International Journal of Advanced Biochemistry Research

ISSN Print: 2617-4693
ISSN Online: 2617-4707
NAAS Rating (2025): 5.29
IJABR 2025; 9(12): 454-460
www.biochemjournal.com
Received: 09-11-2025
Accepted: 02-12-2025

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Cellular senescence and fibrosis as key drivers in the aftermath of acute kidney injury

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DOI: https://www.doi.org/10.33545/26174693.2025.v9.i12f.6532

Abstract
Cellular senescence and fibrosis have become central to the long-term effects that ensue Acute Kidney Injury (AKI), where it was previously viewed as a reversible clinical outcome to a significant risk factor of Chronic Kidney Disease (CKD). In AKI, there is a marked level of oxidative stress, mitochondrial dysfunction and DNA damage in tubular epithelial cells, which can drive the process of senescence involving a permanent cell-cycle arrest with subsequent release of pro-inflammatory mediators, the Senescence-Associated Secretory Phenotype (SASP). Although such a reaction is beneficial to curb the spread of damaged cells, chronic senescence interferes with the regeneration of normal tissues by heightening inflammation, inhibiting epithelial repair, and enhancing a maladaptive microenvironment. The SASP factors enhance fibroblast recruitment and activation, which hastens interstitial fibrosis the technologic of permanent structural injury in the post-AKI kidney. Myofibroblasts then extracellularly deposit too much extracellular matrix that leads to progressive scarring, diminished nephron operations, and gradual loss of renal reserve. Notably, senescence and fibrosis are mutually reinforcing; fibrogenesis is stimulated by senescent cells and the rigid and hypoxic fibrotic niche increases senescence in neighboring epithelial and stromal cells, and is a self-perpetuating mechanism that contributes to AKI-to-CKD progression. Potential methods of breaking this vicious cycle of pathological loops include new forms of therapeutic treatment, including senolytic therapy to selectively kill senescent cells, SASP inhibitors to reduce inflammatory signaling and anti-fibrotic therapy to suppress the activity of myofibroblasts. The additional conception of the crossroad of senescence and fibrosis provides a vital understanding of the importance of maladaptive repair of the kidney and provides new opportunities to prevent long-term kidney damages after acute kidney damage.

Keywords: Acute kidney injury, cellular senescence, fibrosis, maladaptive repair.

1. Introduction
Acute Kidney Injury (AKI) is a medical condition caused by acute injury to the kidney which may or may not but often does lead to Chronic Kidney Disease (CKD). AKI can be characterized as the quick increase in the serum creatinine level and/or the decrease in the urine volume in the short period. The common insidious interplay of senescence and fibrosis following AKI is an evolutionarily preserved, stereotypical reaction to damage of parenchyma, which is a complicated interplay of various renal cell types with the interstitial milieu [1,2]. The intrarenal environment alters the senescence programs that are implemented by various nephron segments, compelling the Proximal Tubule Epithelial Cells (PTEC) to cause an extensive and robust injury-mediated senescence program. Several key determinants in the kidneys, including the cytokine/chemokine signature from the injury site, the ontogeny of resident macrophages, and the proximity of PTECs to the renal vascular supply, govern how perturbed environments interact with essential cellular repair pathways of the senescence programs. Evaluation of markers of senescence at the cellular level, systemic indicators of kidney health, serum creatinine levels, and (semi) quantitative analysis of histologic kidney specimens further confirm the strong correlation between senescence and fibrosis during AKI [3, 4]. Histologically, AKI is typified by tubular cell injury, early inflammatory infiltration, and in certain clinical settings, extensive urinary casts. A diverse collection of cellular events may occur within renal tubular segments besides senescence, metabolic reprogramming, proptosis, and epithelial-mesenchymal transition (EMT) influences renal tubular repair after parenchymal injury [5, 6].

The main actors and the specific events linked to kidney senescence and then interstitial fibrosis involve the initiation of various injuries; the sequential correlation between various renal events; the signals that coordinate fibrotic events; the interaction between epithelial cells and fibroblasts; and, most importantly, the coordination with other renal parenchymal, vascular and immune signals in deciding the response of the kidney to a wide range of external disturbances [7].

