J. Biol. Res. 2011 n.1 - Vol. LXXXIV - Rubbettino - Soveria Mannelli

The human kidney as a regulator of body cytokine homeostasis

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KEY WORDS: inflammation, adipokines, Leptin, IL-6, chronic kidney disease

Abstract

Evidence is accumulating that the human kidney is a major site for the removal of several cytokines and growth factors, which can accumulate in body pools in patients with acute and chronic kidney disease (CKD). In addition, progressive renal failure and the increase in circulating proinflammatory cytokines are associated with mortality, suggesting that altered cytokines handling by the kidney is associated with worse outcome. Also, the kidney itself may be damaged by signals arising by endothelia and peripheral tissues during the course of the metabolic syndrome, type 2 diabetes and obesity. In this paper we provide a review of kidney handling of several adipokines and myokines, with special emphasis to interleukin-6 (IL-6), leptin, resistin and transforming growth factor-beta (TGF-beta).

Renal disposal of adipokines and cytokines

The human kidney is an important site for the catabolism of low molecular weight (m.w. <50.000 Da) plasma proteins and peptides, but its role in the removal of intermediate molecular weight proteins, such as immunoglobulin G (m.w. 160.000 Da) appears to be less important. The kidney catabolism of plasma proteins largely occurs by glomerular filtration and subsequent tubular reabsorption [1]. Convection and diffusion seem to be the main forces involved in macromolecular filtration across the glomerular filtration barrier, which is considered a dynamic barrier, rather than a rigid one [1]. Tri- and di-peptides can be taken up into proximal tubule cells by an active transport mechanism, or they are cleared by the brush-border of the proximal tubule [1]. Megalin and its extracellular binding coadjutor cubilin are involved in proximal tubule reabsorption of different ligands, including albumin. Once internalized, megalin is returned to the cell surface through the recycling endosomes, while albumin may be broken down in the lysosomes. The amount of filtered albumin load is controversial, with different data showing values between 180 mg and 9 g/day. These data suggest that not only the glomerular loss, but also a lack in tubular reabsorption of normally filtered albumin could be responsible for an increase in albumin excretion [1]. Moreover, the amount of protein excreted in urine could be influenced by increased glomerular hydraulic pressure or increased production or concentration of plasma proteins normally filtered in the glomerulus.
Notably, an increase in protein reabsorption due to an overload of filtered proteins may contribute to the development of tubular and interstitial inflammation and fibrosis [2]. Moreover, hyperfiltration of proteins may cause an upregulation of inflammatory and vasoactive genes [2]. The kidney itself can influence the clearance of several cytokines [3]. Accordingly, an altered handling of cytokines by the kidney in CKD might actually cooperate to the microinflammatory state and favour progressive cardiovascular disease (CVD) and renal fibrosis.
In this paper we will review the role of the kidney in the homeostasis of plasma cytokines in the light of recent data based on the kidney handling of cytokines in humans.

Leptin

Leptin is a 16-kDa protein encoded by the *obese* gene and secreted by adipocytes, which controls appetite in rodents and in healthy subjects. Leptin acts also on peripheral tissues and stimulates the inflammatory response by activating the production of tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and interleukin-12 (IL-12) [4]. Leptin receptors are mainly expressed in the lung and the kidney [4]. When labeled 1^{25}I-leptin is injected in humans it is rapidly cleared from plasma and near all the radioactivity appears in the urine [5], suggesting a role of the kidney in the disposal of circulating leptin. We observed that both splanchnic organs and the kidney cooperate in the disposal of leptin, while peripheral tissues add significant amounts of leptin to the circulation [6]. These data suggest that splanchic organs may become a major site for leptin removal in CKD patients. Indeed, leptin concentration do not correlate with residual renal function in CKD patients and dialysis patients may exhibit normal or low leptin levels, even if corrected for BMI [7]. In subjects with normal renal

function, the fractional extraction of leptin by the kidney varies little, from 9 to 13% [6], a percentage which is lower than that of creatinine (~20%). Moreover, leptin fractional extraction across the human kidney is directly related to renal plasma flow [6], suggesting the amount of leptin extracted is proportional to the amount of plasma flow perfusing the kidney. Notably, the percentage of leptin taken up by the kidney relative to the estimated filtered leptin markedly increases along with the increase in plasma flow. These data suggest a progressive role of peritubular uptake in leptin extraction at high plasma flows.

