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Are filtered plasma proteins processed in the same way by the kidney?

W.D. Comper [a,*], L.M. Russo [b], J. Vuchkova [c]

[a] SalAqua Diagnostics, New York and Kantum Diagnostics, NH, United States
[b] Systems Biology, Massachusetts General Hospital, Boston, United States
[c] Department Biochemistry and Molecular Biology, Monash University, Clayton, Victoria, Australia

HIGHLIGHTS

- Albumin processing by the kidney appears very similar to other plasma proteins in the molecular weight range 30–150 kDa.
- Proteins with molecular weight <20 kDa are processed in an entirely different manner.
- The enormous changes in protein clearance in nephrotic states can be explained by inhibition of both the degradation and retrieval pathways.

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ABSTRACT

In order to understand the mechanism of albuminuria we have explored how other plasma proteins are processed by the kidney as compared to inert molecules like Ficolls. When fractional clearances are plotted *versus* protein radius there is a remarkable parallelism between protein (molecular weight range 30–150 kDa) clearance in healthy controls, in Dent's disease, in nephrotic states and the clearance of Ficolls. Although there are significant differences in the levels of fractional clearances in these states. Dent's disease results in a 2-fold increase in the fractional clearance of proteins as compared to healthy controls whereas in nephrotic states there is a further 3-fold increase in fractional clearance. Previous thinking that albumin uptake was controlled primarily by the megalin/cubilin receptor does not explain the albumin urinary excretion data and is therefore an incorrect concept. Protein clearance in nephrotic states approach the fractional clearance of inert Ficolls for a given radius. It therefore appears that there are two pathways processing these proteins. A low capacity pathway associated with megalin/cubilin that degrades filtered protein (that is inhibited in Dent's disease) and a high capacity pathway that retrieves the filtered protein and returns it to the blood supply (without retrieval nephrotic protein excretion will occur and this will account for hypoproteinemia). On the other hand low molecular weight proteins (<20 kDa) are processed entirely differently by the kidney. They are not retrieved but are comprehensively degraded in the kidney with the degradation products predominantly returned to the blood supply.

1. Introduction

The mechanism of albuminuria is still subject to conjecture. There is an ongoing debate as to the major determinants that govern albumin filtration and processing. There is the established glomerular centric view (recently portrayed by Scott and Quaggin (2015)) and the new developing proximal tubular view (Osicka et al., 1996, Eppel et al., 1999, Comper et al., 2008; Dickson et al., 2014). In the light of this debate, it is interesting then to examine how other plasma proteins are filtered and processed by the kidney and to combine all this information to see how this may contribute to the understanding of albumin processing.

2. An update on the renal processing of albumin

2.1. Magnitude of albuminuria

In order to explain albuminuria in nephrotic states then the classic studies of the Myers group have to be explained (Blouch et al., 1997; Guasch et al., 1993; Guasch and Myers, 1994; Scandling et al., 1992) (Fig. 1). The fractional clearances of albumin in nephrotics, when the plasma albumin concentration may be lowered by $>60\%$ due to albuminuria, are very high (range 0.007–0.14) as compared to albumin fractional clearances in healthy controls (range 10^{-5}–10^{-6}). The fractional clearances in nephrotics are considerably higher than what was originally proposed to be the glomerular sieving coefficient (GSC) for albumin as determined by its clearance in Dent's disease (Norden et al., 2001) (Fig. 1) where it

* Corresponding author.
E-mail address: wcomper@hotmail.com (W.D. Comper).

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was assumed that endocytotic uptake by proximal tubule was inhibited. Dent's disease is the result of loss-of-function mutations of chloride channel 5 CLC-5 gene (Lloyd et al., 1996) which causes impaired receptor mediated endocytosis (Gorvin et al., 2013) of a wide range of plasma proteins through the multiligand receptors, megalin and cubilin, which are located on the brush border of proximal tubule cells (Christensen et al., 2012). These results in Fig. 1 then feature that there are two types of albuminuria; a low capacity system associated with megalin/cubilin and a high capacity system that generates albumin clearance in nephrotic patients to be equivalent to Ficoll clearance.

It is then interesting to justify these enormous relative changes in albuminuria (Fig. 2) by various concepts that have been used to explain albuminuria. The concepts are accompanied by their criticism in the contemporary literature.

2.2. Role of size selectivity

The massive changes in albuminuria (see Fig. 2) are not accompanied by any change in size selectivity as determined by the fractional clearance 36 Å radii Ficoll (Fig. 1) (Ficoll is a globular polysaccharide and is an excellent model to simulate globular protein behavior in the kidney). The massive changes in albuminuria have been consistently demonstrated in many other studies (Table 1) in spite of podocyte effacement in many of these conditions.

2.3. Role of charge selectivity

Changes in charge selectivity cannot explain these results (Comper et al., 2008) (Fig. 2). Importantly it has been demonstrated that the transglomerular transport of highly negatively charge molecules, not taken up by renal cells like some proteins are, are simply not affected by the charge on the glomerular filter including the endothelial surface layer (Asgeirsson et al., 2006; Axelsson et al., 2011; Guimarães et al., 2003; Greive et al., 2001b; Schaeffer et al., 2002; Vyas et al., 1996). The proven lack of charge selectivity basically voids the established glomerular centric view of albumin filtration.

