Stages in the Evolution of Kidney Damage

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Acute kidney injury (AKI) is a major clinical problem associated with increased morbidity and mortality. Despite intensive research, the clinical outcome remains poor, and apart from supportive therapy, no other specific therapy exists. Furthermore, acute kidney injury increases the risk of developing chronic kidney disease (CKD) and end-stage renal disease.

Keywords: renal insufficiency ; kidney injury

1. Introduction

The evolution of acute renal damage into chronic renal damage involves various stages in succession up to the repairing processes of the damage, complete or partial depending on the severity of the damage. These processes follow one another with probabilistic and time-dependent mechanisms through different phases involving:

- The endothelium;
- The inflammatory response to endothelial damage;
- Development of fibrosis;
- Damage repair and attempts at functional recovery.

From a pathophysiological point of view, microvascular integrity, changes in the behavior of leukocytes and pericytes, the ability to survive, and the attempt to restore tubular cell function are all characteristics of both AKI and chronic renal failure. The main pathological mechanisms that help to explain the transition from AKI to CKD include:

(i) Endothelial dysfunction, vasoconstriction, and vascular congestion [1];

(ii)Interstitial inflammation and associated infiltration of monocytes/macrophages, neutrophils, T and B cells [2][3];

(iii)Fibrosis via myofibroblast recruitment and matrix deposition [4][5];

(iv)Tubular epithelial damage and dysregulated repair [6].

Thus, after ischemic injury, loss of nephron mass with hyperfiltration of the residual nephron, activation of the renin-angiotensin system (RAS), systemic hypertension, and subsequent glomerulosclerosis, have been described to pave the way from AKI to chronic renal failure [7][8][9][10]. Regardless of the initial insult, evidence of tubular cell loss and scarring, replacement of collagen, and infiltrating macrophages are associated with further renal functional loss and progression to end-stage renal failure. Experimental models have shown that selective epithelial damage could drive capillary rarefaction, interstitial fibrosis, glomerulosclerosis, and progression to chronic renal failure, confirming a direct role for damaged tubular epithelial cells (TEC) [9]. Therefore, tubular epithelial cells have attracted increasing attention. The interaction between endothelial cells, macrophages and other immune cells, pericytes, and fibroblasts often converge in tubular epithelial cells, which play a central role [9]. Recent evidence has reinforced this concept by showing that damaged tubules respond to acute tubular necrosis through two main mechanisms:

- The polyploidization of tubular cells;
- The proliferation of a small population of self-renewing renal progenitors [9].

2. Endothelial Dysfunction and Vascular Congestion

Endothelial dysfunction is characterized by the loss of the mechanisms that regulate vasodilation and vasoconstriction, mediated by endothelium-dependent activity and exerted by nitric oxide (NO), in response to vasomotor stimuli that

involve a variation in systemic blood flow. The endothelial-derived NO is physiologically produced by the activity of eNOS (endothelial nitric oxide synthase) [9][10]. The release of NO involves a multi-level response by reducing the tone of vascular smooth muscle by inducing vasodilation, inhibiting platelet aggregation, and promoting leukocyte activation. In the etiopathogenesis of renal damage, capillary rarefaction and therefore the loss of NO production is traditionally considered an important element linked to the potential progression of chronic renal damage. In fact, the reduction of the oxygen supply leads to an inflammatory reaction, ischemia, and necrosis, making the kidney cells vulnerable, which in the grip of hypoxia lose their function mainly due to a block of mitochondrial activity [9][11]. The inflammatory infiltration resulting from this damage subsequently generates the replacement of functionally active cells with fibrotic tissue [12]. The capillary rarefaction, however, in some way induces a reparative response mediated particularly by the vascular endothelial growth factor (VEGF), an endogenous cytokine produced by epithelial cells and directed to endothelial cells. Its production could constitute a compensatory response to microvascular dysfunctions and morphological changes in the nephron, but the mechanisms governing this process have yet to be known [13][14]. An increase in the production and activity of endothelium-specific transforming growth factor β (TGF-β) and from pericytes of growth factor including PDGF (platelet-derived growth factor), angiopoietin, TGF-β, VEGF, and sphingosine-1-phosphate have been observed to contribute to interstitial fibrosis and, therefore, to chronic damage [15]. Pericytes are cells of undifferentiated mesenchymal origin, with contractile function, partially surrounding the endothelial cells (19). As undifferentiated mesenchymal cellular elements, they can, in response to damage, leave their perivascular site differentiating into myofibroblasts and contributing to both vascular rarefaction and an increase in fibrosis [16].

3. Interstitial Inflammation and the Role of Associated Infiltration of Monocytes/Macrophages, Neutrophils, T and B Cells

After the initial phase of acute kidney injury, early inflammation is followed by pericytes-mediated infiltration of both residents and infiltrating circulating cells, which contribute to disease progression [17][18]. Taking into account their activity in the regulation of inflammation, neutrophils, due to their paracrine effects on tubular epithelial cells, and macrophages can play an important role as determinants of AKI outcomes. In fact, a subset of regulatory T cells (Treg) can act as an inducer of self-tolerance and suppress inflammation by improving immune homeostasis. The $CD4^+$ and $CD8^+$ T lymphocytes could also play a protective role and affect the natural history of AKI although this has only been demonstrated in mouse models [19][20]. Conversely, B lymphocytes and macrophages have been described as elements capable of promoting the evolution of renal damage and making it more severe, contributing to the progression from acute to chronic renal damage [21]. Therefore, an increased presence of macrophages is also related to fibrosis and adverse outcomes [22].

