Credit: Andrzej Rostek/Alamy

the paired immunoglobulin-like receptors (PIRs) as candidates. Mice have six PIR-A isoforms, which bind to distinct MHC class I molecules and are stimulatory, and a single PIR-B protein, which transmits inhibitory signals on binding to a wide spectrum of MHC class I molecules. When antibody was used to block PIR-A and PIR-B, monocyte memory responses to allografts were inhibited in alloimmunized hosts. Moreover, genetic deletion of *Pira* prevented the induction of myeloid cell memory. Lastly, animals treated with PIR-A3–Fc fusion protein, which preferentially blocks PIR-A3 binding to its MHC class I ligand, H-2Dd, also failed to mount myeloid memory responses to H-2Dd⁺ allografts but not H-2K⁺ allografts, confirming specificity of the response.

Closer investigation of the monocyte response showed that immunization with H-2Dd⁺ allogeneic cells led to an increase in the number of monocytes that bind to the H-2Dd tetramer, suggesting clonal outgrowth of monocytes expressing PIR-A3. Single-cell RNA sequencing showed that responding monocytes increased *Pira* expression, reduced *Pirb* expression and increased genes involved in proliferation and immune pathways. This profile is consistent with the important observations that kidney allografts survived long term in PIR-A-deficient recipients, but were rejected in PIR-B-deficient recipients, and treatment with PIR-A3–Fc fusion protein prevented acute allograft rejection in the PIR-B-deficient recipients.

This work identifies a myeloid cell memory response to previously encountered MHC class I alloantigens that potentially could be targeted to improve transplant survival.

Lucy Bird

ORIGINAL ARTICLE Dai, H. et al. PIRs mediate innate myeloid cell memory to nonself MHC molecules. *Science* **368**, 1122–1127 (2020)

Next, the authors used population-level RNA sequencing (RNA-seq) to compare the transcriptional profile of F4/80hiCD102⁺ macrophages from male and female mice, showing that sex accounted for 81% of the transcriptional variance of these cells. Transcripts associated with immune function (such as *Timd4* and *Cd209b*) were more highly expressed in female mice, whereas cell cycle-associated transcripts were more highly expressed in male mice. Population-level differences between male and female mice resulted from differences in gene expression at the single-cell level as well as different frequencies of gene-expressing cells.

Additional single-cell RNA-seq analysis identified six transcriptional clusters associated with both male and female cells. In particular, cluster 5 (characterized by markers of *Timd4*-expressing F4/80hiCD102⁺ macrophages) was more abundant among female cells. Some genes were differentially expressed by male and female cells of all clusters, but more than 50% of differentially expressed genes were unique to one or two clusters.

In *Ccr2⁻/⁻* mice, which have decreased macrophage renewal, a higher proportion of CD102⁺ macrophages express CD209b, suggesting that this might be a marker of length of residency in the peritoneum. In keeping with this, CD209b⁺CD102⁺ macrophages accumulated in female mice but not male mice after sexual maturity, consistent with the higher rate of replenishment from the bone marrow in male mice. By contrast, dimorphic expression of other genes was not affected by CCR2 deficiency.

Thus, both time of residency and local tissue factors seem to result in increased expression of immune function-related genes in F4/80hiCD102⁺ macrophages in female mice. As a result, female mice were shown to better control peritoneal infection with *Streptococcus pneumoniae*.

Kirsty Minton

ORIGINAL ARTICLE Bain, C. C. et al. Rate of replenishment and microenvironment contribute to the sexually dimorphic phenotype and function of peritoneal macrophages. *Sci. Immunol.* **5**, eabc4466 (2020)

IN BRIEF

COVID-19

Preclinical data from SARS-CoV-2 mRNA vaccine

Reflecting the urgency to develop prophylactic approaches against COVID-19, several vaccine candidates have entered clinical trials before showing efficacy in animal models. In this preprint, Corbett et al. describe a preclinical study evaluating an mRNA vaccine candidate by Moderna. Immunization of mice with mRNA encoding stabilized prefusion SARS-CoV-2 spike trimers elicited dose-dependent neutralizing antibody and CD8⁺ T cell responses. Two doses given in prime–boost combination (2 × 1 µg/mouse) protected mice against infection of the nasal mucosa and lungs after challenge with mouse-adapted SARS-CoV-2. Importantly, there was no indication of enhanced immunopathology in animals that received sub-protective doses. A phase III efficacy trial in humans (using a single 100 µg dose regimen) is set to start in July.

ORIGINAL ARTICLE Corbett, K. S. et al. SARS-CoV-2 mRNA vaccine development enabled by prototype pathogen preparedness. Preprint at *bioRxiv* https://doi.org/10.1101/2020.06.11.145920 (2020)

COVID-19

Sex differences in immune responses in COVID-19

In this preprint, Takahashi et al. elucidate differences in the immune response to COVID-19 in 45 male and 48 female patients. Through both single time-point samples (collected before immunomodulatory therapy) and longitudinal analyses, they found that plasma CXCL8 and CCL5 levels were higher in male than in female patients, although other cytokines, such as TNFSF10 and IL-15, correlated with worse outcome in female but not male patients. Of note, female patients had more CD14⁺CD16⁺ monocytes, activated T cells and terminally differentiated CD8⁺ T cells; whereas male patients had a greater subset of CD14lowCD16⁺ monocytes but a poor CD8⁺ T cell response in disease progression. Collectively, these results, in association with clinical parameters, suggest less robust T cell-mediated immunity in male patients with worsening outcome and higher innate cytokine activity in declining female patients.

ORIGINAL ARTICLE Takahashi, T. et al. Sex differences in immune responses to SARS-CoV-2 that underlie disease outcomes. Preprint at *medRxiv* https://doi.org/10.1101/2020.06.06.20123414 (2020)

COVID-19

Roles for eosinophils and basophils in COVID-19?

In this preprint, Rodriguez et al. used mass cytometry and Olink to longitudinally profile immune cells and protein biomarkers in the blood of 39 patients with severe COVID-19 from acute infection to recovery. Partition-based graph abstraction identified IFNγ-induced CD62L⁺ eosinophils, which appeared 2–6 days after hospitalization. In addition, the authors highlight a correlation between IgG responses and circulating basophil numbers. Finally, integrating 148 plasma proteins and 63 immune cell populations in a multi-omics factor analysis identified potential cellular and plasma biomarkers of transition to recovery from severe COVID-19. This work supports further investigation into the role of eosinophils in lung hyperinflammation and the potential role of basophils in enhancing the humoral response to COVID-19.

ORIGINAL ARTICLE Rodriguez, L. et al. Systems-level immunomonitoring from acute to recovery phase of severe COVID-19. Preprint at *medRxiv* https://doi.org/10.1101/2020.06.03.20121582 (2020)

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The authors declare no competing interests.