2. Background: Acute kidney injury and its consequences

Acute kidney injury (AKI) is a serious and widespread clinical issue. Recent estimations indicate that 10% of patients admitted to hospitals and almost a quarter of patients admitted to intensive care units is complicated by AKI which frequently leads to the emergence of chronic kidney disease (CKD) [8, 9]. After damage of the kidney, maladaptive repair usually takes place resulting in interstitial fibrosis, atrophy of the tubules, and nephron mass loss that is functional. The result of this maladaptive repair process is continuous cell cycle arrest of the epithelial cells, a phenomenon also known as cellular senescence, that has now been found to be a determining factor in the development of AKI into CKD [10]. This form of cellular senescence may occur after a wide range of kidney injuries, such as ischemia-reperfusion, drug or contrast agent toxicity and plugging. A typical character of cellular senescence is the senescence-associated secretory phenotype (SASP), which has been noted in epithelial cells of the kidney following AKI and has possibly been involved in the fibrotic repair process [10, 11].

3. Cellular Senescence: Concepts and Mechanisms

Cellular senescence is defined as the permanent arrest of the cell cycle, which in the context of *in vitro* cell culture was originally described as a response of the cell to proliferative stress by the cell. Some inducers encompass telomere shortening, replicative senescence, stress induced premature senescence and oncogene induced senescence. These words show that it is a phenomenon-specific, rather than a universal, process and the indications are where the specific trigger occurs in a particular situation [12]. There is an ever-growing body of evidence pointing to the fact that cellular senescence is the basis of a wide range of conditions, including tissue aging and traumatic injury, and many disease mechanisms. Under the condition of Acute Kidney Injury (AKI), the occurrence of renal injury prompts a chain of events resulting in irreversible cellular changes. The ability to recover decreases with age due to senescence although the restoration of tubular structure/function is believed to be positive during the initial recovery period following injury [13]. Subsequently, tubular cell senescence is involved in the advancement to fibrosis and end-stage renal disease, indicating that it is temporally involved in damage in AKI [14].

Renal senescence involves multiple signal transduction pathways and precise interplay among injury triggers, modules, and serial phases of renal cellular injury and response, necessitating understanding the non-universal mechanisms in each injury or disease context. The relentless commitment to cell fate occurs once the signaling network favors irreversible permanent cell-cycle withdrawal [15]. Accordingly, paradoxical increases in enhancers and repressors that oppose each other maintain the distinct circadian rhythm of synergistic and complementary biosynthesis systems, lying beyond classical concepts of opposing regulators [16].

3.1 Inducers of Renal Cellular Senescence

Severe biopsies and nephrotoxic drugs induce senescence in the kidney, and multiple organs exhibit markers of senescence post-AKI. AKI affects almost all stages of the cell cycle, but G2/M arrest and senescence become persistent post-injury. These persistent alterations correlate with the level of injury and accelerate the development of fibrosis [17].

3.2 Senescence-associated secretory phenotype in the kidney

Cellular senescence is a stress response characterized by a proliferation arrest combined with the expression of the senescence-associated secretory phenotype (SASP), the latter consisting of pro-inflammatory cytokines and growth factors that can influence the behavior of nearby cells [18]. In the context of acute renal injury, the consequences of Tubular Epithelial Cell (TEC) senescence appear to drive the progressive evolution of Acute Kidney Injury (AKI) into Chronic Kidney Disease (CKD) and are likely to curtail recovery in atrophic kidney disease, since senescence is associated with the fibrosis that accompanies repair processes following substantial parenchymal damage. Several groups have reported that TEC upregulate cell cycle inhibitors p16Ink4a and/or p21Cip1 following different acute injury paradigms, which correlates with the development of fibrosis [19]. In experimental models of AKI, the induction of senescence in the kidney-among other organs-occurs very early after injury rather than as a late event in the evolution of the injury, and the functional and morphologic consequences and related secretum continue to evolve thereafter [20]. Experiments involving depletion of p16Ink4a and p21Cip1 in TEC indicated that both are required for maximal upregulation of TGF-β1 and IL-6, members of the SASP originally identified in other cell types [21]. These observations extend earlier work showing that activation of the DNA damage response after AKI preceded the development of fibrosis and indicate that the senescence program in TEC after injury closely resembles that observed in cells undergoing replicative senescence in culture or senescence induced by oncogenic insult. The similar time course and dynamic expression patterns of individual SASP components after acute and chronic damage also suggest that specific paracrine signals produced by senescent TEC following fratricide and regenerative attempts contribute to the pathogenesis of both types of injury [20, 21]. Given their critical role in this process, downstream components of the senescence program that promote these responses offer potential therapeutic targets for blocking the evolution of AKI into progressive CKD [22].

