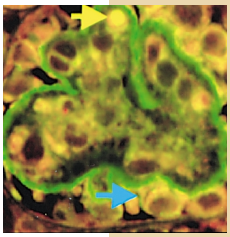
In this issue

By John Ashkenas, Science Editor

Two routes to cell death in the diseased kidney

(See article on pages 807–816.)

Stimulation by the ubiquitous cytokine TGF-β activates the transcription of numerous target genes and leads to an impressive range of biological effects. Central to these responses are intracellular mediators of the SMAD family, which are activated and transported to the nucleus following TGF-β treatment. Schiffer et al. show here that there are surprises left in this widely studied and highly conserved pathway. Overexpression of TGF-β1 under control of the *Albumin* promoter causes apoptosis in renal epithelial cells and yields a model of glomerulosclerosis, a progressive disease involving glomerular fibrosis and degeneration. One protein of the SMAD family, SMAD7, is well known as a negative regulator of TGF-β signaling, and indeed, TGF-β signaling often activates synthesis of SMAD7, establishing a negative feedback system that can limit the pathway's physiological effects. Schiffer and colleagues now find, however, that SMAD7 can also carry its own signals and can work in parallel with TGF-β. In glomerulosclerosis, the cell death induced by the overexpression of the cytokine is accompanied by a dramatic increase in SMAD7, which acts independently in this system to induce apoptosis. Even without TGF-β overexpression, cultured renal podocytes that express SMAD7 are prone to apoptosis. This response activates different apoptotic effectors and is mediated by a signaling pathway distinct from the one induced by TGF-β. Whether SMAD7 must interact with the stimulatory SMAD proteins to exert this novel effect is not yet known.



Rethinking reverse cholesterol transport

(See article on pages 843–850.)

The protective role of HDL, the so-called "good cholesterol," has been attributed to its ability to transport cholesterol to the liver, where it can be incorporated into the bile and eventually excreted. Two players in this pathway have received particular attention: One, the phospholipid/cholesterol transporter ABCA1, is required for the synthesis of HDL — as seen in humans and mice with *ABCA1* mutations, who are almost entirely lacking in this lipoprotein species. The other, the cell surface HDL receptor SR-BI (discussed in the Perspective by Krieger, pages 793–797), is expressed in hepatocytes and other cell types that consume large amounts of HDL cholesterol. Consistent with the commonly accepted model of reverse cholesterol transport, hepatic overexpression of SR-BI increases cholesterol levels in the bile, whereas deletion of the *SR-BI* gene dramatically reduces biliary cholesterol secretion. Now, however, a surprising report from Groen et al. shows that mice lacking a functional *ABCA1* gene secrete normal levels of cholesterol through the bile, despite the nearly complete absence of plasma HDL. The authors note that another mouse line with low HDL levels, this one lacking the HDL apolipoprotein apoA-I, is also capable of normal biliary cholesterol clearance. As the authors suggest, these findings may force the field to reexamine whether HDL plays a major role in this hepatobiliary route of reverse cholesterol transport. Alternatively, it may be that hepatic uptake of cholesterol packaged in some other form, perhaps as VLDL, increases to compensate for the absence of HDL in these systems.

Chemokine expression heightens antibacterial immunity

(See article on pages 917–927.)

Macrophage-derived chemokine (MDC) acts preferentially on Th2 lymphocytes, promoting their migration and setting the stage for antigen-specific B cell responses. Although this chemokine is expressed at low constitutive levels in antigen-presenting cells, Kikuchi and Crystal hypothesized that increasing its expression in dendritic cells (DCs) could allow for more efficient T cell help and a more effective humoral response. Since antibodies are key to the suppression of bacterial infections, these authors tested their idea in a mouse model of bacterial pneumonia. They transduced DCs with a human MDC cDNA and exposed the transgenic cells to pathogenic *Pseudomonas* bacteria, allowing the cells to process and display bacterial antigens. When reintroduced into host mice, these antigen-pulsed DCs effectively suppressed otherwise lethal infections with *Pseudomonas*. As expected, passive transfer of CD4 cells that had been activated by these DCs conferred the same protection to naive hosts, and even simple transfer of the serum from DC recipient animals allowed otherwise untreated recipients to combat the infection. Control DCs that were exposed to the pathogen but that expressed only endogenous, low levels of MDC conferred only minimal protection to recipient animals. This approach allows for specific immunization against this one pathogenic species, but it is fully effective only against certain clinical isolates. Hence if this approach is to be tried for clinical purposes, it may be necessary to expose DCs to multiple bacterial strains. Kikuchi and Crystal also note that increased MDC expression by DCs could promote undesired Th2-dependent immune responses, such as those associated with allergic symptoms.