Chapter 7
How Acute Kidney Injury Contributes to Renal Fibrosis

Li Yang

Abstract Acute kidney injury (AKI) is a widespread clinical syndrome directly associated with patient short-term and long-term morbidity and mortality. During the last decade, the incidence rate of AKI has been increasing, the repeated and severe episodes of AKI have been recognized as a major risk factor chronic kidney diseases (CKD) and end-stage kidney disease (ESRD) leading to global disease burden. Proposed pathological processes and risk factors that add to the transition of AKI to CKD and ESRD include severity and frequency of kidney injury, older age, gender, genetics and chronic health conditions like diabetes, hypertension, and obesity. Therefore, there is a great interest in learning about the mechanism of AKI leading to renal fibrosis, the ultimate renal lesions of CKD. Over the last several years, a significant attention has been given to the field of renal fibrosis with impressive progression in knowing the mechanism of renal fibrosis to detailed cellular characterization and molecular pathways implicated in tubulointerstitial fibrosis. Research and clinical trial are underway for emerging biomarkers detecting early kidney injury, predicting kidney disease progression and developing strategies to efficiently treat AKI and to minimize AKI progression to CKD and ESRD. Specific interventions to prevent renal fibrosis are still experimental. Potential therapeutic advances based on those molecular mechanisms will hopefully offer promising insights into the development of new therapeutic interventions for patients in the near future.

Keywords Acute kidney injury · Fibrosis · Maladaptive repair · Proximal tubular cell · Inflammation

L. Yang (✉)
Renal Division, Department of Medicine, Peking University First Hospital, Beijing, China
e-mail: li.yang@bjmu.edu.cn

Key Laboratory of Renal Disease, Ministry of Health of China, Beijing, China

Key Laboratory of Chronic Kidney Disease Prevention and Treatment (Peking University), Ministry of Education of China, Beijing, China

7.1   Introduction

Acute kidney injury (AKI) is a syndrome of reduced glomerular filtration rate (GFR) and reduced urine production, which can be caused by a large number of diseases, treatment side effects, and complications. Till this day, not a single therapy has been proven to recuperate the outcome of AKI. Traditionally, the renal function decline after AKI has been believed to be a reversible process, the resolution of AKI and the improvement of renal function and parameter have generally been considered to be efficient processes, and that in surviving patients, AKI would have no effect on long-term renal function. Owing to numerous recent studies, this ideology has changed now and its shown that there is a strong connection between AKI and the development to chronic kidney disease (CKD) (Basile et al. 2012).

Apart from reducing kidney function acutely, many diseases can damage the cells in the kidney, which has the ability to repair after mild injury, but if repair mechanisms are disordered, or if the injury-causing stimulus continues, severe damage results in scarring (fibrosis) and an associated progressive loss of kidney function.

Before the last decade, the exact mechanisms involved in CKD progression after AKI were still largely unknown and several different hypotheses were proposed, as this topic has acquired immense interest and studied extensively, now, there is growing evidence that AKI may lead to renal fibrosis when the adaptive responses and dedifferentiation go wrong after the injury (Ferenbach and Bonventre 2015). It is now been largely recognized that AKI is better prevented than being treated lately. As it is now largely known that even the milder form of AKI has an adverse outcome and may progress to renal fibrosis which is final common pathways to various terminal kidney diseases like CKD and ESRD. There is developing confirmation that patients who had survived a scene of AKI, even with clear recuperation in renal function, will have a significant future risk of progressing to chronic kidney disease (CKD) (Chawla et al. 2011; Chawla and Kimmel 2012; Leung et al. 2013). Albeit different clinical factors, for example, preexisting illness and old age assume a part, the severity of AKI is by all accounts the most critical risk factor for future CKD (Heung and Chawla 2014). Quantitative appraisal of the AKI severity may recognize patients who are at a high risk of AKI-CKD transition, so that proper follow-up and secondary prevention may be implemented or studied in this population (Farris and Alpers 2014).

7.2   Epidemiology of AKI to CKD Transition

There is a strong epidemiological indication of a causal clinical connection between the clinical syndrome of acute kidney disease (AKI) and the consequent development of chronic kidney disease (CKD) (Coca et al. 2009; Hsu 2012). AKI and CKD are an interconnected clinical syndrome as AKI leads to worsening of CKD and CKD predisposes to the clinical entity of AKI. The tubules of the kidney play an integral role in the fibrotic response, which ultimately leads to progressive kidney

disease. CKD is gaining in prevalence worldwide and has a strong negative effect on an individual's quality of life both physically and mentally, apart from increasing the morbidity and mortality. In the course of the most recent two decades, the occurrence of CKD has increased more than three times; furthermore, as stated by the World Health Organization (WHO), it will be one of the three most common reasons for death and disability worldwide by 2020 (Lozano et al. 2012). A meta-analysis of observational data demonstrates that AKI increases the risk of CKD by almost eightfold (Coca et al. 2012).

A study in developed nations (USA, Canada, Western Europe, and Australia) estimated 1.5 million AKI survivors per year with approximately 15–20% who progress to advanced CKD within 24-month period resulting in approximately 300,000 cases of advanced CKD per year (Chawla and Kimmel 2012). According to a nationwide survey in China, approximately 3 million adult AKI patients are admitted to the hospitals across the country every year and of whom 50% develop CKD, which would result in 1.5 million cases of CKD per year (Chawla and Kimmel 2012).

The US Centers for Disease Control and Prevention project that 47% of 30-year-olds will develop CKD during their lifetime. Eleven percent of individuals with stage 3 CKD will eventually progress to end-stage renal disease (ESRD), requiring dialysis or kidney transplantation. CKD is also one of the strongest risk factors for cardiovascular disease. The most important AKI-CKD progressing factor identified by the public health system is lack of post-AKI period assessment guidelines, poor follow system, and cost factor.

