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Fatty kidney: A new concept for an old disease

When the 'lipid nephrotoxicity hypothesis' was proposed in 1982 by Moorhead, increasing evidence from our and other laboratories has supported the hypothesis that lipid abnormalities contribute to both atherosclerosis and glomerulosclerosis. The lipid profile of patients with CKD is typified by high circulating levels of VLDL triglycerides/free fatty acids (FAs), and by low plasma levels of HDL cholesterol. The plasma LDL level is not usually increased in patients with CKD and might even be reduced. Surprisingly, low plasma levels of LDL-cholesterol are associated with an increased cardiovascular risk of death in these patients a case of 'reverse epidemiology'. We have demonstrated, both *in vitro* and *in vivo* that inflammatory stress increases intracellular cholesterol influx into vascular smooth muscle cells, mesangial cells and macrophages by inducing scavenger receptor expression. This increased influx disrupts LDL receptor feedback regulation and causes unrestrained LDL receptor-mediated LDL uptake. Inflammation also inhibits ATP-binding-cassette-transporter-1-mediated cholesterol efflux from these cells. Hence inflammatory stress accompanied by CKD modifies cholesterol homeostasis by diverting cholesterol from blood to tissues. This cholesterol redistribution causes cholesterol to accumulate in kidney and vessel wall, and also lowers circulating cholesterol levels. This is why cardiovascular risk is increased up to 33-fold in patients with renal failure, but plasma cholesterol levels are not high. In addition, inflammatory stress causes a degree of statin resistance by overriding the suppression of HMGCoA reductase activity by statins. Albumin carries >99% of plasma FAs. In CKD (especially diabetic kidney disease) the circulating levels of FAs are markedly increased leading to an increase in the FA load per albumin molecule, with a molar FA: albumin ratio of approximately 6 compared to ≤ 1 in health. Serum FAs bound to albumin in glomerular filtrate are reabsorbed by the proximal tubular cells and mediate tubular damage by poorly understood mechanisms. We have demonstrated that palmitic acid (FA) increased CD36 gene expression and protein modifications in HK-2 cells (glycosylations and palmitoylations) which either mediate FA uptake or form complexes with TLR4, activating an inflammatory response. High fat diet increased CD36 expression in the kidneys of mice and enhanced tubulointerstitial lipid accumulation and tubulointerstitial fibrosis all of which would be prevented by knocking-out CD36, suggesting that CD36 acts as a 'bridge' linking high levels of FAs, fatty kidney, inflammatory response and CD36 de-palmitoylation would be a potential molecular target for anti-fibrotic therapy. In conclusion, high levels of FAs induce metabolic inflammatory stress which causes cholesterol redistribution from circulation to kidney and vessels and lowers serum cholesterol levels. This suggests that there is no safe serum cholesterol level in the presence inflammatory stress. Statin resistance suggests that higher concentrations of statin may be required to achieve the same biological and clinical effects in CKD.

Biography

Xiong Z Ruan leads a research laboratory in UCL Centre for Nephrology which is one of the biggest renal-oriented lipid research laboratories in the world, and also act as the Director and Professor of Centre for Nephrology in Shenzhen University and the Joint Centre for Lipid Research in UCL-Chongqing Medical University. He received his MSc in Peking Union Medical College Hospital (PUMCH) in 1994 and PhD from University College London (UCL) in 1999. He is the Vice-President of Chinese Society of Renal Physiology and Associate Editor for BMC Nephrology. His major goal has been to develop an academic research program cross UK and China that investigates the mechanisms of inflammatory stress accompanying with chronic kidney diseases in lipid trafficking control and address clinical problems of lipid mediated tissue injuries associated with kidney disease ('Cardio Kidney Diabetes'). He has published more than 80 papers in *Nature Rev Nephrol*, *J Am Soc Nephrol*, *Kidney Int*, *Lancet Diabete Endocrinology*, *Am J Physiol*, *Arterioscler Vasc Bio*, and *Hepatology* etc.

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