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# CKD Management: A Look into the Future

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## CKD: The Global Challenge

Globally, an increasing number of patients with end stage renal disease (ESRD) are treated by dialysis or transplantation. It is estimated that by 2010 over 2 million individual will be on renal replacement therapy (RRT) worldwide [1]. This global increase in ESRD reflects, to some extent, the ageing of the population in the West and the steady increase in the number of those suffering from diabetes mellitus and diabetic nephropathy. The majority of those having access to RRT live in the West where such facility and resource are available and affordable; those living in the developing countries often die from ESRD with little opportunities for dialysis or transplantation.

Of concern is the fact that ESRD patients represent a small percentage (0.1%) of the population, whilst there may be as many as 10% of the population suffering from chronic kidney disease (CKD), those either will eventually reach ESRD or are more likely to die from cardiovascular complications before reaching that a stage of renal insufficiency. The huge population burden of CKD needs urgent attention as it is likely to increase over the next decade in view of the global rise in chronic, non-communicable, diseases such as diabetes, obesity, hypertension all known to impact on CKD. Furthermore, CKD itself has negative impact on these conditions increasing both their morbidity and mortality.

So far, the management of CKD has been confined to the treatment of its complications namely hypertension and proteinuria with little attempt made to reverse the underlying chronic scarring process. Chronic kidney disease is associated with progressive kidney remodelling and scarring regardless of the initial cause of injury.

## CKD and Kidney Remodelling

Patients with chronic glomerulonephritis, pyelonephritis, hypertensive nephrosclerosis and diabetic nephropathy share some common renal pathological pathways. They are characterised initially by renal cell damage; glomerular or tubular in nature. The nature and extent of the cellular damage will determine the cell's fate; death, metamorphosis or recovery. Death will take place after severe injury either through the process of cell necrosis or apoptosis. These processes can lead to further renal injury through the release of toxic and/or inflammatory cell products. We have shown that apoptosis takes place in both glomerular and tubular cells during the course of experimental renal scarring [2, 3]. Injured renal cells that escape death often undergo a process of transformation aimed at regaining certain immature, embryonic, characteristics allowing them to repair the initial damage through migration and proliferation. These processes when controlled and self-limited will lead to kidney repopulation by mature renal cells, injury repair and healing. If on the other hand, the renal cellular transformation is uncontrolled and progressive, the transformation of renal cells to a new immature and proliferating mesenchymal phenotype will add to the pool of pro-fibrotic cells thus contributing to progressive renal fibrosis and scarring. Other cells engaged in the renal fibrosis response include quiescent renal fibroblasts that could be activated by damaged kidney cells' release products leading to their proliferation as well as their excessive synthesis of extra cellular collagenous matrix (ECM). This leads to irreversible renal fibrosis and scarring.

Kidney fibrosis is characterised by the progressive replacement of renal structure and cells

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by ECM. This is the direct result of the renal cell death and depletion mentioned above and replacement by proliferating fibroblasts. Activated and proliferating fibroblasts produce excessive ECM or ECM altered in such a way that is not amenable to breakdown and clearance by renal collagenolytic enzymes. These enzymes normally have the capacity to effect ECM breakdown and turnover in such a way as to keep renal homeostasis. In pathology, either a collagenolytic enzyme deficiency or resistance to their action leads to ECM accumulation and irreversible fibrosis.

The steps of renal remodelling detailed above often lead to progressive CKD. So far, little attempts have been made in humans to address these changes by therapeutic interventions. This, in spite of a growing body of experimental evidence suggesting that such interventions may prove promising.

**CKD Management: Targeting Cell Death**

Loss of glomerular endothelial, mesangial as well as epithelial cells have all been associated in a range of experimental models with glomerulosclerosis [2]. Similarly, tubular cells apoptosis has been linked to the initiation and progression of tubulointerstitial fibrosis. Renal cells apoptosis has been demonstrated in a number of experimental models affecting both glomerular and tubular cells [4]. Further, intracellular upregulation of pro-apoptotic enzymatic pathways as well as the down regulation of apoptosis inhibitors have also been associated with renal cell injury and death [3, 5]. The intracellular caspase enzymatic system is considered a key pathway for the activation of apoptosis. We sought to target this enzymatic pathway in an experimental model of immune mediated renal fibrosis through the administration of a pan-caspase inhibitor (B-D-FMK). This showed promise as far as reducing both markers of renal inflammation and fibrosis [3]. It also reduced proteinuria, believed by some to be an important contributor to tubulointerstitial fibrosis. Reducing renal cell apoptosis may therefore have therapeutic potential in the management of progressive renal inflammation and fibrosis. However, such a therapy may have a double-edge effect by inhibiting the clearance of pro-inflammatory or pro-fibrotic cells within the remodelling kidney thus hampering its recovery and healing. Further research on the potential of apoptosis manipulation on renal remodelling is needed.