7.3 Risk Factors and Etiologies Affecting the Trajectory of AKI to CKD

Developing evidences during the last several years from epidemiological and experimental findings have revealed that AKI itself is an important risk factor for the development of CKD and may also promote the CKD transition to end-stage renal disease (ESRD), including very few of the studies demonstrating the mechanism of AKI to CKD transition (Chawla et al. 2014; Lewington et al. 2013; Venkatachalam et al. 2010). Evidence has suggested that there exists a population heterogeneity in AKI to CKD continuum, various risk factors both extrinsic and intrinsic play an active role, in an excellent review on risk factors of AKI-CKD transition. Hewitson et al. (2017) have explained the concluded important factors affecting the AKI disease progression. Such factors are explained below. [A] Nature. The nature of the injury, in each case, the degree of fibrosis is driven in part by the extent of the tubule damage, and the duration of injury-causing stimuli, with severity and frequency of tubule injury being shown to determine prognosis (Takaori et al. 2016). Consistent with this, the severity of AKI predicts progression to CKD. [B] Age, a progressive reduction in renal function is common with aging, albeit with wide variability. Both hemodynamic and structural changes occur (Ishani et al. 2009; Zhou et al. 2008)

and aging rats can be shown to have impaired redox homeostasis (Aydin et al. 2012) and angiogenesis (Kang et al. 2001). These changes predispose older kidneys to new acute organ injury as well as aggravating progression of CKD. [C] Genetics, it is estimated that about 25% of incident dialysis patients have close relatives with CKD (Freedman et al. 2005), and the distinct susceptibilities of different rodent strains to experimental CKD strongly suggest that genetic variations affect renal fibrogenesis (Kokeny et al. 2010). Similarly, familial clustering and disparities in the prevalence of CKD across race suggest a strong genetic component to progression. [D] Gender, many studies have also indicated a gender basis to the progression of senescence and CKD, with epidemiological studies showing that females have a lower prevalence and slower rate of progression than males (Yu et al. 2010). Nevertheless, other investigations suggest that the male dominance is due to damaging effects of testosterone (Baylis 1994; Hewitson et al. 2016) rather than the protective effects of estrogen. In addition, there is an acquired evidence that the pathophysiology, clinical characteristics, and prognosis of the cardiovascular and renal disease are totally unique among men and women, which is quite possible since the physiology of both the opposite gender is different. [E] Controllable risk factors like obesity, type 2 diabetes, and hypertension/ischemic nephropathy which are also considered the most common causes of CKD in developed nations are also an important factor which may complicate AKI and recovery from AKI (Goldstein et al. 2013; Moonen et al. 2018). There are numerous causes of AKI, also differing in frequency based on age, gender, environment, and geographical regions. But the most common one is recognized in three categories, such as prerenal associated with hypovolemia, renal acute tubular necrosis, and post-renal acute urinary obstruction. In many patients, AKI presents with an integrated etiology, often having the coexistence of sepsis, ischemia–reperfusion injury (IRI), and exposure to the nephrotoxic drugs. Although the initial injury mechanism is different for AKI with different clinical and biological characteristics, it is generally accepted that all primary causes of CKD share a common pathogenetic path to progressive injury leading to the destructive consequences of scarring (fibrosis) (Nogueira et al. 2017). In a very interesting review, Hultström et al. describe the in-common mechanisms behind tissue damage in AKI caused by different underlying diseases. Comparing six high-quality microarray studies of renal gene expression after AKI in disease models (gram-negative sepsis, gram-positive sepsis, ischemia–reperfusion injury, malignant hypertension, rhabdomyolysis, and cisplatin toxicity) identified 5254 differentially expressed genes in at least one of the AKI models; 66% of genes were found only in one model, showing that there are unique features to AKI depending on the underlying disease. There were in-common features in the form of four genes that were differentially expressed in all six models, 49 in at least five, and 215 were found in common between at least four models (Hultstrom et al. 2018).

7.4 The Proposed Mechanisms of Renal Fibrosis

Acute kidney injury in most circumstances is multifactorial in origin, whether it is associated with ischemia–reperfusion injury, sepsis caused by various infections, toxins or autoimmune disease. During AKI several distinct pathophysiological processes occurs at the same time and in sequence including microcirculatory dysfunction, endothelial cell dysfunction, formation of microvascular thrombi, inflammation and recruitment of different leukocytes and cytokines, tubular cell injury, tubular and renal venous congestion (Bellomo et al. 2017; Sharfuddin and Molitoris 2011). When it comes to AKI, tubular epithelial cell injury and peritubular interaction have great significance for renal fibrosis. Tubular epithelial cells injury occurs early during ischemia and involves alterations to the cytoskeleton and in surface membrane polarity. ATP depletion causes rapid disturbance of the actin cytoskeleton structure, which perturbs tight junctions and in turn leads to back leak of the tubular filtrate. Loss of cell–cell interaction and cell adhesion molecules results in flattened nonpolarized epithelial cells, denuded basement membranes, and expression of mesenchymal markers. Na^+/K^+-ATPase pumps, normally located at the basolateral membrane and tethered by the actin–spectrin cytoskeleton, redistribute to the apical membrane of the proximal tubular cell and are internalized into the cytosol during ischemic injury. Morphologically, proximal tubular cells lose their brush borders, undergo swelling, and blebbing of microvilli during injury, leading to cast formation (Sharfuddin and Molitoris 2011).

Under ideal conditions, injured proximal tubular cells undergo differentiation and subsequent re-epithelization. Recovery of proximal tubular cells begins with integrin reattachment, reassembly of the actin cytoskeleton, repolarization of the surface membranes, and redistribution of the sodium pumps back to their basolateral location and renal function recovers completely after an episode of AKI. The reversal of the pathophysiological process of AKI determines the timeline and the trajectory of renal recovery. However, it is observed under many circumstances that the severe forms of AKI or AKI on previously compromised renal function lead to epithelial dedifferentiation inducing profibrotic signals result in maladaptive repair and chronic kidney disease (CKD). Risk factors for maladaptive repair include increasing age, reduced baseline renal function, and prolonged duration and severity of AKI (Canaud and Bonventre 2015). If the repair process is maladaptive (which will be discussed in detail below) under the influence of profibrotic signals, matrix proteins accumulate in glomerulus which is termed as glomerulosclerosis, whereas tubulointerstitial fibrosis (TIF) is the presence of matrix protein replacing the tubules and/or the surrounding interstitium. Many of the renal injuries may involve both the glomeruli and tubular compartments, but the best predictor of renal survival in CKD of all the etiologies is the amount of TIF in kidney biopsies (Nath 1992).

Recently in laboratory science, several animal models were studied for the pathophysiology and therapy of AKI and for the prevention to renal fibrosis, although no animal model could exactly mimic all the alteration caused by progression of renal disease in humans such as renal fibrosis, because the factors associated with it are not

completely understood; hence, the extrapolation of outcomes from animal models must be done very carefully. Most commonly investigated models in animals are ischemia/reperfusion injury induced by clamping of both the renal pedicles; other less commonly conducted models include toxic injury models, for example, cisplatin and folic acid injury and a sepsis model using cecal ligation and puncture, these models have given us some insights into the causal pathways and mechanism of renal fibrosis and therapeutics options (Nogueira et al. 2017; Schmiedt et al. 2016).

