identical target concentrations ($C_{\text{peak}} = \text{constant}$), the effect might be longer lasting with a prolonged dynamic half-life in renal impairment.

**References**


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**Cross-talk between activated tubular epithelia of human kidney and monocytes: a basis for target cell-specific pharmacotherapy**

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Changes in the tubulointerstitial compartment govern the progression and outcome in most patients suffering from renal diseases. Under pathological conditions, the influx of monocytes into the kidney and local proliferation of blood-derived macrophages releasing proinflammatory and fibrogenic cytokines contribute to structural and functional deterioration [1]. In addition, cell lesions may result directly from cooperative but maladapted cell interactions between ‘activated tubular cells’ which are capable of recruiting and stimulating monocytes to invade the glomeruli and/or the tubulointerstitium, thus resulting in progressive sublethal injury, necrosis and fibrosis. In the present work, we summarize our experimental and clinical data which support an engaged interaction (cross-talk) of tubular epithelia of proximal and distal origin with monocytes/macrophages in human renal diseases [2–4].

**Human renal proximal and distal tubular cells.**

Human renal proximal (PTC) and distal (DTC) tubule cells were isolated immunomagnetically as described earlier, applying monoclonal antibodies raised against distinct segments of the human nephron [2]. PTC were strongly positive for aminopeptidase M (CD13); however, DTC were negative for CD13 antigen. Ultrastructural analyses of PTC primary isolates revealed a highly preserved brush border, whereas DTC showed multiple basolateral invaginations and many fewer apical microvilli. Both cell types formed tight junctions and expressed cytokeratin and vimentin, whereas stains for desmin, $\alpha$-actin and von Willebrand’s factor were negative. A different response after hormonal stimulation [parathyroid hormone (PTH), calcium] was found where cAMP production was especially high in DTC after challenge with PTH [2,5].

**Activated tubule cells**

After incubation of cultured cells with a mix of 25 U/ml interleukin (IL)-1$\beta$, 10 ng/ml tumour necrosis factor-$\alpha$ (TNF-$\alpha$) and 200 U/ml interferon-$\gamma$ (IFN-$\gamma$), the production of RANTES, a chemokine for monocytes, increased dramatically in both PTC and DTC [6]. Compared with basal conditions, the release of RANTES into the supernatant was 107- to 133-fold increased up to 364 pg/48 h/10$^5$ cells. In parallel, expression of HLA-DR and interstitial cell adhesion molecule-1 (ICAM-1) increased significantly, as analysed by flow cytometry. Unstimulated PTC and DTC did not express HLA-DR; DTC expressed ICAM-1 constitutively in very small amounts.

**Effect of anti-inflammatory drugs**

Glucocorticoids such as dexamethasone ($10^{-6}$ M) as well as cyclooxygenase II inhibitors down-regulated...
the synthesis of RANTES in cytokine-stimulated PTC/DTC \( (P < 0.05; \text{Baer et al., submitted for publication}) \). Lipopolysaccharide (LPS) from *Escherichia coli* 128:B12 (5 ng/ml) did not modulate HLA-DR and ICAM-I expression of PTC and DTC.

**Monocytes/macrophages**

In healthy subjects, 92% of circulating blood monocytes (median 336 cells/\( \mu l \)) expressed an endotoxin receptor, the CD14 antigen, at a high rate [7]. A minor population (median 8%) revealed an immunophenotype of CD14\(^+\) cells which co-expressed the CD16 antigen, an Fc\(\gamma\)RIII molecule [3,7].

