammatory M2 macrophage markers in the young mice and are important for maintenance of cardiac homeostasis (Pinto et al., 2012). Markers of M1 macrophages include interleukin (IL)-6 and tumor necrosis factor (TNF) −α, and are increased with age, while the M2 marker Fizz-1 is decreased with age, indicating M1 > M2 polarization in the aged LV (Toba et al., 2015). The increase in pro-inflammatory cytokines from M1 macrophages likely stimulates the further accumulation of macrophages in the LV.

Cardiac inflammation causes ECM fibrillar collagen accumulation by stimulating the release of fibrogenic cytokines and growth factors (Wynn, 2008), particularly transforming growth factor (TGF)-β (Biernacka & Frangogiannis, 2011). In humans without CVD history, collagen content increases from 3.9 ± 0.8% at 20–25 years of age to 5.9 ±0.8% at 67–87 years of age; and similar rates of change are seen in mice (Chiao et al., 2012; Gazoti Debessa, Mesiano Maifrino, & Rodrigues de Souza, 2001; Toba et al., 2016; Toba et al., 2017). Of note, mice do not develop hypertension with age, making them a good model to study aging only effects. In the aged murine LV, TGF-β-induced protein (Tgfbi) and phosphorylated Smad2 increase and correlate with the modest but significant picrosirius red-positive collagen deposition (Chiao et al., 2012). Mechanisms of TGF-β-induced fibrosis include enhanced fibroblast proliferation and myofibroblast transdifferentiation, ECM protein synthesis, and matrix preservation by suppressing MMP activity by inducing protease inhibitors (Biernacka & Frangogiannis, 2011).

Fibroblasts are a predominant non-cardiomyocyte cell type in the heart (human, rat, mice) and play a pivotal role in regulating ECM maintenance (Camelliti, Borg, & Kohl, 2005). TGF-β is the primary fibrogenic factor that promotes cardiac fibrosis not only by inducing synthesis of ECM proteins and decreasing collagen degradation but also by cardiac fibroblast transdifferentiation to myofibroblast. TGF-β signaling play a crucial role in myofibroblast differentiation by inducing α-smooth muscle actin transcription (Pardali, Sanchez-Duffhues, Gomez-Puerto, & Dijke, 2017). Cardiac fibroblasts derive from activation and proliferation of resident fibroblasts and recruitment from other cell types (Camelliti et al., 2005). Mice deficient in plasminogen activator inhibitor-1 exhibit increased collagen deposition and TGF-β-induced epithelial-mesenchymal transition (EMT) in the aged heart, indicating that EMT contributes to age-related cardiac fibrosis (Ghosh et al., 2010).

The rate of newly-synthesized collagen in the rat myocardium remains steady until the age of 15 months and then begins to decreases around 24 months (Mays, McAnulty, Campa, & Laurent, 1991). ECM post-translational modifications play more critical roles in collagen accumulation than new synthesis. This is consistent with the phenotype of aging LV fibroblasts, which exhibit decreased proliferative and migratory capacities (Lindsey et al., 2005). Collagen solubility changes with age in the LV, indicating an alteration in collagen type and degree of crosslinking. In human hearts, the number of large diameter collagen fibrils increases with age, indicating more collagen crosslinking (Mendes et al., 2012). Lysyl oxidase, which stabilizes fibrillar collagen by producing covalent crosslinking of collagen fibrils, increases with age (Thomas, Cotter, Li, McCormick, & Gosselin, 2001).

Collagen type I and III are the most abundant collagens in the heart, with collagen I predominating (Meschiari, Ero, Pan, Finkel, & Lindsey, 2017). Old hearts exhibit the decreased ratio of collagen I to collagen III content. Since collagen I has high tensile strength and collagen III is more distensible, the alteration of collagen types as well as increased total collagen content may contribute to age-related myocardial stiffness (Meschiari et al., 2017). An increase in the collagen III proportion is also reported (Table 2) (Biernacka & Frangogiannis, 2011).

Age-related alterations in the immune system, characterized by a shift from Th1 to Th2 cytokines, occur in humans and animal models (Cieslik et al., 2011). Along with the increased shift to a Th2 phenotype, numbers of $CD45^+$ myeloid-derived fibroblasts that contain procollagen I increase, along with the development of diastolic dysfunction in the aging mouse heart, indicating immunoinflammatory dysregulation in the aging heart stimulates interstitial fibrosis (Cieslik et al., 2011).

3.2. Kidney

3.2.1. Physiology—In human subjects, GFR shows an age-related decline (averaging 0.75–1.0 ml/min/1.73m^2/year) from the age of 30–40 years (Bolignano, Mattace-Raso, Sijbrands, & Zoccali, 2014; Denic, Glassock, & Rule, 2016; Rule et al., 2010; Wetzels, Kiemeney, Swinkels, Willems, & Heijer, 2007; Zhou, Saxena, Liu, Vaziri, & Silva, 2008). Functional reserve is declines from 20% in the young to approximately 15% in the elderly (Fliser, Zeier, Nowack, & Ritz, 1993). Effective renal perfusion, an important determinant of GFR, decreases about 10% per decade in healthy elderly volunteers after the age of 30 (Fliser et al., 1993). The decrease is profound in the cortex, largely due to an increase in renal artery resistance that may result from blunted vasodilatory responses to acetylcholine with intact or enhanced responses to vasoconstrictors such as angiotensin (Fliser et al., 1997; Gekle, 2017; Goldberg & Finkelstein, 1987).

The filtration fraction (ratio of GFR to renal plasma flow) is slightly enhanced with age and starts to significantly increase from the age of 60. An enhanced filtration fraction indicates the extent of drop in renal blood flow is larger compared to the GFR drop and that the age-related increase in vascular resistance occurs mainly in efferent arterioles. Increased filtration fraction, depending on the resistance in efferent arterioles, results in glomerular pressure overload and hyperfiltration (Gekle, 2017). These changes damage glomerular

capillaries, resulting in elevated albumin excretion, even though the increase is still preserved within the normal physiological range (Fliser et al., 1997).

Age-related sclerotic changes may reduce intrarenal pressure and shift the pressure-natriuresis relationship to rightward because additional systemic blood pressure elevation is needed to excrete sodium. In addition, atrophy of nephrons may cause the requirement of higher systemic blood pressure, while less sodium intake may require less blood pressure, which blunting the slope (Levy et al., 2009). These changes may induce hypertension, in particular salt-sensitive hypertension, in elderly population.

The decreased expression of the most important water channel, AQP-2, and medullary hypotonicity in the elderly (humans and animal models) suggest that the abilities of concentrating urine is impaired despite a normal circulating level of vasopressin (Bolignano et al., 2014; Preisser et al., 2000). The proximal sodium reabsorption is enhanced, and reabsorption at the thick ascending loop of Henle and the distal tubes is reduced, suggesting a reduced control range. The protein levels of the $Na^+ -K^+ -2Cl^-$ cotransporter NKCC2/BSC1 and the epithelial sodium channel ENaC and reduced in the aged rats compared to the young (Tian et al., 2006). The reduced levels of these sodium transporters may also, at least in part, contribute to the reduced maximal urine osmolality in aged rats. Together with reduced levels of renin and aldosterone and diminished responses to their stimuli, the elderly are at a high risk of volume depletion and sodium excretion (Gekle, 2017; Schaeffner et al., 2012). Potassium secretion is impaired, which corresponds to impaired sodium reabsorption across the Na^+/K^+ -ATPase transporters in the distal nephron and collecting duct, explaining the high risk for hyperkalemia in the elderly (Schaeffner et al., 2012).

Endocrine function, including renin release, is impaired with age, but serum erythropoietin levels are normal or slightly increased to compensate for age-related blood loss or increased erythropoietin resistance (Bolignano et al., 2014; Fliser et al., 1997; Gekle, 2017).

3.2.2. Structure—Arterial sclerosis (intimal fibrosis of the interlobular arteries) is found in the aged kidneys, which leads to the regional ischemia in nephrons, arteriolar hyaline, and fibrotic changes in the smaller distal branches (Takazakura et al., 1972). Deposition of hyaline and matrix in the mesangium leads to expansion of the mesangial compartment, collapse of glomerular and capillary tufts and intracapsular fibrosis (glomerulosclerosis), and globally sclerotic glomeruli may eventually atrophy. Corresponding tubules are atrophied; proximal convoluting tubes are shortened, and the size of the proximal tubular epithelial cells decreases (Abdel-Kader & Palevsky, 2009). Fibrillar collagens accumulate in tubulointerstitial space (Denic et al., 2016).

Glomerulosclerosis occurs primarily in the surface cortex, with losing the cortical glomeruli 30% - 50% by the age of 70 years (Abdel-Kader & Palevsky, 2009), which eventually contributes to the loss of parenchyma in the cortex (Emamian, Nielsen, Pedersen, & Ytte, 1993; Gourtsoyiannis, Prassopoulos, Cavouras, & Pantelidis, 1990; Kaplan, Pasternack, Shah, & Gallo, 1975). The remaining glomeruli are hypertrophied to compensate for the decline of functional glomeruli, and the medullary volume increases through the age of 40–50 years, in part due to the deposition of renal sinus fat and the hypertrophy of remaining

and compensating functional juxtamedullary glomeruli and tubules (Bolignano et al., 2014; Zhou, Saxena, et al., 2008).

Podocytes support and maintain glomerular basement membrane filtration mechanisms, and with age become hypertrophied and detached (Bolton & Sturgill, 1980; Ortmann et al., 2004; Wiggins, 2009). Another type of arterial change seen in the juxtamedullary area is alomerular arterioles, where the afferent and efferent arteries communicate directly each other due to the loss of glomeruli (Takazakura et al., 1972).

3.2.3. Renal inflammaging and fibrosis—In the aged kidney, VEGF decreases and anti-angiogenic factors angiostatin and thrombospondin-1 increase, with decreased peritubular capillaries (Satoh et al., 2013). Mitochondrial dysfunction and NO deficiency are associated with the decline in VEGF and upregulation of angiostatin (Kang et al., 2001; Satoh et al., 2011). Endostatin, an anti-angiogenic factor, is elevated in the blood and kidney of aging mice, and elevated endostatin associates with the degree of renal injury in elderly patients (Lin et al., 2014; Ruge et al., 2014). Peritubular capillary loss contributes to interstitial hypoxia, oxidative stress, MCP-1 and IL-18 upregulation, and tubulointerstitial fibrosis, with proteinuria and increases in serum creatinine, suggesting the critical role of vessel rarefaction in renal aging (Satoh et al., 2011; Satoh et al., 2013).

Accumulation of macrophages and lymphocytes is observed in the aged kidney, along with increased expression of intracellular adhesion molecule (ICAM)-1 and osteopontin. The number of F4/80-positive monocytes and macrophages doubles in mice from 3 months to 24 months old (Zhang et al., 2006). This increase in macrophage number is much lower than the diseased kidney. For example in the unilateral ureteral obstruction (UUO) mouse model, kidneys have 100–120 F4/80-positive cells/×200 field, compared to 5–10 F4/80-positive cells/×200 field for sham (Tan et al., 2013). The M1 macrophage marker inducible NOS increases and the M2 macrophage marker arginase 1 decreases with age in the kidney, indicating M1 > M2 polarization (Son et al., 2017). Chronic inflammation induces renal cell senescence, and senescent cells secrete cytokines and chemokines to propagate the cycle of inflammation (Mei & Zheng, 2009).

Inflammatory cells release cytokines and growth factors, including platelet-derived growth factor (PDGF)-β, IL-1β, TNF-α, IL-6, and TGF-β (Bolignano et al., 2014; Hewitson, 2012). TGF-β is a potent fibrogenic growth factor produced from all cell types in the kidney, and the mechanisms of TGF-β-induced fibrosis is inducing myofobroblast formation from fibroblasts, pericytes, endothelial cells *in vitro*, stimulating the ECM gene transcription in tubular, endothelial, and mesangial cells and stimulating cell proliferation and ECM accumulation via activation of connective tissue growth factor (Lawson, Elliott, Wheeler-Jones, Syme, & Jepson, 2015). TGF-β induces EMT via Smad2/3 and p38 mitogen-activated protein (MAP) kinase signaling. In addition to fibrogenic effects, TGF-β causes tubular epithelial cell apoptosis and inflammatory cell accumulation.

The number of macrophages correlates with the degree of interstitial fibrosis in the aging kidney, and glomerulosclerosis and tubulointerstitial fibrosis are major hallmarks of renal aging (Denic et al., 2016; Gagliano et al., 2000; Lim et al., 2012; Maric, Sandberg, &

Hinojosa-Laborde, 2004). The picrosirius red stained fibrosis area is about 7.5% in 2 month old male Fischer rats and doubles to about 15% at 20 months (Sangaralingham et al., 2016). Collagen I, III, and IV, laminin, and fibronectin levels are higher in the aged kidney (Table 2) (Gagliano et al., 2000; Hou et al., 2016; Maric et al., 2004; Zhang et al., 2006).

Aging kidneys exhibit increased ECM crosslinking and a 2–4 fold significant increase in transglutaminase 2, an enzyme that catalyze Ca^{2+} dependent cross-links ECM proteins (Lin et al., 2016). Transglutaminase 2 is a molecular partner of endostatin, and overexpression of endostatin in young mice leads to interstitial fibrosis. Subcapsular injection of transglutaminase 2 or endostatin into a young kidney results in cellular senescence, and cotreatment exerts cumulative effects resulting in apoptosis, illustrating that endostatin and transglutaminase 2 synergistically promote fibrosis (Lin et al., 2016).

