Insights into renal albumin handling

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The appearance of albumin in the urine (microalbuminuria) is an important marker of renal impairment. The clinical importance of albuminuria as a major, independent risk factor for cardiovascular disease is now becoming widely appreciated and underscores the importance of understanding the mechanisms of albuminuria. The traditional view of albumin handling is that the glomerulus presents a charge and size selective barrier that prevents substantial amounts of albumin entering the tubules. The small amount of albumin that is filtered is rapidly reabsorbed by receptor-mediated endocytosis, broken down in the lysosomes and resultant amino acids returned to the blood. In disease, the glomerular filtration barrier is compromised, excess albumin leaks into the tubules which in turn disrupts the endocytic mechanism leading to microalbuminuria. This disruption of tubular endocytosis also implicates impaired lysosomal function in the development of microalbuminuria. This conventional paradigm is currently under challenge on two broad fronts. The first is the charge selectivity of the glomerular filtration barrier and the amount of albumin that crosses the barrier. The second is the nature of the mechanisms for the tubular uptake of albumin. Recent studies in transgenic animals have shown that removal of most of the negative charge from the glomerular capillary wall does not induce heavy albuminuria as predicted by the theory of glomerular charge selectivity. Real time *in vivo* imaging of albumin filtration in the normal kidney has challenged our view of glomerular permeability. These data suggest that albumin is highly permeable across the glomerular filtration barrier and that albumin is retrieved intact by an as yet uncharactersied high capacity retrieval pathway. Key to the understanding of these proposed pathways is the ability to distinguish between intact and degraded albumin as it is taken up by the proximal tubule. We have recently developed a method using a conjugate of albumin that only fluoresces when it is degraded to track the albumin degradation pathway in the nephron. Our data are consistent with significant levels of albumin being rapidly taken up and degraded by the proximal tubule and suggest that the conventional model of renal albumin handling may require re-examination.