Over the last several years, with the help of the knowledge gained from this animal model's research experiments, many different theories and mechanism have been proposed on this abnormal recovery of AKI which may lead to renal fibrosis if the disease progresses.

The hypothesis of epithelial–mesenchymal transition (EMT) states that after injury, the kidney tubular cells undergo a phenotypic transition characterized by loss of epithelial markers and gain of mesenchymal features. Liu proposed four key events occur in tubular EMT in renal fibrogenesis, based on the studies of tubulointerstitial changes following experimental unilateral ureteric obstruction (UUO) in vivo and on the response of epithelial cells in vitro to TGFβ1, an inducer of EMT. These are the following events: loss of epithelial adhesion, cytoskeletal reorganization, de novo synthesis of α-SMA, disruption of the tubular basement membrane, and finally enhanced cell migration and invasion of the interstitium (Liu 2004, 2010). However, such concept has been debated; recent studies have demonstrated that genetic cell lineage tracing could not confirm a direct contribution of epithelial cells to the myofibroblast population in the fibrotic kidney (Kriz et al. 2011).

The idea of EMT was again supported by two studies and offered new insights into the potential role of tubular EMT in the development of renal fibrosis. These studies found out that tubular epithelial cells undergo a partial EMT; during the progression of the disease, the cell expresses the markers for both epithelial and mesenchymal cells and remains associated with the basement membrane. Lovisa et al. have further demonstrated that this partial EMT is sufficient to induce tubule function impairment through the arrest of cell cycle in the G2 phase leading to an abnormal recovery of tubular epithelial cells which will further progress to renal fibrosis (Lovisa et al. 2016).

Endothelial-to-mesenchymal transition (EndMT) is a subtype of EMT where specific epithelial cells known as endothelial which are a single layer of cells lining vessels serving as a permeable membrane transition into a mesenchymal cell type. EndMT has also been described in several publications as a contributor to the development and progression and renal fibrosis (Cruz-Solbes and Youker 2017). Zeisberg et al. carried out a landmark experiment to confirm the contribution of EndMT in renal fibrosis in three different types of animal models: unilateral ureteral obstruction nephropathy UUO, streptozotocin-induced diabetic nephropathy, and a surrogate for Alport syndrome (Zeisberg et al. 2008). The result showed that approximately 30–50% of fibroblasts co-expressed the endothelial marker CD31 and mesenchymal markers FSP-1 and αSMA; they confirmed this finding with endothelial lineage tracing using dual transgenic mice. Li et al. also confirmed that EndMT occurs and contributes to the early development of diabetic renal interstitial fibrosis. They did so

by looking at a streptozotocin-induced diabetic nephropathy model using endothelial lineage-traceable mice to identify if EndMT occurred in diabetic renal interstitial fibrosis (Li et al. 2009).

However, recent development in the understanding of renal fibrosis has come up with new and reasonable evidence for the mechanism responsible for normal and abnormal repair and drew an important link between injury, abnormal repair, and development of fibrosis, stating that fibrosis is a characteristic of maladaptive repair (Fiorentino et al. 2018) that can result when the regenerating tubules become growth arrested, fail to differentiate, and undergo atrophy, these tubules also exhibit pathological signaling, paracrine, and autocrine activity that perturbs normal interaction between different renal and renal interstitial cells. There is a significant cellular cross talk between tubular epithelial–epithelial cell, tubular epithelial–fibroblast, epithelial–endothelial cells, and epithelial–inflammatory cells. One of the main changes is the interaction of pericytes and peritubular capillary endothelium. The maladaptive process results in dissociation of pericytes from capillaries is leading to capillary disintegration and microvascular rarefaction, pericyte to myofibroblast transformation, endothelial dysfunction, chronic inflammatory infiltrates, renin–angiotensin system (RAS) activation, mitochondrial dysfunction and epigenetic changes, all the pathological changes ultimately causing renal fibrosis (Chou et al. 2017). Maladaptive repair and progression of tubulointerstitial fibrosis is a complex process that involves several different types of cells and molecular pathways. Renal biopsies from the human with AKI and also CKD patients offer us a snapshot in time and usually shows all these pathological changes at once, making it difficult to decide the relative importance of each cellular compartment and sequence of events leading to renal fibrosis. In recent years a lot of attention was focused on myofibroblast and its origin (Chang et al. 2012), as this interstitial cell is thought to be the main producers of ECM, but new findings have highlighted the role of the proximal tubule and proximal tubular epithelial cell (PTEC) a specialized tubular segment just adjacent to the glomerulus, as not only the target of injury but also an important mediator of renal fibrosis progression (Bonventre 2014).

In the below section, we will discuss the maladaptive changes in cells and molecular mechanism implicated in tubulointerstitial fibrosis

7.5 The Maladaptive Repair

7.5.1 The Role of Proximal Tubular Epithelial Cells in Maladaptive Repair

The tubulointerstitium consists of multiple cell components including tubular epithelial, mesenchymal (fibroblast and pericytes), endothelial, and inflammatory cells all of which contribute to fibrosis progression.

Researches done over a period of several years have made clear that proximal tubular epithelial cells (PTECs) play an important role in the histopathology of renal injury, both in AKI and CKD. After an acute ischemic or toxic insult, PTECs (mostly those of proximal S3 segment) are most susceptible to injury (Bonventre and Yang 2011). Ischemia–reperfusion injury and drug-induced renal injury lead to a significant increase in production of reactive oxygen species (ROS) heavily contributing to PTEC injury (Granger and Kvietys 2015; Hosohata 2016). The PTECs are highly sensitive due to (i) the high metabolic activity/demand of these cells; (ii) medullary region is highly prone to hypoxia; and (iii) increased exposure to intra-tubular toxins due to upstream water absorption (Canaud and Bonventre 2015). The innate immune features of PTECs facilitate them to act as immune responders to a wide range of insults, with the subsequent production and release of bioactive mediators that drive the interstitial inflammation.