In normal adults, senescent resident renal cells are replaced by proliferating resident cells or differentiated stem cells. Stem cells have a potential to differentiate into tubular epithelial cells, endothelial cells, mesangial cells, and podocytes. Stem cell aging delays this replacement process, leading to renal fibrosis. Young bone marrow cell transplantation into radiated old mice reduces renal fibrosis and senescence markers (Yang et al., 2011). Thus, stem cell aging as well as parenchymal cell aging contributes to age-related renal fibrosis (Yang et al., 2011).

4. Common mechanisms of cardiac and renal aging

Among possible biological mechanisms of aging, the heart and kidney share a number of commonalities, which lead to cellular senescence and functional disorder.

4.1. Oxidative stress

In the 1950s, Harman et al. proposed the free radical theory of aging, where aging is a generative process driven by the oxidative-damaged macromolecules (proteins, lipids, and DNA) (Harman, 1956). An increased systemic oxidative stress marker and a reduced anti-oxidant enzyme activity are observed in the healthy elderly compared to young subjects (Bouzid, Hammouda, Matran, Robin, & Fabre, 2014). Once the imbalance between the production of ROS and its quenching system occurs, oxidative stress results in cellular oxidative damage. ROS triggers downstream inflammatory signaling and cascades related to cellular proliferation and growth signals, which further generate ROS (Benigni, Cassis, & Remuzzi, 2010; Lithgow & Kirkwood, 1996).

Impaired electron transport function in mitochondria contributes to elevated electron leakage and ROS generation (Dai, Rabinovitch, & Ungvari, 2012). Mitochondria DNA is susceptible to oxidation, because it lacks protective histones and in proximity to high ROS levels (Yakes & Van Houten, 1997). The heart requires a large amount of energy, and mitochondria are critical to provide ATP to meet the demands of the myocardium (Dai, Rabinovitch et al., 2012). Mitochondria of aged murine hearts are more damaged and produce more ROS than young hearts (Roh et al., 2016). Mice with mitochondrial DNA mutation show exacerbated cardiac aging phenotypes, which are partially suppressed by mitochondrial catalase overexpression (Dai et al., 2010; Kujoth et al., 2005).

Because reabsorption of fluid and minerals by the renal tubular cells demand energy and consume ATP, mitochondria are abundant in renal tubular cells (Eirin, Lerman, & Lerman, 2017). Mitochondrial ROS production is greater in old rat kidney with impaired mitochondrial function, which is suppressed by enalapril and losartan (de Cavanagh et al., 2003).

NADPH oxidase is composed with membrane-bound subunits (a gp91phox homologue, NOX and p22phox) and cytosolic subunits (p67, p47, Noxa1, Rac)(Sahoo, Meijles, & Pagano, 2016). Various factors including angiotensin II, mechanical forces, environmental factors, and agonistic stimulation by aldosterone, endothelin-1, PDGF, TGF-ß, and TNF-α, most of which relate to pathological states and increase with age, stimulate NADPH oxidase, and produce ROS (Wang et al., 2010).

Aged cardiomyocytes show enhanced p47phox and ROS generation with prolonged TR(90), reduced tolerance to high stimulus frequency, and slowed intracellular Ca^{2+} rise and clearing rates (Ren et al., 2010). NOX4 is a major source of ROS in mitochondria of failing hearts, and cardiac-specific overexpression of NOX4 results in mitochondrial dysfunction, oxidative stress, and exacerbated age-related cardiac phenotypes in mice (Ago et al., 2010).

In old rats, renal ROS, dysfunction, and structural injury as well as cell senescence markers are increased compared to the young and associated with overexpression of NOX4 and p22phox in the kidney (Simao et al., 2011). The senescence-accelerated mouse prone-8 (SAMP8) shows higher levels of renal NOX2 expression and NADPH oxidase activity at the age of 1 month than the senescence-accelerated-resistant mouse (Baltanas et al., 2013).

Catalase, Cu/Zn-super oxide dismutase, and Mn-super oxide dismutase levels all decrease, and the renal antioxidant potential declines, with age in the rat kidney and plasma (Hou et al., 2016; Lim et al., 2012). These changes may contribute to the marked increase in oxidative stress and more severe renal injury after ischemia/reperfusion compared to young controls (Wang, Bonventre, & Parrish, 2014). Renal glutathione levels in aged rats is not different from young controls at baseline, but levels decrease more rapidly after ischemia/reperfusion in old rats (Shimizu, Araujo, Borges, de Tolosa, & Seguro, 2004). Induction of heme oxygenase-1 is blunted in the aged kidney, leading to worse ischemic injury (Ferenbach et al., 2011). Disorders in antioxidant system may explain high susceptibility of aging kidney to nephrotoxicity.

4.2. Renin-angiotensin system (RAS)

Numerous evidence demonstrates the protective effects of RAS inhibition on progressive cardiac and renal dysfunction in animals and humans (Lakatta, 2015; Sargento, Simoes, Longo, Lousada, & Reis, 2016; Spannella et al., 2018). Plasma renin activity and aldosterone levels show age-related decreases, due to limited synthesis and release of renin. Despite a suppressed systemic RAS, pharmacological inhibition of RAS with angiotensin converting enzyme (ACE) inhibitors, AT1 receptor blockers, or AT1 receptor deletion attenuates age-related cardiac and renal alterations and increases survival, suggesting an exacerbating role of local RAS in cardiorenal aging (Benigni et al., 2009; de Cavanagh, Inserra, & Ferder, 2015; Ferder, Romano, Ercole, Stella, & Inserra, 1998). Indeed, the

protein expression of angiotensin II, AT1 receptor, ACE, and aldosterone are markedly increased in hearts of older rats, while kidney localized RAS has been reported to both increase or decrease in aged kidneys, depending on the study (Li, Cao, Bai, Lin, & Shi, 2010; Lu, Li, Li, Li, & Wang, 1996; Schulman et al., 2010).

By binding to AT1 receptor, angiotensin II exerts various effects, including induction in inflammation, cell proliferation, ECM synthesis, and ROS production (Benigni et al., 2010; de Cavanagh et al., 2015; Feng, Wang, & Li, 2011; Ferrario, 2016; Ito et al., 2007; Mezzano, Ruiz-Ortega, & Egido, 2001; Wang & Shah, 2015). Angiotensin II-induced NADPH oxidase activation plays pivotal roles in both cardiac and renal aging (Benigni et al., 2010; Ito et al., 2007). For example, the increased levels of NADPH oxidase expression, NADPH oxidase-derived ROS, cardiomyocyte hypertrophy, and vascular remodeling in aged rat hearts are reproduced by the angiotensin II infusion in young rats (Wang, Zhang, et al., 2010). Regular exercise training improves cardiac function in elderly populations and recuses collagen deposition in rat hearts, which relates to the downregulation of cardiac angiotensin II and AT1 receptor and the concomitant suppression of NADPH oxidase-derived superoxide production (Lee, Kwak, Hord, Kim, & Lawler, 2015).

Aldosterone, the final product of the RAS pathway, induces the over-expression of cell senescence markers, including β-galactosidase, p21, and p53, as well as the reduction in an anti-senescence molecule Sirtuin1 through mineralocorticoid receptor stimulation in rat kidneys (Fan et al., 2011). Aldosterone infusion induces the overexpression of gp91phox, p47phox, and p67phox and increased oxidant levels in the kidney (Shibata, Nagase, Yoshida, Kawachi, & Fujita, 2007).

Chymase is a mast cell-derived serine protease that catalyzes conversion of angiotensin I to angiotensin II in humans, dogs, and hamsters (Miyazaki & Takai, 2006). Chymase inhibition suppresses cardiac fibrosis in a model of cardiomyopathy and improves hemodynamics and survival rates after myocardial infarction (Takai, Jin, & Miyazaki, 2012). Substrates of chymase include not only angiotensin I but also latent forms of TGF-β1 and MMP-9, producing their active forms (Takai, Jin, & Miyazaki, 2010). Chymase expression and activity increase with age and are reduced by exercise (Froogh et al., 2017). There are a wide range of effects chymase has in the heart that may accelerate cardiac aging.

The existence of intramitochondrial RAS is reported to regulate mitochondrial functions such as NO production and respiration through AT2 receptor stimulation (Abadir et al., 2011). Mitochondrial AT2 receptor is abundant in renal tubular cells from young mice, while mitochondrial AT1 receptor expression is very rare or not observed. Mitochondrial AT2 receptor decreases with age in the renal tubular cells, paralleled by increased levels of the mitochondrial AT1 receptor. Chronic treatment with losartan prevented the age-related decrease in mitochondrial AT2 receptor expression (Abadir et al., 2011).

Investigations into renal RAS will provide efficient and a wide range of potential therapeutic targets against cardiac and renal aging. Together with its hemodynamic and metabolic effects, RAS inhibitors may become comprehensive anti-aging agents against cardiorenal aging.

4.3. NO deficiency

One of the most important roles of endothelial cells of large arteries is producing NO, a critical vasodilator. Aged endothelial cells exhibit a decline in eNOS activity and NO production (Ma et al., 2014; Trinity et al., 2016). NO deficiency facilitates endothelial cell senescence (Ghebre et al., 2016). Because NO inhibits vascular inflammation, platelet aggregation, and aberrant cell proliferation, NO deficiency and inactivation results in significant vasomotor dysfunction and atherosclerotic vascular change (Kawashima & Yokoyama, 2004).

NO deficient mice show increased mortality and a shorter lifespan, supporting the favorable effects of NO to suppress aging. Nevertheless, the expression of NOS is reported to be both increased and decreased with age (Cau, Carneiro, & Tostes, 2012). Even if NOS levels increase with age, eNOS concentrations do not always correlate with the amount of NO; uncoupled eNOS produces superoxide (Lee, Zeeshan, Kim, & Chae, 2017). Oxidative stress in aging causes a functional inactivation of NO, and peroxynitrite, synthesized by binding superoxide to NO, and is also a very strong oxidant.

Asymmetric dimethylarginine (ADMA) is an endogenous NOS inhibitor, which is synthesized when arginine residues in proteins are methylated and then hydrolyzed (Vallance & Leiper, 2004). ADMA levels increase in aging rats and humans (Sverdlov, Ngo, Chan, Chirkov, & Horowitz, 2014). In the elderly, a high level of ADMA predicts cardiovascular events and death and correlates positively with reduced renal per-fusion, suggesting a key role of ADMA in cardiorenal aging (Zoccali, 2006).

Aged animals and humans exhibit reduced endothelium-dependent vasodilation in a number of arteries including the coronary artery. With age, coronary flow reserve is impaired, in part due to the multiple protective actions of NO that are blunted, leading to atherosclerotic changes in the coronary artery.

NO also plays an important role in cardiac contractility and Ca^{2+} channel functions in cardiomyocytes, either by cyclic guanosine monophosphate (cGMP) formation or by cGMP-independent protein modifications (S-nitrosation). The number and the activity of cardiac L-type Ca^{2+} channel increases, and L-type current inactivates more slowly, in myocytes with age. The prolonged Ca^{2+} transience and contraction may underlie the reduction in early diastolic filling and diastolic dysfunction. A dietary nitrate supplementation improves diastolic function associated with an accelerated cardiomyocyte calcium handling and augmented NO-cGMP-protein kinase G signaling in aged mice (Borlaug, 2016; Rammos et al., 2016).

In the aged rat kidney, NO content and acetylcholine-induced endothelium-dependent vasodilation is reduced, resulting in increased vasoconstriction and reduced renal perfusion (Long et al., 2005). Ischemia/reperfusion causes more severe functional and structural damage with a drastic increase in vasoconstriction in the kidney of old rats (Wang et al., 2014). Administration of the NO precursor L-arginine attenuates ischemia/reperfusion-induced renal injury in both young and old rats, to a greater extent in old rats, suggesting a

significant role of NO in increased susceptibility to ischemia in the aged kidney (Sabbatini et al., 1994).

In addition to regulation of renal and glomerular hemodynamics, NO exerts other important physiological functions, including the maintenance of medullary perfusion, mediation of pressure-natriuresis, blunting of tubuloglomerular feedback, inhibition of tubular sodium re-absorption, and modulation of renal sympathetic nerve activity. Age-related NO deficiency causes subclinical renal pathology in all of these processes (Mount & Power, 2006).

4.4. Advanced glycation end product (AGE)

AGEs accumulate in various aged organs and tissues including the heart and kidney (Son et al., 2017). During normal aging, AGEs accumulate primarily in proteins with long turnover rates (e.g., collagens), because the glycation reaction proceeds slowly (Simm et al., 2015). Serum AGE levels increase with age in healthy adults and correlate with circulating oxidative and inflammatory markers (e.g., 8-isoprostanes, vascular cell adhesion molecule 1, TNF-α, and C-reactive protein) (Uribarri et al., 2007). Plasma AGE levels correlate with all-cause and CVD mortality in the elderly (≥65 year old men and women) and diastolic dysfunction in aging men (43–78 years old) undergoing coronary artery bypass graft surgery (Campbell et al., 2012). Reduction of AGEs by dietary control suppresses development of CKD and improves survival rates (Vlassara et al., 2009).

Glycated enzymes and growth factors are unable to exert their essential biological activities, resulting in functional decline. For example, AGEs inhibit eNOS activation and impair endothelium-dependent vasodilation (Xu et al., 2003). AGEs also cause diastolic dysfunction by prolonging Ca^{2+} transient decay time, which is associated with crosslinked AGE modification of sarcoplasmic reticulum proteins in cardiomyocytes (Neviere, Yu, Wang, Tessier, & Boulanger, 2016).

