The role of the tubular epithelial cell in renal fibrogenesis

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Abstract
Changes in the tubulointerstitial compartment play an important role in the progression of chronic renal disease to endstage renal failure. These changes consist of interstitial inflammation and subsequent fibrosis. The tubular epithelial cell plays a key role in the formation of interstitial inflammation. Stimulated by proteinuria and morphokines in the tubular fluid, the tubular epithelial cell responds by synthesizing chemokines, which, in turn, results in the influx of inflammatory mononuclear cells. Increased tubular expression of adhesion molecules, such as intercellular adhesion molecule (ICAM)-1 and vascular adhesion molecule (VCAM)-1, as well as major histocompatibility complex (MHC) class II antigens, in conjunction with costimulatory molecules, may have additional effects. However, the tubular epithelial cell does not only mediate interstitial inflammation, it also stimulates interstitial fibroblasts via the secretion of cytokines such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF)-2, and transforming growth factor (TGF)-β. Furthermore, tubular epithelial cells have the capacity to participate in the synthesis of extracellular matrix either directly or indirectly via their transformation into mesenchymal-like fibroblasts. This process of epithelial-mesenchymal transformation (EMT) depends on cytokines such as TGF-β1 and epidermal growth factor (EGF), as well as disruption of the tubular basement membrane (TBM). The contribution of epithelial cell apoptosis to tubular atrophy is actively under investigation.

Key words Fibrosis · TGF-β1 · FGF-2 · Fibroblast · Autocrine stimulation · Transdifferentiations

Introduction
The number of patients with endstage renal disease is increasing worldwide, although at different growth rates.1 Whereas in the United States, the incidence increased by more than 7% a year over the past decade to more than 73 000 in 1996,2 the increases were more moderate in Europe and Japan.3 Diabetic nephropathy, chronic glomerulonephritis, chronic tubulointerstitial disease, hypertensive nephrosclerosis, and polycystic kidney disease represent the most common causes of endstage disease. Usually, deterioration of renal function progresses slowly over many years. This decline may be due to persistent damage, as in diabetic nephropathy. However, progression of chronic renal failure often occurs even when the primary disease process (such as glomerular inflammation) becomes inactive, indicating that secondary factors play a key role in progressive injury.4 These secondary factors (also known as progression promoters) include systemic and intraglomerular hypertension, glomerular hyperfiltration, systemic and intraglomerular hypertension, glomerular and tubular hypertrophy, and tubulointerstitial changes (reviewed in reference 4).

Histologic sections from kidneys with chronic renal failure display characteristically glomerular and tubulointerstitial scarring. These lesions often have similar appearances regardless of the primary insult, and point to a final common pathway for endstage renal disease. Of particular importance in human studies and experimental models is the involvement of the interstitial (inter-tubular) spaces. The anti-Thy 1.1 model of glomerular disease, for example, is characterized by spontaneous resolution in the absence of interstitial lesions, but can progress to endstage renal failure when severe interstitial damage is present.5 In human kidney diseases, Bohle and coworkers observed an inverse association between histologic changes in the tubulo-interstitium and renal function that is now widely accepted...
(reviewed in reference 6). In studies on mesangio-
proliferative,7 membranous,7 membranoproliferative,7 and focal-sclerosing8 glomerulonephritides, the group con-
irmed a strong relationship between the morphometrically 
measured interstitial volume and renal function (deter-
ded by serum creatinine). Both the extent of interstitial 
filtration and the degree of interstitial fibrosis were rela-
tively accurate predictors of renal function 5 or more years 
later.11 Moreover, the group established the prognostic 
fuction of the tubulointerstitial space not only for primary 
glomerular diseases but also for secondary forms of 
glomerulopathies, such as glomerular amyloidosis12 and dia-
etic glomerulosclerosis.13 Conversely, even severe glom-
erular changes did not correlate with renal function in 
membranoproliferative glomerulonephritis, diabetic glom-
erulosclerosis, and renal amyloidosis, as long as the cortical 
tubulointerstitial space was not affected.14 These findings were 
confirmed and extended by Jepsen and Mortensen,15 Katafuchi and co-workers,16 Abe et al.,17 Alexopoulos and 
co-workers,18 Lane et al.,19 and Ziyadeh20 Moreover, tubu-
lointerstitial changes are equally important in non glo-
merular diseases, such as chronic pyelonephritis,21 
nephrosclerosis,22 and polycystic kidney disease.23 In dia-
etic nephropathy, tubulointerstitial changes have long 
been ignored until recently.24

Thus, interstitial fibrosis represents a final common path-
way of response by the kidney to sustained inflammation, 
independent of its origin. There is probably a point-
of-no-return where progressive renal failure invariably 
ensues despite resolution of the inflammatory process. 
Tubulointerstitial fibrosis is characterized by tubular atro-
phy, tubular dilatation, and increased interstitial matrix 
deposition. Because the tubular epithelial cell is directly 
involved in the formation of tubular atrophy and dilatation, 
its key role in fibrogenesis should come as no surprise. This 
review addresses the central role of the tubular epithelial 
cell in renal fibrogenesis.