**CKD Management: Targeting Cell Transformation**

A large body of literature supports the concept of renal epithelial cells to mesenchymal transformation (EMT) in response to injury. The acquisition by these cells of mesenchymal, myofibroblastic, characteristics allows their migration, proliferation and production of ECM to achieve wound healing and renal recovery. On the other hand, the proliferation of myofibroblasts within injured glomeruli or tubulointerstitium may play a major role in fibrogenesis. A number of mediators have been implicated in EMT including transforming growth factor-beta1 (TGF-?1), connective tissue growth factor (CTGF), epidermal growth factor (EGF) as well as interleukin-1 [6]. On the other hand, bone morphogenetic protein-7 (BMP-7), an endogenous TGF-?? 1 antagonist, has been shown to inhibit and even reverse EMT [7]. Consequently, a number of reports have shown that the inhibition of TGF-?? 1 or the administration of BMP-7 attenuate experimental renal fibrosis [8]. Whether such approaches will be translatable to the bedside remain to be demonstrated.

**CKD Management: Targeting Cell Proliferation**

The proliferation of myofibroblasts, be it of the quiescent renal fibroblasts pool or from transformed epithelial cells, is driven by a number of cytokines and growth factors activating intracellular signaling pathways. Of these platelet-derived growth factor (PDGF) is a potent renal and fibroblast mitogen. Targeting PDGF by a number of agents has been shown to be effective in reducing renal proliferation as well as fibrosis [9].

Also the targeting of intracellular effectors of cell proliferation such as the tyrosine kinase, the cyclins, the ras-raf-mek-erk and rho kinase (ROCK) pathways has shown promise in reducing experimental renal cell proliferation and fibrosis. For instance, Imitanib mesylate, a c-abl tyrosine kinase inhibitor, has been shown to reduce fibrosis in animal models of chronic allograft nephropathy, obstructive as well as diabetic nephropathy. The synthetic cyclin kinase inhibitor roscovitine attenuated the histological changes observed in an experimental model of proliferative glomerulonephritis [10]. This anti-proliferative agent also shows considerable promise in the inhibition of tubular cell proliferation and cyst

Table

| Target | Intervention | Mechanism of action | Evidence level |
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| **TGF-β1** | Bone morphogenetic protein-7 (BMP-7) | Inhibitor of the TGFβ1-Smad signalling pathway | Experimental models of kidney disease |
| | Hepatocyte growth factor (HGF) | Inhibits nuclear translocation of receptor-regulated Smads and up regulates the expression of Smad corepressors | Experimental models of kidney disease and trials in promoting angiogenesis |
| | Inhibition of connective tissue growth factor (CTGF) | Mediator of TGF-β1-induced fibrosis | Experimental of kidney disease and phase II trial completed in Diabetic Nephropathy |
| | Tranilast | Inhibits TGF-β1-induced ECM synthesis | Experimental models of kidney disease, early clinical data in diabetic nephropathy and used in the treatment of hypertophic scars and scleroderma |
| | Decorin | Sequesters TGF-β1 in the extracellular matrix | Experimental models of kidney disease |
| **Proliferative mitogens** | Anti platelet derived growth factor (PDGF) e.g PDGF aptamers, Imatinib Mesylate, CR002, Trapidil. | Imatinib mesylate - kinase inhibitor of PDGF transduction. CR002 monoclonal antibody targeting PDGF-D. | Experimental data indicates potential of CR002 in mesnagioproliferative disease –phase I trial completed. Cardiotoxicity limits use of Imatinib Mesylate in clinical use in oncology and beneficial effects in experimental models of kidney disease. Use limited by cardiotoxicity |
| | Anti epidermal growth factor (EGF) | Inhibition of renal fibroblast proliferation and collagen expression | Experimental models of kidney disease. |