Glycation-induced changes in protein structure and function also induce crosslinking of collagens elastic proteins, leading to tissue stiffening. AGE actions to reduce NO availability and enhance myocardial stiffness may contribute to diastolic dysfunction and high susceptibility to ischemic injury in aged human and animals (Ramasamy & Schmidt, 2012).

Another important mechanism of AGEs-induced aging exerts through the receptor of AGE (RAGE). The binding of AGEs to RAGE induces several intracellular signaling pathways, including MAP kinase, Janus kinase/signal transducers and activators of transcription, and activation of nuclear factor-κB (Heidland, Sebekova, & Schinzel, 2001; Simm et al., 2015; Stinghen, Massy, Vlassara, Striker, & Boullier, 2016). AGE binding to RAGE activates these signaling pathways in cardiac and renal cells by upregulating ROS (Inagi, 2016; Lu et al., 2004; Neviere et al., 2016). NADPH oxidase activation is the principle mechanism of ROS generation by the AGE-RAGE axis (Neviere et al., 2016). These signaling pathways increase synthesis of various ECM proteins, including collagens, fibronectin, and laminin through upregulation of growth factors (e.g. TGF-β), and production of inflammatory cytokines and adhesion molecules (Inagi, 2016; Lu et al., 2004; Neviere et al., 2016).

RAGE null mice are resistant to ischemia/reperfusion-induced cardiac cell apoptosis, as shown by decreased caspase 3 activity and cytochrome c and decreased Bcl-xL, along with suppressed phosphorylation of JNK and STAT5 (Tsoporis et al., 2010). RAGE-induced inhibition of autophagy through ERK and AKT pathways also induces cardiomyocyte apoptosis (Neviere et al., 2016). Age-related AGE/RAGE accumulation, therefore, may explain the high sensitivity of aging hearts to ischemic damage.

AGEs and their precursors are excreted from the body by kidney (glomerular) filtration. Methylglyoxal and 3-deoxyglucosone, representative precursors of AGEs, are uremic toxins. The age-related decline in GFR induces deficient clearance and excessive accumulation of AGEs and uremic toxins, which leads to vicious cycle leading to further renal injury.

The glycoxalase system catalyzes toxic metabolites (e.g. AGE precursors) and subsequently protects organs from glycative stress (Inagi, 2016). In older rat kidney, glycoxalase 1 activity is lower, concomitant with higher oxidative stress markers, compared to younger rats (Ikeda et al., 2011). Glycoxalase transgenic overexpression blunts age-dependent increases in oxidant markers in the kidney and urine and reduces senescent marker expression in tubules, age-related interstitial thickening, and renal dysfunction (Ikeda et al., 2011). Glycoxalase 1 protects against vascular endothelial cell senescent phenotypes and age-related NO deficiency, which may also contribute to not only renal protection but also cardiac protection (Inagi, 2016). Preserving the defense system against AGEs may be one therapeutic method for cardiorenal aging.

4.5. Lifestyle approaches to anti-aging

Regular exercise, healthy diet, and caloric restriction are the most evidenced lifestyle approaches to anti-aging (Seals, Brunt, & Rossman, 2018). During aging, regular exercise reduces risk of all-cause mortality, chronic diseases, and premature death (Baltaci, Mogulkoc, & Baltaci, 2016; Mora & Valencia, 2018). Exercise leads to anti-oxidant protections of organism both in young and old subjects (Lawler & Powers, 1998; Leeuwenburgh & Heinecke, 2001). Physically active elderly individuals exert similar levels of antioxidant activity and lipid peroxidation to those of young sedentary subjects. Furthermore, muscle cells release cytokines, interleukins, and other proteins that play important roles in the protection against low-grade inflammation such as atherosclerosis (Golbidi, Badran, & Laher, 2012; Pedersen, 2011). Increased physical activity achieving a 30% energy deficit compared to controls increases average life span but does not expand maximal lifespan in rodents. While there are no data whether physical activity will expand lifespan in humans, it may be achieved at least in part by preventing chronic disease (Blair et al., 1989; Holloszy, 1997; Holloszy, Smith, Vining, & Adams, 1985). In addition to increasing endogenous antioxidants by exercise, nutritional antioxidants, including vitamin E, vitamin C, carotenoids, ubiquinone, polyphenols, and flavonoids, have been the focus of attention to reduce oxidative stress (Simioni et al., 2018). The mechanisms of exogenous antioxidant actions are neutralizing free radicals, repairing oxidized membranes, decreasing ROS production, and neutralizing ROS by short-chain free fatty acids and cholesteryl esters via lipid metabolism (Berger, 2005).

Caloric restriction is the only reproducible strategy that delays senescence and prolongs lifespan in yeast, worms, and rodents (Alfaras et al., 2016). In both the heart and the kidney, caloric restriction is reported to delay the aging process by increasing Sirtuins, which are demonstrated to moderate aging in yeast to mammals (Haigis & Sinclair, 2010).

In addition to reduced metabolic rate, alteration in insulin sensitivity, hormonal secretion, sympathetic nerve activation, and gene expression may contribute to anti-aging effects of caloric restriction (Heilbronn & Ravussin, 2003). Caloric restriction exerts anti-aging effects by reducing oxidative stress (Lee & Yu, 1990; Sohal & Weindruch, 1996). Short-term caloric restriction also reduces markers for inflammation (e.g. C-reactive protein) in obese and non-obese subjects, whereas the effects of long-term caloric restriction in human are unknown (Bastard et al., 2000; Heilbronn, Noakes, & Clifton, 2001; Mavri et al., 2001; Velthuis-te Wierik, Meijer, Kluft, & van den Berg, 1995). Recent clinical study reports that subjects who have sleeping difficulty have a shorter relative telomere length compared to those with no sleeping difficulties, suggesting that poor sleep may be an accelerator of or response to aging (Zgheib et al., 2018).

5. Common ECM targets for cardiac and renal aging

The ECM provides structural support for cells, and the major component of cardiac and renal ECM is collagen. The ECM also regulates inflammation and fibrosis, in part by serving as a reservoir for the sequestration of growth factors and inflammatory cytokines. Below, we discuss ECM proteins relevant to both cardiac and renal physiology and pathophysiology.

5.1. Osteopontin

Osteopontin, initially identified as a bone matrix protein, is increased in various pathological states in both the heart and kidney (Irita et al., 2011; Singh, Foster, Dalal, & Singh, 2010; Xie et al., 2001). Osteopontin promotes inflammation via cell adhesion, chemotaxis, and signal transduction including NF-κB activation, and angiotensin II is reported to increase osteopontin expression (Singh et al., 2010; Xie et al., 2001).

In the normal adult heart, osteopontin expression is low and does not show an age-related increase in the absence of injury (Table 2) (Singh et al., 2010). Following ischemia/reperfusion, osteopontin protein is 1.5-fold higher in old (6 years old) compared to young (2 years old) dogs (Jugdutt, Palaniyappan, Uwiera, & Idikio, 2009). The higher susceptibility to injury in the elderly may be due in part to the exacerbated induction of osteopontin. On the other hand, old mice (>2 years old) show worse systolic dysfunction and dilative and hypertrophic remodeling post-myocardial infarction and reperfusion compared to young mice (2–3 months old), which is associated with decreased and delayed neutrophil and macrophage infiltration and reduced osteopontin expression in the infarcted myocardium (Bujak et al., 2008).

Osteopontin expression in the adult human kidney is present at low levels and localized to distal tubular segments. The degree of tubular expression correlates with the number of macrophages and monocytes in the kidney (Bujak et al., 2008; Xie et al., 2001). Renal

osteopontin expression shows age-related increases (Table 2), which is correlated with blood nitrogen levels, suggesting a role for osteopontin in age-related renal dysfunction (Liang & Barnes, 1995). Macrophage accumulation in the kidney may be caused by osteopontin and may cause further osteopontin generation. Though renoprotective effects of osteopontin in the recovery process after ischemia injury are reported, osteopontin may be one of the critical promoters of renal aging (Xie et al., 2001).

5.2. Secreted protein acidic and rich in cysteine (SPARC)

SPARC is expressed during morphogenesis and re-induced during tissue remodeling (Brekken & Sage, 2000). SPARC is a procollagen-binding matricellular protein, which chaperones procollagen processing (Bornstein & Sage, 2002; Bradshaw & Sage, 2001). SPARC is induced under fibrotic conditions in a variety of organs and tissues, including the heart and kidney (Pichler et al., 1996; Wu et al., 1997). SPARC increases the aged LV (Table 2), along with increases in myocyte hyper-trophy, LV stiffness, and insoluble fibrillar collagen content (Bradshaw et al., 2009; Bradshaw et al., 2010). Furthermore, SPARC promotes not only post-translational processing but also collagen I production and a disintegrin and metalloproteinase with thrombospondin-like motifs 1 (ADAMTS1) induction in cardiac fibroblasts (Toba et al., 2016). ADAMTS1 is an ECM protease that increases with age in the mouse LV, along with a decrease in its substrate, versican (Toba et al., 2016).

SPARC deletion reduces inflammation in a lipopolysaccharide-induced footpad model and dextran sodium sulfate-induced murine colitis, while the function of SPARC in regulating inflammatory processes depends on its cellular origin (Ng et al., 2013; Rempel et al., 2007; Sangaletti et al., 2011). Plasma levels of SPARC positively correlate with hypersensitive C-reactive protein and white blood cell numbers in gestational diabetes, indicating that SPARC is upregulated in the setting of inflammation (Xu et al., 2013).

In the heart, SPARC is detected primarily in fibroblasts and, at lower levels, in endothelial cells, cardiomyocytes, and macrophages (McCurdy et al., 2011; Ridinger et al., 2009). SPARC deletion delays age-related increases in macrophage infiltration and proinflammatory marker expression. Age-related increases in markers of M1 macrophage polarization and decreases in a marker of M2 macrophage polarization are blunted in SPARC-null murine hearts, indicating SPARC acts as a mediator of age-related cardiac inflammation by facilitating M1 > M2 polarization (Toba et al., 2015).

There is no direct study investigating the role of SPARC in renal aging, and only one report shows that SPARC mRNA decreases with age (Table 2) (Hultstrom et al., 2012). However, there are many reports demonstrating pro-inflammatory and fibrogenic roles of SPARC in renal diseases. In addition, SPARC treatment increases M1 > M2 polarization in isolated peritoneal macrophages, and this direct effect of SPARC to macrophages suggests that SPARC may induce inflammaging by M1 polarization not only in the hearts but also the kidney (Toba et al., 2015). Serum SPARC levels are elevated in patients with fibrotic renal injury (Kanauchi, Nishioka, & Dohi, 2000). In subtotal nephrectomized renal injury model, induced by right subcapsular nephrectomy and ligation of approximately two-thirds of the left kidney, SPARC expression is increased in both the sclerotic glomerulus and damaged tubulointerstitium (Wu et al., 1997). SPARC gene deletion reduces the expression of MCP-1

and IL-1ß, and TGF-ß, as well as reduces macrophages and collagen deposition in the perivascular and tubulointerstitial regions and leads to significant functional improvement in angiotensin II-induced hypertensive mice (Socha, Manhiani, Said, Imig, & Motamed, 2007). The decrease in SPARC mRNA levels in the aged kidney may be due to negative feedback.

In addition to studies showing angiotensin II treatment induces SPARC expression in mesangial cells and in animals, ACE inhibition or AT1 receptor blockade reduces renal SPARC expression in subtotal nephrectomized rats (Socha et al., 2007; Wu et al., 1997).

ADAMTS1 is expressed during kidney development, and its expression becomes lower after birth (Thai & Iruela-Arispe, 2002). Lipopolyssacharide up-regulates renal ADAMTS1 expression, suggesting a significant role for ADAMTS1 in inflammation (Kuno et al., 1997; Thai & Iruela-Arispe, 2002). In rats, ischemia/reperfusion injury induces ADAMTS1 expression and reduces VEGF in proximal tubules in the first week after reperfusion (Basile, Fredrich, Chelladurai, Leonard, & Parrish, 2008). In the UUO kidney, ADAMTS1 mRNA is induced in the renal tubular epithelial cells in the outer stripe of the outer medulla, localized to the area damaged by the acute kidney injury (Nakamura, Sakai, Ohata, & Komurasaki, 2007). ADAMTS1 may accelerate acute injury in the aging kidney by inducing inflammation, vascular rarefaction, and fibrosis.

6. Aging effects on MMPs in the heart and kidney

There are 25 members of reported mammalian MMPs, which are classified into collegenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs, and other MMPs (Iyer, Patterson, Fields, & Lindsey, 2012). MMPs are endogenously inhibited by the tissue inhibitors of metalloproteinases (TIMPs: TIMP1–4). All TIMPs inhibit pro-and active MMPs with relatively low selectivity, by forming tight non-covalent 1:1 complexes. MMPs are important key regulators of ECM turnover by remodeling and degrading ECM components. Age-related changes in MMPs and TIMPs are summarized in Table 3.

6.1. MMPs in the aging heart

Among the MMPs, collagenases (e.g. MMP-1 and MMP-13), gelatinases (e.g. MMP-2 and MMP-9), stromelysin (e.g. MMP-3), matrilysin (e.g. MMP-7), metalloelastase (MMP-12), and the membrane-type MMP (e.g. MT1-MMP; MMP-14) are highly related to myocardial remodeling and consequently cardiac function (Kwak, 2013; Lindsey & Zamilpa, 2012).