3.3 Detection and Biomarkers of renal senescence

Following Acute Kidney Injury (AKI), renal tissues initiate a repair response that involves the removal of damaged cells; however, this repair process can become maladaptive and lead to long-term fibrosis, which ultimately contributes to the progression of Chronic Kidney Disease (CKD). Cellular senescence has been established as a universal phenomenon that occurs in various organs and cell types

during aging and may represent one of the principals signaling pathways involved in this maladaptive repair response [23]. Initially described as an irreversible cell cycle arrest phenomenon in response to replicative and stress-induced telomere shortening that prevents aberrant cell proliferation and promotes tissue homeostasis, cellular senescence has more recently been recognized to engage specific secretory pathways that can exert detrimental paracrine effects on neighboring cells. In the kidney, senescence has been linked to AKI, AKI-CKD transition, CKD progression, and transplant rejection [24].

Cellular events that activate senescence in epithelial cells of the proximal tubule following AKI include telomere shortening, elevated formation of reactive oxygen species, DNA damage, persistent endoplasmic reticulum stress, and engagement of mitochondrial apoptotic pathways. Macrophage-mediated propagation of these senescent signals has also been documented. In the kidney, tubular cells account for a significant proportion of senescent cells and remain the cell type in which the senescent phenotype has been studied most extensively [25]. Other forms of cells, like the glomerular cells like podocytes and endothelial cells, have also been identified to experience senescence in AKI, thus leading to the progression of glomerulosclerosis. There are other types of cells within the kidney that need to be further studied such as mesangial, parietal, and glomerular cells whose association with senescence needs to be explained. Lastly, immune cells have also become another important type of cell that becomes senescent in AKI and other chronic kidney diseases. T cell senescence, Natural Killer T (NKT) cell senescence, and macrophage senescence facilitate the progressive worsening of a kidney disease by facilitating the release of inflammatory and fibrotic messages [25, 26].

4. Fibrosis following acute kidney injury

Renal fibrosis is one of the frequent complications after acute kidney injury (AKI), yet the mechanisms of such pathological process are not fully understood. In spite of constant therapeutic progress, the incidence of the chronic kidney disease (CKD) in the patients with AKI has been on the increase [27]. Data deriving from both experimental models and human samples suggest that a sustained state of cellular senescence might be a pivotal mechanism linking AKI with subsequent renal fibrosis, therefore establishing this process as a potential target for therapeutic intervention. Cellular senescence is induced by a broad spectrum of forms of cellular stress, and recent findings indicate that, following AKI, it can be triggered by cell-intrinsic factors that are still poorly defined [28].

Activated myofibroblasts represent the most prominent source of extracellular matrix (ECM) and they dramatically contribute to renal fibrogenesis [28]. Myofibroblasts develop from different cell types within the kidney, including resident fibroblasts, pericytes, endothelial cells, epithelial cells and, potentially, circulating fibrocytes. Loss of adult nephron epithelial cells triggers compensatory proliferation of surviving cells; however, in settings where proliferation remains arrested, such as after G1/S or G2/M phase cell-cycle checkpoints have been induced, the secretion of specific factors can stimulate remaining epithelial cells to adopt a myofibroblast phenotype. This illustrates the existence of a secondary level of communication in the interstitial renal fibrotic compartment, whereby signals from senescent [29]. epithelial cells activate pericyte, fibroblast or endothelial cell-to-myofibroblast switches without the need for direct cell-cell contact [30].

