allogeneic neutrophils. The spheroids readily induced NETosis, which was inhibited in the presence of reparixin. When tumour cell-targeted cytotoxic lymphocytes (CTLs) and/or NK cells were added, tumour cell spheroids with NETs showed much better survival than spheroids that had been stripped of their NETs with DNase I.

In mice that received xenografted human tumour cell lines (HT-19 colorectal carcinoma) and human neutrophils, abundant NETs were detected in the tumours; however, these were significantly reduced if the animals were treated with reparixin or pertussis toxin. The in vivo relevance of the protective role of NETs in tumours was demonstrated in mouse models of breast cancer (4T1 metastasis), where treatment of the animals with DNase I or the small molecule GSK484, an inhibitor of NETosis, reduced the number of micrometastases. However, the treatment did not have any effect in mice that lacked both T cells and NK cells, confirming that NETs provide protection from these cells. In mice with established 4T1 tumours, treatment with GSK484 showed a synergistic effect with dual checkpoint inhibition (anti-PD1 and anti-CTLA4), and this was dependent on the presence of CTLs.

Further in vitro experiments, as well as intravital microscopy in mice injected with Lewis lung carcinoma (LLC) cells, demonstrated that NETs reduce the physical contact between tumour cells and cytotoxic lymphocytes. The authors speculate that the shielding may extend beyond the physical separation as NETs may contain proteins that are detrimental to NK cells and CTL cytotoxicity. Moreover, it indicates that inhibitors of NETosis may be of value in combination with checkpoint inhibitors.

Alexandra Flemming

IN BRIEF

COVID-19

SARS-CoV-2-reactive T cells in patients and healthy donors

In this preprint by Braun et al., CD4+ T cell responses to SARS-CoV-2 infection were characterized in 18 patients with COVID-19 and 68 seronegative healthy donors (HDs). Peripheral blood mononuclear cells from patients and HDs were stimulated with peptide pools derived from the SARS-CoV-2 spike (S) protein. S protein–specific CD4+ T cells were found in most of the patients with COVID-19, but also in a portion of HDs. CD4+ T cells from patients with COVID-19 had a phenotype of recent activation in contrast to those from HDs. The authors suggest that S protein–specific T cells in HDs may be cross-reactive clones developed following a previous exposure to human endemic coronaviruses that cause common cold. Further validation with larger cohorts and more functional assessment, including the use of control peptides, are needed to establish whether these T cells are truly reactive to SARS-CoV-2.

ORIGINAL ARTICLE Braun, J. et al. Presence of SARS-CoV-2-reactive T cells in COVID-19 patients and healthy donors. Preprint at bioRxiv https://doi.org/10.1101/2020.04.17.20061440 (2020)

COVID-19

Inactivated vaccine for SARS-CoV-2

In this preprint, Gao et al. describe the first evidence of vaccine efficacy against COVID-19 in non-human primates. A patient-derived SARS-CoV-2 isolate was expanded then inactivated with β-propiolactone. Rhesus macaques were immunized three times with inactivated virus plus alum, then challenged 1 week later with a virus from a different isolate. Although SARS-CoV-2 infection of rhesus macaques doesn’t fully recapitulate human pathophysiology, vaccinated macaques had no symptoms and a rapid decrease in viral loads. Vaccine safety was assessed in additional macaques that showed no immediate adverse effects. This inactivation technique is well known and adaptable for production in other facilities, which argues for scalability. Phase I and II clinical trials are underway.

ORIGINAL ARTICLE Gao, Q. et al. Rapid development of an inactivated vaccine for SARS-CoV-2. Preprint at bioRxiv https://doi.org/10.1101/2020.04.17.20068015 (2020)

COVID-19

Impaired interferon signature in severe COVID-19

In this preprint, Hadjadj et al. analyse the late-stage immune response in 50 patients with COVID-19 spanning a range of disease severity but controlled for age, duration from symptom onset and comorbidities. Compared with mild or moderate cases, severe and critically ill patients have a profoundly impaired type I interferon response, despite comparable viral loads as measured by nasal swab. In addition, clinical severity correlated with increased IL-6, TNF and chemokine signatures. These findings suggest that type I interferon may hold promise for prognostic and therapeutic strategies. Further studies of these cytokines earlier in disease and with more precise quantification of viral load in the respiratory tract will be crucial to validate the result.

ORIGINAL ARTICLE Hadjad, J. et al. Impaired type I interferon activity and exacerbated inflammatory responses in severe COVID-19 patients. Preprint at bioRxiv https://doi.org/10.1101/2020.04.10.20068015 (2020)

Luisanna Pia, Emma Risson and Conor Gruber

Sinai Immunology Review Project, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: Sinai.immunology@gmail.com

The authors declare no competing interests.