MMP-1 and MMP-2 are abundant in normal LV (Iyer et al., 2012; Lindsey & Zamilpa, 2012). Abundant expression of MMP-1 and MMP-2 suggests a homeostatic role of these MMPs in the heart. Cardiac pro-MMP-1 and MMP-2 activity in rats decrease with age by 45% and 40%, respectively (Robert et al., 1997). MMP-14 (MT1-MMP) is detected in normal LV (Iyer et al., 2012; Lindsey & Zamilpa, 2012). In sedentary old (31 months old) rats displaying fibrillar collagen deposition, active MMP-1, MMP-2, and MMP-14 in the ECM fraction of the LVs are reduced, and TIMP-1 and TGF-β elevated compared to young (3 months old) group (Kwak et al., 2011). Exercise training reduces these age-related changes in collagen contents and imbalance of MMPs and TIMPs (Kwak et al., 2011). Cardiomyocyte restricted overexpression of human MMP-1 in mice results in a marked

deterioration of systolic and diastolic function at older age associated with loss of cardiac interstitial collagen and compensatory cardiac hypertrophy (Kim et al., 2000). At physiological levels, MMP-1, MMP-2, and MMP-14 are anti-fibrotic factors. With age, MMP-2 and MMP-14 activity increases, along with NADPH oxidase, inflammatory cytokines, and collagen content (Batkai et al., 2007; Horn et al., 2012; Wang, Zhang, et al., 2010).

In humans with no evidence of CVD, circulating levels of MMP-2, MMP-7, TIMP-1, TIMP-2, and TIMP-4 increase with age, and the levels of MMP-7, TIMP-1, and TIMP-4 correlate with the decline in early to late (E/A) LV filling ratio (Bonnema et al., 2007). Upregulation of MMP-7 and TIMPs contributes to diastolic dysfunction in elderly populations. We found that MMP-3, MMP-8, MMP-9, MMP-12, and MMP-14 increase in the insoluble protein fraction of old (23 months old) mouse LV compared with young (3 months old) and/or middle-aged (15 months old) mouse LV, suggesting enhanced ECM degradative and pro-fibrotic capacity in the aging LV (Lindsey et al., 2005). Indeed, cardiomyocyte-restricted overexpression of MMP-14, yielding approximately a 200% increase in MMP-14 expression, induces fibrillar collagen in young (3 month old) LV and exacerbates the age-related increase in LV fibrillar collagen deposition by >2-fold by middle age (14 months) (Spinale et al., 2009). These mice also display LV dilation and systolic dysfunction. A greater activation of TGF-β and its signaling, displayed with increased expression of low molecular weight latency-associated TGF-binding protein and phosphorylated Smad2 in the middle-aged LV, is further enhanced by MMP-14 overexpression. Age-related enhancement of MMP expression and activity actually leads to elevated collagen deposition and consequent LV stiffness in the aging heart.

MMP-9 is predominantly expressed in leucocytes and also produced by cardiomyocytes, fibroblasts, vascular smooth muscle, endothelial cells, neutrophils, and mast cells (Lindsey & Zamilpa, 2012). The normal LV septum and free wall express MMP-9, but at very low levels compared to injury LV such as post-myocardial infarction (Iyer et al., 2012; Lindsey & Zamilpa, 2012). Aged mice exhibit elevated circulating MMP-9 levels, which positively correlate with plasma MCP-1 and enddiastolic dimension (Chiao et al., 2011). MMP-9 mRNA increases after the age of 12–15 months in the murine LV, and MMP-9 protein from the age of 26–34 months (Chiao et al., 2012). MMP-9 may be an indicator of accelerated cardiac aging.

6.2. MMPs in the aging kidney

Ten members of MMPs (MMP-1, MMP-2, MMP-3, MMP-9, MMP-13, MMP-14, MMP-24, MMP-25, MMP-27, MMP-28) and three members of TIMPs (TIMP-1, TIMP-2, TIMP-3) are expressed in the kidney (Catania, Chen, & Parrish, 2007; Tan & Liu, 2012). Under basal conditions, MMPs are at low levels and are tightly regulated. Since a high rate of ECM turnover is required during kidney development, MMPs are highly expressed in the developing kidney, playing important roles in nephron formation. Among MMPs expressed in adult kidneys, MMP-1, MMP-2, MMP-3, MMP-9, MMP-13, and MMP-14 have been extensively studied (Giannandrea & Parks, 2014; Tan & Liu, 2012).

In 2, 6, 12, and 19 month old Sprague Dawley rats, MMP-1 protein decreases and the collagen I protein, not mRNA, increases in the renal cortex with age, which is associated with age-related fibrosis and glomerular and tubular histological injury. Collagen III protein decreases with age, potentially due to the progressive replacement with collagen I. The adverse accumulation of collagen I, due to insufficient degradation, is caused by age-related decrease in MMP-1 (Gagliano et al., 2000). MMP-13, a murine interstitial collagenase, is produced from fibroblasts and degrades collagen I, II, and III. Different from MMP-1, renal MMP-13 protein expression increases with age (Dasgupta, Kar, Van Remmen, & Melendez, 2009). MMP-1 and MMP-13 are redox-sensitive enzymes, and Cu/Zn-super oxide dismutase deletion exacerbates age-related increase in MMP-13 and adverse loss of collagen in the Bowman's capsule, which is crucial for filtration (Dasgupta et al., 2009). Age-related oxidative stress contributes to excessive and adverse collagen degradation through MAP kinase signaling and MMP-13 over-expression. MMP-1 increases in renal fibrosis in the settings of dialysis, kidney transplants, and progressive kidney scarring. Fibroblasts from patients with various premature aging diseases release high levels of MMP-1.

MMP-7 is not detected in normal human kidney, but is upregulated in distal tubular epithelium in various pathological conditions including polycystic kidney disease in humans and UUO in mice, and acute folic acid nephropathy in mice (Catania et al., 2007). Due to its inducible expression, MMP-7 has been proposed as a new screening marker for kidney damage. The correlation between fibrotic changes and MMP-7 activation are reported in the kidney, as well as in the lung and liver (Bauer et al., 2017; Huang et al., 2005). Aging increases renal expression of MMP-7, along with elevated renal and urinary kidney injury molecule-1 (Chen et al., 2007). Susceptibility to ischemic injury is increased in kidneys with age, characterized by elevated lactate dehydrogenase release and exacerbated structural damage and corrected by caloric restriction (Chen et al., 2007). Caloric restriction inhibits age-related MMP-7 upregulation and fibrotic collagen deposition, suggesting a significant role for MMP-7 induction in age-related renal fibrosis (Oelusarz et al., 2013). MMP-7-overexpressed in kidney cells *in vitro* show increases in collagen Ia2 and collagen IIIa1 transcription mediated by phosphoinositide 3-kinase, p38, ERK, Src, and protein kinase A signaling, independently of inflammation (Oelusarz et al., 2013). Interestingly, these effects may be caused by pro-MMP-7, because the authors detect no active form of MMP-7 in the aging kidney. MMP-7 activates MMP-2 and MMP-9, both of which are well-reported to contribute to renal pathogenesis and fibrosis.

TIMP-3 protein expression in renal parenchymal tissues at autopsy correlates with advancing age, not gender, ethnicity, diabetes, hyper-tension, or smoking status. Renal TIMP-3 is not detected in subjects under 20 years old and becomes strongly induced in the 40s. TIMP-3 is expressed around small and intermediate-sized arterioles and occasionally the afferent arterioles of the glomerulus (Macgregor, Eberhart, Fraig, Lu, & Halushka, 2009). In contrast, TIMP-3 expression in the renal medulla is lower in old mice (2 years old) than the young mice (12 weeks old) (Kassiri et al., 2009).

The renal TIMP-1 levels increase with age, and transgenic overexpression of TIMP-1 accelerates age-related downregulation of MMP-2 and MMP-9 expression and activity, collagen III and IV accumulation, fibrosis, and renal dysfunction (Zhang et al., 2006). An

imbalance in MMPs and TIMPs causes ECM accumulation in the aging kidney (Sangaralingham et al., 2016). Because TIMP-1 overexpression also promotes age-related increases in ICAM-1, macrophage infiltration, and TGF-ß, increases in TIMP-1 mediates age-related renal fibrosis at least in part by enhancing inflammation through ICAM-1 upregulation (Zhang et al., 2006).

MMP-2 and MMP-9 are produced from mesangial cells, glomerular cells, epithelial cells, endothelial cells, tubular cells of collecting ducts, fibroblasts, and macrophages in the kidney (Tan & Liu, 2012). Renal MMP-2 and MMP-9 are at low levels in the absence of pathology. Advancing age causes decreases in MMP-2 and MMP-9 mRNA, protein, and activity and increases TIMP-1, which contribute to the decline in fibrillar collagen degradation (Oelusarz et al., 2013). Likewise, old (12 month old) female Dahl-salt sensitive rats receiving low (0.1%) salt chow exhibit an aging physiological and structural phenotype, with increased TGF-β and reduced activity of MMP-2 and MMP-9 (Maric et al., 2004). MMP-2 and MMP-9 increases with age can be inhibited by caloric restriction (Oelusarz et al., 2013). Kidneys from old rats (20 month old) express higher levels of MMP-9 protein compared to younger rats, and atorvastatin improves age-related pathological changes by reducing MMP-9 (Zhao et al., 2016).

7. MMP-9 as a potential therapeutic target for cardiorenal aging

MMP-9, first known as neutrophil gelatinase or gelatinase b, processes a variety of ECM substrates such as collagens, elastin, entactin, fibronectin, gelatin, laminin, and proteoglycans and non-ECM substrates such as endothelin-1, IL-1β, IL-6, IL-8, osteopontin, latent TGF-β, TNF-α, VEGF, and even other MMPs (MMP-2 and MMP-13) and itself. Because of the wide range of substrates, MMP-9 plays important roles in the process of cardiorenal aging and the pathogenesis of CVD and CKD. MMP-9 also has strong association with common mechanisms of cardiac and renal aging. For example, angiotensin II, RAGE, and oxidative stress are reported to induce upregulation of MMP-9, and physiological levels of NO produced by eNOS decreases MMP-9 (Cipollone et al., 2003; O'Sullivan, Medina, Ledwidge, Radomski, & Gilmer, 2014; Pushpakumar et al., 2013; Ridnour et al., 2007; Stacy, Yu, Horak, & Larson, 2007).

7.1. MMP-9 in the aging heart

In the setting of myocardial infarction, older mice show a more drastic increase in LV MMP-9 and a higher risk of cardiac rupture despite a greater extent of collagen content and crosslinking than the young mice (Yang et al., 2008). MMP-9 deletion improves survival and blunts age-related LV dilation post-myocardial infarction (Yabluchanskiy et al., 2016). Macrophages isolated from MMP-9-null infarct LVs demonstrate enhanced expression of M2 markers, including TGF-ß1. Promoted macrophage M2 polarization may contribute to the increased collagen accumulation, which results in a stiffer infarct region and limits LV dilation and further adverse remodeling in MMP-9-null aged mice (Voorhees et al., 2015). Hence, inhibition of MMP-9 is expected to be a promised therapeutic strategy against myocardial infarction in the elderly.

Cardiac MMP-9 expression and activity increases with age, while plasma MMP-9 increases in mice and decreases in humans. The role of MMP-9 as an age accelerator is supported by evidence that global MMP-9 gene deletion attenuates age-related LV diastolic dysfunction and fibrosis (Chiao et al., 2012). MMP-9 expression in healthy murine LV doubles with age (Chiao et al., 2012; Yabluchanskiy et al., 2014). In senescent mice (>23 months of age), MMP-9 co-localizes with macrophages (Chiao et al., 2011). MMP-9 in cardiac fibroblasts actually declines beginning at middle-age in mice, supporting that macrophages are major source of MMP-9 in the aging LV (Lindsey et al., 2005).

MMP-9 deletion leads to increased angiogenic factors in the plasma (von Willebrand factor) and the LV (VEGF and integrin αv), which support an increase in the number of vessel numbers in the aging LV (Yabluchanskiy et al., 2014). In MMP-9 null LV, vascular permeability is also attenuated, indicating that deleterious effects of MMP-9 on cardiac capillaries include both promoting vessel rarefaction and vascular leakiness (Yabluchanskiy et al., 2014).

Age-related increases in the expression of pro-inflammatory genes, including Ccr7, Ccr10, IL-1f8, IL-13, and IL-20, are blunted by MMP-9 gene deletion (Yabluchanskiy et al., 2014). While macrophages produce MMP-9, MMP-9 also affects macrophage polarization. With advancing age, wild type mice show a linear increase in cardiac M1 macrophages and decrease in cardiac M2 macrophages; in MMP-9-null mice, these linear changes are abolished. Aged LVs from MMP-9 null mice have a higher cardiac M2 macrophage ratio than age-matched wild type LVs, indicating that MMP-9 facilitates macrophage M2 to M1 polarization. MMP-9 stimulated young peritoneal macrophages show an M1/M2 mid-transition polarization state (Ma et al., 2015). MMP-9 promotes cardiac inflammaging by changing macrophage polarization without affecting the number of macrophages.

MMP-9 deletion inhibits fibrillar collagen deposition by inhibiting TGF-β signaling, characterized by decreased TGF-β-induced protein (Tgfbi) and Smad2 phosphorylation, and its downstream pro-fibrotic periostin and connective tissue growth factor (Chiao et al., 2012). Fibro-blasts play principal roles in controlling ECM homeostasis, and MMP-9 expression in fibroblasts from middle-aged and old murine LVs decreases compared to the young (Lindsey et al., 2005). MMP-9 may play important roles in maintaining physiological function of fibroblasts when produced locally and at a physiological amount.