Senescent epithelial cells and G2/M cell cycle arrest of epithelial cells is an important mediator of CKD. Senescence is a cell fate decision when cell cycle arrest becomes permanent. Although this is generally the case, some senescent cells that do not express p16INK4a can resume growth after inactivation of p53 (Beausejour et al. 2003). Senescence has been studied extensively in response to DNA damage where some cell types undergo apoptosis, whereas others, particularly epithelial cells, undergo a senescence response. Besides serious levels of DNA damage, high levels of reactive oxygen species (ROS) are considered a major cause of senescence induction (Munoz-Espin and Serrano 2014; Sturmlechner et al. 2017). DNA damage leads to the activation of the ATM/ATR pathway, following CHK2 activation which phosphorylates cdc25 and p53, causing the G2/M arrest by CDK1 inhibition (Goodarzi et al. 2003; Yan et al. 2016). An important finding validating the involvement of G2/M arrest in renal injury was reported by Yang et al. in 2010 (Yang et al. 2010). By inspecting tubular epithelial cell cycle behavior after renal injury, they noted a causal association between epithelial cell cycle arrest at the G2/M phase and subsequent development of renal fibrosis due to maladaptive repair. They characterized the cell cycle profile of PTECs after an acute insult in five experimental mouse models of AKI: moderate bilateral ischemia–reperfusion injury (IRI), severe bilateral IRI, unilateral IRI, aristolochic acid nephropathy (AAN), and unilateral ureter obstruction (UUO). These models resemble the three most common causes of AKI seen in humans: ischemia, toxic exposure, and obstruction (Le Clef et al. 2016). All animal models, except moderate IRI, showed that the injury led to the development of severe fibrosis demonstrating the chronic fate of the kidney. They also found that many tubular cells arrested in the G2/M phase of the cell cycle result in activation of the DNA repair response with the resultant production and secretion of profibrotic factors, such as transforming growth factor beta (TGFβ), Collagen 1 (Col I), and CCN2, formerly known as connective tissue growth factor (CTGF) (Moonen et al. 2018). Mounting evidence has also shown that the injured PTEC that is transformed into a secretory phenotype and can recruit a variety of proinflammatory cytokines that drive the immune response in an autocrine manner or indirectly through infiltrating leukocyte in a paracrine manner, thus causing tubulointerstitial inflammation. A variety of cytokines and profibrotic factors have been shown to be

produced by activated TECs, including IL-1b, IL-18, IL-15, IL-16, TNF-a, TWEAK, Fas ligand, CTGF, and vascular endothelial growth factor, platelet-derived growth factor (PDGF). Proinflammatory cytokines and profibrotic growth factor produced or recruited by injured TEC are listed in Table 7.1.

Transforming growth factor-β1 (TGF-β1) is one of the most crucial soluble mediators of renal fibrosis. Both angiotensin II exposure and Snail1 overexpression induce TGF-β1 production in tubular cells (Grande et al. 2016; Macconi et al. 2014), particularly when TEC is under arrest in the G2/M phase. Elevated TGF-β1 expression leads to a variety of paracrine and autocrine effects on target cells. TGF-β1 is a potent mitogen for fibroblasts and causes myofibroblast transformation (Meng et al. 2015). TGF-β1 also causes tubular cell apoptosis and induces the EMT program, leading to the production of an increased matrix. It also causes tubular cell hypertrophy, which may be closely linked to increased matrix production (Gewin et al. 2012; Lopez-Hernandez and Lopez-Novoa 2012). Stress-induced activation of the c-Jun amino-terminal kinase (JNK) pathway in cells of the glomerular and tubulointerstitium is a common feature of chronic kidney disease. JNK signaling acts to increase TGF-β1 expression, to promote activation of latent TGF-β1, and to promote transcription of profibrotic molecules via direct phosphorylation of the linker region of Smad3 (Grynberg et al. 2017). Ample progress has been made in identifying miRNA molecules which regulate TGF-β/Smad3 induced fibrosis. TGF-β specifically promotes fibrosis by increasing levels of miR21, miR-433, and miR-192 which amplify TGF-β signaling and stimulate dedifferentiation of tubular epithelial cells (Chung and Lan 2015). One of the main therapies for chronic kidney disease is inhibition of the production or action of angiotensin II (Ang II) as Ang II is an inducer of TGF-β production and activation (Macconi et al. 2014). Autocrine TGF-β signaling increases PTEC production of PDGF-β and CTGF/CCN2 that can signal neighboring fibroblast and induce TIF (Geng et al. 2012). CTGF is an essential cofactor for TGF-β signaling. CTGF interacts directly with the TGF-β receptor, downregulation of Smad7 activity, and inhibition of bone morphogenetic protein 7. CTGF can also bind LRP6, stimulating β-catenin activity (Kok et al. 2014). CTGF also promotes inflammatory cell infiltration in the renal interstitium by activating NF-kappaB pathway (Rodrigues-Diez et al. 2015). PDGF is another profibrotic growth factor produced by the epithelial cell that interacts with fibroblast. PDGF-β produced by injured TEC may increase PDGF-receptor phosphorylation and consequent signaling on neighboring fibroblast promotes TIF (Tang et al. 1996). The intrarenal renin–angiotensin system activation plays an important role in CKD progression; there is extensive research available that the major fraction of Ang II in renal tissues is produced from angiotensinogen by PTECs and it is converted to Ang I (Kobori et al. 2007). RAS production in the kidney has also shown to be Wnt/β-catenin dependent (Zhou et al. 2015). As discussed above, Ang II can stimulate TGF-β expression in cultured murine PTECs to promote inflammatory and fibrotic responses. Wnt/β-catenin signaling is a pathway involving the renal recovery from AKI. In the acute phase of injury, Wnt/β-catenin is likely to be protective. A lot of nephrotoxic events lead to marked accumulation of β-catenin in renal tubules (Zhou et al. 2016). In both renal ischemia/reperfusion injury and folic acid nephropathy, tubule-specific ablation of β-catenin has been shown

Table 7.1 Proinflammatory cytokines and profibrotic growth factors induced by injured TEC

