KU LEUVEN

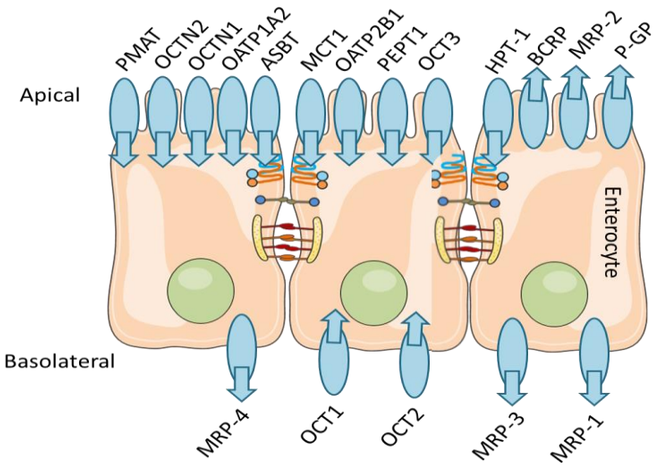
TARGID & Nephrology Department

Colon transporters in chronic kidney disease: a potential target to reduce microbiome-derived uremic toxins?

M. Lauriola, S. Dejongh, R. Farré, B. Meijers

INTRODUCTION

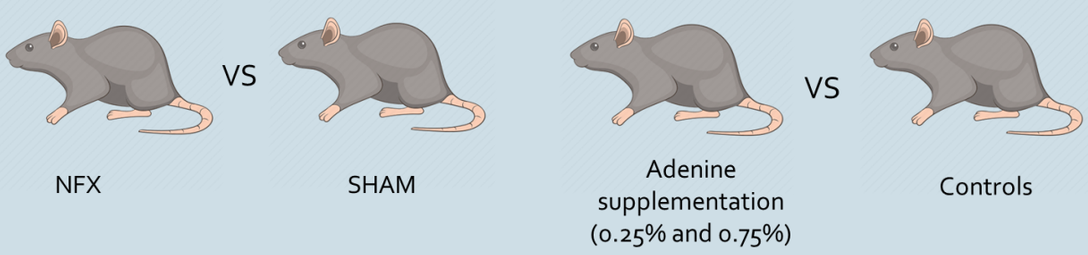
Chronic kidney disease (CKD) is associated with an increased risk of cardiovascular disease mortality. Advanced CKD is marked by the so-called uremic syndrome i.e. an accumulation in plasma of solutes called uremic toxins such as indoxyl sulfate(IS) and p-cresyl sulfate(PCS) which cannot be excreted by the kidneys and that mediate a series of detrimental metabolic and cardiovascular events. A significant part of the uremic retention solutes is produced by the gut microbiome. Due to their binding to plasma proteins, those are hard to be removed via the most effective renal replacement therapies such as hemodialysis and hemodiafiltration. We sought to determine the impact of CKD on gut transporters and to define differences between the two most common CKD rodent models: the 5/6 nephrectomy model (NFX) and the adenine supplementation model.



Overview of colon transporters

METHOD

Study design



Euthanasia after different timepoints (4, 8, 12, 16 weeks)

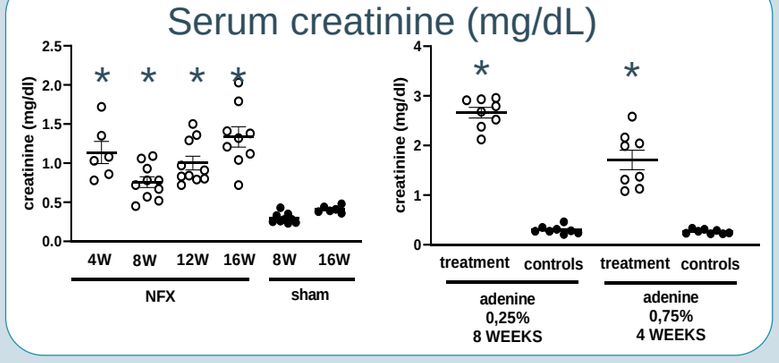
Sampling

- Relative transporters gene expression by qPCR
- Relative protein transporters expression by Western Blot
- Plasma uremic toxic quantification by UPLC-MS/MS

