P2X7 receptors and klotho

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The authors of the paper entitled ‘P2X7 siRNA targeted to the kidneys increases klotho and delays the progression of experimental diabetic nephropathy’ in the current issue of purinergic signalling have consolidated their earlier work confirming the increase in renal tissue expression of the pro-inflammatory P2X7 receptor (P2X7R) in the widely used streptozotocin-treated (STZ) rat model of diabetes mellitus and associated kidney disease. Having previously shown an increase in the functional expression of P2X7R at the whole kidney level, its relationship to markers of oxidative stress, and amelioration of P2X7R expression by the antioxidant N-acetylcysteine and aerobic exercise [1], these authors went on to explore in the same model the relationship of renal P2X7R expression to that of klotho [2]. Klotho was chosen because of its antioxidant and antiapoptotic actions, and evidence for a protective role in the kidney, and a relative deficiency of klotho seen in diabetes, and in chronic kidney disease (CKD) more generally.

Klotho is a membrane-bound protein that is expressed mainly in the kidney, and it was originally identified as having anti-ageing properties in mice. It also exists as a membrane-cleaved, soluble form, and levels decrease as renal function declines, and inversely with circulating FGF23 (derived from bone) with which klotho interacts as a co-receptor in the gut and kidney to control phosphate absorption and excretion, respectively. The concept of supplementing or restoring tissue and circulating levels of klotho is topical as a potential treatment for CKD.

In their second paper, the authors again showed an increase in oxidative markers in the STZ rat (reduced NO and increased lipid peroxidation-TBARS) and that renal P2X7R expression increased at both the mRNA and protein levels,

and that klotho decreased, although there was an initial increase in its expression that fell significantly after the peak of P2X7R expression; they hypothesised that this pattern may reflect klotho-dependent phosphate loss and an effect on ATP synthesis preventing an early increase in P2X7R expression, which may in turn suppress klotho expression.

In the third and current publication, the authors have gone on to test this hypothesis by targeting P2X7R with a small interfering RNA (siRNA) in the same STZ rat model. Again, the authors show an increase in renal P2X7R expression and in tissue oxidation, associated with reduced NO and increases in the endogenous antioxidant catalase and SOD1, and a reduction in membrane (renal tissue) and soluble klotho. These changes were reversed in diabetic rats treated with the P2X7R siRNA and were also associated with significant reductions in proteinuria, plasma creatinine concentration, water intake and a trend toward increases in body weight and reduced hyperglycaemia.

The importance of this publication lies in its confirmation and reinforcement of a growing body of evidence that the P2X7R may play an important pathogenic role in the development and progression of diabetic kidney disease (DKD), which remains a major therapeutic challenge, accounting for almost 40% of patients worldwide with CKD. Moreover, targeting P2X7R with small molecules has so far proved problematic, at least in humans, and this may be related to the presence and tissue distribution of alternative transcripts. That said, an siRNA approach looks promising, especially since a number of therapeutic siRNAs are already being used successfully in the clinic for other disease targets. The present findings support further exploration and development of a P2X7 siRNA for the treatment of DKD and also raise the possibility that the benefit is in some way related to changes in klotho abundance and function.

However, the main limitations of these findings are the STZ animal model of DKD, which does not strictly reproduce the more widespread (glomerular and tubular) changes seen in human DKD, especially the more common type 2 (non-insulin-dependent) form, and that the available histology does not

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easily localize P2X7R or klotho within the kidney, showing a general increase and decrease, respectively, in the intensity of immunostaining, and that the improvement in histological features of DKD with treatment is not striking; this limits any deeper mechanistic insights at this time. Confirmation of these findings and the effect of siRNA treatment really need to be shown in at least one other animal model, preferably of type 2 diabetes with insulin resistance, as in humans, rather than with insulin deficiency. On the positive side, the measures of NO, TBARS and klotho itself may provide the potential for these soluble biomarkers to be used to monitor and confirm a clinical response to treatment in patients with DKD. Finally, it seems that the ‘ups and downs’ of P2X7R as a therapeutic target may once again be in the ascendance!

Compliance with ethical standards

Conflicts of interest Robert Unwin is Professor Emeritus of Nephrology at UCL and is currently employed by AstraZeneca BioPharmaceuticals

R&D, Early Development Cardiovascular, Renal and Metabolism (CVRM)

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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