Cytokines/factors	Effects	References
IL-6	Proinflammation	Yard et al. (1992)
IL-18	Triggers proinflammatory cytokines	Yang et al. (2015)
IL-34	Neutrophil and macrophage recruitment	Baek et al. (2015)
IL-6	Proinflammation	Yard et al. (1992)
IL-15	CD103$^+$ T-cell recruitment	Wong et al. (2003)
IL-1β	Triggers proinflammatory cytokines and initiates acute-phase responses	Leemans et al. (2014) Anders (2016)
IL-16	CD4$^+$ T-cell recruitment	Wang et al. (2008)
CSF-1	Macrophage recruitment and adhesion	Menke et al. (2009)
	Polarization into an M2 phenotype	Wang et al. (2015) Huen et al. (2015)
TNF-α	Triggers proinflammatory cytokines innate and adaptive immunity apoptosis	Al-Lamki and Mayadas (2015)
Fas ligand	Apoptosis	Lorz et al. (2000)
TWEAK	Cell death in the presence of TNF-α/IFN-γ	Sanz et al. (2014)
	Proinflammation	Sanz et al. (2011)
VEGF	Macrophage recruitment	Schrijvers et al. (2005)
	Endothelial cell proliferation and survival	Ninichuk et al. (2006)
CTGF	Triggers proinflammatory cytokines	Rodrigues-Diez et al. (2015)
	Profibrotic fibroblast proliferation	Geng et al. (2012)
PDGF	Profibrotic	Kimura et al. (2005)
	Fibroblast proliferation Fibroblast to myofibroblast differentiation	Chen et al. (2011)
TGF-β	Profibrotic	Wu et al. (2013)
	Tubular cell dedifferentiation	Meng et al. (2015)
	Fibroblast to myofibroblast differentiation	Lamouille et al. (2014)
Hh	Profibrotic	Fabian et al. (2012)
	Fibroblast to myofibroblast differentiation	Ding et al. (2012)
	Pericyte to myofibroblast differentiation	Zhou et al. (2014)
Notch	Profibrotic	Murea et al. (2010)

Table 7.1 (continued)

Cytokines/factors	Effects	References
	Epithelial–mesenchymal transition	Bielesz et al. (2010)
Wnt	Fibroblast to myofibroblast differentiation	Maarouf et al. (2016)
	RAS↑	Tan et al. (2014)
RAS components	Proinflammatory	Liu et al. (2006)
	Triggers growth factors (TGF-b, CTGF)	Wolf et al. (1999) Chen et al. (2006)
ET-1	Proinflammatory	Gerstung et al. (2007)
	Profibrotic	Gomez-Garre et al. (2001) Zager et al. (2013)
Exosome	Fibroblast to myofibroblast differentiation	Borges et al. (2013)
	Epithelial–mesenchymal transition	Zhou et al. (2013b)
Complement	Epithelial–mesenchymal transition	Tang et al. (2009)
	RAS activation	Zhou et al. (2013a)

to exacerbate kidney injury by increasing TEC apoptosis (Zhou et al. 2012). However, persistent activation of Wnt signaling has a decisive role in driving AKI-CKD progression because sustained Wnt signaling causes uncontrolled fibroblast activation, RAS activation, inflammation, and excessive deposition of ECM (Maarouf et al. 2016). The relationship between mitochondrial dysfunction and CKD has been long suspected, but the exact mechanism connecting mitochondrial dysfunction to CKD has remained indefinable (Galvan et al. 2017). Also, mitochondrial dysfunction is thought to be pathogenic in AKI (Che et al. 2014; Hall and Schuh 2016). The proximal tubules are densely packed with mitochondria; PTEC generates ATP mainly via mitochondrial oxidative phosphorylation, whereas other renal cells like endothelial cells, podocytes, and mesangial cells exhibit more flexibility in their glycolytic capacity to generate energy (Wirthensohn and Guder 1986). Under stressful condition, mitochondrial fragmentation and permeability alteration contribute significantly to tubular dysfunction and cell death. Funk and Schnellmann demonstrated persistent disruption of mitochondrial homeostasis after AKI, which in turn may result in decreased cellular respiration accompanied by a reduction in cellular adenosine triphosphate, all contributing to the development of ensuing CKD (Funk and Schnellmann 2012). Plenty of evidence suggests that a mitoprotective drug like SS-31 can target the mitochondrial membrane to prevent the permeability transition and is very effective in diminishing ischemic AKI and the development of interstitial fibrosis (Liu et al. 2014).

7.5.2 The Role of Endothelial Dysfunction in Maladaptive Repair

AKI-induced endothelial injury has long-term chronic disease implications. Basile and colleagues documented that renal vascular network is significantly compromised following acute ischemic injury (Basile 2007). Hörbelt M and colleagues have also confirmed this finding; they found a nearly 45% drop in vascular density 4 weeks after an ischemic insult. This reduction in capillary vascular density is termed as a capillary rarefaction (Horbelt et al. 2007). Capillary rarefaction in the kidneys is thought to promote hypoxia, impair hemodynamic responses, and predispose to chronic kidney disease (CKD) progression and hypertension development. Consistent with decreased renal oxygenation in CKD is the increased expression of the oxygen-sensitive α-subunit of hypoxia-inducible factor (HIF). These heterodimeric basic helix-loop-helix transcription factors HIF-1 and HIF-2 are key mediators mediating a cellular adaptation to hypoxia by regulating glycolysis, angiogenesis, erythropoiesis, and cell survival decisions. HIF-1 and HIF-2 are furthermore involved in the regulation of biological processes that are relevant to wound healing, tissue repair, and fibrogenesis, such as extracellular matrix synthesis and turnover, cell adhesion and migration, and epithelial to mesenchymal transition (EMT) (Haase 2012). There is conflicting opinions regarding the effect of HIF on CKD pathophysiology, which seems to depend on the pathological discourse. At one point, stimulation of HIF and HIF-regulated genes by CoCl2 has been shown to exert renoprotective role in the hypoxic tubulointerstitium in rats with nephritis (Tanaka et al. 2005) and hypertensive type 2 diabetes (Ohtomo et al. 2008).

At another point, an inappropriate and prolonged activation of HIF is well known to play a pivotal role in initiating and promoting renal fibrogenesis via regulation of multiple signaling pathways in CKD. HIF activation can stimulate inflammatory cell proliferation and recruitment to the site of injury in animal models of CKD, which plays a role in setting up the fibrous scar formation. Additionally, activated HIF binds to its profibrogenic downstream genes and induces maladaptive expression of matrix modifying factors directly in hypoxic TECs, such as collagen I, plasminogen activator inhibitor 1 (PAI1), endothelin-1 (ET-1), connective tissue growth factor (CTGF), matrix metallopeptidase 2 (MMP-2), and tissue inhibitor of metalloproteinase 1 (TIMP1), which lead to increased production of interstitial collagen and decreased degradation of ECM (Liu et al. 2017).

