

## Continuous Medical Education

# Pathogenesis of primary tubulointerstitial nephritis

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Primary tubulointerstitial nephritis (TIN) is the term applied to conditions characterized by tubulointerstitial inflammation and damage with relative sparing of glomeruli and vessels. Both acute and chronic forms exist (table 1). In addition, TIN can be present with primary glomerular diseases affecting the kidney.<sup>1</sup> Although interstitial nephritis can be a primary cause of renal failure, it usually follows glomerular injury, which probably initiates secondary interstitial disease as a consequence of persistent proteinuria and cytochinuria from leaky glomeruli.<sup>2</sup> TIN may be the final common pathway to renal failure.<sup>3</sup> Regardless of the etiology, the interstitial changes are characteristic and include macrophage accumulation, mononuclear inflammation, proteolysis, and tubular atrophy with concomitant fibrosis.<sup>4</sup>

Many forms of tubulointerstitial injury involve exposure to drugs or other nephrotoxic agents (table 1). Currently, acute TIN is mainly drug induced. Non-steroidal anti-inflammatory drugs (NSAID) are the most frequent cause of permanent renal insufficiency after acute TIN.<sup>5</sup>

### Pathophysiology

The tubulointerstitial lesions in all forms of TIN are characterized by predominantly T-cell lymphocytic infiltrates, suggesting immune-mediated mechanisms of renal injury. Such mechanisms may initiate tubular injury or amplify damage induced by both immune and non immune causes.<sup>6</sup> Cell mediated immune mechanisms seem to be more important than humorally mediated mechanisms in the pathogenesis of TIN.<sup>7</sup>

### Cell mediated immunity

Cell mediated responses are initiated by T-cell recognition of relevant antigen presented in the context of appropriate major histocompatibility complex (MHC) molecules.<sup>8</sup> The cause for antigen expression is unknown. Tubular epithelial cells normally do not express costimulatory molecules such as CD80 and CD86 which likely limits their ability to present antigens under physiologic conditions.<sup>9</sup>

**Table 1.** Etiology of interstitial nephritis.

#### Acute tubulointerstitial nephritis

- Drugs e.g. penicillins, cephalosporins, erythromycin derivatives, sulfa drugs, non-steroidal anti-inflammatory drugs, diuretics, cimetidine, cyclosporine
- Immunologic diseases ( associated with lupus, Goodpasture syndrome)
- Acute transplant rejection
- Infections
  - Bacterial associated with acute pyelonephritis
  - Viral (cytomegalovirus, hantavirus, HIV, hepatitis B, Epstein Barr, adenovirus)
  - Parasitic (Toxoplasma)
- Idiopathic

#### Chronic tubulointerstitial nephritis

- Drugs (analgesics, lithium, cyclosporine, tacrolimus)
- Heavy metals ( lead, cadmium, mercury)
- Obstructive uropathy, nephrolithiasis, reflux disease
- Immunologic diseases
  - Lupus, Sjögren syndrome, primary glomerulopathies, sarcoidosis
  - Vasculitis, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, Wegener granulomatosis
  - Chronic transplant nephropathy
- Infections (as the acute)
- Metabolic diseases (e.g. hypercalcemia, cystinosis, hyperoxaluria)
- Genetics (e.g., Alport syndrome, medullary cystic disease)
- Miscellaneous (e.g., Balkan endemic nephropathy, Chinese herb nephropathy, radiation, neoplasm)
- Idiopathic

*Modified from Dell and Avner<sup>1</sup>*

Genetic susceptibility may play a factor in antigen expression and consequent immune response.<sup>10</sup> Other mechanisms, such as drugs or infectious agents, may serve as inciting agents of cell-mediated responses targeting the kidney.<sup>11</sup> Drug specific T cells are activated locally and orchestrate a local inflammation via secretion of various cytokines. Immunohistochemistry of kidney biopsies of patients with drug induced IN revealed cell infiltrations that consisted mostly of

T cells (CD4<sup>+</sup> and/or CD8<sup>+</sup>). An augmented presence of IL-5, eosinophils, neutrophils, CD68<sup>+</sup> cells and IL-12 was observed.<sup>12</sup>

