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 F4/80+CD102+ 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 Tmem4 and C2d09b) 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 Tmem4-expressing F4/80+CD102+ 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 could 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 F4/80+CD102+ macrophages in female mice. As a result, female mice were shown to better control opportunistic infection with Streptococcus pneumoniae.

Kirsty Minton

Original Article: Bain, C. C. et al. Rate of replacement and microenvironment contribute to the sexually dimorphic phenotype and function of peritoneal macrophages. Sci. Immunol. 5, eabc4466 (2020)

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-2Kd allografts, confirming specificity of the response.

Closer investigation of the monocyte response showed that