There is a bidirectional relationship between tubular epithelial cells and capillary endothelial cells. Primary tubular epithelial cell injury promotes capillary rarefaction (Bonventre 2012) and capillary rarefaction further promotes hypoxic tubular cell injury, thus creating a vicious circle. There are several examples in which tubular injury precedes capillary rarefaction. Additionally, capillary rarefaction decreases tubular blood and oxygen supply, promoting the loss of tubular cell viability and tubular atrophy and interstitial fibrosis (Kida et al. 2014). Various mechanisms have been suggested to play a role in the development of capillary rarefaction; the very first hypothesis proposed nearly 20 years ago was that excessive collagen production by

myofibroblasts reduces peritubular blood flow, causing tubular hypoxia and nephron dropout (Fine et al. 1998); following this hypothesis, a huge interest is shown in this field, and various other mechanisms were inflammation, an altered endothelial-tubular epithelial cell cross talk, a relative deficiency in angiogenic growth factors, increased activity of TGF-β1 and thrombospondin-1, loss of pericytes, vitamin D deficiency, a link to lymphatic neoangiogenesis and INK4a/ARF (cyclin-dependent kinase inhibitor 2a; CDKN2A) (Afsar et al. 2018).

Basile et al. have also shown that acute ischemia decreases the expression of angiogenic vascular endothelial growth factor (VEGF) while raising the expression of the VEGF antagonist, a disintegrin, and metalloproteinase with thrombospondin motif 1 (ADAMTS-1) (Basile et al. 2008). By contrast, administration of a VEGF fragment (VEGF-121) during repair preserved microcapillary density, indicating that VEGF agonism may be a therapeutic approach to prevent AKI-induced capillary rarefaction (Leonard et al. 2008). Pericyte–endothelial interactions also play an important role in capillary rarefaction. Pericytes produce angiopoietin-1, a growth factor that stabilizes the microvasculature by activating the endothelial Tie2 receptor. After renal injury, endothelium-derived angiopoietin-2, an antagonist of angiopoietin-1, increases, favoring capillary leakiness and pericyte loss (Tsai et al. 2014). Pericyte disintegration and loss lead to structural instability of blood vessels and to capillary rarefaction. Furthermore, detached pericytes are key precursors of myofibroblasts. Pericytes-turned myofibroblasts contribute to interstitial fibrosis that leads to further capillary rarefaction (Kramann and Humphreys 2014).

During hypoxia, TGF-β1 directly causes endothelial cell apoptosis and capillary pruning finally leading to vascular dropouts (Ballermann and Obeidat 2014). Thrombospondin-1 could enhance the fibrotic response by both activating TGF-β and employing antiangiogenic actions, thus leading to capillary rarefaction (Gewin et al. 2017). Inhibition of thrombospondin expression ameliorated tubulointerstitial fibrosis by promoting VEGF production and restoring peritubular capillary density.

7.5.3 The Role of Inflammatory Cells in the Maladaptive Repair

The interstitial inflammatory cells specifically macrophages and dendritic cells are important modulators of CKD. Generally, the macrophages and dendritic cells populate the uninjured renal interstitium, act as an antigen-presenting cell, and also carry out their phagocytic function; these inflammatory cells expand both through local proliferation and infiltration of circulating monocytes and subsequent differentiation after the renal injury. This persistent leukocyte accumulation and activation inside the kidney would promote extended periods of ischemia due to vascular congestion and may induce direct tubular and endothelial cell damage by the release of inflammatory mediators (Nelson et al. 2012; Weisheit et al. 2015).

Macrophages and dendritic cells in the injured kidney display appreciable plasticity and functional heterogeneity with different overlapping roles. These cells are identified with different markers by multicolor flow cytometry, for example, macrophages (CD11b, F4/80, and CD68) and dendritic cells (CD11c, MHCII, and CD80/86) (Weisheit et al. 2015). Macrophages can be classified into many subtypes, but they are broadly classified either as M1 (classically activated) or M2 (alternatively activated) macrophages. During AKI, M1 macrophages are known as proinflammatory and make cytokines such as IL-1, IL-6, and TNF-a, and they promote inflammation whereas M2 are mainly reparative and anti-inflammatory, they express arginase, mannose receptor, IL-10, and IL-4 receptor-a. However, in CKD M2 macrophages may stimulate tubulointerstitial fibrosis through the production of various profibrotic growth factors. A variety of experimental cell depletion strategies have shown that decreasing the number of interstitial macrophages reduces kidney fibrosis (Mosser and Edwards 2008).

Recent reviews and studies have shown that there is a significant cross talk between injured TEC and inflammatory cells. Injured renal epithelia induce the inflammatory response by the production of chemokines and chemoattractant cytokines that bind to receptors on inflammatory cells to promote migration of macrophages and dendritic cells to the site of injury. Injured proximal tubules can also promote local macrophage proliferation through the production of macrophage colony-stimulating factor (Gewin et al. 2017).

The macrophage phenotype, the timing relative to PTEC injury, and local microenvironment affect the epithelial/inflammatory cell cross talk leading to progression of CKD. Animal models of AKI, a risk factor for CKD progression, suggest that a proinflammatory, M1 macrophage phenotype predominates at 1–3 days post-injury. Depleting macrophages using clodronate or genetic methods may improve injury in this phase. However, at later time points, there is a switch to a reparative, M2 macrophage subtype that promotes recovery from injury. Depletion of macrophages at this later stage can impair renal recovery and lead to CKD (Vinuesa et al. 2008). In CKD, unlike AKI, the M2 phenotype is likely to promote TIF due to the production of factors like TGF-β, PDGF, and galectin-3 (Henderson et al. 2008). Therefore, a continuous epithelial injury may affect TIF progression through chemokine-dependent, increased M2 macrophage infiltration. Although injured epithelia also alter DC polarization through cytokine production, there are fewer data to support a role for DCs in TIF progression (Kitching 2014; Machida et al. 2010). Other inflammatory immune cells like (lymphocytes, natural killer cells) have also shown to play a role in CKD, but there are not many studies to mention here.

7.5.4 The Role of Myofibroblast in the Maladaptive Repair

Tubulointerstitial fibrosis is marked by an exuberant and pathological deposition of extracellular matrix (ECM) consisting of collagen I, III, and IV, laminin, fibronectin, perlecan, and heparin. Research on animal models of kidney disease has identified

myofibroblasts as major matrix-producing cells contributing to fibrosis after injury. Myofibroblasts can be defined by being α-smooth muscle actin (α-SMA) positive and are mainly located in the renal interstitium and to a lesser extent in glomeruli in various animal models of renal fibrosis. The amount of myofibroblasts is proportionally related with severity of renal fibrosis. However, the diverse lineage and mixed phenotypic heterogeneity of myofibroblasts make them a difficult therapeutic target. Due to their central importance, the cellular origin of these cells is a critical question that has been extensively studied in animal models, but contradictory data leave this as a subject of an ongoing debate.

