from tumour cells compared with cultures of normal control tissue, and breast cancer cells from patients showed upregulation of the histamine synthesizing enzyme HDC. This suggested that increased synthesis of histamine may limit antitumour immune responses through effects on macrophages in the TME.

Indeed, in mouse tumour models, deficiency or blockade of macrophage HRH1 was associated with enhanced antitumour T cell activity and with improved antitumour responses. Detailed analyses indicated that HRH1 signalling in macrophages promotes a more immunosuppressive M2-like phenotype and promotes membrane localization of the immune inhibitory molecule VISTA. Notably, treatment with the H1-antihistamine fexofenadine reduced tumour expression of VISTA and improved ICB outcomes in several mouse tumour models.

As allergies are associated with high levels of histamine release, the authors examined how allergy impacts tumour immunity and ICB. In a mouse model of allergic airway disease, allergic mice showed accelerated growth of transplanted EMT6 mammary or CT26 colon tumours compared with non-allergic animals, but tumour growth could be blocked by fexofenadine treatment. EMT6 and CT26 tumours are normally susceptible to ICB, but allergic mice with these tumours became resistant to ICB. Strikingly, fexofenadine treatment restored the sensitivity of the tumours in these animals to ICB. Finally, the authors found that patients receiving ICB for various cancers, who had allergies or high plasma histamine levels before ICB therapy, also experienced poorer clinical outcomes.

Together, these data suggest that H1 antihistamines could represent useful adjuvant therapies for patients receiving ICB for cancer. As H1 antihistamines are relatively inexpensive, this could represent an important breakthrough in the clinic.

**ORIGINAL ARTICLE**

Lii, H. et al. The allergy mediator histamine confers resistance to immunotherapy in cancer patients via activation of the macrophage histamine receptor H1. Cancer Cell 2021.11.001 (2021)

**RESEARCH HIGHLIGHTS**

## IN BRIEF

### COVID-19

**Defective viral genomes can protect against SARS-CoV-2 variants and other respiratory viruses**

Based on the unexpected observation that the Sabin Poliovirus vaccine not only protects against polio but also against other viruses, Andino and colleagues explored whether virus-like entities can be used as broad-spectrum antivirals to stimulate innate immune defences. They generated a liposome-encapsulated poliovirus-derived defective viral genome (eTIP1) that was administered intranasally to mice infected with different respiratory viruses, including influenza, SARS-CoV-2 and its Alpha, Delta and Epsilon variants. eTIP1 reduced viral loads, facilitated adaptive immune responses and prevented lethal infections when given up to 48 hours before to 24 hours after viral exposure. Protection was dependent on eTIP1 being replication competent. The authors hypothesize that, by mimicking natural infection, eTIP1 recruits different arms of immunity, providing a potentially powerful broad-spectrum prophylactic and therapeutic weapon.

**ORIGINAL ARTICLE**

Xiao, Y. et al. A defective viral genome strategy elicits broad protective immunity against respiratory viruses. Cell 2021.11.023 (2021)

### COVID-19

**Dexamethasone restrains neutrophils in severe COVID-19**

Dexamethasone reduces mortality in patients with severe COVID-19, but the mechanism has been elusive. Using single-cell RNA sequencing and plasma proteomics, Rosin, Yipp, Biernaske and colleagues investigated immune cell dynamics in patients with severe COVID-19 and acute respiratory distress syndrome (ARDS) who either did or did not receive dexamethasone, and compared these to patients with bacterial ARDS and healthy volunteers. COVID-19 seemed to promote the enrichment of specific neutrophil states characterized by enhanced type I interferon (IFN) activation (IFNactive) or by prostaglandin signalling. Dexamethasone treatment was associated with global alterations in neutrophil sub-states, a suppression of IFN networks, a depletion of IFNactive neutrophils and an expansion of immature and immunosuppressive neutrophils, indicating that dexamethasone limits neutrophil pathogenicity.

**ORIGINAL ARTICLE**

Sinha, S. et al. Dexamethasone modulates immature neutrophils and interferon programming in severe COVID-19. Nat. Med. 2021.11.037 (2021)

### COVID-19

**Cross-reactive memory T cells abort SARS-CoV-2 infection**

A study in health-care workers showed that some people, despite likely exposure to SARS-CoV-2, never develop PCR or antibody positivity. Swadling et al. hypothesized that pre-existing cross-reactive memory T cells, as described in pre-pandemic samples, may lead to abortive seroengenic infections in these individuals. Indeed, they found T cell and innate transcript evidence for abortive infections. They also showed that these individuals frequently had memory T cells directed at the early transcribed replication transcription complex, which has high sequence conservation between human seasonal coronaviruses and SARS-CoV-2. Boosting such T cells with vaccines may allow for pan-reactivity against endemic and emerging coronaviruses.

**ORIGINAL ARTICLE**

Swadling, L. et al. Pre-existing polymerase-specific T cells expand in abortive seroengenic SARS-CoV-2. Nature 2021.11.037 (2021)

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