Secretion of the epithelial sodium channel chaperone PCSK9 from the cortical collecting duct links sodium retention with hypercholesterolemia in nephrotic syndrome.

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Objective/Aim/Hypothesis:
85% of US chronic kidney disease patient presenting nephrotic syndrome (NS) have high levels of low density lipoprotein cholesterol (LDL-c), compared to 31.5% in the general population. The Proprotein convertase subtilisin/kexin type 9 (PCSK9) is highly expressed in the liver where it plays a significant role in the pathogenesis of hypercholesterolemia. PCSK9 is also expressed in intestine, and in the collecting duct (CD), where it functions as a chaperone for the epithelial sodium channel (ENaC). As we found increased PCSK9 expression in the CCD in kidney biopsies of patients with primary glomerular disease, we explored a possible relationship with hypercholesterolemia of nephrotic syndrome.

Design/Approach/Methods:
(1) Rrm2b Control (+/+) and knock-out (-/-) mice were followed weekly between the age 5 and 12 weeks. (2) Buffalo/Mna rats were followed monthly between the age 12 and 32 weeks. (3) We use nephrotoxic serum to induce NS in CCD-specific PCSK9 deficient mice. (4) 8 week-old *Rrm2b* mice were treated or not with Amiloride, a specific inhibitor of ENaC located in the renal CCD. Albuminuria/proteinuria, PCSK9 and cholesterol serum levels were assessed. PCSK9 gene and protein expression in liver and kidney was studied by RealTime PCR, Western blot, and confocal microscopy.

Results:
$Rrm2b^{+/+}$ mice do not develop albuminuria, hypercholesterolemia, or high levels of serum PCSK9. $Rrm2b^{-/-}$ develop albuminuria from the age of 7 weeks (425±239 μg/18h, $P<0.001$) and serum PCSK9 and total cholesterol levels significantly increase from the age of 8 weeks (19.75±5.21 ng/ml, $P<0.05$, and 124.16±10.27 mg/dl, $P<0.05$, respectively). Buffalo/Mna rats develop proteinuria from the age 6 weeks and onwards. Significantly elevated serum PCSK9 and cholesterol levels were noted in both animals models. Furthermore, increased expression of PCSK9 in the kidney occurred when liver expression was reduced in mice and rats. Mice with selective deficiency of PCSK9 expression in the collecting duct failed to develop hypercholesterolemia after induction of nephrotic serum by injection of nephrotoxic serum. Finally, blocking epithelial sodium channel activity with Amiloride in *Rrm2b-/-* mice resulted in increased expression of its chaperone PCSK9 in the CCD, followed by elevated plasma levels and worsening hypercholesterolemia.

Conclusion:
Our data suggest that PCSK9 in the kidney plays a role in the initiation of hypercholesterolemia in nephrotic syndrome and make a case for depletion of PCSK9 early in patients with nephrotic syndrome to prevent development of hypercholesterolemia.