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RENAL DEVELOPMENT AND CYSTIC DISEASES

FP063 INFLAMMATION TRIGGERS RENAL EXPRESSION OF FGF23 IN POLYCYSTIC KIDNEY DISEASE

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Introduction and Aims: Fibroblast growth factor 23 (FGF23) regulates phosphate homeostasis and is directly linked to all-cause mortality in chronic kidney disease (CKD). FGF23 rises in patients with CKD stages 2-3 whereas in patients with autosomal dominant polycystic kidney disease (ADPKD), the increase of FGF23 precedes the first measurable decline in renal function. Similar, in PKD animal models such as Han:SPRD rats and Pkd1 conditional KO mice plasma FGF23 levels are elevated while renal function and phosphate homeostasis are unchanged. FGF23 is mainly expressed in bone but in PKD animals also the polycystic kidney is a source of FGF23 production. In this study, we examined hypoxia and inflammation as possible factors regulating FGF23 expression in cyst lining epithelial cells of polycystic kidneys.

Methods: Using Pkd1 conditional KO mice as well as bone cell models we investigated the regulation of renal FGF23 expression in PKD.

Results: Renal FGF23 expression in Pkd1 conditional KO mice was accompanied by up-regulation of bone marker genes such as dentin matrix protein 1 and runt-related transcription factor 2 as well as nuclear receptor related 1 protein (Nurr1) transcription factor. Nurr1 is known to modulate FGF23 expression in bone and can be activated by PTH or Vitamin D as well as inflammatory markers such as tumor necrosis factor (TNFa). Primary bone cells treated in vitro with TNFa or lipopolysaccharides showed increased FGF23 mRNA expression levels. TNFa mRNA expression was highly upregulated in polycystic kidneys of Pkd1 conditional KO mice where it could be a trigger for renal FGF23 expression.

It has been shown that in iron deprived mice as well as in UMR106 osteosarcoma cells FGF23 expression is regulated by hypoxia. Hypoxia is present in cystic kidneys of human as well as PKD animals. We found that MC3T3-E1 mouse preosteoblast cell line did not display intrinsic FGF23 expression. Nevertheless after two weeks differentiation of MC3T3-E1 along the osteogenic lineage FGF23 expression could be induced by 1.25 (OH)2 vitamin D3. Vitamin D3 induced FGF23 expression was totally repressed when cells were cultured for 24 or 48h under hypoxic conditions. Primary bone cells intrinsically expressed FGF23 but expression levels were unchanged under hypoxic conditions.

Conclusions: In conclusion, inflammation but not hypoxia could be a trigger for renal FGF23 expression in polycystic kidney disease.