Cover story

Our colourful front cover features a knee joint of a mouse lacking IL-23 receptor signaling during antigen-induced inflammatory arthritis. The cartilage layers of both the patella (left) and femur (right) are intact as is the bone and there is hardly any inflammation present in the joint without IL-23 receptor signaling. This indicates that IL-23 receptor signaling is important during the progression of inflammatory arthritis. The picture is a representative H&E staining and is taken from Razawy et al. (pp. 245–255). The colour of the image has been digitally altered for the cover.

First demonstration of a successful antigen-specific plasma cell depletion in vivo

Long-lived memory plasma cells (PCs) secreting pathogenic antibodies emerged as promising therapeutic target in autoimmune diseases, since they are resistant to conventional immunosuppressive agents and treatments targeting B cells. Available therapies deplete all PCs equally, regardless of whether they produce pathogenic or protective antibodies. In this issue, Cheng et al. created a conjugate which consists of an antigen-of-interest (here ovalbumin, OVA) and an anti-CD138 antibody for PCs labeling. After injection in mice, this conjugate labels all PCs in the bone marrow and spleen with ovalbumin, followed by a significant depletion of OVA-specific PCs and reduction of serum anti-OVA antibody levels, while PCs secreting antibodies of other specificities, such as chicken gamma globulin are not affected. The mode of action uses the fact that PCs secrete antibodies against ovalbumin, which is present on their cell surface as component of the conjugate, commit suicide through antibody-mediated mechanisms. This concept offers a unique therapeutic approach for (auto)antibody-mediated diseases sparing the humoral immunity.

Battle it out: Pannexin-1 takes on gasdermin D for cell death and inflammasome activation

Inflammasomes are multiprotein signalling platforms that are assembled upon microbial challenge or cellular stress. Detection of cytoplasmic lipopolysaccharide during Gram-negative bacterial infections induces the ‘non-canonical’ inflammasome pathway that enables activation of the cysteine-protease, caspase-11. Active caspase-11 cleaves gasdermin D, a pore-forming protein, to induce plasma membrane damage and pyroptosis. In this issue, by using two different lines of Panx1 knockout mice and three different pannexin-1 inhibitors, Chen et al. demonstrate that pannexin-1 is dispensable for non-canonical inflammasome signalling but confirm the requirement for gasdermin D in driving pyroptosis and NLRP3 inflammasome activation upon cytosolic LPS detection. In addition, the authors report that pannexin-1 channel activity is indeed required for NLRP3 inflammasome assembly in apoptotic cells, and that it involves caspase-3-dependent pannexin-1 cleavage and the release of potassium that serves as a signal for NLRP3 activation.
Type I interferons fine-tune effector responses of TCR-activated MAIT cells

Mucosal-associated invariant T (MAIT) cells are an abundant unconventional T cell subset, comprising 1–10% of T cells in humans. The MAIT cell T cell receptor (TCR) recognises bacteria-derived vitamin B2 metabolites presented by MHC class I-related protein (MR1). Bacteria, however, not only produce vitamin B2 metabolites but also multiple pathogen-associated molecular patterns (PAMPs). How PAMPs regulate MAIT cell activation is yet to be determined. Type I interferons were recently shown to cooperate with innate cytokine signals during viral infection to activate MAIT cells. However, the role of type I interferons in regulating TCR-mediated MAIT cell activation is undefined. In this issue, Lamichhane et al. demonstrate a co-stimulatory role for type I interferons during TCR-mediated activation of human blood and liver MAIT cells. A role for type I interferons was observed with both viral and bacterial stimulation. Therefore, in both bacterial infection and viral co-infection, type I interferons fine-tune MAIT cell effector responses to TCR stimulation.

