ENDOGENOUS PENTRAVIN 3 INHIBITS NEPHROCALCINOSIS AND PROTECTS FROM HYPEROXALURIA-INDUCED CHRONIC KIDNEY DISEASE

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INTRODUCTION AND AIMS: Patients with primary hyperoxaluria type 1 have an elevated endogenous oxalate production leading to intrarenal calcium oxalate crystal deposition (nephrocalcinosis) and CKD progressing to end-stage renal disease. The acute phase protein Pentraxin 3 (PTX3) exerts a variety of regulatory functions in acute and chronic tissue inflammation. In particular, PTX3 acts as an opsonin for a variety of pathogens and endogenous particles. We hypothesized, that PTX3 would exhibit opsonin-like functions also on calcium oxalate crystals and inhibiting crystal growth and nephrocalcinosis.

METHODS: Direct effects of PTX3 on calcium oxalate crystals were investigated in chemico using standard imaging techniques. To study the role of PTX3 in vivo, we used a murine model of hyperoxaluria induced nephrocalcinosis where Pttx3-deficient B6.129 mice or their PTX3-competent littermates were fed with a high-oxalate diet for 21 days. PTX3 protein levels were assessed by Western blot and immunohistochemistry. Assessment of nephrocalcinosis and CKD progression was conducted by histology, flow cytometry and fluorescein isothiocyanate-labeled sinistrin clearance using non-invasive, transcutaneous imagers.
RESULTS: Adding PTX3 to supersaturated calcium and oxalate in-chemico dose-dependently inhibited crystal growth, while an isomolar albumin control did not (A). PTX3 protein was undetectable in the urine of wildtype mice under physiological conditions but increased within 3 weeks of feeding an oxalate-rich diet to induce nephrocalcinosis. Most likely the urinary PTX3 originated directly from tubular epithelial cells, as immunohistochemistry of kidney sections indicated a high induction of protein expression in these cells. To test for a functional role of PTX3 we designed an in vivo experiment where Ptx3−/− mice as well as their wildtype littermates were exposed to oxalate-rich diet for 3 weeks, although mice of this specific genetic background are not susceptible to hyperoxaluria-induced nephrocalcinosis. However, lack of PTX3 induced profound nephrocalcinosis in B6;129 mice associated with interstitial inflammation and fibrosis as well as a linear decline in glomerular filtration rate (B-D). Nephrocalcinosis and CKD were absent in their Ptx3+/+ littermates (B-D).

CONCLUSIONS: Thus, PTX3 is an endogenous inhibitor of calcium oxalate crystallization even in profound hyperoxaluria. It will be interesting to look into the precise mechanism of action and to develop therapeutic strategies to exploit this novel found function of PTX3 to prevent nephrocalcinosis in primary hyperoxaluria, a disease with currently very few treatment options.