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The role of epigenetic regulation in foetal programming to chronic kidney disease

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Chronic kidney disease (CKD) is a major health burden that is increasing globally at an annual rate of between 6-12%, driven largely by the increased incidence of obesity and diabetes. Metabolic perturbations in the intrauterine environment clearly predispose to CKD, which underpins the notion of foetal programming of chronic disease. 30-40% of patients with diabetes develop CKD for unknown reasons and the rate of CKD progression varies substantially from patient to patient, even among those with similar co-morbidities. Epigenetic modifications are implicated in the development of chronic disease. DNA methylation is the best understood epigenetic modification in the context of kidney disease. It occurs in response to environmental stimuli including diet, metabolic fluctuations, exercise, oxidative stress, inflammation, drugs and toxins and can be modulated by the cellular milieu. In this study we hypothesised that epigenetic regulation, specifically DNA methylation, is responsible for CKD development and progression, which can be pharmacologically modified and thus reduce CKD due to obesity and maternal obesity. To determine whether DNA methylation can identify animals with progressive CKD, we completed a longitudinal study using a high fat-fed animal model which we have recently demonstrated to induce features of type 2 diabetes by 9 weeks (adolescence) and significant renal structural damage and albuminuria in 30-40% of the animals by 32 weeks (adulthood), thus reflecting human epidemiology. Blood was collected at 9 and 32 weeks post weaning and DNA methylation was determined using reduced representation bisulfite sequencing. Animals were sacrificed by pericardiectomy at 32 weeks under anaesthetic (using 2% Isoflurane, nitrous oxide (2L/min) and Oxygen (1L/min)) and kidneys collected for pathological assessment. To confirm the role of DNA methylation in obesity related CKD and fetal programming to CKD, we assessed the effect of low dose hydralazine, which has a demethylating activity, on HFD induced CKD development and on maternal obesity induced CKD development in the offspring. Biometric and metabolic parameters, and markers of renal function and pathology including oxidative stress, inflammation and fibrosis were assessed. Global DNA methylation and gene methylation profile were also determined in the kidneys at week 32. We demonstrated that animals with progressive kidney disease exhibit differential gene methylation at week 9 compared to animals with non-progressive disease, when biomarkers of kidney disease ie albuminuria was not different. In total 48 genes were identified to be differentially methylated in the mice blood BEFORE the development of DKD. Pathways analysis revealed alteration in signalling pathways related to kidney development, structure and fibrosis suggesting relevance to the kidney and supporting the role for DNA methylation as potential biomarkers predictive of the future development and progression of CKD. We additionally demonstrated that low-dose hydralazine administration had renoprotective effects against CKD induced by obesity and transmissible factors inherent in maternal obesity. The mechanism of effect involves epigenetic regulation and DNA oxidation. In conclusion, epigenetic modifications especially DNA methylation is involved in the development and progression of CKD due to dietary obesity and in maternal obesity-induced CKD in the offspring. Our data supports the use of hydralazine or epigenetic modulators to limit obesity and maternal obesity-related CKD.