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Glomerular filtration rate and quantification of glomerular number and size in mouse

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According to Brenner hypothesis of hyperfiltration, kidneys compensate a loss of nephrons by increasing the single nephron glomerular filtration rate (SNGFR). This might cause, at later stages, focal glomerulosclerosis, further reduction of nephron number and loss of function.
The validity of Brenner hypothesis has never been rigorously investigated so far.
Robust and reliable methods for assessing functional and morphological parameters are essential for providing a comprehensive description of the phenomenon.
Fluorescein isothiocyanate (FITC)-labelled sinistrin was successfully employed to assess renal function transcutaneously in conscious mice by using a device that excites and detects its fluorescence. A compartment model was used to fit the acquired kinetics and derive FITC-sinistrin half-life ($t_{1/2}$) that provides a quantification of the renal function. The method was validated against gold standard plasma clearance.
In parallel, a test bench was implemented for the quality control of the transcutaneous devices and the effect of new strategies for the technical optimization was tested *in-vivo*. Preliminary results showed that targeted adjustments of the hardware and the device package will allow realizing a new generation of highly sensitive devices, which will allow reducing the necessary dosage of renal marker per measurement.
A new approach based on magnetic resonance imaging (MRI) was used in this study for counting and sizing mouse glomeruli and successfully validated against gold standard stereology. This method, unlike stereology, has the significant advantage of providing quantitative information on the whole kidney. Besides, this technique does not imply the destruction of the sample. The technology was adjusted to allow the estimation of the glomerular endowment in whole mouse kidneys.
Taken together, renal function, glomerular number, size and size distribution were analyzed according to Brenner hyperfiltration hypothesis.
The study was conducted on mice belonging to wild-type Balb/c and C57BL/6 strains and on one group *glial cell line-derived neurotrophic factor* (GDNF) heterozygous mice. Cationized ferritin (CF) was used to label the glomeruli that appeared as black object in *ex-vivo* MR images and were automatically quantified.
Our dataset showed that left and right kidneys of Balb/c and C57BL/6 mice are highly comparable in terms of weight and glomerular numberand size distribution. An age-associated reduction of the glomerular number and an overall increase of glomerular size were observed in C57BL/6 mice until the age of 34 weeks. Together with a limited reduction of the renal function over the same period, these results are in agreement with the compensatory hypothesis of hyperfiltration. However, the measurement performed in two 83 weeks old kidneys indicates shrinkage of the glomeruli at later stages.
Body weights, kidney weights and renal function of GDNF heterozygous mice with two kidneys were comparable with wild-type values. However, they present fewer and bigger glomeruli. These mice therefore reveal substantial hyperfiltration, according to the Brenner hypothesis: the kidney compensates for a reduction in filtration surface with glomerular hypertrophy in order to maintain the total glomerular filtration rate unvaried. The phenomenon was found considerably more pronounced in heterozygous mice with solitary kidney.
This work validated the main aspects of Brenner hypothesis; in particular the complementarity among renal function, glomerular number and size. Age has been newly introduced as a factor substantially affecting glomerular morphology and function. Follow-up studies involving new technologies are necessary to further our knowledge on the mechanisms arising hyperfiltration.