4.1 Pathophysiology of renal fibrosis

Renal fibrosis is a consequence of acute kidney injury (AKI) and it can occur following severe and/or prolonged disruptions to normal physiological conditions. Renal fibrosis often becomes manifest following renal insult. Both the location and the type of functional change in the kidney tissue generally correlate with the degree of the original acute interstitial event; therefore, fibrosis is believed to represent a more chronic or advanced stage of renal tissue injury [31,32]. Fibrosis is characterized by the excessive production and deposition of extracellular matrix (ECM) components, which ultimately leads to disruption of the natural architecture of the kidney tissue. In the kidney, several factors are involved in the initiation and progression of the fibrotic response. The components of the fibrotic response in kidney injury have been well studied, and knowledge of the specific cellular mediators acting in the kidney has increased over the years. Myofibroblasts are the predominant cells responsible for the synthesis and deposition of extracellular matrix (ECM) in scar tissue after injury to most organs [33]. The specific transcription factors involved in cell plasticity between resident renal cells and myofibroblasts in different pathophysiological conditions have not yet been identified [34].

The renal damage caused by pyelonephritis, ischemia, rhabdomyolysis, and nephrotoxicity almost invariably leads to the development of renal interstitial fibrosis and prevents restoration of normal renal function. More than 20 different cell types reside in the kidney, and understanding of cell-type heterogeneity is improving steadily [35]. Renal rehabilitative mechanisms and persistent or progressive fibro-genic pathways vary according to the cellular source of pro-fibrotic mediators, which ultimately influence therapeutic strategies. The cellular sources of pro-fibrotic mediators that drive profibrotic signal transduction and the type of injury that preceded the fibrotic signal can also be linked with straight-line trajectories of fibrosis onset [36]. For instance, the injury induced by angiogenesis inhibitors and the anti-neoplastic 5-fluorouracil exclusively affects proximal epithelial cells and triggers a fibro-proliferative form of fibrosis through the liberation of secretory phospholipase A2-IIA into the tubular lumen. In contrast, injury induced by growth factor excess, including insulin and hepatocyte growth factor, acts through either smooth muscle or pericyte cell types at the perivascular niche and stimulates purely adipo-genic or lipogenic processes [37]. Therefore, connective-tissue-growth-factor-dependent pro-fibrotic signaling can act through extensive and wholly renal-soup-containing cell-type heterogeneity to maintain either a clarion-of-competent-regeneration/fibro-proliferative/fibro-scas-dependent fibrotic-response program [38].

4.2 The role of myofibroblasts and extracellular matrix remodeling

The fibro-genic phenotype associated with Chronic Kidney Disease (CKD) is mainly due to the abnormal activation of fibroblasts into myofibroblasts, a process known as trans differentiation. Resident fibroblasts in the kidney respond to various insults by converting into myofibroblasts that

produce extracellular matrix proteins, greatly contributing to the progression of fibrotic diseases [39]. Pericytes and epithelial cells (proximal tubular and podocytes) can also transdifferentiate into myofibroblasts, although the cells of origin may differ depending on the type of insult. Tubular cell trans differentiation may initially occur as an adaptive process, but if the injury is unresolved and tubular-effector senescence becomes prominent, this process may become maladaptive and foster fibrosis. Different types of renal insults and diseases affect the origin and activity of myofibroblasts involved in renal fibrosis [40, 41].

4.3 Interplay between senescence and Fibrosis

Following AKI, the secretion of factors associated with the SASP can worsen kidney conditions. Myofibroblasts are one cell type activated in the damaged kidneys that may respond to these factors released by senescent cells and stimulate renal fibrogenesis. During interstitial fibrosis repair after acute injury, pathways leading to renal senescence activation are already functional weeks after parenchymal injury. In one study of mouse models, partial nephrectomy induced multiorgan and renal senescence and promoted myofibroblast activation and renal fibrosis even when the final kidney parenchymal injury was limited [42]. Renal fibrosis, thus, might follow, and if additional injury occurs, CKD may develop. However, the interaction between cellular senescence and fibrosis in the same organ after parenchymal injury has not been investigated in kidney diseases [43].