2.4. Streaming potentials

It has been proposed that streaming potentials are responsible to restrict albumin transport across the glomerular filter (Hausmann et al., 2010). Streaming potentials are a well established physical phenomenon that occurs when you have fluid flow (in the case of the kidney it is water flow through the filter termed glomerular filtration rate (GFR)) past the fixed charges of the glomerular filter generating a charge separation with the small counterion which is generally sodium. But this proposal has three problems (i) no-one has demonstrated any significant charge effects for transglomerular transport as described above that would require a 'streaming potential' and (ii) there is no established relationship between GFR (that would generate the streaming potential) and albuminuria. For example, renal insufficiency patients (with GFR < 60 ml/min 1.73 m^2, > 40% below normal) have varying degrees of albuminuria; 20–25% are normoalbuminuric (MacIsaac and Jerums, 2011; MacIsaac et al., 2004). Also patients with minimal change disease who are nephrotic (with a 60% reduction in their plasma albumin) may have no change in their GFR despite an increase of 730-fold in albumin excretion rate (Blouch et al., 1997). Furthermore, patients undergoing hyperfiltration, that would further minimize the possibility of albuminuria due to an enhanced 'streaming potential' are actually albuminuric (Premaratne et al., 2015). (iii) the theoretical justification of streaming

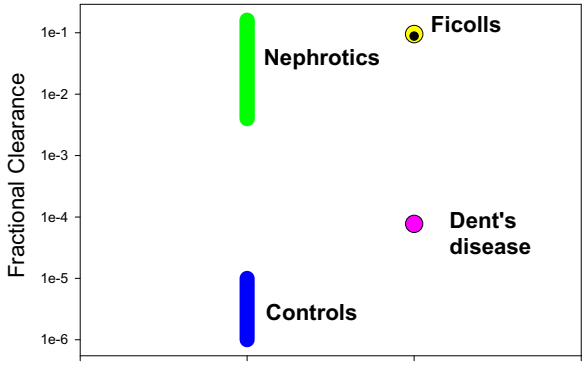

Fig. 1. Range of fractional clearances (y-axis) of albumin in healthy controls (blue bar) and nephrotic patients (green bar) (Blouch et al., 1997; Guasch et al., 1993; Guasch and Myers, 1994; Scandling et al., 1992) and in Dent's disease (red) (Norden et al., 2001). Fractional clearances of 36 Å radii Ficoll from healthy controls (yellow) and nephrotic patients (black) are also presented (Blouch et al., 1997). It is to be noted that the assignment of radii is not accurate as generally dilute solution Stokes-Einstein radii are quoted whereas in plasma, where there is a high osmotic environment, proteins and Ficolls will shrink (Smit et al., 1996). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

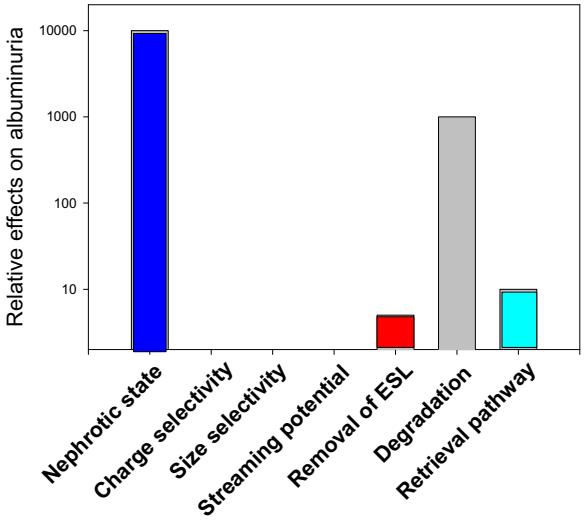

Fig. 2. The effects of various phenomena on the relative change in albumin clearance. ESL is the endothelial surface layer. The relative influence of the degradation pathway and retrieval pathway on albuminuria may be species dependent. In humans it appears more like ~100-fold effect of degradation and ~100-fold effect of retrieval in humans (Fig. 1) whereas in rats the effect is more dominated by inhibition of the degradation pathway (Fig. 2). While the degradation pathway appears to be inhibited first in disease (Table 2) we cannot eliminate that there is a simultaneous partial inhibition of the retrieval pathway without significant albumin plasma loss and this too may be species dependent.

Table 1
Albumin clearance in renal disease/podocytopathies increases 100-10,000 plus-fold whereas no change in dextrans and Ficolls same size as albumin.

Humans
Diabetic nephropathy (Deckert et al., 1988; Myers et al., 1982; Scandling et al., 1992; Scandling and Myers, 1992; Fox et al., 1995; Lemley et al., 2000)
Non-diabetic nephrotic syndrome (Blouch et al., 1997)
Minimal change disease (Guasch and Myers, 1994)
Diffuse proliferative lupus nephritis (Scandling et al., 1992)
Focal segment glomerulosclerosis (Scandling et al., 1992)
Membranous glomerulopathy (Scandling et al., 1992)
Rats
Anti-GBM disease (Greive et al., 2001b)
PAN (Olson et al., 1981; Osicka et al., 1999; Greive et al., 2001b; Koltun et al., 2005)
Adriamycin nephrosis (Weening and Rennke, 1983)
Sclerosis after renal ablation (Olson et al., 1982)
Membranous glomerulopathy (Groggel et al., 1988)
Nephrotoxic serum nephritis (Alfino et al., 1988)