4. Fibrosis

The interaction between activated macrophages, damaged cells, endothelial cells, and the growth factors connected to the damage is responsible for the development of a pro-fibrotic environment. This environment activates the pericytes to proliferate and evolve into myofibroblasts, further inducing the deposition of the extracellular matrix, the deposition of collagen, fibronectins, and other glycoproteins, and therefore extending renal fibrosis and promoting subsequent CKD evolution [23]. Although recognized as the main prognostic factor for CKD, according to current studies fibrosis is considered to be self-sustaining in its process, and a causal relationship between ECM deposition, fibrosis, and damage has not yet been identified in chronic renal damage [24]. According to some studies, the premature presence of fibrosis after initial damage could be a positive element capable of stimulating healing processes by representing a demarcation zone between damaged cellular elements and those spared or not affected by the damage [25]. Therefore, it would appear that fibrosis is not such an important element in the transition from AKI to CKD and that the progression of renal damage requires further phenomena independent of the apposition of fibrotic tissue. On the basis of experimental models, other authors have shown that selective epithelial damage inducing interstitial fibrosis and glomerulosclerosis led inexorably to the progression to chronic renal failure, confirming a direct role of fibrosis in the loss of renal function [9]. Furthermore, it is necessary to specify that even the role of myofibroblasts is somewhat ambiguous in situations of the evolution of renal damage. This is because if they are naturally the main cellular elements that trigger and condition the severity and extent of the fibrosis, contrarily, they can acquire the ability to produce retinoic acid, supporting the integrity and repair of the epithelium and reducing the pro-inflammatory activity of macrophages [26]. Some studies [27][28] suggest that it is essential to better understand the cellular and molecular processes that underlie fibrosis in AKI for the development of therapeutic strategies to arrest the progression of AKI into CKD. However, it would be useful to first establish the exact role of fibrosis and also to identify the elements or mechanisms that underlie the resistance of renal cells to acute damage.

5. Tubular Damage and Damage Resistance Capacity

All of the molecular and cellular mechanisms described so far lead to the dysfunction of the tubular epithelial cells, which represents the true cause of the progression of renal damage towards CKD [29]. In fact, the failure to recover the integrity of the tubular structure is directly proportional to the risk of the development and progression of CKD, which in turn is closely linked to the severity of the acute episode [29]. However, the severity of the acute episode is not the only determinant of the progression of kidney damage. It is believed that the age of the affected person may also be important, especially in the processes of survival and resistance of kidney cells as well as the resumption of normal activity [30]. The most acute damage in kidney cells occurs in the tubular epithelial cells of the proximal S3 segment of the outer cord stripe. These cells carry out intense activity and require an enormous metabolic and energy potential that comes only in a limited way from the production of ATP, and therefore exploit energy substrates obtained in anaerobiosis or from alternative metabolic pathways [9]. Precisely for this reason, these cells are extremely vulnerable to hypoperfusion, renal hypoxia, and mitochondrial damage [9]. After acute injury, the kidney can overcome the injury and restore its functionality in the right state [31][32][33]. In fact, after a mild injury event, the kidney may return to a structural and functional state that is indistinguishable from normal. Both the cortex and medulla of the kidney tissue can be senescent, including renal tubular epithelial cells (TECs), podocytes, vascular smooth muscle cells, endothelial cells, and mesenchymal cells, among which renal TECs are the most common cells that undergo senescence [31][32]. This is due to the strong compensatory ability of mature kidney cells, which can quickly re-enter the cell cycle from a resting state within 24 h after injury. If the kidney is severely impaired or damaged, it will cause a variety of pathological changes and interstitial fibrosis [31][32]. It has been observed that the most vulnerable cellular elements, once damaged, undergo a process of dedifferentiation. This allows them to return to an undifferentiated state and therefore able to generate new cellular elements that carry out rapid repair in the case of acute injuries, thus preventing chronic damage [34]. It is known that cellular reprogramming is the process of reverting differentiated cells to the pluripotent state, and the pluripotent state can be differentiated into various functional cells [35]. There are different modes of reprogramming. Cells can first return to a pluripotent state and then differentiate into the desired lineages. Alternatively, one cell type can directly convert into another cell lineage by expressing specific factors [35]. Senescence can be improved by initiating reprogramming, which plays a crucial role in blocking the progression of AKI to CKD. Acute senescence causes the cell cycle to be temporarily blocked, which helps the cells to avoid uncontrolled mitosis and provides more time for DNA repair [36]. Other studies have demonstrated that cell senescence in the process of AKI proliferation and repair is not an irreversible process, and its cell phenotype changes dynamically. In the process of tissue damage and repair, cell senescence after an injury is an important factor leading to cell reprogramming [37][38]. Regeneration of tubular epithelial cells is mainly due to a larger renal progenitor population in the S3 segment of the proximal tubule. This explains the high proliferation of tubular epithelial cells observed in this area, but such activity has also been observed in the S2 segment of the proximal tubule and in other uninjured areas of the nephron [39][40][41]. However, it would seem that the entry of these cells into a phase of senescence does not involve the re-reception and therefore the formation of two new differentiated daughter cells. Nevertheless, they undergo an endoreplication program by which the cells replicate their genome without division, becoming polyploid. Polyploidization increases gene replication in response to increased metabolic demands, constantly maintaining differentiated and specialized cell functions. This allows for hypertrophy and functional recovery [39][42].

The researchers reported that the targeting TC (tubular cells) polyploidization after the early AKI phase can prevent the AKI-CKD transition without influencing AKI lethality. Senolytic treatment prevents CKD by blocking repeated TC polyploidization cycles [43].

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