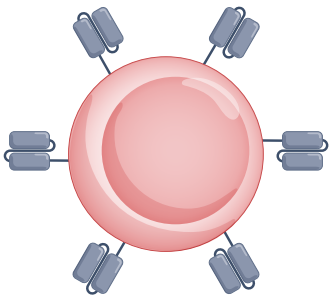
Autoimmune disease

Treatment of SLE with anti-CD19 CAR-T cells



A new study reports the successful use of anti-CD19 chimeric antigen receptor (CAR)-T cell therapy in five patients with treatment-refractory systemic lupus erythematosus (SLE). T cells from the patients were transduced with a lentiviral anti-CD19 CAR vector and expanded in vitro to generate anti-CD19 CAR-T cells. The patients were then lymphodepleted before infusion of their autologous CAR-T cells.

Following infusion, the CAR-T cells rapidly expanded, leading to B cell depletion, loss of double-stranded DNA autoantibodies and improvements in the clinical symptoms and organ manifestations of SLE, including glomerulonephritis. Remission was achieved in all patients at 3 months after CAR T cell infusion and was sustained, even after reconstitution of B cells, during a median follow-up of 8 months.

The researchers conclude that these data provide new therapeutic possibilities to control SLE disease activity through engineered autologous cells.

Ellen F. Carney

Original article: Mackensen, A. et al. Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. *Nat. Med.* **28**, 2124–2132 (2022)

Genetics

Genetics of posterior urethral valves

Posterior urethral valves (PUV) can cause bladder outflow obstruction and are the most common cause of kidney failure in children. Although various lines of evidence have suggested that PUV have an underlying genetic component, the genetic causes remain unclear. New findings from a whole genome sequencing-based genome-wide association study (seqGWAS) have uncovered novel susceptibility genes.

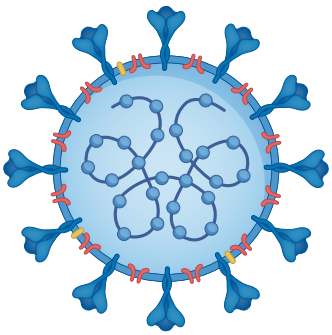
To investigate how common, low-frequency and rare variations may contribute to PUV, Chan and colleagues performed seqGWAS in 132 unrelated male patients with PUV and 23,727 controls of diverse ancestries. These analyses and subsequent replication studies identified significant associations with common and rare variations in *TBX5* and *PTK7*, respectively. The protein products of these genes are expressed in the urinary tract of developing embryos, prompting the researchers to suggest that alterations in their regulation may perturb normal urogenital development. The researchers also identified enrichment of rare duplications and inversions that affected candidate *cis*-regulatory elements as possible causes of PUV. The researchers emphasize that further studies are needed to explore the underlying biologic mechanisms by which the variants contribute to disease.

Susan J. Allison

Original article: Chan, M. M. Y. et al. Diverse ancestry whole-genome sequencing association study identifies *TBX5* and *PTK7* as susceptibility genes for posterior urethral valves. *eLife* **11**, e74777 (2022)

COVID-19

AngII autoantibodies after SARS-CoV-2 infection



Entry of SARS-COV-2 into mammalian cells is mediated by angiotensin-converting enzyme 2 (ACE2). This binding and consequent ACE2 endocytosis have potential to disrupt blood pressure regulation by interfering with ACE2-mediated cleavage of angiotensin II (AngII). Now, Swartz and colleagues suggest that SARS-CoV-2 infection might also dysregulate vascular tension in patients with severe COVID-19 by promoting the formation of anti-AngII autoantibodies.

The researchers detected anti-ACE2 antibodies in serum from hospitalized patients with COVID-19, and the antibody levels correlated strongly with blood pressure dysregulation and disease severity (based on blood oxygenation levels). Mouse monoclonal anti-AngII antibodies cross-reacted with recombinant SARS-CoV-2 spike protein, indicating that epitope mimicry might contribute to the generation of autoantibodies in infected individuals. In vitro, monoclonal anti-ACE2 antibodies interfered with binding of AngII to AngII receptor type 1, suggesting antagonism of AngII function.

Monica Wang

Original article: Briquez, P. S. et al. Severe COVID-19 induces autoantibodies against angiotensin II that correlate with blood pressure dysregulation and disease severity. *Sci. Adv.* **8**, eabn3777 (2022)

Organoids

Derivation of collecting duct organoids

Although robust methods have been developed for the production of kidney organoids representing metanephric-derived components, similar methods for efficient derivation of organoids representing the branching ureteric bud (UB) and its derived functional epithelia are lacking. Now, Min Shi and colleagues describe the development of UB and collecting duct (CD) organoids that progress through normal developmental stages and morphologic processes.

The researchers used a stepwise strategy to first differentiate human pluripotent stem cells into pronephric intermediate mesoderm and nephric duct spheroids, which subsequently underwent iterative branching and development of organized tip–stalk radial polarity with localization of RET to the distal tip domains. In a chimeric fetal kidney explant culture system, organoid-derived cells incorporated into the UB tips of the progenitor niche, suggesting appropriate responses to patterning cues.

The developing UB organoids differentiated into epithelia, representative of the inner medullary CD. These contained AQP2- and ENaC-expressing principal cells, which were capable of electrogenic sodium transport. Induction of FOXI1 expression induced the differentiation of intercalated cells with V-type ATPase proton pump activity.

Susan J. Allison

Original article: Shi, M. et al. Human ureteric bud organoids recapitulate branching morphogenesis and differentiate into functional collecting duct cell types. *Nat. Biotechnol.* https://doi.org/10.1038/s41587-022-01429-5 (2022)