PATHOPHYSIOLOGY OF TUBULOINTERSTITIAL INJURY

Proximal Tubular Cell Physiology and Pathology

Albumin handling by proximal tubular cells: mechanisms and mediators

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Clinical nephrologists have long recognized the association between heavy proteinuria and the tendency for progression of renal failure. Progressive renal impairment is characterized by progressive interstitial scarring and tubular atrophy, and proteinuria is strongly implicated in the pathogenesis of this tubulo-interstitial lesion. Proximal tubular cells are exposed to filtered protein, most notably albumin, in health, but are exposed to much higher concentrations in diseases of reduced glomerular permselectivity. Traditional dogma, however, suggests that albumin is a benign molecule, and the mechanisms by which it may induce adverse pathophysiological events in the kidney have not been clear. Thus the mechanism of interaction of albumin with the proximal tubule is of considerable interest to nephrologists.

Filtered albumin is reabsorbed by the proximal tubular epithelium, and these cells are often heavily vacuolated in nephrotic patients. The vacuoles contain predominantly protein reabsorbed from the proximal tubular fluid, but lipid accumulation is also observed. Cellular architecture is disturbed markedly by this vacuolation, and it is likely that cells with such disordered architecture also have disordered function. Albumin reabsorption in the proximal tubule occurs by receptor-mediated endocytosis. Using opossum kidney cells as a model, albumin has been shown to bind to both high-affinity low-capacity, and low-affinity high-capacity receptor systems [1,2]. The characteristics of the higher affinity system suggest that this receptor would be capable of mediating the reabsorption of the albumin normally crossing the glomerular filtration barrier in health. The identity of the receptor(s) remains unresolved. Megalin has been shown convincingly to bind albumin in proximal tubular segments [3], but it is possible that other lower molecular weight receptors may also participate in the albumin reabsorptive process.

After binding, albumin reabsorption occurs by endocytosis into an intracellular vesicular trafficking system, with delivery of the majority of the reabsorbed albumin to a lysosomal compartment. Here it is degraded to its component amino acids which are then returned to the circulation rather than being excreted in the urine. The endocytic process itself is subject to complex regulation by heterotrimeric GTP-binding proteins, and the enzyme phosphatidylinositol 3-kinase (PI 3-kinase) [4,5].

Albumin is not simply an inert piece of cargo reabsorbed and degraded by the proximal tubular epithelium. Indeed, a growing body of evidence also implicates albumin as an important regulator of function and dysfunction in a number of other cell types. In endothelial cells, albumin modulates vascular permeability possibly via inducing changes in intracellular calcium [6]. Albumin binding to endothelial cells not only precedes its endocytosis, but also initiates an intracellular tyrosine kinase cascade with phosphorylation of multiple substrates [7]. Survival of endothelial cells in serum-free conditions is greatly enhanced by albumin, although the mechanism of this effect is unknown [8]. Some authors have postulated an important role for albumin in the pathogenesis of brain injury when the blood–brain barrier is breached. Again it is thought that albumin may induce changes in intracellular calcium in astrocytes and glia [9].

Cultured proximal tubular cells proliferate in response to albumin in serum-free conditions. The use of yeast recombinant albumin eliminates the possibility that this effect may be mediated by a serum-derived factor bound to albumin. Upon binding to proximal tubular cells, recombinant albumin stimulates the activity of a kinase cascade involving PI 3-kinase and pp7056 kinase [10]. The proliferative effect of recombinant albumin is dependent on the activity of both these enzymes. Interestingly, activation of these enzymes by albumin is observed at concentrations likely to prevail in the proximal tubule in health, indicating that under physiological conditions albumin may play a role in the maintenance of proximal tubular homeostasis and

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integrity. Chronic or over-stimulation of this pathway in proteinuria may contribute to the disturbance of proximal tubule growth, which is a hallmark of progressive renal tubulo-interstitial disease.

Therefore, in vitro, albumin is mitogenic when applied to proximal tubular cells. The situation in vivo is more complex. Proximal tubular cell turnover has been studied in protein overload proteinuria. In this model, albumin is administered to rats via the intraperitoneal route daily for 7 days. These animals quickly develop heavy proteinuria in the absence of any classical immune response. If these animals are sacrificed after 7 days, evidence of tubular cell proliferation is seen by in situ hybridization for histone mRNA. However, widespread apoptosis both of proximal tubular cells and of cells in the interstitium is more prominent [11]. The balance of these two opposing processes favours apoptosis and thus provides a potential explanation for the tubular atrophy seen to occur in progressive renal disease. This increased turnover of proximal tubular cells in proteinuric animals is accompanied by a heavy infiltrate of macrophages into the cortical interstitium.

It is unclear whether the apoptosis observed in the proximal tubules of proteinuric animals is a direct result of the interaction of albumin with the cells, whether it may occur as a response to interstitial inflammation or, indeed, whether it may be due to the effects of a ligand bound to albumin. It is possible that lipids bound to albumin may exert a biological effect on proximal tubule cells in proteinuria. If protein overload is induced in rats using delipidated fatty acid-free albumin, apoptosis and interstitial inflammation are considerably less marked than if protein overload is induced with fatty acid-carrying albumin.

In conclusion, albumin is able to interact with proximal tubular epithelial cells and modulate their growth and survival both in vitro and in vivo. A number of intracellular signalling cascades are activated by albumin, and these pathways are likely to be important in both health and disease. In proteinuric renal diseases, other molecules carried with albumin, particularly lipids, are also probable contributors to the development of tubulo-interstitial disease.

References