

Rosuvastatin prevents cardiovascular events in people with elevated C-reactive protein

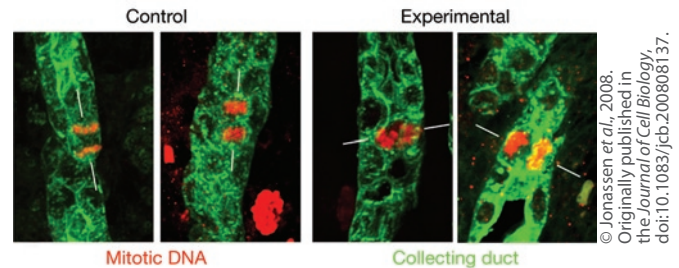
Increased levels of the inflammatory biomarker high-sensitivity C-reactive protein predict cardiovascular events. Since statins lower levels of high-sensitivity C-reactive protein as well as cholesterol, the authors of a new study hypothesized that people with elevated high-sensitivity C-reactive protein levels without hyperlipidemia might benefit from statin treatment.

Ridker *et al.* randomly assigned 17,802 apparently healthy men and women with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg/dl (3.4 mmol/l) and high-sensitivity C-reactive protein levels of 2.0 mg/l or higher to 20 mg daily of rosuvastatin, or placebo, and followed them for a number of years. The combined primary end point was defined as myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. The trial was stopped after a median follow-up of 1.9 years (maximum, 5.0). Rosuvastatin reduced LDL cholesterol levels by 50% and high-sensitivity C-reactive protein levels by 37%. The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively ($P < 0.00001$). Consistent effects were observed in all subgroups evaluated. The rosuvastatin group did not have a significant increase in myopathy or cancer but did have a higher incidence of physician-reported diabetes. The authors conclude that in this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events. (*N Engl J Med* 2008; **359**: 2195–2207)

Marc De Broe

Misorientation of the mitotic spindle and cystic kidney disease

Primary cilia project from the surface of most vertebrate cells and are thought to be sensory organelles. Defects in the cilia of the epithelial cells lining kidney tubules underlie nearly all types of human cystic kidney diseases. It is currently believed that increased proliferation of mutant epithelial cells, along with defects in planar cell polarity, plays a role in the development of cystic kidney diseases. However, the function of the primary cilia in controlling kidney architecture and preventing cyst formation is not understood. Cilia and flagella are assembled and maintained by intraflagellar transport (IFT). During IFT, large protein complexes called IFT particles are transported along the ciliary microtubules under the ciliary membrane and carry precursors from the



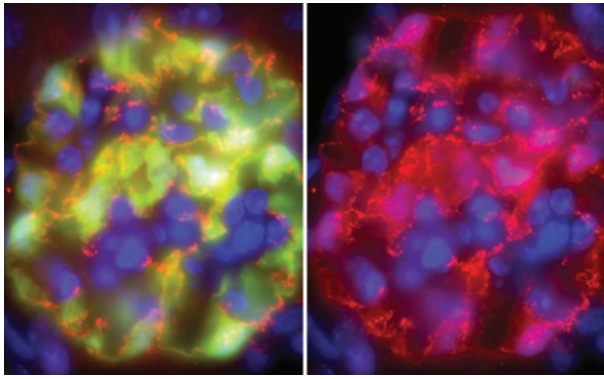
Deletion of *Ift20* leads to mitotic spindle misorientation in collecting duct cells. In normal kidney tubules, mitotic spindles (phospho-histone H3, red) typically orient their axes (white lines) parallel to the long axis of the collecting duct (*Dolichos biflorus* agglutinin, green).

site of synthesis in the cell body to the site of ciliary assembly. The particles comprise approximately 20 unique subunits organized into A and B complexes. In a recent report, Jonassen *et al.* characterized the function of IFT20, a complex B subunit, by generating a floxed allele of *Ift20* and deleting this gene specifically in kidney collecting duct epithelium. Deletion of the gene prevented cilia formation and resulted in rapid postnatal cystic expansion of the kidney. Of great interest is their finding that dividing collecting duct cells in early stages of cyst formation failed to properly orient their mitotic spindles along the tubule (Figure), whereas non-dividing cells improperly positioned their centrosomes. Mitotic spindle orientation is thought to be controlled by the non-canonical branch of the Wnt pathway, but the authors found that at later stages, cells lacking cilia had increased canonical Wnt signaling and increased rates of proliferation. While cilia can function as chemoreceptors and as mechanosensors, several other studies suggest that these functions are not involved in cytotogenesis. Hence, the current study suggests that the cilia provide spatial information to control Wnt signaling. It also shows that IFT20 couples extracellular events to cell proliferation and differentiation. (*J Cell Biol* 2008; **183**: 377–384; doi:10.1083/jcb.200808137)

Juan Oliver

Pericytes and perivascular fibroblasts are a source of collagen-producing cells in obstructive kidney fibrosis

Understanding the origin of scar-producing myofibroblasts is a vital component in understanding the mechanisms by which fibrosis develops in response to inflammatory injury. Lin *et al.* used a transgenic reporter mouse model expressing enhanced green fluorescent protein (GFP) under the regulation of the collagen type I, $\alpha 1$ (*coll1a1*) promoter and enhancers to



Reprinted from *Am J Pathol* 2008; 173: 1617–1627, with permission from the American Society for Investigative Pathology.