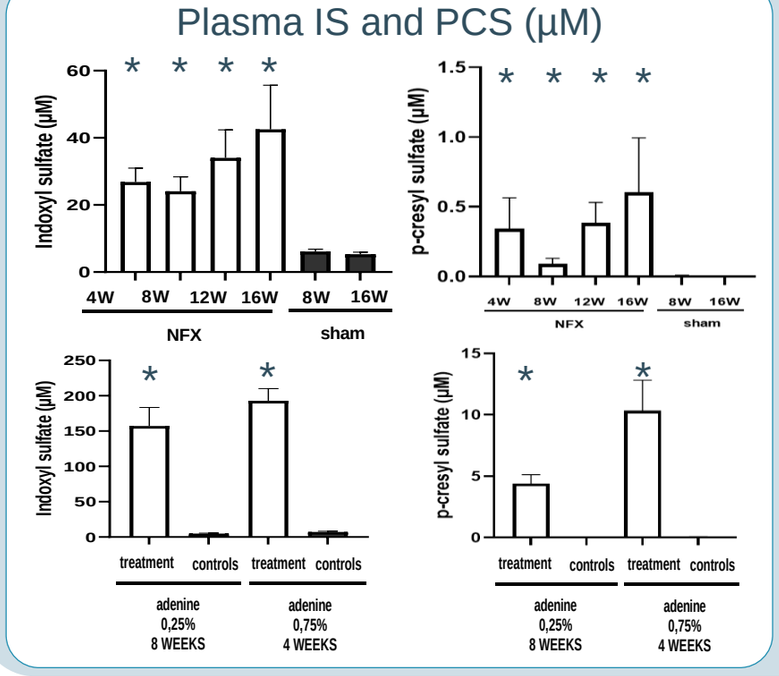
RESULTS

*p value<0,05

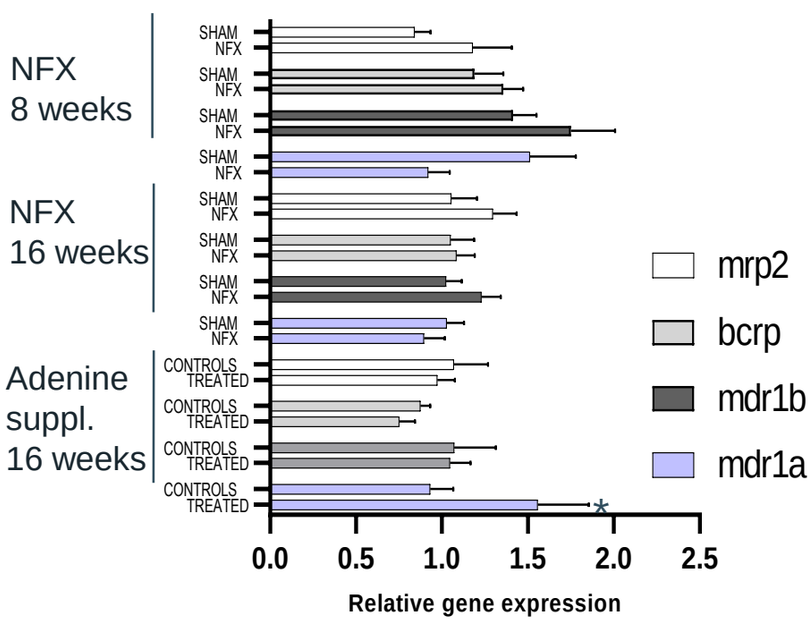
Serum creatinine (mg/dL)

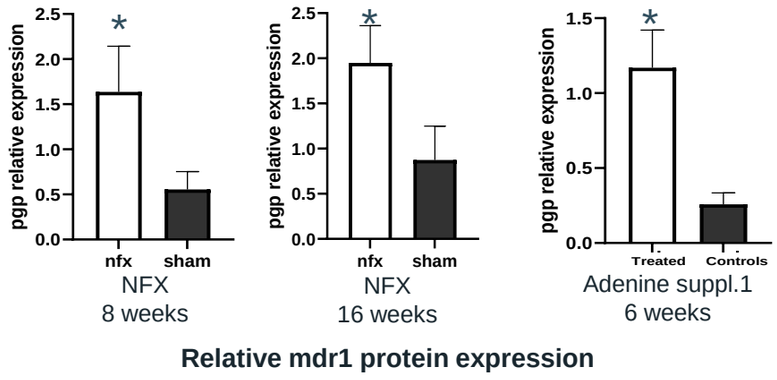


Plasma IS and PCS (µM)