### Regular wound healing and renal fibrogenesis

The normal interstitium consists of interstitial cells and a 
loose matrix of interstitial collagens (mainly types I and III) 
and proteoglycans. Interstitial cells are comprised of 
matrix-producing resident fibroblasts, macrophages, den-
dritic, and endothelial cells.25 Physiologically, a balance ex-
ists between matrix formation and degradation. This 
balance is impaired in fibrogenesis, due to both increased 
matrix production and decreased matrix degradation, as 
well as unregulated fibroblast proliferation. A better under-
standing of the process of renal fibrogenesis is possible by 
comparison with the regular wound healing process.

The physiology of wound healing has been studied most 
extensively in the skin.26 Three different phases can be dis-
tinguished: induction, matrix deposition, and resolution. 
Analogous to the dermal wound healing process, fibro-
genesis in the kidney has been divided into the same three 
phases;27 the induction phase, a phase of inflammatory ma-
trix synthesis, and a phase of postinflammatory matrix syn-
thesis. Table 1 gives an overview of the three phases. How-
ever, progressive renal fibrosis differs from regular wound 
healing in that no true resolution of fibrogenesis seems to 
occur. Instead, matrix synthesis and fibroblast proliferation 
continues in parallel with progressive destruction of normal 
organ architecture and eventual loss of organ function. As 
outlined above, matrix synthesis often persists despite ap-
parent resolution of the primary inflammatory stimulus. In 
resemblance to the regular wound healing process, how-
ever, three phases can be distinguished in renal fibrogenesis. 
These three phases will be discussed in more detail below, 
with particular emphasis on the role of the tubular epithelial 
cell.

### Induction phase

The first phase of renal fibrogenesis is the phase of intersti-
tial inflammation, which is characterized by the influx of 
infiltrating mononuclear cells.28 The infiltrating cells are 
made up of monocytes or macrophages and lymphocytes, 
mainly T lymphocytes.29 The degree of interstitial inflam-
ation is inversely related to renal function and longterm kid-
ney survival.30 This relationship is apparent, for example, in 
membranous glomerulonephritis and lupus nephritis.31

<table>
<thead>
<tr>
<th>Phases of renal fibrogenesis</th>
<th>I. Induction Phase</th>
<th>II. Inflammatory matrix synthesis</th>
<th>III. Postinflammatory matrix synthesis</th>
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<td>• Release of chemokines by tubular epithelial cells</td>
<td>• Increased matrix synthesis and deposition</td>
<td>• Cessation of the primary inflammatory stimulus</td>
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<td></td>
<td>• Infiltration of mononuclear cells</td>
<td>• Continued release of profibrogenic cytokines by infiltrating cells</td>
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<td></td>
<td>• Release of profibrogenic cytokines</td>
<td>• Autocrine proliferation of (myo)fibroblasts</td>
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<td>• Activation and proliferation of resident fibroblasts</td>
<td>• Fibroblast formation by epithelial-mesenchymal transformation</td>
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Müller et al.32 have shown that the number of infiltrating 
CD4+ (and somewhat weaker CD8+) cells was associated 
with renal function. Conversely, no correlation was found 
between infiltrating CD14+ monocytes or macrophages in 
that study, although these results were not confirmed by all 
investigators.33 Whereas there is a predominance of CD4+ 
helper cells in most forms of interstitial infiltrates, CD8+ T 
cells predominate in allograft rejection, lupus nephritis, and 
puromycin aminonucleoside (PAN) nephrosis.34 Both 
subtypes of T lymphocytes have the capacity to induce 
fibrosis, as was demonstrated by Piguet and coworkers35 in 
a model of pulmonary fibrosis. After induction of fibrosis 
with bleomycin, rats were treated with neutralizing anti-
CD4 or anti-CD8 antibodies, which resulted in significant 
decreases in matrix deposition. Moreover, treating the 
animals with both neutralizing antibodies simultaneously 
caused a complete abrogation of fibrosis.35