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| **Intracellular transduction cascade** | Ras-Raf-Mek-Erk pathway inhibition by<br>1- Ras: prenylation inhibitors (statins), prenyltransferase inhibitors, farnesylthiosalicylic acid (FTS),<br>2- Raf & Mek kinase inhibitors | Inhibition of cellular proliferation, differentiation and apoptosis. | Experimental model and phase II clinical trial in cancer treatment. Role of statins in progressive CKD not yet defined |
| | Rho kinase inhibition: Fasudil | Interference with cell proliferation, tubulointerstitial fibrosis and glomerular haemodynamics | Experimental models of kidney disease and phase II studies in ischaemic heart disease Fasudil in clinical use in Japan for cerebral vasospasm |
| | p38 mitogen-activated protein kinase inhibitors | Inhibition of pro-inflammatory and profibrotic mediators. | Experimental models and clinical trials in rheumatoid arthritis and type 1 diabetes mellitus. |
| | Protein kinase C inhibitors such as Ruboxistaurin | Inhibition of cell growth most evident in diabetic nephropathy. | Experimental models. Early clinical data with Ruboxistaurin in patients with early diabetic nephropathy |
| **Cell Cycle Inhibitors** | Cyclin-dependent kinases inhibitors such as Roscovitine | Inhibition of cell-cycle progression. | Experimental models and phase II trials in cancer. |
| **Immuno-suppressive agents** | Mycophenolate mofetil (MMF) | Inhibitor of inosine monophosphate dehydrogenase inhibiting cell proliferation | Experimental data. No clear data on efficacy in progressive CKD. |
| | Rapamycin | Interference with cell proliferation by regulating ribosomal biogenesis and protein translation | Experimental models variable but can induce proteinuria. No clinical data on efficacy in progressive CKD. |
| **Other Agents** | Pentoxyfylline | Phosphodiesterase inhibitor interfering with cell proliferation and EMT | Experimental models of CKD. Ongoing clinical trials assessing role in proteinuric CKD. |
| | Endothelin Antagonists | Reduce cellular proliferation and intra-glomerular hypertension. | Experimental models. Ongoing clinical trials in diabetic nephropathy. |

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| | Pirfenidone | Inhibits ECM accumulation | Experimental models of CKD. Phase II trials in diabetic nephropathy and phase III in pulmonary fibrosis |
| | Peroxisome proliferator-activated receptor-gamma agonists | Reduce cell growth, inflammation. Antiproteinuric effect. | Experimental and clinical data. Reduces proteinuria in diabetic nephropathy. On going clinical trials in diabetic and non-diabetic CKD. |
| | Prolyl hydroxylase domain (PHD) inhibitors e.g. Cobalt chloride, FG-2216 | Upregulation of HIF-regulated genes such as VEGF and EPO. | Experimental models. Phase II clinical trials of FG-2216 underway for the treatment of anaemia |
| | N acetyl-cysteine (NAC) | Antioxidant. | Experimental models. No clinical evidence in CKD |
| | Tocopherols | Antioxidant. | Experimental models. Tocopherols and alpha lipoic acid in clinical trials in CKD |

formation in an experimental model of polycystic kidney disease (PKD). ROCK inhibitors attenuate renal fibrosis in following experimental unilateral ureteric obstruction, subtotal nephrectomy and hypertensive glomerulosclerosis [11].

Whether such approaches can be safely applied to humans remain to be determined. Imatinib was shown to be cardiotoxic. Also, it is important to appreciate that renal cell proliferation is part of the reparative process in response to injury; its inhibition may compromise renal healing.

**CKD Management: Targeting ECM Deposition**

Transforming growth factor-beta1 plays a pivotal role in the ECM accumulation during the progression of experimental CKD. TGF-?1 is capable of increasing ECM synthesis as well as decreasing its breakdown through the inhibition of collagenolytic proteases (matrix metalloproteinases [MMPs]) as well as through the activation of protease inhibitors such as plasminogen activator inhibitor-1 (PAI-1). Consequently, as mentioned above, the inhibition of TGF-????has proved very effective at reducing ECM accumulation in experimental models of CKD [12]. Other strategies may involve the activation of MMPs, the activation of their inhibitor (TIMPs) and PAI-1; these interventions would in theory have the objective of reducing ECM deposition and/or increasing its clearance. However, it is important to bear in mind that these proteases and their inhibitors have numerous functions and interference with their activities may not be without side effects.

Another approach aimed at controlling ECM deposition may rely on the inhibition of tissue transglutaminase, an enzyme produced in the kidney and known to make ECM more resistant to collagenolytic breakdown. Our own work in the field showed that tissue transglutaminase is raised during the course of experimental and clinical scarring and that its inhibition considerably attenuates renal fibrosis [13]. This could prove to be a major breakthrough in the prevention of progressive renal fibrosis and scarring.

This review has explored some aspects of kidney remodelling in response to injury and suggested some future interventions, based on promising results in experimental models of CKD, that may have therapeutic potential for the management of patients with progressive CKD. The list of intervention (Table 1) is far from comprehensive as agents aimed at reducing renal inflammation, inhibiting putative cytokines and chemokines as well as those based on the administration of agents capable of affecting renal angiogenesis, hypoxia or glomerular permeability may also prove effective.

The next decades will undoubtedly see proof of concept intervention trials aimed at addressing many of the concepts highlighted in this review; a number of clinical trials are already underway (see www.clinicaltrials.gov).

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