5. Experimental evidence linking senescence and fibrosis in AKI

Following acute kidney injury (AKI), parenchymal tubular and vascular cells incur damage that, in certain circumstances, triggers a series of interwoven reparative responses from which complete recovery does not occur. Sustained renal repair characterized by cellular senescence is believed to significantly drive the development of chronic kidney disease (CKD) [44].

Senescent cells accumulate with time in rodent models and also in human kidneys following an acute ischemic insult [45]. Studies on various models of AKI have linked the induction of cellular senescence in renal parenchymal cells to a clear profibrotic response and to the emergence of a pro-fibrotic senescence-associated secretory phenotype (SASP). Under circumstances where tubular parenchyma exposure to sub-lethal ischemia remains confined to acute injury without long-term kidney dysfunction, tubular cells engaged in a G2/M cell cycle arrest reported the transient expression of canonical senescence markers that did not correlate with subsequent fibrogenesis, suggesting that other factors contribute to channeling kidney injury into a profibrotic trajectory [44, 45]. Furthermore, tubular parenchyma subjected to extensive but early recovery ischemic insults subsequently revert to normal structure and function, and do not initiate subsequently and exhibit progressive fibrosis [46].

5.1 Animal models of AKI-Induced senescence and fibrosis

In the clinical setting, the relevance of cellular senescence in kidney injury is observed following acute kidney injury (AKI), a condition that initiates an irreversible deposition of Extracellular Matrix (ECM) and subsequently leads to Chronic Kidney Disease (CKD). When compared to young controls, the kidneys of aged mice (i) present a more pronounced and persistent G2/M cell cycle arrest and (ii) exhibit a substantially large number of CDKIs positive cells post-AKI insult. Aged mice display an increased abundance of several profibrotic cytokines such as TGFβ1, CTGF, IL-6, and IL-1α in kidneys after AKI [47, 48]. Kidney senescence associated-secretory phenotype (SASP) expression is also intensified in aged kidneys and is mainly produced by G2/M arrested cells. Furthermore, senescence is exacerbated in aged animals undergoing cisplatin treatment. In mice undergoing warm ischemia-reperfusion (WIR), the cellular senescence markers P16INK4a, P21CIP1/WAF1, and the cellular senescence-associated β-galactosidase activity remain elevated up to 3 months following an insult and the senescent cells are preferentially located in the inner cortical region of the nephron, most notably in proximal tubular epithelial cells at the time of injury [48]. Renal senescence ASB accompanied by delayed proliferative restoration eventually results in peritubular capillaries endothelial dysfunction, ECM depositor elevation, and progressive interstitial fibrosis. In different species including rats, tubular epithelial cells, and pericytes undergo cellular senescence post-AKI insult, indicating that renal cellular senescence is a conserved key element following kidney injury. In humans, kidney specimens obtained from living transplant donors demonstrate greater P16INK4a and P21WAF1 expression associated with connective tissue growth factor, fibronectin deposition, and more advanced interstitial fibrosis in diabetic and hypertensive individuals when compared to subjects with no previous history of kidney disease [49].

5.2 Human Studies and Clinical Correlates

Cellular senescence and kidney fibrosis are critically involved in the prolonged loss of nephron function after acute kidney injury (AKI) the so-called post-AKI chronic kidney disease. Such connections have been firmly established in experimental models, and evidence from human studies supports involvement of these processes in the human kidney. During the quest to identify suitable translational indicators of renal senescence and fibrosis, informative patterns of gene expression, notably those in the kidney tissue or urine associated with the senescence marker p21CIP1, have emerged. Key findings of studies correlating senescence with kidney fibrosis, conventional measures of disease severity (levels of serum creatinine), and causative factors of AKI (e.g., sepsis, nephrotoxic drugs) are also instructive. Together, these insights focus attention on the pursuit of effective interventions for preventing or delaying the development of post-AKI chronic kidney disease, which is expected to benefit a large number of patients [50, 51].

