IN BRIEF

COVID-19

Crossreactivity not so helpful after all?

Crossreactive CD4+ T cells to SARS-CoV-2, thought to originate from immune responses to common cold coronaviruses (CCCs), have been reported in up to 80% of SARS-CoV-2-naive individuals. This led to the hypothesis that encounters with CCCs may provide a degree of cross-protective immune memory. Now, a study in *Immunity* shows that SARS-CoV-2-crossreactive CD4+ T cells can be detected in almost all individuals tested and that these cells generally have a low functional avidity. At the same time, the authors identified highly expanded populations of low-avidity CD4+ T cells as a hallmark of severe COVID-19. This challenges the idea of a protective function of crossreactive CD4+ T cells and even raises the possibility that these cells may contribute to the risk of developing severe COVID-19. However, given the correlative nature of the study, causal links remain to be verified.

ORIGINAL ARTICLE Bacher, P. et al. Low-avidity CD4+ T cell responses to SARS-CoV-2 in unexposed individuals and humans with severe COVID-19. *Immunity* **53**, 1258–1271 (2020)

COVID-19

Genetic clues for predisposition to severe disease

The course of disease in individuals infected with SARS-CoV-2 is hugely variable, ranging from asymptomatic infections to severe COVID-19 and death. The GenOMICC genome-wide association study, published in *Nature*, now identifies significant associations of severe disease with several genes involved in antiviral defence mechanisms or in host-driven inflammatory lung injury. These include a cluster of genes that encode antiviral restriction enzyme activators (*OAS1*, *OAS2* and *OAS3*), *TYK2*, encoding a tyrosine kinase, the dipeptidyl peptidase gene *DPP9* and the interferon receptor gene *IFNAR2*. Mendelian randomization revealed a causal link between severe disease, low expression of *IFNAR2* and high expression of *TYK2*. Moreover, a transcriptome-wide association study showed the monocyte/macrophage chemotactic receptor CCR2 is associated with severe COVID-19. These findings indicate opportunities for the potential repurposing of existing drugs.

ORIGINAL ARTICLE Pairo-Castineira, E. et al. Genetic mechanisms of critical illness in Covid-19. *Nature* https://doi.org/10.1038/s41586-020-03065-y (2020)

COVID-19

Deciphering the protective features of the antibody response

The serological features that determine clinical outcomes in patients with COVID-19 are currently ill defined and there has been considerable controversy regarding the duration of antibody responses to SARS-CoV-2. A study in *Science Immunology* now reports a longitudinal investigation of plasma samples from 79 hospitalized patients with COVID-19, as well as 175 outpatients and asymptomatic SARS-CoV-2-positive individuals. Overall, outpatients and asymptomatic individuals had higher ratios of spike protein receptor-binding domain-specific IgG versus nucleoprotein-targeted IgG antibodies than hospitalized patients. In hospitalized patients, increases in antibody titres correlated with decreases in viral titres, but antibody responses during acute illness were insufficient to predict outcomes. In all patients, antibody titres started to wane around 1 month after disease onset.

ORIGINAL ARTICLE Röltgen, K. et al. Defining the features and duration of antibody responses to SARS-CoV-2 infection associated with disease severity and outcome. *Sci. Immunol.* **5**, eabe0240 (2020)

AUTOIMMUNITY

Targeting pathogenic T cells by metabolic checkpoint inhibition

CD4+ T cells that react inappropriately to microbiota antigens are thought to drive pathology of inflammatory bowel disease. A study in *Science Immunology* describes a new approach to selectively eliminate these microbiota-specific pathogenic T cells by activating them in the presence of metabolic inhibition.

Naive and memory CD4+ T cells undergo a profound metabolic transition to aerobic glycolysis when stimulated through the T cell receptor (TCR) that supports their activation and expansion. This metabolic checkpoint is primarily controlled by the mammalian target of rapamycin (mTOR) complex. Zhao et al. hypothesized that interfering with this metabolic checkpoint during T cell activation — using the mTOR inhibitor rapamycin or metformin to activate the negative regulator of mTOR, 5′-AMP-activated protein kinase — would lead to death or anergy of pathogenic naive and memory CD4+ T cells.

To investigate this in the setting of experimental colitis, the authors engineered a multi-epitope peptide (MEP) comprising multiple flagellin peptides from commensal bacteria that could activate flagellin-specific TCR-transgenic CD4+ T cells. Application of this MEP to transgenic CD4+ T cells in vitro together with rapamycin inhibited mTOR signalling, reduced glucose uptake and promoted cell death of more than 90% of proliferating cells. Moreover, concomitant MEP and rapamycin favoured differentiation of the remaining CD4+ T cells into regulatory T (T_{reg}) cells, which were shown to provide antigen-specific and bystander suppressive effects.

To test the effects of rapamycin in vivo, colitis was induced by adoptive transfer of flagellin-specific TCR-transgenic CD4+ T cells

COVID-19

Immune readouts from the Oxford COVID-19 vaccine

The vast majority of COVID-19 candidate vaccines are designed to target the SARS-CoV-2 spike (S) protein, but the precise vaccine-mediated immune correlates of protection remain to be determined. Two recent reports from the Oxford COVID-19 vaccine team detail the immune outcomes observed in a phase I/II trial of their ChAdOx1 nCoV-19 vaccine, in which volunteers received a single standard dose or various two-dose regimens.

The ChAdOx1 nCoV-19 vaccine comprises a non-replicating chimpanzee adenovirus vector (ChAdOx1) that is genetically modified to express the full-length S protein of SARS-CoV-2. Trial participants were healthy adults aged between 18 and 55 years, with the paper by Ewer et al. describing the immune responses seen in 88 individuals who received either a single dose of ChAdOx1 nCoV-19 or a control vaccine. The paper by Barrett et al. details immune responses in 52 volunteers who were vaccinated with a standard dose of ChAdOx1 nCoV-19 and then received a standard dose ($n = 20$) or half-dose ($n = 32$) booster 56 days later. Previously published data on trial participants who received two standard doses 28 days apart were also included for comparison.

A key finding in the single-dose paper is that a sole vaccination induced S-protein-reactive CD4+ T and CD8+ T cells with a T helper 1 (T_H1)-type cytokine bias as well as CD8+ T cells with a cytotoxic phenotype. This is important as T_H1-type immunity is thought to mediate protective antiviral immunity whereas T_H2-type responses have been linked with potentially adverse vaccine effects.