Interstitial myofibroblasts have been proposed to originate from one or more of five sources: fibroblasts, pericytes, bone marrow-derived myofibroblast, tubular epithelial–mesenchymal transition (EMT), or endothelial/mesenchymal transition EndMT. However, the role of EMT in renal fibrosis is rigorously challenged by lineage tracing studies and other recent scientific evidence (Sun et al. 2016).

Fibroblasts are inactive cells found within the interstitial space, important for maintaining the structural integrity of kidneys by producing a basal level of the extracellular matrix. Injured epithelia are potent producers of growth factors and cytokines such as TGF-β, PDGF, hedgehog, and Wnt ligands. Injured PTECs have paracrine effects on surrounding cells such as fibroblasts, causing them to transform into myofibroblasts. Activated fibroblasts have increased stress fibers, and they proliferate and produce ECM components such as collagens leading to progressive TIF (Baum and Duffy 2011).

The recent discovery of a functionally distinct subset of extracellular matrix-producing cells called pericytes might be another major source of myofibroblasts. Pericytes are stromal cells which stay in close contact with interstitial capillary endothelial cells and regulate capillary permeability. An interesting study by Kramann et al. identified a group of Gli1-positive perivascular mesenchymal-like pericytes such as myofibroblast progenitors, as shown by lineage tracing and cell ablation. Using transgenic Gli1-CreERt2/tdTomato mice in an experimental model of fibrosis, Gli1þ cells proliferated within the interstitial region and acquired expression of NG2 and α-SMA as myofibroblasts (Kramann et al. 2015).

Myofibroblasts may also originate from bone marrow-derived cells (BMDCs) which migrate into the kidney in response to injury. In the UUO model of kidney fibrosis, transplantation of transgenic bone marrow expressing the red fluorescent protein (RFP) under the control of α-SMA promoter (α-SMA-RFP) demonstrated 35% of the myofibroblasts was derived from bone marrow cells (LeBleu et al. 2013).

Fibrocytes are hematopoietic or bone marrow-derived collagen-producing cells expressing vimentin and CD34 marker; they infiltrate renal parenchymal tissue and may contribute to fibrogenesis. Patients with chronic allograft nephropathy with interstitial fibrosis had a large number of myofibroblasts derived from the recipient. Immunostaining of hematopoietic markers like CD11b, CD34, CD45, CD115, and Gr1, together with intracellular collagen I, was used to identify fibrocytes in kidneys. Specific cell ablation of αSMA-positive fibrocytes after bone marrow transplantation showed a significant reduction of renal fibrosis (Mack and Yanagita 2015).

TGF-β1 is synthesized by injured TEC in the kidneys as latent complexes covalently bound to the extracellular matrix (Huang et al. 2008). Active TGF-β1 is released via proteolytic cleavage from the extracellular matrix and binds to the TGF-βII receptor and starts Smad-dependent and Smad-independent signaling pathways. Phosphorylated Smad2/3 complex together with Smad4 translocates into the nucleus to modulate transcription of a number of target genes. TGFβ1 promotes progressive renal fibrosis by stimulating extracellular matrix synthesis, preventing its degradation, mediating tubular epithelial cells and endothelial cells to undergo EMT or EndoMT, respectively (Li et al. 2009).

7.6 Biomarkers Implicated in AKI—CKD Transition

New biomarkers of AKI are significant recent developments and typically indicates a specific component of AKI pathophysiology, such as epithelial tubular injury, cell cycle arrest, systemic inflammatory pathways, and glomerular filtration. AKI biomarkers will hopefully beneficial in different clinical processes, including diagnosing AKI earlier, prognostication of clinical outcomes, and prediction of response to therapy.

Biomarkers of AKI can be used to inference the short- and long-term adverse outcomes in various patient care settings. The commonly observed short-term outcomes are in-hospital mortality, need for renal replacement therapy (RRT), and length of stay. At present, there are evidences that biomarkers of AKI are related to long-term mortality, but the data are lacking to suggest that biomarkers of AKI are related to other important long-term patient outcomes, such as cardiovascular events and CKD, although prospective studies are ongoing like ASSESS-AKI study. The Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI) study is prospectively studying the long-term outcomes in hospitalized patients, with or without chronic kidney disease, after an episode of acute kidney injury, to ascertain the natural history of acute kidney injury and define the risk factors for progression and for the development of complications, including cardiovascular disease, and the relationship between putative biomarkers and long-term outcomes (Go et al. 2010). Some of the AKI biomarkers may yield additional predictive information beyond that is provided by the AKI event itself. Several long-term follow-up studies have identified a subgroup of patients who suffer from "subclinical AKI." While these patients do not have AKI as defined by serum creatinine, they have elevated biomarkers of tubular injury and fare worse than patients without elevated biomarkers of AKI (Haase et al. 2011). This proposes that biomarkers of AKI may provide additional prognostic information beyond that offered by serum creatinine and serum creatinine-based current AKI definitions.

7.6.1   Serum and Urine Kidney Injury Molecule 1

KIM-1 expression is markedly upregulated after ischemia–reperfusion injury reflecting the proliferating dedifferentiated epithelial cells of the proximal tubules, and it appears to peak at approximately 48 h. It is known to promote epithelial cell regeneration and regulates tubule cell apoptosis. In murine AKI models, KIM-1 overexpression reduces kidney fibrosis and the development of ESRD (Humphreys et al. 2013). Sustained KIM-1 elevation in blood, however, indicates persistent tubular injury, which would be a risk for the development of CKD/ESRD. Urinary KIM-1 shows a similar correlation of kidney injury; hence, the persistent KIM-1 levels may be used to prognosticate development of ESRD.

7.6.2   Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Intrarenal NGAL is highly upregulated following ischemic or nephrotoxic kidney injury. A urinary NGAL has been proposed as a potential marker of kidney disease progression to ESRD in animal models (Ko et al. 2010). Human studies, though small and few, have shown the possible utility of high baseline levels of plasma and urinary NGAL in predicting progression [reference]. The area under the receiver operating characteristic curve (AUC) is estimated at 0.78 for baseline urine NGAL and 0.70 for baseline serum NGAL (Bolignano et al. 2009), suggesting potential utility in prognostication post-AKI kidney disease progression.