6. Therapeutic Implications and Interventions

Acute Kidney Injury (AKI) is a clinical syndrome characterized by a sudden decrease in kidney function with a multifactorial etiology. After AKI, some pathologies such as chronic kidney disease (CKD) develop at an increased rate, which is an urgent health issue. Cell loss is subjected to senescence by the influence of such harmful conditions as nephrotoxins, ischemia, and oxidative stress, which in the end results in an abnormal secretum and the capability to regulate neighboring tissues. When nephrons are lost, the survivors are exposed to mechanical stress because of

hyperfiltration in the glomeruli, causing abnormal signaling and activation of kinases that create a cellular set point that favors senescence [52]. The set of these signals results in the formation of an environment where the senescence-associated secretory phenotype ensures proinflammatory and pro-fibrotic signals. This process maintains the path to the kidney senescence and facilitates CKD. An accumulating amount of evidence is suggesting the activation of cell senescence and fibrosis after AKI and that the two processes are associated with the following chronic kidney disease. Regulating stress factors that promote senescence is a promising approach to postpone the development of postinjury kidney disease [53, 54].

6.1 Targeting Cellular Senescence

Cellular senescence is a concept that is relevant to the consideration of AKI. It is a dynamic process which results as a consequence of cell stress and damage to DNA which causes cell cycle arrest and a possible maladaptive repair process. Moderate and reversible AKI is linked to restore kidney functions in 7 days and alterations in kidney cellular proliferation which are limited to G1 and, therefore, do not progress into fibrosis in the long term. Conversely, in severe AKI, there is a sustained G2/M cell cycle arrest and G2/M-arrested cells accumulation, which is associated with a markedly exertive interstitial fibrotic reaction that is evidently a sign of a maladaptive cure. Accumulation of G2/M-arrested cells elicits aberrant activation of a number of signal transduction pathways among them the JNK pathway resulting in increased secretion of a variety of profibrotic cytokines and growth factors that further amplify the fibrotic process [55]. Such G2/M accumulation and associated fibrosis also occur in the kidneys of individuals exposed to noxious stimuli who display no overt renal dysfunction at any time. Intervention with small molecule inhibitors that specifically target pathways such as the ATM/p53/p21 or the p38 MAPK/c-Fos/JUN/FosB pathway has been shown to mitigate renal G2/M cell cycle arrest and interstitial fibrosis, indicating that such pathways represent promising therapeutic targets [56].

Acute Kidney Injury (AKI) triggers renal cellular senescence and fibrosis. Experimental evidence from rodent models of AKI and studies in human specimens has established a strong link between senescence and the fibrotic responses that accompany the injury [57]. Renal cell senescence, detectable from day 3 to day 30 after injury, is accompanied by the appearance of profibrotic factors and is tightly associated with the accrual of interstitial fibrosis. In humans, expression of the senescence-related protein p16INK4a and the senescence-associated secretory phenotype is significantly increased in kidneys from both AKI patients and non-AKI chronic kidney disease subjects, correlating with markers of renal fibrosis [58].

6.2 Anti-fibrotic strategies and combination approaches

Cellular senescence and renal fibrosis following acute kidney injury share common mechanistic pathways and often colocalize in animal models while the expression of pro-fibrotic genes is upregulated in senescent cultured renal cells [59]. Efforts aimed at either mitigating senescence or reducing fibrosis consequently have the potential to achieve dual therapeutic benefits within the context of acute kidney injury. Several anti-fibrotic agents are currently in late preclinical or early clinical stage studies targeting a range of pro-fibrotic pathways [60]. Neutralizing (regarding pro-fibrotic activity) selective modulators of extracellular matrix proteins such as peptide aptamers, monoclonal antibodies, and lytic phages also represent a novel experimental approach for mitigating renal fibrosis. Combination treatments targeting both renal senescence and fibrosis might be considered a highly attractive strategy. Metformin has shown preliminary evidence for Seno-lytic behavior and diminishment of cellular senescence following acute kidney injury [60].