Image of the normal glomerulus of a coll-GFP mouse colabeled with antibodies against podocin (red), and nuclei labeled with 4,6-diamidino-2-phenylindole (DAPI; blue). The right panel shows red and blue channels only. Podocytes exclusively express GFP in the glomerulus and colocalize with podocin.

examine the origins of *coll1a1*-producing cells in the kidney (Figure). The authors showed that in the normal kidney, both podocytes and pericytes generated *coll1a1* transcripts, as detected by enhanced GFP, and that in the fibrotic kidney, *coll1a1*-GFP expression accurately identified myofibroblasts. To determine the direct contribution of circulating immune cells to scar production, wild-type mice, chimeric with bone marrow from coll-GFP mice, underwent ureteral obstruction to induce fibrosis. Histological examination of kidneys from these mice showed recruitment of small numbers of fibrocytes to the fibrotic kidney, but these fibrocytes made no significant contribution to interstitial fibrosis. Instead, using kinetic modeling and time-course microscopy, the authors identified *coll1a1*-GFP-expressing pericytes as the major source of interstitial myofibroblasts in the fibrotic kidney. These studies suggest that either vascular injury or vascular factors are the most likely triggers for pericyte migration and differentiation into myofibroblasts. Therefore, the authors propose that fibrosis research should perhaps be refocused to injury of the vasculature rather than injury of the epithelium. (*Am J Pathol* 2008; 173: 1617–1627; doi:10.2353/ajpath.2008.080)

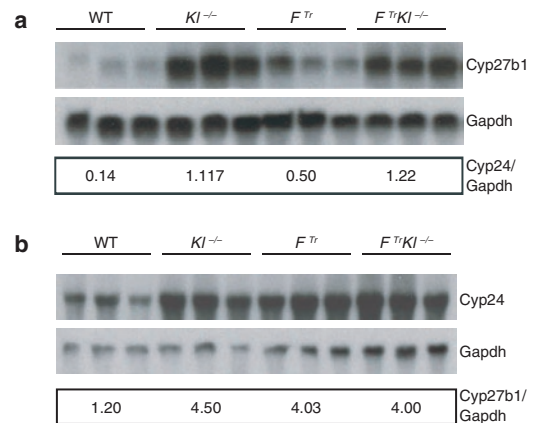
Marc De Broe

Essential role of Klotho for FGF23 action

Fibroblast growth factor-23 (FGF23) induces urinary excretion of phosphorus by decreasing its reabsorption in renal proximal tubules. Concurrently, FGF23 reduces circulating $1,25(\text{OH})_2\text{D}$ by both decreasing its biosynthesis and increasing its metabolism. Recent studies have shown that to bind and signal through its receptor, FGF23 requires Klotho (KL) as a cofactor. Klotho and FGF receptor-1(IIIc) form a heterodimeric, high-affinity receptor for FGF23. The Klotho gene encodes a single-pass transmembrane protein, that is expressed in limited tissues, notably in kidney tubules and

parathyroid. Klotho likely has additional functions, since the extracellular domain of the Klotho protein is shed from the cell surface. This soluble Klotho appears to regulate multiple growth factor signaling pathways. Mice severely hypomorphic for *Klotho* ($Kl^{-/-}$) display a variety of skeletal and biochemical abnormalities similar to those seen in mice with deletion of *Fgf23*. Furthermore, circulating levels of FGF23 are elevated in $Kl^{-/-}$ mice, suggesting that resistance to FGF23 action occurs in this animal. In addition, many *in vitro* studies suggest a functional cross-talk between Klotho and FGF23. To examine the role of Klotho in FGF23 action on mineral and skeletal homeostasis *in vivo*, Bai *et al.* used a genetic approach. They crossed transgenic mice (F^{Tr}) expressing a mutant form of human FGF23 (R176Q), which is resistant to protease degradation, and $Kl^{-/-}$ mice to introduce the FGF23 (R176Q) transgene onto the $Kl^{-/-}$ genetic background. They found that the biochemical abnormalities (hypophosphatemia, phosphaturia, abnormal $1,25(\text{OH})_2\text{D}_3$ metabolism) and skeletal abnormalities (rickets and osteomalacia) attributable to FGF23 action were abrogated in the $F^{Tr}/Kl^{-/-}$ mice, which had features similar to those of the $Kl^{-/-}$ mice. Importantly, whereas in the mice with excess human FGF23, renal expression of *Cyp27b1* was decreased and that of *Cyp24* was increased (Figure), resulting in decreased serum levels of $1,25(\text{OH})_2\text{D}_3$, in $F^{Tr}/Kl^{-/-}$ mice, increased *Cyp27b1* expression was associated with raised circulating levels of the hormone, implying increased protein expression and/or enzymatic activity of the elevated *Cyp27b1*. Thus, the lack of Klotho protein in $F^{Tr}/Kl^{-/-}$ mice appears to prevent FGF23 inhibition of *Cyp27b1* renal hydroxylase enzymatic activity. Moreover, the increase in *Cyp24* may have occurred in response to elevated $1,25(\text{OH})_2\text{D}_3$ and likely prevented the serum concentrations of $1,25(\text{OH})_2\text{D}_3$ from being more elevated. These findings substantiate the essential role of Klotho in the mechanism of action of FGF23 *in vivo*. (*Am J Physiol Endocrinol Metab* advance online publication, 4 November 2008, doi:10.1152/ajpendo.90539.2008)

Juan Oliver



Northern blot analysis of renal hydroxylase expression. (a) *Cyp27b1* and (b) *Cyp24* expression levels in kidneys from wild-type (WT), $Kl^{-/-}$, F^{Tr} , and $Kl^{-/-}/F^{Tr}$ mice. *Gapdh* expression was used as loading control.