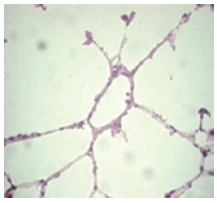
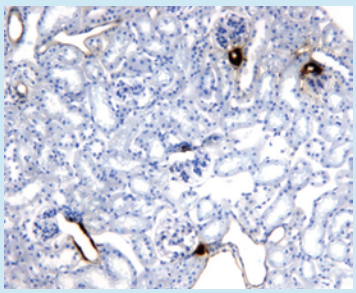
New way to treat pulmonary hypertension?



Pulmonary arterial hypertension (PAH) is a severe vascular disease that leads to progressive right heart failure and premature death. There is no cure for PAH. However, recent advances in understanding the pathogenesis of PAH have led to new, clinically beneficial therapeutic approaches. In this issue (2888–2897), Hara and colleagues provide new insight into the pathogenesis of PAH that leads them to suggest that inhibiting multidrug resistance–associated protein 4 (MRP4, also known as Abcc4) could provide a new way to treat individuals with PAH. Their initial analysis indicated that expression of MRP4 was markedly higher in lung samples from patients with clinical pulmonary hypertension than in those from healthy individuals. Consistent with a role for MRP4 in the development of PAH, mice lacking MRP4 were protected from pulmonary hypertension induced by exposure to hypoxia for 4 weeks. Furthermore, treatment of wild-type mice with an MRP4 inhibitor reversed hypoxic pulmonary hypertension. Mechanistic analysis in vitro indicated that the protective effects of the MRP4 inhibitor were linked to its ability to increase intracellular levels of cAMP and cGMP. These data provide the rationale for the authors' suggestion that MRP4 could be targeted for the treatment of PAH.

Long live intrarenal dopamine



The best-characterized function of dopamine is as a neurotransmitter. However, it also exerts effects on peripheral organs, such as the kidney, which itself synthesizes dopamine through the actions of aromatic amino acid decarboxylase (AADC) in the proximal tubule. The relative contribution of extrarenal and intrarenal dopamine to the regulation of renal function has not been previously determined. To address this issue, Zhang and colleagues generated mice lacking AADC in the kidney proximal tubules (mice that they referred to as pt*Aadc*$^{-/-}$ mice) (2845–2854). Analysis of pt*Aadc*$^{-/-}$ mice revealed that they were more susceptible to salt-sensitive hypertension and had a substantially shorter life span than wild-type mice. Mechanistically, pt*Aadc*$^{-/-}$ mice exhibited increased expression of renin, the peptide hormone that cleaves angiotensinogen to yield angiotensin I, and altered renal expression of angiotensin receptors (AT): expression of AT1b was increased, while expression of AT2 and Mas (also known as angiotensin 1–7 receptor) was decreased. These changes were associated with increased renal injury in response to angiotensin II. The authors therefore conclude that the intrarenal dopaminergic system buffers renal responses to angiotensin II to regulate salt and water homeostasis and thereby exert blood pressure control.

Divide to conquer triple-negative breast cancer

A diagnosis of triple-negative breast cancer (TNBC) — so called because the tumor cells lack expression of estrogen receptor and progesterone receptor and lack amplification of the human epidermal growth factor receptor 2 (*HER2*) gene — is associated with poor clinical outcome. There are several reasons for this, including the high heterogeneity among TNBCs. If TNBCs could be subtyped, identifying good molecularly targeted treatment options would be easier. Lehmann and colleagues have now generated new insight into this issue by analyzing gene expression profiles from 587 TNBC cases (2750–2767). Using this approach, 6 subtypes of TNBC were defined and cell lines characteristic of each identified. The gene expression profiles allowed Lehmann and colleagues to predict what signaling pathways drove the development and progression of each TNBC subtype. Pharmacologic targeting of these pathways in the corresponding cell lines demonstrated the utility of gene expression analysis for therapy selection. For example, the luminal androgen receptor (LAR) subtype was characterized by androgen receptor (AR) signaling, and LAR cell lines were uniquely sensitive to an AR antagonist. The authors hope that their data will help physicians target therapeutic strategies more effectively in TNBC patients, improving clinical outcome.

A miR reduction in atherosclerosis

High levels of plasma HDL are associated with a decreased risk of atherosclerosis. This suggests that therapeutics that increase HDL levels could be clinically useful. However, better understanding of the mechanisms underlying HDL biogenesis and regulation is needed if the potential of HDL-raising therapeutic strategies is to be realized. Recent data indicate that miR-33 indirectly lowers HDL levels, leading to the hypothesis that targeting this microRNA might be atheroprotective. Rayner and colleagues have now generated data in mice that support this hypothesis and define the underlying mechanism (2921–2931). Treating LDL receptor–knockout mice (*Ldlr*$^{-/-}$ mice) that had established atherosclerotic plaques with a 4-week course of an antagonist of miR-33 increased circulating HDL levels. Importantly, it also reduced plaque size and lipid content and increased expression of markers of plaque stability. Mechanistically, miR-33 antagonism was shown to enhance expression of the cholesterol transporter ABC transporter A1 (ABCA1) in both the liver and macrophages within the atherosclerotic plaques, thereby enhancing HDL biogenesis in the liver and cholesterol removal from plaque macrophages. The authors therefore suggest that miR-33 antagonism might provide a promising strategy to treat individuals with atherosclerosis.