Interleukin-6 (IL-6)

IL-6 is the ligand of the IL-6-receptor (IL-6R) which binds with the glycoprotein gp130 to activate STAT3 [8]. An important function of IL-6 is the induction of acute phase response proteins in the liver. In patients with CKD, plasma levels of IL-6 are often elevated and are associated with mortality [9]. Although endothelia and circulating cells are major contributors to plasma IL-6, recent evidence shows that somatic cells participate actively in plasma IL-6 balance. Adipocytes are estimated to account for ~30% of IL-6 produced under normal conditions [10]. Notably, in a recent study Witasp *et al.* [11] found a threefold increase in the expression of IL-6 gene in abdominal subcutaneous adipose tissue of CKD patients (stage V), as compared to healthy controls.
Skeletal muscle, a common target of inflammation, contributes to the release of several cytokines [12]. IL-6 mRNA is expressed in resting human muscle and is rapidly increased by contraction. The high prevalence of inflammatory changes in CKD patients could stem from an increased IL-6 production associated with a blunted removal. We recently found IL-6 release from the forearm in CKD patients with evidence of inflammation [13], suggesting that peripheral tissues release may play a major role in the altered IL-6 homeostasis.
IL-6 has a m.w. of 26 kD, which allows a renal catabolism of this protein. The human kidney removes about 8% of arterial IL-6 after a single passage [14]. IL-6 clearance by kidney and splanchnic organs is estimated to be ~50 and 130 ml/min respectively [14]. As already observed for leptin, also the renal removal of IL-6 depends on renal plasma flow, but not on glomerular filtration rate or filtered IL-6 [14].

Resistin

Resistin is a 12.5 kDa peptide, member of a family of cysteine-rich secretory proteins, called resistin-like molecules [15]. In rodents resistin is almost exclusively produced by fat tissue and induces insulin resistance [15]. In humans resistin is expressed in inflammatory cells and stimulates the expression of adhesion molecules and the production of proinflammatory cytokines [16]. Moreover, resistin may play a role in atherogenesis [17], while its possible role in insulin-resistance is not yet completely understood. Plasma resistin levels are inversely correlated with eGFR [18] suggesting a possible role of resistin in the determination of CKD and, on the other hand, a possible role of CKD in the retention of resistin. Moreover, Axelsson *et al.* [19] found an association between resistin levels and inflammatory biomarkers (such as IL-6, CRP and TNF-α), but not with insulin resistance, in CKD patients.

TGF-beta

Transforming growth factor beta (TGF-beta) is a member of the TGF-beta superfamily, which is produced both by immune and somatic cells. TGF-beta binds to a membrane receptor complex with serine-threonine kinase activity, which activates several intracellular signaling pathways, including Smads, p38 and Jun kinase [20]. TGF-beta can contribute to the development of CKD through different mechanisms. First, TGF-beta determines tubulointerstistial fibrosis, both by stimulating resident fibroblasts, myofibroblasts and tubule epithelial cells to produce extracellular matrix components and also by activating an epithelial-to mesenchimal transition process [20]. Moreover, TGF beta has a proapoptotic effect on different cell lines, including renal cells [21], by inhibiting thymidine incorporation and arresting cell-cycle in the G1 phase [21]. Data from artero-venous samplings obtained during elective cardiac catheterization [22] have shown the presence of a net renal production of TGF-beta in patients with type II diabetes, while it is taken up by the kidney in healthy subjects. This suggests a possible role of kidney-derived TGF-beta in accelerated vascular disease, a major feature of diabetic nephropathy.

Conclusions

Inflammation is commonly observed in CKD patients and is considered among the major non-traditional risk factors for the increased cardiovascular morbidity and mortality observed in these patients'population. Although changes observed in CKD patients may be due to the activation of proinflammatory pathways specific to uremia and associated comorbidities, a reduced kidney handling of proinflammatory molecules may facilitate the occurrence of a inflammatory response. Since at least some proinflammatory cytokines are metabolized or excreted by the kidney, CKD may directly decrease plasma cytokine removal and favor inflammation.

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