Elastin microfibril interface-located protein-1 (EMILIN-1), an adhesive glycoprotein, is secreted by myocytes, endothelial cells, vascular smooth muscle cells, and adventitial fibroblasts. Myocardial EMILIN-1 expression decreases with age, and global gene deletion of MMP-9 attenuates age-related EMILIN-1 downregulation (Padmanabhan Iyer et al., 2016). EMILIN-1 deficiency is associated with vascular stiffening and hypertension (Zacchigna et al., 2006). Thus, MMP-9-induced cardiac aging and stiffness may be mediated by EMILIN-1 reduction.

MMP-9 cleaves osteopontin, and MMP-9-cleaved osteopontin fragments increase fibroblast migration *in vitro* (Lindsey, Zouein, Tian, Padmanabhan Iyer, & de Castro Bras, 2015). Though the total levels of osteopontin expression does not show age-related increase in the

normal heart (Singh et al., 2010), MMP-9-cleaved osteopontin fragment may increase with age and play important roles in cardiac fibrosis by migrating fibroblasts.

Citrate synthase, a rate limiting enzyme of tricarboxylic acid cycle and a marker of mitochondrial function, is a MMP-9 substrate *in vivo* and *in vitro* (de Castro Bras et al., 2014). The citrate synthase activity decreases in the infarct LV of wild type mice, but not in MMP-9-null mice, suggesting that MMP-9 promotes mitochondrial dysfunction after myocardial infarction (de Castro Bras et al., 2014). Because mitochondrial dysfunction is a strong cell senescent factor, MMP-9 may contribute to cardiac aging by cleaving citrate synthase.

7.2. MMP-9 in the aging kidney

MMP-9 is expressed in the developing metanephric mesenchyme and is decreased in the adult murine kidney, with very low to no expression in collecting duct epithelial cells and glomeruli. MMP-9 null mice display no significant differences in renal phenotype in the absence of injury (Andrews et al., 2000). MMP-9 is elevated in a variety of kidney disease models and humans, including patients with IgA nephritis, Henoch-Schönlein nephritis, non-IgA mesangial proliferative glomerulonephritis, lupus nephritis, and Alport syndrome (Urushihara, Kagami, Kuhara, Tamaki, & Kuroda, 2002). In serum of polycystic kidney disease patients, MMP-9 and collagen IV are elevated. In allograft rejection after kidney transplantation, MMP-9 is increased and the immunosuppressive agent rapamycin decreases MMP-9 (Tan & Liu, 2012).

MMP-9 is colocalized in scattered neutrophils within diseased glomeruli in acute poststreptococcal glomerulonephritis (Urushihara et al., 2002). In UUO mice, renal MMP-9 activity increases, and the major sources of MMP-9 are tubular epithelial cells, myofibroblasts, and macrophages. Peritubular endothelial cells also express MMP-9, which has potential to induce endothelial-to-mesenchymal transition (EndMT) (Abadir et al., 2011; Catania et al., 2007; Tan et al., 2013; Zhao et al., 2013; Zhao et al., 2017). MMP-9-induced EMT in UUO rats is STAT3-dependent, and mesenchymal stem cells protect against renal fibrosis by suppressing the STAT3-MMP-9-EMT axis (Matsui et al., 2017). A neutralizing antibody for MMP-9 given at early- and late-stages reduces MMP-9-cleaved osteopontin, macrophage infiltration, tubular cell EMT, and fibrosis in the kidney (Tan et al., 2013).

MMP-9 mRNA, protein, and activity increase or decrease with age in the rat kidney, depending on the strain evaluated. Even in the same strain, renal MMP-9 mRNA increases or decreases depending on the studies. In a mouse model of anti-glomerular basement membrane nephritis, MMP-9 null mice exhibit severe renal dysfunction and fibrin deposition, suggesting a protective role of MMP-9 (Lelongt et al., 2001). TGF-ß-induced Wnt/ß-catenin signaling, the fibrogenic pathway, induces MMP-9 transcription, indicating a link between MMP-9 expression and fibrogenic signals (Wang, Dai, Li, & Liu, 2011). In renal fibroblasts, tissue-plasminogen activator induces MMP-9 gene and protein expression (Hu et al., 2006). As a posttranslational regulation, the interaction between MMP-9 and neutrophil gelatinase-associated lipocalin (NGAL), a renal injury marker, prevents MMP-9 degradation, suggesting prolonged MMP-9 action in renal pathology.

The anti-angiogenic factor angiostatin is produced by plasminogen cleavage by several MMPs, including MMP-9 (Patterson & Sang, 1997). In the arteries of diabetic CKD patients, upregulation of MMP-9 and angiostatin correlate with impaired angiogenesis, endothelial dysfunction, and vessel stiffening (Chung et al., 2009). In acute kidney injury, renal angiostatin is generated due to MMP-9 activation (Basile, Fredrich, Weihrauch, Hattan, & Chilian, 2004). Age-related increases in angiostatin with decreased MMP-9 expression and activity have also been reported in the aging rat kidney (Satoh et al., 2013).

In wild type mice with nephritis, the macrophage number per kidney is 2000, in MMP-9 null mice with nephritis, this number decreases to 500 (Kluger et al., 2013). Bone marrow transplantation of wild type-derived donor cells to MMP-9-deficient mice prior to the induction of nephritis cancels the suppression of renal tissue injury and macrophage recruitment, suggesting a crucial role of leucocyte-derived MMP-9 in recruiting pro-inflammatory macrophages (Kluger et al., 2013). MMP-9 cleaves osteopontin, and cleavage enhances macrophage migration *in vitro*, suggesting MMP-9 is essential for inflammatory cell migration directed by osteopontin cleavage (Tan et al., 2013). Among the leucocyte subpopulations, activated macrophages are reported to be the major source of MMP-9 (Kluger et al., 2013). Because macrophage number increases with age in the kidney, the macrophage is presumed to be a major source of MMP-9 in aging kidney. The fact that MMP-9 polarizes M1 > M2 macrophages *in vitro* and that M1 > M2 polarization increases in aging kidney suggest MMP-9 may play roles in renal inflammaging.

Tubular epithelial cells that are cultured with activated macrophage-conditioned media undergo EMT, which is suppressed by a MMP-2/9 inhibitor or MMP-9 knockout, suggesting a significant role of macrophage-derived MMP-9 in EMT (Tan et al., 2010). Since less EMT occurs in MMP-9-ablated tubular epithelial cells than WT cells, tubular epithelial cells are also the origins of MMP-9.

MMP-9 causes fibrosis as a consequence of interactions with the inflammatory process and also by direct signaling. In addition to catalyzing pro-TGF-β to its active form, MMP-9 directly mediates EMT in renal cells downstream and independent of TGF-β (Wang et al., 2010). For example, MMP-9 deletion decreases EMT and collagen deposition without affecting TGF-β. *In vitro*, even without TGF-β stimulation, increased MMP-9 can promote EMT by digesting matrigel that mimics native tubular basement membrane, suggesting that MMP-9 promotes EMT by tubular basement membrane destruction (Wang, Zhou, et al., 2010).

TGF-ß-induced EndMT and concomitant production of collagen I and fibronectin in cultured mouse renal peritubular endothelial cells is suppressed by MMP-9 deletion, showing that MMP-9 promotes renal fibrosis through EndMT (Zhao et al., 2017). In the same study, MMP-9-mediated EndMT is demonstrated to be mediated by Notch signaling.

8. Potential therapeutic targets for CVD and CKD in the elderly

Both physiological aging and pathological premature aging in the heart and kidney induce inflammation and subsequent fibrosis. However, in pathological states, more numbers of

macrophages are detected in the heart and the kidney compared to what is seen with physiological aging. For example, macrophage numbers increase approximately 10 times in hypertensive heart failure and 100 times in myocardial infarction (days 3–5 post-myocardial infarction) compared to non-diseased controls (Halade et al., 2013; Lindsey et al., 2006; Xia et al., 2009). In addition to macrophages, various inflammatory cells contribute to disease progression. While macrophages play roles in hypertensive heart failure, neutrophils and macrophages increase after the onset of myocardial infarction (Halade et al., 2013; Lindsey et al., 2006). In diseased kidney, myocytes, macrophages (hypertensive nephrosclerosis, diabetic nephropathy, and acute kidney injury), lymphocytes (diabetic nephropathy), and neutrophils (acute kidney injury) participate in the pathogenesis (Duran-Salgado & Rubio-Guerra, 2014; Ferenbach & Bonventre, 2015; Meyrier, 2015).

8.1. For CVD

In hypertensive heart failure, TGF-β is induced at day 7, when macrophage numbers start to decline, suggesting that TGF-β may bridge the inflammatory and reparative phases (Xia et al., 2009). As pressure overload is not associated with significant cardiomyocyte loss, TGF-β-induced matrix deposition results in fibrotic remodeling (Kuwahara et al., 2004; Xia et al., 2009). Aged mice show worse outcome after pressure overload, while there is also a study reporting that aged mice exhibit less LV remodeling and higher survival than young mice following size-appropriate transverse aortic constriction (Geng et al., 2017).

Macrophage activation after coronary artery occlusion is biphasic with both M1 and M2 macrophages being present. While M1 macrophages promote ECM degradation, M2 macrophages contribute to scar formation by releasing TGF-β, IL-10, and VEGF (Nahrendorf, Pittet, & Swirski, 2010). Fibrillar collagen content increases approximately 10 to 20-fold on days 7–15 post-myocardial infarction (Cleutjens, Verluyten, Smiths, & Daemen, 1995). Increased collagen content and collagen crosslinking during the maturation phage leads to LV stiffness and heart failure. Insufficient fibrillar collagen formation, in contrast, results in inadequate wound healing and scar formation and can lead to excessive wall thinning and cardiac rupture.

Transverse aortic contraction induces an approximate 4-fold increase in SPARC expression (Bradshaw et al., 2009). In SPARC-null mice, pressure overload-induced increases in fibrillar collagen content and myocardial stiffness are attenuated (Bradshaw et al., 2009). In a mouse model of myocardial infarction, SPARC expression increases in the LV, colocalizing with myofibroblasts and leukocytes (Schellings et al., 2009). SPARC deletion preserves LV systolic function at the early stage (day 3) after coronary ligation (McCurdy et al., 2011). In contrast, SPARC deletion results in increased mortality from an increased incidence of cardiac rupture and failure day 7 post-myocardial infarction due to immature collagen formation (Schellings et al., 2009). Suppression of SPARC may not be beneficial but rather deleterious for the long term treatment in the settings of myocardial infarction.

MMP-9 deletion attenuates LV remodeling and dysfunction after transverse aortic constriction (Heymans et al., 2005). The adverse effect of MMP-9 in the pressure-overloaded heart is strengthened by a recent study that demonstrates that angiotensin II facilitates cardiac hypertrophy through MMP-9 activation (Wang et al., 2017).

In a murine myocardial infarction model, a robust increase in MMP-9 activity is corresponding with infiltration of neutrophils (day 1) and macrophages (day 4) (Halade et al., 2013). Robustly increased MMP-9 from inflammatory cells raises the possibility that MMP-9 facilitates early LV injury post-myocardial infarction (Yabluchanskiy, Ma, Iyer, Hall, & Lindsey, 2013). Whereas MMP-9 gene deletion attenuates LV dilation in both young and old murine models of myocardial infarction, pharmacological inhibition of MMP-9, decreasing MMP-9 activity by 30%, prevents neutrophil apoptosis, which leads to prolonged inflammation, insufficient scar formation and enhanced matrix degradation, suggesting a critical role of MMP-9 in inflammatory process for a subsequent adaptive scar formation (Iyer et al., 2016).

Restricted overexpression of human MMP-9 in aged mice exacerbates age-related hypertrophy, vessel rarefaction, inflammation, and fibrosis (Toba et al., 2017). Overexpression of macrophage MMP-9 in aged mice superimposed on myocardial infarction causes decreased angiogenesis and increased macrophage infiltration with M2 macrophage phenotype. While collagen content after myocardial infarction is greater in transgenic mice than wild type mice, overexpression of macrophage MMP-9 results in reduced collagen crosslinking, attenuated cardiac stiffness, and improved diastolic function (Zamilpa et al., 2012). One interpretation is that the diverse actions of macrophage MMP-9 in aged hearts depend on the physiological or pathological context, the concentration of MMP-9, and the indirect downstream effects on vascular cells, inflammatory cells, and fibroblasts.

8.2. For CKD

Histopathological features of hypertensive nephrosclerosis include microvascular changes with hyalinesis of the preglomerular vessel walls and thickening of the intima and reduplication of the internal elastic lamina of the arcuate and interlobar arteries, leading to glomerulosclerosis and patchy tubular atrophy, which are associated with inflammation and tubulointerstitial fibrosis (Hill, 2008; Klanke et al., 2008; Meyrier, 2015). Aging kidneys display lesions close to hyper-tensive nephrosclerosis even without hypertension (Marin, Gorostidi, Fernandez-Vega, & Alvarez-Navascues, 2005). Animal models of hypertensive nephrosclerosis demonstrate that angiotensin II plays major roles in creating microvascular lesions and stimulating inflammatory cascades that end in renal fibrosis (Mezzano et al., 2001). Comorbidities of metabolic disorders such as metabolic syndrome and obesity increase oxidative stress and inflammation directly and through an increase of angiotensin II. Since angiotensin II plays pivotal roles in renal aging, high levels of age-related angiotensin II in the kidney may contribute to the susceptibility to hypertensive renal injury in the elderly populations.