7.6.3   Liver-Type Fatty Acid-Binding Protein

Liver-type fatty acid-binding protein is considered as a renal protective protein in general. It binds to and promotes the metabolism of fatty acids and has antioxidant properties. Urinary L-FABP levels are elevated almost immediately after AKI and peak within 6 h correlating strongly with renal ischemic time (Susantitaphong et al. 2013). L-FABP levels are also increased in patients with known renal disease risk factors of hypertension and diabetes in the absence of overt kidney damage, further improving its potential to be used to identify patients at increased risk.

7.6.4   Interleukin-18

Interleukin-18 (IL-18) is a 22-kD proinflammatory cytokine formed in the proximal tubular cells. Urinary IL-18 is elevated following renal injury (Parikh et al. 2004). The mature IL-18 induces inflammatory response through upregulating NF-kappaB

pathway including TNF-α, iNOS, chemokines MCP-1, and MIP-2, which causes inflammation by macrophage and neutrophils induction (Wu et al. 2008). IL-18 worsens tubular necrosis in ischemia–reperfusion injury (Parikh et al. 2004) and animal models via Fas/Fas ligand pathways (Yano et al. 2015). Interrupting the IL-18 signaling has consistently shown to decrease kidney injury.

7.6.5 Renin–Angiotensin System Activation

Renin–angiotensin system (RAS) activation, especially intrarenal activation, causes progression of AKI and transition from acute to chronic kidney injury. Urinary angiotensinogen is considered a novel prognostic marker for AKI. AKI patients with elevated urinary angiotensinogen have been shown to progress to higher stages of AKI with higher mortality rates (Alge et al. 2013b). In patients with post-cardiac surgery AKI, elevated urinary angiotensinogen had an AUC of 0.75 for predicting progression of AKI to stage 3 and predicting mortality (Alge et al. 2013a). Measurement of urinary angiotensinogen can help with delineating AKI patients who are at risk of having accelerated CKD and could possibly benefit from RAS blockade agents.

7.7 Renal Antifibrotic Treatment

Renal fibrosis is the common final outcome of different progressive kidney diseases and, in the majority of chronic kidney diseases, becomes a leading target for antifibrotic interventions. The current therapeutic approaches for the reversal or inhibition of progression of many chronic kidney diseases are either not enough effective or safe to be used as treatment regimen in the clinical practice; because of this reason, drugs to cure kidney fibrosis are not in clinical yet. At present, the available medications for the treatment of renal fibrosis are angiotensin-converting enzyme (ACE) inhibitors (e.g., captopril), angiotensin II receptor blockers (ARBs), and renin inhibitors. They are used only to improve the symptoms and delay the progression of chronic kidney diseases, but this drug also comes with serious limitations. The safety and efficacy of these medications depend on different key factors such as the stage and type of chronic kidney disease, the causal fibrosis leading molecular mechanisms, and the patient medical history. The present research work done on the pathways and mechanisms of fibrogenesis has revealed impressive preclinical evidence showing that fibrosis can be slowed, arrested, or even be reversed. Research indicates that multiple ligands of TGF-β/Smads are the direct mediators for renal fibrosis; hence, inhibition of the TGF-β/Smads signaling pathway using various strategies can significantly reduce renal fibrotic lesions and ameliorate kidney injury, suggesting that targeting the TGF-β/Smads signaling pathway could be a new strategy for effective therapies.

Other drugs that are being developed for CKD-related fibrosis are targeting the key players that are known in the molecular mechanisms of fibrosis such as CTGF, endothelin-1, mothers against decapentaplegic homolog (SMAD) 3 and 4, phosphodiesterase type 5, bone morphogenetic protein (BMP)-7, and NADPH oxidase (NOX) 1 and 4 (Nastase et al. 2018).

7.8 Conclusion

Currently, there are not many therapeutic strategies for preventing progression after AKI. However, staggering advancements have been made in recent years to determine the risk factors, mechanisms, the role of cellular cross talk, molecular pathways involved, maladaptive repair under the influence of proinflammatory cytokines, profibrotic growth factor (Fig. 7.1), and the role of novel biomarkers in AKI-CKD transition. It is highly surprising that the planned clinical follow-up of the patients who survived AKI is very low, given the increasing incidence of AKI and its association with the progression to CKD. More information can be acquired with the proper clinical follow-up of AKI survivors, which can help with short- and long-term clinical trials and research by making a better animal model that can elaborate the understanding of AKI-CKD transition which is ultimately necessary for preventing TIF and developing more effective therapies to halt TIF progression to CKD.
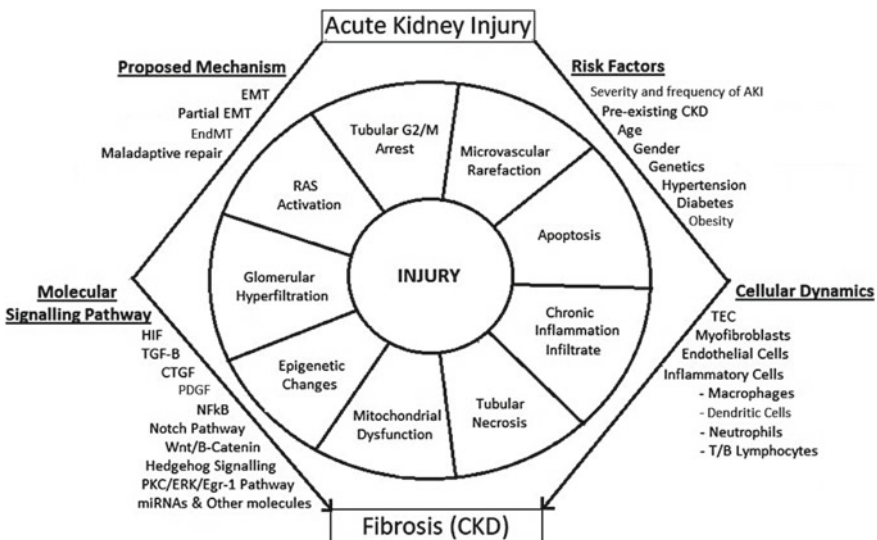
Fig. 7.1 Acute kidney injury to chronic kidney disease transition. Depicting the risk factors, proposed mechanisms, cellular dynamics, and molecular signaling pathway of fibrosis development after acute kidney injury

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