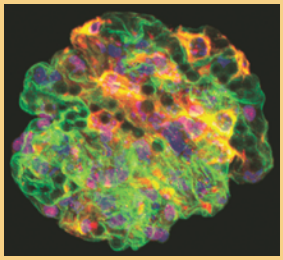
Kidney maintains its integrity with Arhgap24

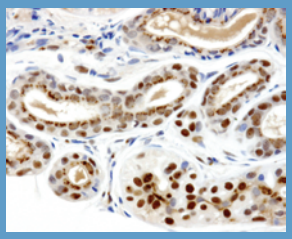


Focal segmental glomerulosclerosis (FSGS) is a proteinuric kidney disease caused by breakdown of the glomerular filtration barrier in the kidney. Podocytes are a key cellular component of the glomerular filtration barrier; efficient barrier function requires dynamic regulation of the podocyte actin-based cytoskeleton. In this issue (4127–4137), Akilesh and colleagues report human genetic and cell biological data that support the idea that disruption of the podocyte cytoskeleton contributes to the development of FSGS. Initial analysis indicated that expression of the actin regulatory protein Rho GTPase–activating protein 24 (Arhgap24) was upregulated in mouse podocytes as they differentiated. Increased Arhgap24 levels were associated with a decrease in membrane ruffling and cell motility, which are likely important for podocyte maintenance of glomerular filtration barrier integrity. These data have clinical relevance, since further analysis identified a mutation in the *ARHGAP24* gene in affected members of a family with FSGS. The mutation impaired the Rac1 GTPase–activating protein activity of Arhgap24, leading the authors to suggest that modulating Arhgap24 activity could provide a new way to treat FSGS.

B cells outFOX(O3A)ed by HIV

Infection with HIV-1 leads to severe immunodeficiency in most individuals, but little is known about the profound deregulation of B cell physiology, homeostasis, and function that is detectable soon after infection. In this issue (3877–3888), van Grevenynghe and colleagues detail their investigation of the molecular mechanisms responsible for the progressive depletion of peripheral $CD27^+$ memory B cells in individuals chronically infected with HIV-1. Initial analysis indicated that infected individuals who had been successfully treated (ST subjects) had fewer $CD27^+$ memory B cells than infected individuals whose immune system was naturally controlling the virus (elite controllers) and that this was a result of increased apoptosis. Detailed molecular studies determined that the increased apoptosis of $CD27^+$ memory B cells from ST subjects was a result of their decreased capacity to respond to IL-2, which triggered signaling pathways that increased Foxo3a transcriptional activity and expression of the proapoptotic Foxo3a target gene *TRAIL*. These data provide potential targets for enhancing B cell function and thereby restoring antibody responses, including toward HIV-1, in individuals infected with HIV-1.

Mutation-mechanism-disease



Autoinflammatory syndromes are rare conditions characterized by episodes of fever and inflammation in the absence of infection. There are several different autoinflammatory syndromes identified by distinct symptoms. Etiologic genetic mutations have been identified for some of these conditions. Using exome analysis, Kitamura and colleagues have now determined that a homozygous missense mutation (G197V) in immunoproteasome subunit, β type 8 (*PSMB8*) causes Japanese autoinflammatory syndrome with lipodystrophy (4150–4160). Proteasomes are converted to immunoproteasomes when their 3 constitutively expressed catalytic β subunits are substituted for 3 alternative β subunits, expression of which is induced by IFN-γ. Kitamura and colleagues found that the G197V *PSMB8* mutation caused decreased expression of PSMB8 protein and that the encoded mutant protein disrupted immunoproteasome assembly, leading to decreased proteasome function and accumulation of ubiquitin-coupled proteins in patient tissues. The low levels of PSMB8 expression resulted in increased IL-6 expression and disturbed adipocyte differentiation. The authors therefore conclude that the G197V *PSMB8* mutation causes autoinflammation through increased IL-6 production and lipodystrophy through disrupted adipocyte differentiation.

BVES butts heads with epithelial cancers

A key step in the progression of an in situ primary epithelial carcinoma to one that is invasive and metastatic is the acquisition of a mesenchymal phenotype by some of the cancer cells. Cellular junctional complexes, including tight junctions (TJs) and adherens junctions (AJs), are regulators of epithelial-mesenchymal transition (EMT), and loss of the junctional molecules E-cadherin and p120 has been associated with increased tumor invasiveness. In this issue (4056–4069), Williams and colleagues report that the junctional protein blood vessel epicardial substance (BVES; also known as Popeye 1 [POP1]) regulates epithelial-mesenchymal phenotypes. Initial analysis revealed that BVES expression was reduced in all stages of human colorectal carcinoma (CRC). Decreased expression of *BVES* in CRC cell lines was a result of promoter DNA hypermethylation. Treatment of CRC cell lines with a DNA-demethylating agent restored *BVES* expression. Restoring BVES expression promoted CRC lines to assume epithelial phenotypes and decreased their in vitro and in vivo tumorigenic characteristics. Mechanistically, these effects were associated with changes in AJ and TJ composition and related signaling. These data indicate that BVES acts as a tumor suppressor by regulating EMT and lead the authors to suggest that BVES could be a therapeutic or preventative target in CRC.