Diacylglycerol kinases control mucosal-associated invariant T cell development

Mucosal-associated invariant T (MAIT) cells are abundant in human but extremely rare in mouse. It has been known that signal from the invariant TCR expressed on MAIT cells is critical for their development. However, signal pathways downstream of the TCR that control MAIT cell development are still poorly understood. Diacylglycerol (DAG), a critical second messenger generated by PLCγ1 following TCR engagement, activates multiple signal cascades in conventional T cells. DAG kinases (DGKs) terminate DAG by conversion to phosphatidic acid (PA). In this issue, Pan et al. show that accelerated conversion of DAG to PA due to enhanced DGK function inhibits late stage MAIT cell maturation. The authors demonstrate further that DGKα and ζ double deficiency also severely inhibits MAIT cell maturation. These data reveal that DAG is not only critical but also need to be tightly regulated by DGKs for proper development of MAIT cells.

Journal roundup

Neutrophils suppress tumor-infiltrating T cells in colon cancer via matrix metalloproteinase-mediated activation of TGFβ

High T-cell infiltration in colorectal cancer (CRC) correlates with a favorable disease outcome and immunotherapy response. This, however, is only observed in a small subset of CRC patients. A better understanding of the factors influencing tumor T-cell responses in CRC could inspire novel therapeutic approaches to achieve broader immunotherapeutic responsiveness. In a recent issue of EMBO Molecular Medicine, Germann et al. investigated T cell-suppressive properties of different myeloid cell types in an inducible colon tumor mouse model. The most potent inhibitors of T-cell activity were tumor-infiltrating neutrophils. Gene expression analysis and combined experiment tests indicated that T-cell suppression is mediated by neutrophil-secreted metalloproteinase activation of latent TGFβ. CRC patient neutrophils similarly suppressed T cells via TGFβ, and public gene expression datasets suggested that T-cell activity is lowest in CRCs with combined neutrophil infiltration and TGFβ activation. Thus, the interaction of neutrophils with a TGFβ-rich tumor microenvironment may represent a conserved immunosuppressive mechanism in CRC.
PTPN2 phosphatase deletion in T cells promotes anti-tumour immunity and CAR T-cell efficacy in solid tumours

Although adoptive T-cell therapy has shown remarkable clinical efficacy in haematological malignancies, its success in combating solid tumours has been limited. In a recent issue of the *EMBO Journal*, Wiede et al. report that PTPN2 deletion in T cells enhances cancer immunosurveillance and the efficacy of adoptively transferred tumour-specific T cells. T-cell-specific PTPN2 deficiency prevented tumours forming in aged mice heterozygous for the tumour suppressor p53. Adoptive transfer of PTPN2-deficient CD8\(^+\) T cells markedly repressed tumour formation in mice bearing mammary tumours. Moreover, PTPN2 deletion in T cells expressing a chimeric antigen receptor (CAR) specific for the oncoprotein HER-2 increased the activation of the Src family kinase LCK and cytokine-induced STAT-5 signalling, thereby enhancing both CAR T-cell activation and homing to CXCL9/10-expressing tumours to eradicate HER-2\(^+\) mammary tumours in vivo. The authors’ findings define PTPN2 as a target for bolstering T-cell-mediated anti-tumour immunity and CAR T-cell therapy against solid tumours.

Fetal monocytes possess increased metabolic capacity and replace primitive macrophages in tissue macrophage development

Tissue-resident macrophages (MΦTR) originate from at least two distinct waves of erythro-myeloid progenitors (EMP) arising in the yolk sac (YS) at E7.5 and E8.5 with the latter going through a liver monocyte intermediate. The relative potential of these precursors in determining development and functional capacity of MΦTR remains unclear. In a recent issue of the *EMBO Journal*, Li et al. studied development of alveolar macrophages (AM) after single and competitive transplantation of different precursors from YS, fetal liver, and fetal lung into neonatal Csf2ra\(^{-/-}\) mice, which lack endogenous AM. Fetal monocytes, promoted by Myb, outcompeted primitive MΦ (pMΦ) in empty AM niches and preferentially developed to mature AM, which is associated with enhanced mitochondrial respiratory and glycolytic capacity and repression of the transcription factors c-Maf and MaFβ. Interestingly, AM derived from pMΦ failed to efficiently clear alveolar proteinosis and protect from fatal lung failure following influenza virus infection. Thus, the authors’ data demonstrate superior developmental and functional capacity of fetal monocytes over pMΦ in AM development and underlying mechanisms explaining replacement of pMΦ in fetal tissues.