Diabetic nephropathy is characterized with mesangial expansion, thickening of basement, tubular, and glomerular membrane, and ECM accumulation in these membranes that eventually cause tubular atrophy, tubulointerstitial and glomerular fibrosis, and glomerulosclerosis (Duran-Salgado & Rubio-Guerra, 2014; Li et al., 2008). Metabolic changes due to hyperglycemia lead to AGE generation, poly pathway activation, abnormal PKC activation, and oxidative stress. Among various cytokines, chemokines, and adhesion molecules, which are involved in the inflammatory response in diabetic nephropathy,

circulating MCP-1 and vascular cell adhesion molecule-1 and renal TNF-α correlate with the severity of albuminuria in diabetic patients and animals. TGF-β is one of the principle mediators of fibrosis in diabetic nephropathy, and its concentration is higher in diabetic patients with albuminuria (Duran-Salgado & Rubio-Guerra, 2014; Li et al., 2008).

In many cases, progression of renal failure is due to a secondary insult (e.g. shock, sepsis, surgery, and administration of nephrotoxic agents), associated with transient intrarenal hypoperfusion (acute kidney injury) rather than worsening of primary renal disease (Ferenbach & Bonventre, 2015). Ischemia-reperfusion injury particularly affects the outer stripe of the outer medulla where baseline hypoxia exists. Following insult, the kidney has the ability to return to normal function, whereas functional recovery potential declines with age (Schmitt & Cantley, 2008). Vascular injury remains for several days, and injured vasculatures show impaired NO generation, adhesion molecules expression, and high permeability. Within the first 24 h, resident immune cells release a burst of chemotactic signals, and injured tubular and endothelial cells promote neutrophil migration, followed by monocyte recruitment, which differentiations predominantly M1 macrophages. Day 5, macrophage polarization shifts to M2 subsets, which are necessary for renal repair by releasing various factors including TGF-β. Depending on the background (e.g. aging, hypertension, and diabetes) and the extent and frequency of injury, acute kidney injury leads to being arrested in dedifferentiated tubular cells with production of profibrogenic factors, resulting in maladaptive repair and developing CKD. In maladaptive repair, increased numbers of myofibroblasts are key players in the collagen deposition (Ferenbach & Bonventre, 2015). Pathological stimulus results in more prominent injury in the elderly people who potentially have levels of basal inflammation and fibrosis. Despite the cause of injury, inhibiting maladaptive repair which results in excessive fibrosis is the common and critical target for renal aging and CKD.

Inhibitors for MMPs suppress proteinuria and glomerular injury with or without anti-hypertensive action (Williams et al., 2011). In spontaneously hypertensive rats, which show proteinuria a fibrillar collagen deposition, renal MMP-9 levels are higher compared to normotensive control, while spontaneously hypertensive stroke-prone rats shows progressive inflammatory cell infiltration and severe fibrosis with decreased levels of MMP-9 (Camp, Smiley, Hayden, & Tyagi, 2003; Gianella et al., 2007).

Type 2 diabetic Goto-Kakizaki rats demonstrate high expression of MMP-9, collagen I, collagen III, and fibronectin during the early stages before functional and histological pathology emerge (Portik-Dobos et al., 2006). MMP-9 deletion attenuates nephropathy in the streptozotocin-induced type 1 diabetic model (Li et al., 2014). These reports highlight the exacerbating roles of MMP-9 in diabetic nephropathy. Indeed, administration of the MMP inhibitor doxycycline to patients with diabetic nephropathy receiving ACE inhibitors and angiotensin II receptor blockers significantly reduce proteinuria for the short duration of 3 months (Aggarwal et al., 2010).

As described above, MMP-9 contributes to decreases in renal capillary density after ischemia by generating angiostatin (Basile et al., 2004). MMP-9 deletion stabilizes microvascular density after ischemia/reperfusion by preserving renal VEGF (Lee et al.,

2011). In addition to vessel rarefaction, ischemia-induced degradation of the tight junction protein zonula occludens-1 in glomerulus is associated to the increased MMP-9 activity (Caron, Desrosiers, & Beliveau, 2005).

9. Sex differences in cardiorenal aging

Sex-differences in cardiorenal aging have been under-investigated. The age-related progression of cardiovascular and renal diseases is slower in premenopausal women compared with men (Keller & Howlett, 2016; Perry 3rd., 1999; Reckelhoff, 2001; Silbiger & Neugarten, 2003).

In the heart, the number of LV myocytes declines through apoptosis with age in male human and animals but not in the female (Olivetti et al., 1995; Olivetti, Melissari, Capasso, & Anversa, 1991; Zhang et al., 2007). In addition to myocyte apoptosis, the decrease in peak Ca^{2+} transients/contractions in myocytes from aged male animals but not female control may be one of the reasons why heart failure are seen more in older men than older women (Dibb, Rueckschloss, Eisner, Isenberg, & Trafford, 2004; Dunlay & Roger, 2012; Feridooni, Dibb, & Howlett, 2015). Risk factors for heart failure differ between genders with myocardial ischemia playing a critical role in men and hypertension being important in women (Greiten, Holditch, Arunachalam, & Miller, 2014).

In the healthy population, the age-related decline in GFR starts from approximately the age of 30 in men, while GFR remains stable beyond the age of 50 in women. Renal plasma flow is also preserved in aging women, whereas it falls with age in men (Berg, 2006; Kielstein et al., 2003). Plasma ADMA levels increase with age and correlate with renal plasma flow declines in healthy aging men (Kielstein et al., 2003). In women, age-related increases in ADMA delay until approximately 50 years old and correlate with endothelial dysfunction (Celermajer et al., 1994; Schulze et al., 2005).

Angiotensin II-overexpressed aged male myocytes maintain contractile function but exert the increased vulnerability to arrhythmic activity. In contrast, female myocytes from intracardiac angiotensin II-transgenic mice are more susceptible to age-related contractile deficit and exhibit a low level of spontaneous activity in the pressure of prolonged Ca^{2+} release, suggesting compensatory mechanisms to prevent spontaneity in the pro-arrhythmogenic setting (Mellor et al., 2014). Despite the controversy, the majority of reports support that ACE inhibitors have lower efficacy in women than men, and ARBs should be chosen for women (Sullivan, 2008). Males have greater levels of AT1 receptor expression in the kidney and higher AT1 receptor bindings in glomeruli (Sullivan, 2008).

There is accumulating evidence that estrogens protect cardiovascular tissue (Baylis, 2012; Zheng et al., 2003). In addition to subsequent renal protection by improving cardiovascular function, estrogens exert direct kidney protection. Though some studies demonstrate that estrogens induce worse renal pathology, estrogens inhibit ECM accumulation and vascular smooth muscle and mesangial cell growth (Baylis, 2012). Estrogen receptor α gene deletion accelerates age-related albuminuria and glomerular damage and develops age-related hypertension (Elliot et al., 2007; Zhu et al., 2002). Estrogens inhibit RAS by various

mechanisms, whereas androgens stimulate it (Diz, 2008; Komukai, Mochizuki, & Yoshimura, 2010). Estrogens exert NO stimulatory effects by direct and indirect actions (Baylis, 2012). The effects of sex hormones on the cardiac and renal RAS and NO bioavailability may influence the sex differences in aging.

In 699 Framingham Study participants free of heart failure and previous myocardial infarction (mean age, 57 years, 58% women), plasma MMP-9 associates with increased LV diastolic dimensions, increased wall thickness, and higher LV mass in men but not in women (Sundstrom et al., 2004). In 832 consecutive outpatients with chest pain (mean age 53.7, 516 men, 346 women), serum MMP-9 levels independently correlates with the diagnosis of non-calcified and mixed plaques in women but not in men (Gu et al., 2017).

17β-estradiol treatment increases MMP-9 expression and activation in mesangial cells (Potier et al., 2001). In the aged (12 months old) rat kidney, ovariectomy increases TGF-β expression and decreases cortical MMP-9 activity, which are reversed by 17β-estradiol replacement (Maric et al., 2004). Age-related and postmenopausal renal dysfunction may be induced by insufficient ECM degradation by MMP-9, but the relationship between sex difference and MMP-9 in renal aging is not clarified.

Further investigation into the sex-specific variation in aging and pathological mechanisms, including MMP-9, will be needed for adequate and effective therapeutic strategy against cardiorenal aging and CVD and CKD in the elderly population.

10. Conclusions

Common mechanisms of cardiac and renal aging that affect each other include RAS activation and stimulation of the AGE-RAGE axis to induce oxidative stress, which decreases NO bioavailability. These mechanisms all have strong bidirectional relationships with MMP-9, and a major conclusion of this review is that macrophage-derived MMP-9 promotes cardiorenal aging by vessel rarefaction, inflammation, and fibrosis. In terms of ECM, SPARC and osteopontin interact closely with MMP-9 may be a therapeutic target for cardiorenal aging. The wide MMP-9 network provides strong rationale for examining MMP-9 as a comprehensive therapeutic cross-organ target (Figs. 3 and 4).

Although we conclude that MMP-9 inhibition is critical for age-related CVD and CKD, no MMP-9-specific inhibitor has not become in clinical use yet and in fact it may be inhibition of specific MMP-9 substrate targets will be more effective. Until clinically available selective MMP-9 inhibitors have been developed, alternative MMP-9 inhibition with clinically available agents would be helpful. For example, peroxisome proliferator-activated receptors α and γ ligands downregulate the MMP-9 expression in lipopolysaccharide-treated human monocytic THP-1 cells (Shu et al., 2000). Since angiotensin II induces MMP-9 expression and angiotensin II-induced cardiomyocyte hypertrophy is mediated by MMP-9, tissue protective actions by RAS inhibitors may be at least in part by MMP-9 inhibition (Wang, Cheng, et al., 2017). In addition to these agents, suppression of inflammation by lifestyle modification and treatment of diseases results in the decline in inflammatory cells, which are the major source of MMP-9.

Future studies to determine the extent and timing of MMP-9 inhibition and the background which divides the effects of MMP-9 and to develop clinically available selective MMP-9 inhibitors will provide further possibility of macrophage-derived MMP-9.

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Abbreviations:

CVD	cardiovascular disease
CKD	chronic kidney disease
MMP	matrix metalloproteinase
ECM	extracellular matrix
GFR	glomerular filtration rate
SASP	senescence-associated secretory phenotype
LV	left ventricle
VEGF	vascular endothelial cell growth factor
NO	nitric oxide
eNOS	endothelial NO synthase
ROS	reactive oxygen species
IL	interleukin
TNF	tumor necrosis factor
Ccl	chemokine (C-C motif) ligand
Ccr	CC chemokine receptor
Mif	macrophage migration inhibitory factor
MCP	monocyte chemoattractant protein
TGF	transforming growth factor
EMT	epithelial-mesenchymal transition
ICAM	intracellular adhesion molecule
PDGF	platelet-derived growth factor

MAP	p38 mitogen-activated protein
UUO	unilateral ureteral obstruction
ROS	reactive oxygen species
RAS	renin-angiotensin system
ACE	angiotensin converting enzyme
ADMA	asymmetric dimethylarginine
cGMP	cyclic guanosine monophosphate
AGE	advanced glycation end product
RAGE	receptor of AGE
SPARC	secreted protein acidic and rich in cysteine
ADAMTS	a disintegrin and metalloproteinase with thrombospondin-like motifs
TIMP	tissue inhibitors of metalloproteinase
EMILIN-1	elastin microfibril interface-located protein-1
SD	Sprague-Dawley
DS	Dahl salt-sensitive

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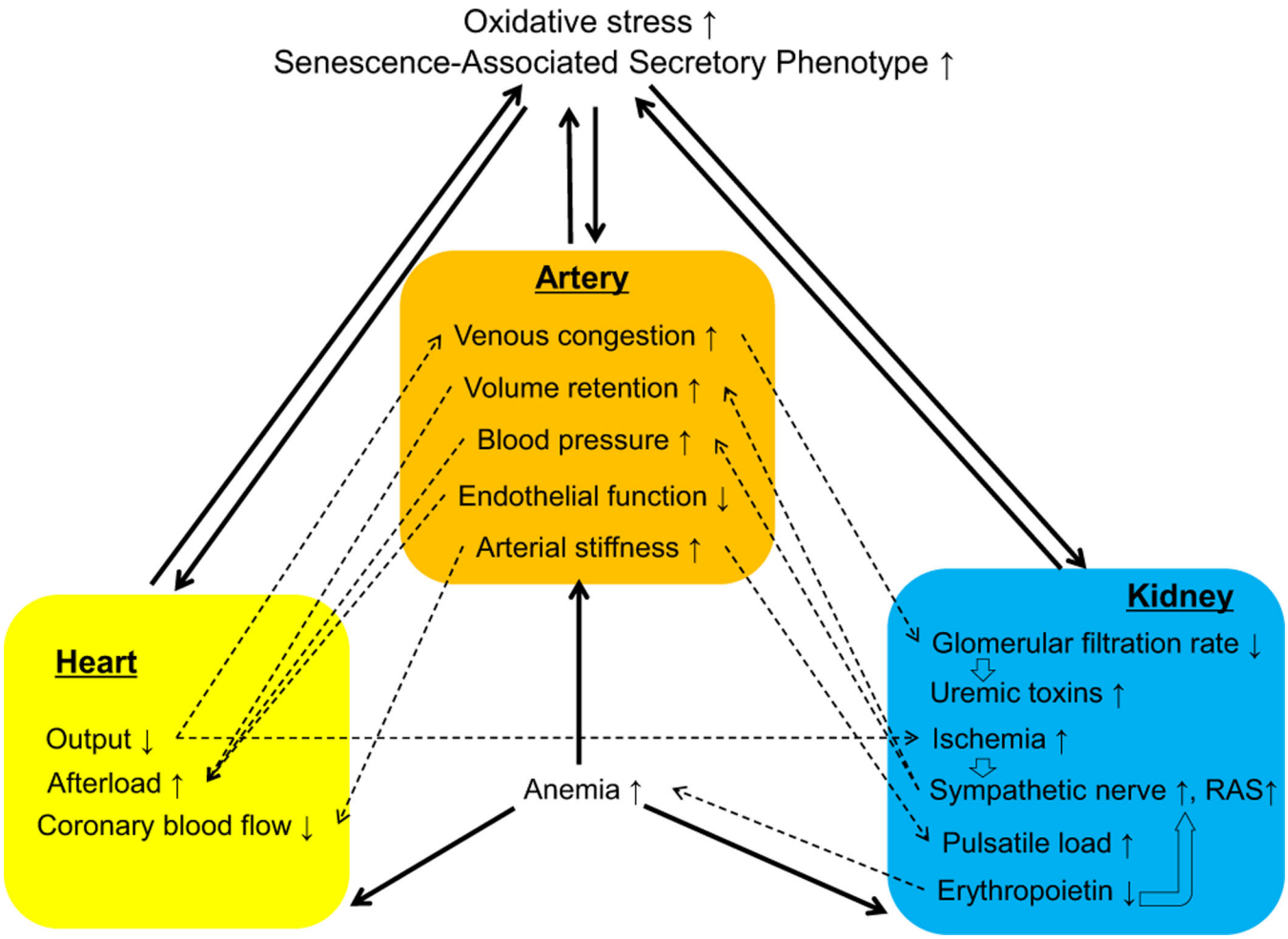

Fig. 1.