#### ***Antibody mediated immunity***

Antibody mediated TIN is occasionally seen. Anti-tubular basement membrane (TBM) staining often occurs as part of anti-glomerular basement membrane (GBM) disease but at times it appears to be a primary phenomenon resembling experimental anti-TBM disease. Anti-TBM antibodies can be seen at times in association with drug-induced TIN and in the setting of renal transplantation due to the presence of foreign antigens in the transplanted kidney<sup>13</sup>. Antitubular basement membrane disease is a form of primary interstitial nephritis mediated by T cells and alpha TBM antibodies. In mice and humans, the nephritogenic immune response is directed to a glycoprotein (3M-1) found along the proximal tubule of the kidney.<sup>14</sup>

#### ***Local and extra-renal antigens***

Two main categories of antigens can induce experimental TIN (1) endogenous renal antigens which can be either non-collagenous components of TBM or proteins synthesized by tubular cells, and (2) non-renal antigens.<sup>4,15</sup>

#### ***Mechanisms whereby a drug or (one of its metabolites) can induce acute interstitial nephritis (AIN):<sup>16</sup>***

(A) The drug can bind to a normal component of the TBM and act as hapten.

(B) The drug can mimic an antigen normally present within the TBM or the interstitium and induce an immune response that will be directed against this antigen.

(C) The drug can bind to the TBM or deposit within the interstitium and act as an implanted antigen.

(D) The drug can elicit the production of antibodies and become deposited in the interstitium as circulating immune complexes. Circulating immune deposits that settle in the interstitium can cause TIN. This might be the case in SLE, and IgA nephropathy.<sup>17</sup>

#### ***Cytokines and amplification of injury***

Experimental studies and analysis of renal biopsies have shown that macrophages, lymphocytes and activated tubular cells can produce many cytokines that can induce a proliferation of fibroblastic cells, and /or increase the production of extracellular matrix.<sup>18,19</sup> For

example, inflammatory cells can produce transforming growth factor- $\beta$  (TGF- $\beta$ ), interleukin-1 (IL-1), IL-4, and lipid peroxidation products, which increase the production of extracellular matrix proteins by fibroblastic cells in vitro. Similarly, tubular cells can synthesize TGF- $\beta$ , insulin like growth factor-1 (IGF-1), endothelin-1 (ET-1), and lipid peroxidation products. In vivo only three of these molecules induce fibrotic reactions within the renal interstitium: TGF- $\beta$ , ET-1, and platelet derived growth factor-BB (PDGF-BB).<sup>16</sup>

#### ***Fibrogenesis and atrophy***

Interstitial fibrosis is the final common pathway for a variety of glomerular and tubular disorders, particularly when associated with massive glomerular proteinuria or the presence of inflammatory cells in the tubulointerstitial compartment. Tubulointerstitial scars are primarily composed of collagen types 1 and 3, fibronectin, and tenascin. Early in the development of a scar, the fibrotic tissue may contain monocytes, tubular cells, and fibroblasts. The source of fibroblasts in the tubulointerstitium is yet unknown. There are several lines of evidence suggesting that they may arise from transformation of resident cells like the tubular epithelium. This mechanism is called epithelial mesenchymal transformation (EMT). The transformation is probably activated by immune-mediated mechanisms and various cytokines. EMT plays an important role in organ remodeling during fibrogenesis. In the kidney, EMT can be induced efficiently in cultured proximal tubular epithelium by incubation of TGF- $\beta$ 1 and epidermal growth factor (EGF). Moreover, fibroblast growth factor-2 (FGF-2) makes an important contribution to the mechanisms of EMT by stimulating microenvironmental proteases essential for disaggregation of organ-based epithelial units. Tubular epithelial to myofibroblast transition is an orchestrated, highly regulated process involving four key steps including: 1) loss of epithelial cell adhesion, 2) de novo  $\alpha$ -smooth muscle actin expression and actin reorganization, 3) disruption of tubular basement membrane, and 4) enhanced cell migration and invasion.<sup>20-26</sup>

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