**Activated monocytes and drug response**

In cultured monocytes, membrane CD14 and release of soluble CD14 (sCD14) were dramatically up-regulated in the presence of LPS, where the LPS-binding capacity [of fluorescein isothiocyanate (FITC)-labelled LPS] was correlated directly with monocyte CD14 expression (\( r = 0.89, P < 10^{-4}; \) ref. [7]). Endotoxin-induced stimulation of CD14\(^+\) and sCD14 synthesis was markedly (but not completely) abolished by various glucocorticoids following a sigmoid curve dose dependency [7]. In addition, glucocorticoids significantly decreased the secretion of IL-1 of LPS-activated monocytes. Blood monocytes expressing both the CD14\(^+\) and CD16\(^+\) antigen constituted a proinflammatory subtype, which exhibited features of tissue macrophages. CD14\(^+\)/CD16\(^+\) monocytes and sCD14 were highly increased in patients with infectious and non-infectious inflammatory diseases [8,9]. They also disclosed an augmented HLA-DR expression and phagocytic activity compared with CD14\(^-\)/CD16\(^-\) cells [9]. CD14\(^+\) (and CD68\(^+\)) cells accumulated up to 10-fold in kidneys of patients with progressive renal damage and in allografts with chronic rejection, as shown by immunohistochemistry. Glucocorticoid therapy selectively affected the CD14\(^+\)/CD16\(^+\) subset of monocytes not only by down-regulating CD14 expression and sCD14 release but also by inducing a rapid decline in the amount of the circulating proinflammatory cells [3,7].

**Cross-talk of tubular epithelia and monocytes**

Tubular epithelia may cross-talk with monocytes through mechanisms described above (Figure 1). Various stimuli such as immune complexes, ischaemia, oxygen radicals and cytokines (IL-1, IFN, cytomix as shown) activate tubule cells to synthesize and secrete monocyte-attracting chemokines MCP-1 and RANTES. Cytokines, which stimulate tubule epithelia to overexpress HLA-DR and adhesion molecules (ICAM-1), are released by ‘activated’ monocytes or lymphocytes at an increased rate. In the presence of LPS, oxidized lipoproteins or other stimuli, transform blood monocytes (CD14\(^+\)/CD16\(^-\)) into a proinflammatory subtype carrying the CD16 epitope as described [10]. This cell type may pass the endothelial barrier, and accumulate (proliferate) within the glomeruli and the tubulointerstitial space. Experimental and clinical studies reveal a tight association of macrophage accumulation and proliferation with local renal damage. Release of profibrogenic cytokines and growth factors by activated monocytes/macrophages (IL-1, TNF, prostaglandins, etc.) may amplify progressive cell

![Fig. 1. Cross-talk of tubular epithelia of human kidney and monocytes capable of transforming into the proinflammatory macrophage-like subtype (CD14\(^+\), CD16\(^-\), HLA-DR\(^+\)) which invades the kidney. Pre-lethally damaged or cytokine-activated tubular cells may present antigens to lymphocytes and release chemokines (RANTES) to attract activated monocytes/macrophages. oLip = oxidized lipoproteins, LPS = lipopolysaccharide (endotoxin), O* = oxygen radicals. For details, see text.](https://academic.oup.com/ndt/article-abstract/14/suppl_4/8/1806416/1806416)
injury, interstitial fibrosis, glomerulosclerosis and functional deterioration. Anti-inflammatory drugs positively interfere the cross-talk of both cell types.

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Role of the protein kinases A and C and of the calcium/calmodulin-dependent protein kinase II in the regulation of the renal basolateral PAH and dicarboxylate transporters

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The kidneys have a major role in the elimination of drugs and their metabolites. The elimination mechanism involves mainly glomerular filtration, but drugs which are organic bases (cations) or acids (anions) may, in addition, be actively secreted by the proximal tubules. The secretory system accepts a wide variety of pharmacologically highly active drugs or their metabolites [e.g. antibiotics, non-steroidal anti-inflammatory drugs, loop and thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, AT1 receptor antagonists].

There are two transport systems present in the kidneys by which drugs can be secreted from blood into urine, one for organic anions and another for organic cations. The transport proteins, which recently have been cloned, reside predominantly in the S2 segment of proximal tubules [1]. Regarding the renal transport system for organic anions, of which p-aminobenzamidopropionate (PAH) is the prototype, the active step in the secretion process is confined to the basolateral membrane. The current model (Figure 1) indicates that the cellular uptake of organic anions across the basolateral cell membrane is mediated by a tertiary active process. The primary event is hydrolysis of ATP.

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