Mechanisms of cardiorenal interaction, showing the association among cardiac, renal and vascular dysfunction. While aging itself and common diseases such as hypertension, diabetes, and dyslipidemia are important risk factors for cardiovascular disease and chronic kidney disease, cardiac, renal, and vascular dysfunction exacerbate each other. Hatched lines show physiological interactions, and solid lines indicate the adverse interactions among organs.

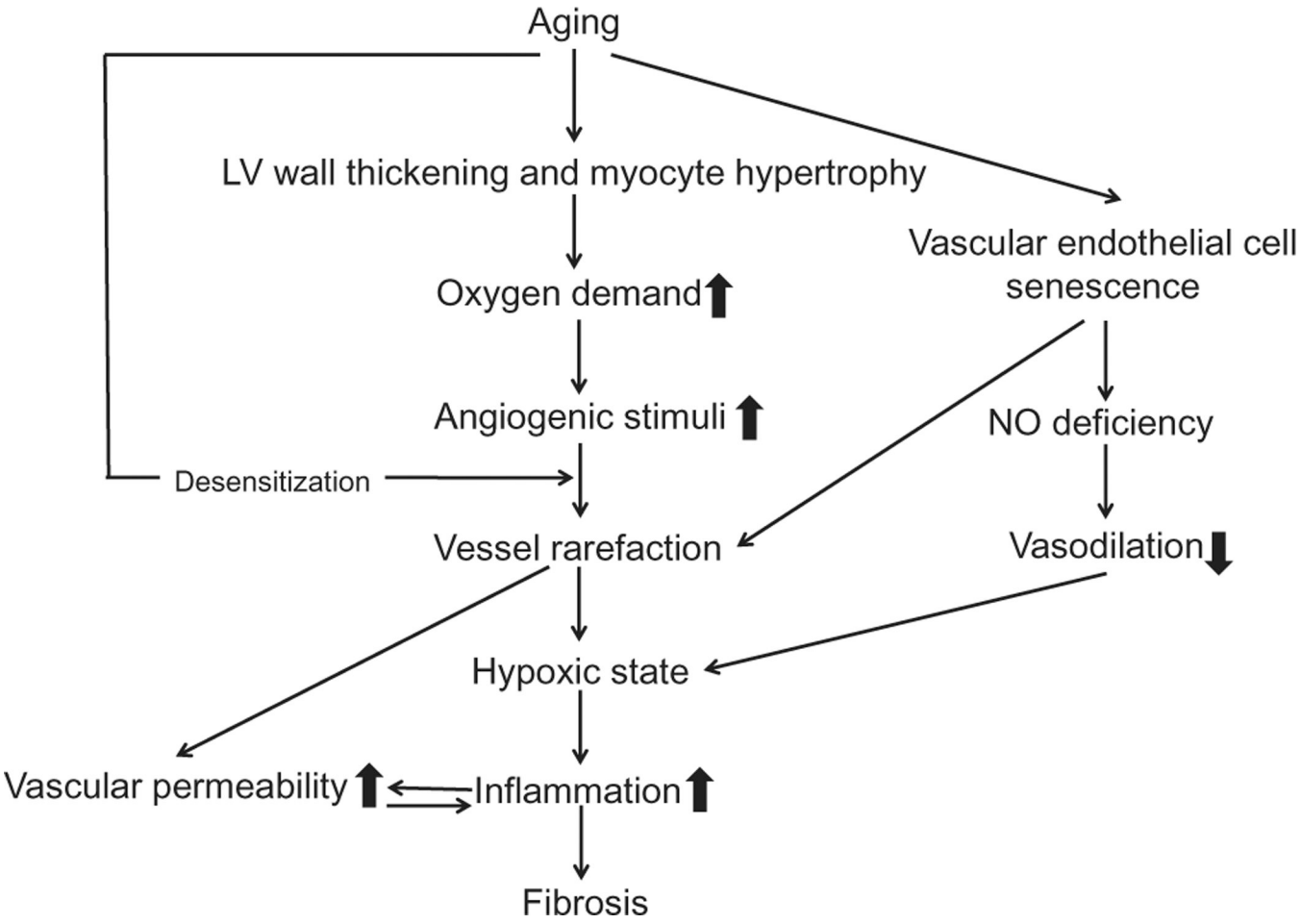

Fig. 2.

Mechanistic figure showing the development process of inflammation and fibrosis in the aging left ventricle (LV). Age-related LV wall thickness and myocyte hypertrophy generate an additional oxygen demand, which in turn increases the production of angiogenic stimuli. Despite the production of angiogenic stimuli, blood vessel numbers do not increase in aging LV. Together with nitric oxide deficiency due to endothelial cell senescence, vessel rarefaction leads to an hypoxic state, which triggers inflammation and subsequent fibrosis.

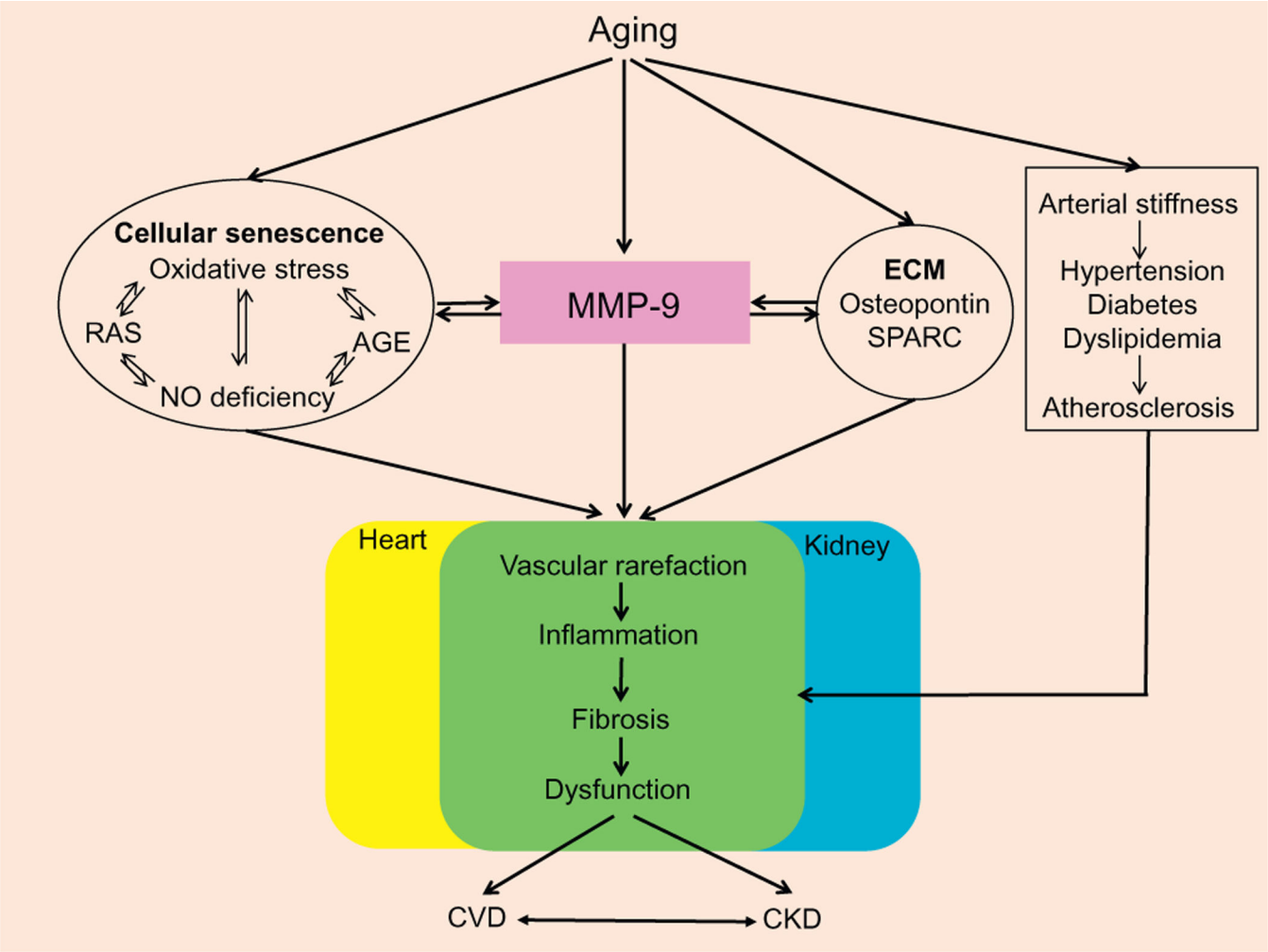

Fig. 3.

Mechanistic diagram showing effects of macrophage-derived matrix metalloproteinase (MMP)-9 in cardiorenal aging. In addition to reported common aging mechanisms such as oxidative stress, renin-angiotensin system (RAS), nitric oxide (NO) deficiency, and advanced glycation end product (AGE), all of which cause cellular senescence, and extracellular matrix (ECM) components including osteopontin and secreted protein acidic and rich in cysteine (SPARC), macrophage-derived MMP-9 causes inflammation and fibrosis dependent and independent vascular rarefaction in the heart and kidney. Age-related systemic changes and comorbidities of risk factors (hypertension, diabetes, dyslipidemia) facilitates cardiorenal aging. Cardiovascular disease (CVD) and chronic kidney disease (CKD) interact each other, exacerbating their dysfunctional changes.

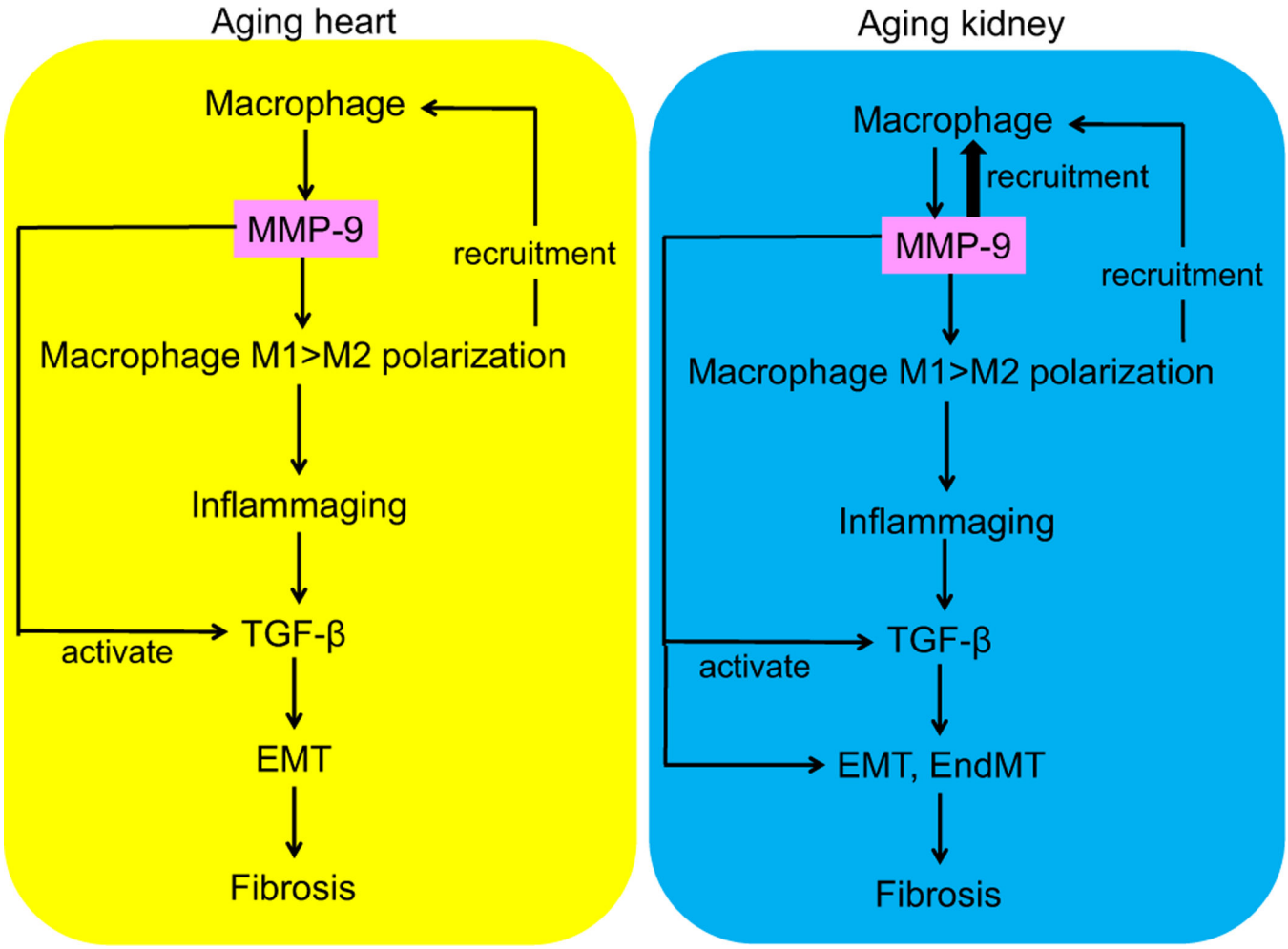

Fig. 4.