EFFLUX TRANSPORTERS

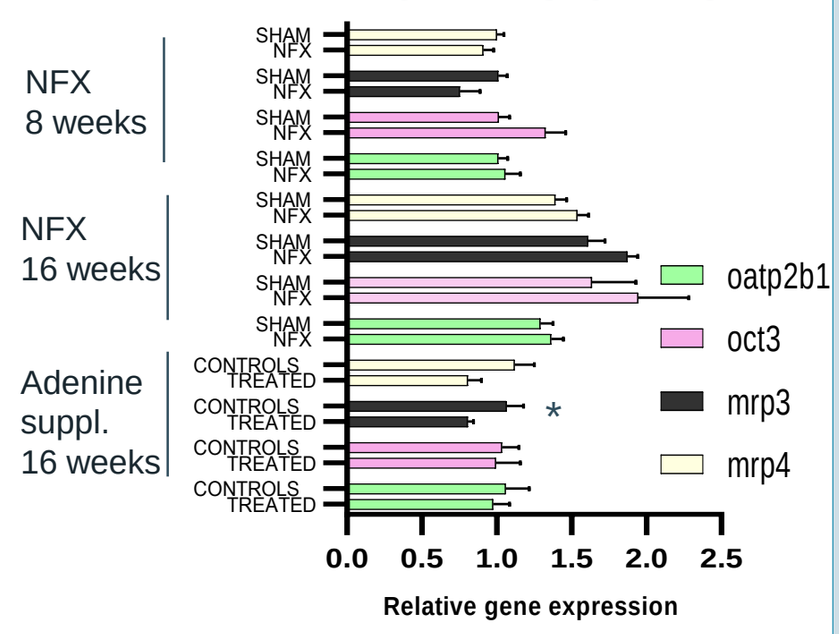


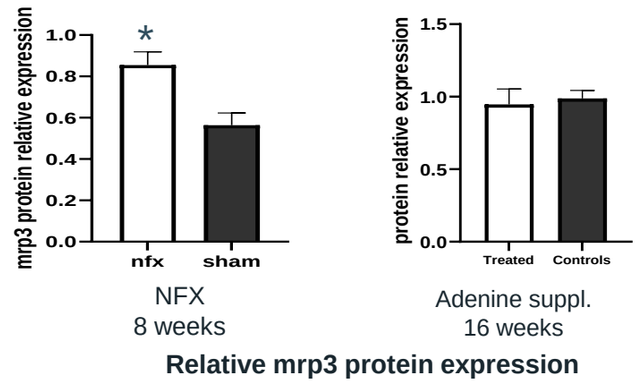


NFX 8 weeks | NFX 16 weeks | Adenine suppl.1 6 weeks

Relative mdr1 protein expression

INFLUX TRANSPORTERS





NFX 8 weeks | Adenine suppl. 16 weeks

Relative mrp3 protein expression

CONCLUSIONS

- 5/6 nephrectomy and adenine supplemented diet use can be used as **useful CKD rodent models** to study uremic toxins impact on the gut in CKD.
- 5/6 nephrectomy caused a **medium-severe** loss of kidney function, with an average **4-8 times** increase of indoxyl sulfate and an average **6-18 times** increase of p-cresyl glucoronide.
- Adenine model caused a **severe** loss of kidney function, with an average **27-32 times** increase of indoxyl sulfate and an average **26-32 times** increase of p-cresyl glucoronide.
- **Mrp3** (or Multi drug resistant protein 3) relative expression is significantly higher only in CKD nephrectomized rodent models after 8 weeks, while expression decreases after 16 weeks at a mRNA level in both adenine (significantly) and NFX (not significantly) models.
- **P-gp** (or Multi drug resistant protein 1) relative expression is significantly higher in all the CKD rodent models.