Renal dysfunction is transmitted to third generation offspring born to a growth restricted mother or father

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Introduction. Being born small increases cardio-renal disease risk, with males exhibiting more severe phenotypes than females. These disease risks are not limited to the first generation (F1) but may be transmitted to subsequent generations (F2 and F3). The F3 maternal line represents the first generation that is not directly exposed to the initial insults. There is limited evidence of paternal line transmission. We characterized nephron number and cardio-renal phenotype of F3 offspring born to normally grown and growth restricted (F1) mothers or fathers.

Methods. Late gestation rat uteroplacental insufficiency was induced (Restricted) or sham (Control) surgery in F0. Rats were anaesthetized with 4% isoflurane and 650ml.min⁻¹ oxygen flow (reduced to 3.2% isoflurane and 250ml.min⁻¹ oxygen flow when suturing). To generate F3 paternal line offspring, F1 Control and Restricted males were mated with normal females and the F2 Control and Restricted males were then mated with normal females. F3 maternal line offspring were similarly generated. F3 body weights were measured from birth to 12 months. Nephron number was quantified using unbiased stereology at postnatal day 35. 24h renal excretions, creatinine clearance and tail cuff blood pressure were measured at 6 (maternal and paternal lines) and 12 (maternal line only) months of age. All data were analysed by t-test within a gender and line.

Results. Although F1 offspring were born small, F2 and F3 offspring (both maternal and paternal lines) had normal birth weights. F3 body weight was not different from birth to 12 months of age with no differences in kidney, heart or adipose weights at 6 months between groups or lines. F3 male and female nephron endowment and blood pressure was not different between groups for paternal and maternal lines. F3 maternal line renal function was normal at 6 months of age. However, at 12 months, although creatinine clearance (eGFR) was normal, renal dysfunction emerged in F3 maternal line males (proteinuria) and females (increased urinary creatinine excretion). F3 offspring from fathers born small had evidence of impaired eGFR (reduced creatinine clearance).

Conclusions. F3 offspring, born to F1 growth restricted mothers or fathers are not programmed to be born of low birth weight but developed renal dysfunction in the absence of obesity. The proteinuria that emerged with aging in the F3 maternal line male offspring in the absence of nephron deficits, hypertension and reduced eGFR, suggests tubulointerstitial injury mediated either through podocyte dysfunction/depletion or solely via proteinuria. In contrast, F3 paternal line offspring had glomerular dysfunction (reduced eGFR), indicative of glomerular filtration deficits. Our paternal line results highlight sustained transgenerational inheritance of renal dysfunction. Since nephron number was preserved our results propose the progression of renal dysfunction via the “fibrosis hypothesis” rather than the “Brenner hypothesis”. Our findings provide novel evidence of transgenerational transmission of renal dysfunction to F3 offspring from both maternal and paternal lines.