Suggested roles of matrix metalloproteinase (MMP)-9 in inflammaging and fibrosis in the heart and the kidney. MMP-9, produced from recruited macrophages in the aging heart, promotes inflammaging by increasing macrophage M1 polarization, not macrophage recruitment. Macrophage-derived MMP-9 in the aging kidney induces both macrophage M1 polarization and leucocyte mobilization. MMP-9 converts latent TGF-β to active form, which leads to fibrosis. Epithelial-mesenchymal transition (EMT) in the kidney is both TGF-β-dependent and independent. *EndMT*; endothelial-to-mesenchymal transition.

Table 1

Characterization of Aging Effects on Physiology and Structure in Heart and Kidney.

			Age-related changes
Heart	Physiology		Diastolic function ↓, Systolic function ↔, Maximum heart rate ↓
			End diastolic and systolic volume in response to postural maneuvers and during exercise ↓
	Structure		Left ventricular concentric hypertrophy ↑, Cardiomyocyte number 4, Cardiomyocyte size ↓, Amyloid and lipofuscin accumulation ↑, Vessel density ↓, Inflammation ↑, Perivascular and interstitial fibrosis ↑
Kidney	Physiology		
		Glomerular	Glomerular filtration rate ↓, Hyperfiltration ↑
		Tubular	Urine concentration ↓, Electrode reabsorption and secretion regulation ↓
			Acid secretion↔
		Endocrine	Renin release ↓, Erythropoietin production ↔, Conversion from 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D ↓
	Structure		
		Global	Kidney mass ↓, Parenchymal thickness ↓, Cortex volume ↓, Medullary volume ↑
			Renal sinus fat ↑, Parenchymal, parapelvic, and hyperdense cysts ↑, Angiomyolipomas ↑
			Nephron number ↓, Inflammation ↑
		Glomerular	Global glomerulosclerosis ↑, Podocyte injury and loss ↑, Basement membrane thickness ↑
		Tubular	Tubular atrophy ↑, Intratubular cast ↑, Peritubular capillary ↓, Tubulointerstitial fibrosis ↑, Basement membrane thickness ↑
		Vascular	Arteriosclerosis ↑, Alomerular arterioles ↑

↑ increase, ↓decrease, ↔ unchanged.

Table 2

Summary of Age-related Changes in ECM in Heart and Kidney.

		Change with age	Sample type	Species	References
Heart	Collagen I	↑	Protein	C57BL/6, human	(Cieslik et al., 2011; Gazoti Debessa et al., 2001)
		↓	mRNA	C57BL/6, SD rat, Fischer rat, FBNF1 rat	(Annoni et al, 1998; Kwak et al, 2011; Thomas, Zimmerman, Hansen, Martin, & McCormick 2000; Toba et al, 2016)
		↔	mRNA	Sheep	(Horn et al, 2012)
		↓	mRNA	C57BL/6J	(Chiao et al, 2012)
	Collagen III	↓	protein	C57BL6/J	(Padmanabhan Iyer et al, 2016)
		↓	mRNA	C57BL/6, SD rat, Fischer rat, C57BL/6J	(Annoni et al, 1998; Chiao et al, 2012; Thomas et al, 2000; Toba et al, 2016)
	Collagen IV	↓	mRNA	C57BL/6	(Toba et al., 2016)
	Collagen V	↓	mRNA	C57BL/6	(Toba et al., 2016)
	Collagen XV	↓	Protein	C57BL6/J	(Padmanabhan Iyer et al, 2016)
	Fibronectin	↓	mRNA	C57BL/6	(Toba et al., 2016)
	Laminin	↑	mRNA	C57BL/6	(Toba et al., 2016)
		↓	mRNA	C57BL/6	(Toba et al., 2016)
	Osteopontin	↓	mRNA	C57BL/6, SD rat	(Chiao et al, 2012; Graf et al, 1997)
	SPARC	↑	Protein	C57BL/6,C57B16/SV129, sheep	(Bradshaw et al, 2010; Horn et al, 2012; Toba et al, 2016)
		↓	mRNA	C57BL/6	(Toba et al., 2016)
	Thrombospondin-1	↑	Protein	Kunming mouse	(Cai, Yuan, Fei, & Zhao, 2012)
Kidney	Collagen I	↑	Protein	SD rat, C57BL/6	(Gagliano et al., 2000; Hou et al., 2016)
		↔	Protein	Human	(Eikmans, Baelde, de Heer, & Bruijn, 2001)
		↑	mRNA	Human, Fischer rat	(Eikmans et al, 2001; Oelusarz et al, 2013)
		→	mRNA	Fischer rat, SD rat	(Gagliano et al., 2000; Sangaralingham et al, 2016)
		↓	mRNA	Wistar rat	(Hultstrom et al., 2012)
	Collagen III	↑	Protein	NIH mouse, C57BL/6	(Hou et al, 2016; Zhang et al, 2006)
		↓	Protein	SDrat	(Gagliano et al., 2000)
		↑	mRNA	Fischer rat	(Oelusarz et al., 2013)
		→	mRNA	SDrat	(Gagliano et al., 2000)
		↓,↔	mRNA	Fischer rat	(Sangaralingham et al., 2016)
		↓	mRNA	Wistar rat	(Hultstrom et al., 2012)
	Collagen IV	↑	Protein	NIH mouse, human, mouse, DSrat	(Eikmans et al, 2001; Maric et al, 2004; Schneider et al, 2017; Zhang et al, 2006)

	Change with age	Sample type	Species	References
	↔	mRNA	Human	(Eikmans et al., 2001)
	↓	mRNA	Wistar rat	(Hultstrom et al., 2012)
Collagen VI	↓	mRNA	Wistar rat	(Hultstrom et al., 2012)
Fibronectin	↑	Protein	C57BL/6	(Hou et al., 2016)
	↓	mRNA	Wistar rat	(Hultstrom et al., 2012)
Laminin	↑	Protein	DSrat	(Maric et al., 2004)
Osteopontin	↑	mRNA	Wistar rat	(LiangS Barnes, 1995)
SPARC	↓	mRNA	Wistar rat	(Hultstrom et al., 2012)
Thrombospondin-1	↑	Protein	SDrat	(Kang et al., 2001)

↑ increased, ↓decreased, ↔ unchanged, *ECM* extracellular matrix, *SPARC* secreted protein acidic and rich in cysteine, *SD* Sprague-Dawley, *DS* Dahl salt-sensitive.

Table 3

Summary of Age-related Changes in MMPs in Heart and Kidney.

		Change with age	Sample type	Species	References
Heart	MMP-1	↓	Protein	SD rat, FBNF1 rat	(Kwak et al, 2011; Thomas et al., 1998)
		↓	mRNA	Rat	(Robert et al., 1997)
	MMP-2	↓	Protein	FBNF1 rat	(Kwak et al., 2011)
		↓	mRNA	rat	(Robert et al., 1997)
		↑	Protein	Sheep	(Horn et al., 2012)
		↑	mRNA	FBN rat, mouse, C57BL/6	(Batkai et al., 2007; Toba et al., 2016; Wang, Zhang, et al., 2010)
		↑	Protein (plasma)	Human	(Bonnema et al., 2007)
		↔	Protein (soluble, insoluble)	CB6F1	(Lindsey et al., 2005)
	MMP-3	↑	Protein (soluble)	FBNF1 rat	(Kwak et al., 2011)
		↔	Protein	FBNF1 rat	(Kwak et al., 2011)
		↑	mRNA	C57BL/6	(Toba et al., 2016)
		↓	Protein (soluble)	CB6F1	(Lindsey et al., 2005)
		↑	Protein (insoluble)	CB6F1	(Lindsey et al., 2005)
	MMP-7	↑	Protein (plasma)	Human	(Bonnema et al., 2007)
		↔	Protein (soluble)	CB6F1	(Lindsey et al., 2005)
	MMP-8	↔	Protein (soluble)	CB6F1	(Lindsey et al., 2005)
		↑	Protein (insoluble)	CB6F1	(Lindsey et al., 2005)
	MMP-9	↑	mRNA	mouse, C57BL/6	(Batkai et al., 2007; Toba et al., 2016)
		↓	Protein (plasma)	Human	(Bonnema et al., 2007)
		↑	Protein (plasma)	C57BL6/J	(Chiao et al., 2011)
		↑	Protein	C57BL6/J	(Chiao et al., 2012)
		↑	mRNA	C57BL6/J	(Chiao et al., 2012)
	MMP-12	↓	Protein (soluble)	CB6F1	(Lindsey et al., 2005)
	MMP-13	↓	mRNA	C57BL/6	(Toba et al., 2016)
		↓	Protein (soluble)	CB6F1	(Lindsey et al., 2005)
	MMP-14	↓	Protein	FBNF1 rat	(Kwak et al., 2011)
		↑	mRNA	FBN rat	(Wang, Zhang, et al., 2010)
		↓	Protein (soluble)	CB6F1	(Lindsey et al., 2005)

		Change with age	Sample type	Species	References
		↑	Protein (insoluble)	CB6F1	(Lindsey et al., 2005)
	MMP-15	↓	mRNA	C57BL/6	(Toba et al., 2016)
	MMP-28	↓	Protein	C57BL/6J	(Ma et al., 2012)
	TIMP-1	↑	Protein	FBNF1 rat	(Kwak et al., 2011)
		↔	Protein	Sheep	(Horn et al., 2012)
		↑	Protein (plasma)	Human, C57BL6/J	(Bonnema et al., 2007; Chiao et al., 2011)
	TIMP-2	↔	Protein	FBNF1 rat, sheep	(Horn et al., 2012; Kwak et al., 2011)
		↓	mRNA	FBN rat	(Wang, Zhang, et al., 2010)
		↑	Plasma	Human	(Bonnema et al., 2007)
		↔	Protein (soluble)	CB6F1	(Lindsey et al., 2005)
	TIMP-3	↔	Protein	Sheep	(Horn et al., 2012)
		↔	Protein (soluble)	CB6F1	(Lindsey et al., 2005)
		↓	Protein (insoluble)	CB6F1	(Lindsey et al., 2005)
	TIMP-4	↔	Protein	Sheep	(Horn et al., 2012)
		↑	Protein (plasma)	Human	(Bonnema et al., 2007)
		↔	Protein (soluble)	CB6F1	(Lindsey et al., 2005)
Kidney	MMP-1	↓	Protein	SDrat	(Gagliano et al., 2000)
	MMP-2	↔	Protein	SDrat	(Gagliano et al., 2000)
		↓	mRNA, protein	NIH mouse	(Zhang et al., 2006)
		↑	mRNA	Fischer rat	(Oelusarz et al., 2013)
	MMP-3	↓	mRNA	Fischer rat	(Oelusarz et al., 2013)
	MMP-7	↑	mRNA, protein	Fischer rat	(Chen et al., 2007)
		↑	mRNA	Fischer rat	(Oelusarz et al., 2013)
	MMP-9	↓	Protein	DS rat, SD rat	(Maric et al., 2004; Satoh et al., 2013)
		↑	mRNA, protein	Wistar rat	(Zhao et al., 2016)
		↓	mRNA, protein	NIH mouse	(Zhang et al., 2006)
		↑	mRNA	Fischer rat	(Oelusarz et al., 2013)
		↓	mRNA	Fischer rat	(Sangaralingham et al., 2016)
	MMP-12	↑	mRNA	Fischer rat	(Oelusarz et al., 2013)
	MMP-13	↑	Protein	C57BL/6J	(Dasgupta et al., 2009)
	MMP-14	↑	mRNA	Fischer rat	(Oelusarz et al., 2013)

	Change with age	Sample type	Species	References
MMP-16,17,19,20,23,25	↑	mRNA	Fischer rat	(Oelusarz et al., 2013)
TIMP-1	↑	mRNA, protein	NIH mouse	(Zhang et al., 2006)
	↑	mRNA	Fischer rat	(Oelusarz et al., 2013; Sangaralingham et al., 2016)
TIMP-2	↑	mRNA, protein	NIH mouse	(Zhang et al., 2006)
TIMP-3	↑	Protein	human	(Macgregor et al., 2009)
	↓	Protein	C57BL/6	(Kassiri et al., 2009)

↑ increased, ↓ decreased, ↔ unchanged, *MMP* matrix metalloproteinase, *TIMP* tissue inhibitor of metalloproteinases, *SD* Sprague-Dawley, *DS* Dahl-salt sensitive.