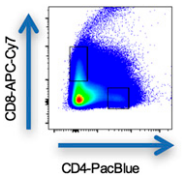
This Month's Highlights

BRIEF COMMUNICATION

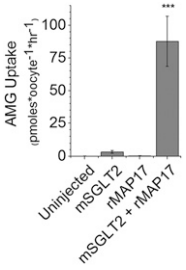
Pathogenic CD8$^+$ T Cells in Anti-Myeloperoxidase GN



In ANCA-associated vasculitis, an active CD8$^+$ T cell phenotype indicates poor prognosis, but whether these cells contribute to ANCA-associated GN remains unclear. Here, Chang *et al.* report that depletion of CD8$^+$ T cells in the effector phase of disease protects against anti-myeloperoxidase (MPO) GN in mice, likely through the observed reduction in glomerular macrophage infiltration and renal levels of inflammatory cytokines and chemokines. In immunodeficient mice, adoptively transferred CD8$^+$ T cell clones specific for a pathogenic MPO epitope exacerbate glomerular injury induced by cotransferred MPO-specific CD4$^+$ T cells and alone cause injury if MPO is deposited in glomeruli. These data support a pathogenic role for MPO-specific CD8$^+$ T cells in GN. *See Chang et al., pages* 47–55.

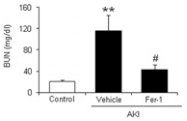
BASIC RESEARCH

Accessory Protein Increases SGLT2 Transport Activity *In Vitro*



Inhibitors of the Na$^+$-coupled glucose cotransporter SGLT2 are used to increase urinary glucose excretion in patients with diabetes. However, the lack of transport activity exhibited by ectopically expressed SGLT2 has hindered mechanistic study of these inhibitors in model systems. Here, Coady *et al.* identified 17 kDa membrane-associated protein as an accessory protein that increases SGLT2 transport activity in cotransfected oocytes and kidney cells. This finding advances our understanding of the mechanisms regulating SGLT2 function and should facilitate studies regarding the physiologic effects of SGLT2 inhibition. *See Coady et al., pages* 85–93.

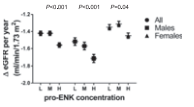
Ferroptosis in Folic Acid-Induced AKI



Necrotic cell death and inflammation contribute to AKI, but the specific pathways involved are not fully characterized. In this issue, Martin-Sanchez *et al.* demonstrate that the ferroptosis inhibitor ferrostatin-1 decreases histologic injury, tubular cell death, and oxidative stress and preserves renal function in a mouse model of folic acid-induced AKI (FA-AKI). In contrast, inhibiting specific molecular mediators of necroptosis and/or apoptosis does not prevent renal injury in this model. Indeed, knockout of a key regulator of necroptosis, mixed lineage domain-like protein, exacerbates FA-AKI. These findings may inform therapeutic development to limit kidney injury and inflammation in AKI. *See Martin-Sanchez et al., pages* 218–229.

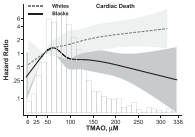
CLINICAL EPIDEMIOLOGY

Fasting Plasma Proenkephalin-A and CKD



High plasma concentrations of proenkephalin-A (pro-ENK) have been linked to eGFR decline and AKI. Schulz *et al.* conducted a prospective population-based study of 2568 participants without CKD to evaluate the association between circulating pro-ENK levels and CKD risk. Participants with the highest fasting levels of pro-ENK at baseline exhibited greater annual decline of eGFR, increased creatinine levels, and increased CKD incidence over a mean 16.6 years. Genome-wide association analysis identified a single nucleotide polymorphism that associates with higher pro-ENK levels and risk of CKD, suggesting a causal relationship between the two. Clinical assessment of circulating pro-ENK concentration may identify patients at high risk of developing CKD. *See Schulz et al., pages* 291–303.

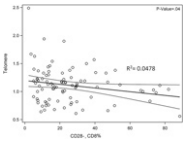
Toward Understanding the Race-Survival Paradox in Dialysis



Why is the risk of death higher in white hemodialysis patients than in black hemodialysis patients? Using serum from 1232 patients of the Hemodialysis Study, Shafi *et al.* analyzed the longitudinal association of trimethylamine *N*-oxide (TMAO), a proatherogenic metabolite, with cardiovascular outcomes. Serum concentrations of TMAO did not differ between blacks and whites. However, higher TMAO concentration associated with linear increases in the risk of any-cause death, cardiac death, and sudden cardiac death in whites, whereas TMAO concentration associated nonlinearly with cardiac death in blacks. Identification of the environmental or genetic mechanisms underlying these differential associations may inform the design of clinical trials. *See Shafi et al., pages* 321–331.

CLINICAL RESEARCH

T Cell Maturation in Pediatric CKD



The state of T cell maturation may affect an individual's response to immunosuppressive therapy; whether the immune repertoire differs in children with renal disease is unknown. In their study of T cell phenotypes in 20 healthy children and 80 children with renal failure, George *et al.* found that children with renal disease had greater variability in phenotypes and often exhibited evidence of premature immune maturation and even exhaustion or senescence. These findings were most significant in patients with previous exposure to immunosuppressive drugs. Understanding the immune repertoire disturbances in children with renal disease or other diseases may improve risk stratification and treatment outcomes. *See George et al., pages* 359–367.