6.3 Timing, Safety, and Translational Considerations

Acute kidney injury (AKI) is an abrupt loss of kidney function associated with high mortality and rapid progression to permanent kidney dysfunction in up to 60% of survivors. Kidney function is commonly assessed by serum creatinine and urine output, but these variables can remain unchanged while critical events still occur. A marked increase in serum creatinine and a progressive decline in estimated glomerular filtration rate frequently occur in non-urinary conditions such as heart failure, liver failure, advanced malignancy, and sepsis [61]. Acute neutron dose to any tissue is considered by many to convey a high risk for tissue injury, regardless of previous total dose. In certain tumor volumes, however, high single doses are intentionally delivered in order to cause immediate or rapid cell destruction, sometimes even to prevent further treatment; and experiments have shown that stem cell recruitment can follow such irregular patterns [62]. Mitochondrial dysfunction and silencing of juxta-cellular signal genes are important for many cell types. Central signaling proteins, pathways, RNA species, and epigenetic entities participate extensively in molecular responses to various types of acute injury.

7. Gaps in knowledge and Future Directions

There is substantial evidence linking cellular senescence to acute kidney injury (AKI) and its consequent fibrosis and chronic kidney disease progression. Nevertheless, significant gaps in knowledge remain, several of which are outlined in the present section. First, although the senescence-associated secretory phenotype (SASP) and other features of renal senescence are recognized as biomarkers of progressive kidney pathology, further clarification is necessary regarding the extent to which these features are observed following AKI and whether they exhibit temporal variations [63, 64]. Second, further insight into the mechanisms of renal injury and subsequent tissue responses under conditions of less extreme parenchymal injury including the unilateral ischemia and nephrotoxin model would be beneficial to the understanding of pathways mediating between initial injury and late fibrotic alterations and would create conditions to design therapeutic approaches to these events [64].

Other questions involve the investigation of the therapeutic potential of anti-senescence measures that suppress the formation or progression of the senescence program per se or the outcome of its execution; the consideration of cell type-specific senescence attributes that can be employed to customize and optimize therapeutic interventions; the detailed delineation of the fibrotic program that senescence activates in a particular cell type and the identification of the specific mediators of the senescence-induced recruitment, activation, and/or reprogramming of interstitial

myofibroblasts All these areas provide promising areas of future research to help mainstream the complex interaction between cellular senescence, fibrosis, and AKI [65].

8. Conclusion

The causes of acute kidney injury (AKI) include ischemia-reperfusion injury, obstruction of the ureters, and nephrotoxic substances, which activate complement, toll-like receptors, and the release of DAMPs. Approximately 70 percent of patients with AKI have tubule-glomerular fibrosis and thus AKI is an expanding healthcare issue particularly due to the ageing of population and increased comorbidities. Injured cells tend to enter senescence and cease proliferation while retaining a pro-inflammatory, pro-fibrotic secretum which stimulates fibroblast activation and chronic fibrosis. Thus, it is necessary to get rid of senescent cells. Tubular epithelial cells, especially around the medulla, are very susceptible, and they undergo G2/M arrest and MAPK-induced senescence following ischemia, cisplatin toxicity, or obstruction. The transition between acute injury and chronic disease is prompted by DAMP release, G2/M arrest, Akt activation and p21-mediated HIF-1 expression. Mitochondrial dysfunction and ATP depletion induce p53 and maintain p21 programs, which increase chronic HIF-1 signaling. Long-term renal damage can be avoided by the inhibition of mitochondrial fission or supplementing with ATP to limit early HIF-1 activity.

9. Declaration of Competing Interest

The authors say they don't have any known personal or financial relationships or financial interests that could have seemed to affect the work in this study.

10. Acknowledgment

This review article is supported by Department of Basic Sciences, College of Dentistry, University of Basrah.

11. Funding

There is no funding

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