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# In This Issue

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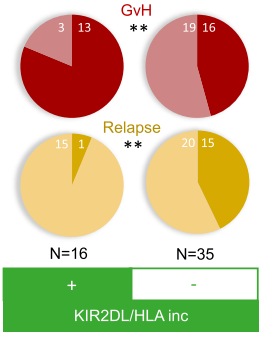
## Incompatibility Issues for NK Cells

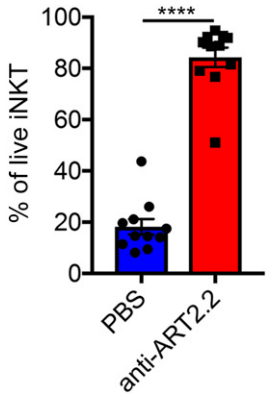



Allogeneic hematopoietic stem cell transplantation (HSCT) can be an effective treatment for hematologic malignancies but requires identification of HLA-haploidentical bone marrow donors. These transplants are also prone to causing graft-versus-host disease (GvHD) in recipients due to the presence of alloreactive donor T cells. In this issue, Willem et al. (p. 2141) examine how incompatibility of killer cell Ig-like receptors (KIR), which are expressed by NK cells and are specific to different HLA allotypes, influence clinical outcomes in HSCT patients who underwent T cell–replete HSCT. The authors observed a higher incidence of acute GvHD but decreased relapse in recipients with inhibitory KIR/HLA incompatibility, and that recovery of KIR2DL2/3$^+$ and KIR3DL1$^+$ NK cells 30 d posttransplant was inversely affected by KIR/HLA incompatibility. Patients who developed GvHD also had more NK cells with differentiated and activated phenotypes. These data suggest that KIR/HLA incompatibility can play a critical role in donor/recipient selection and transplant outcomes.

## Factoring for Complement Control

The complement system is a critical part of innate immunity and uses several mechanisms to differentiate between self and nonself. The alternative pathway (AP) of complement activation is relatively indiscriminate and is engaged in constant surveillance of cell surfaces, but is tightly regulated by Factor H (FH) or the splice variant FH-like protein 1 (FHL-1). Dopler et al. (p. 2082) examined how FH and FHL-1 can regulate AP activity on self and nonself surfaces. They observed that FH had greater selectivity overall as it exhibits greater regulatory activity on self surfaces compared with FHL-1 and a greater regulatory penalty on nonself surfaces. FHL-1 was also shown to be rapidly cleared from plasma in mice and was detected at very low levels in human plasma. Together, these results provide deeper insights into how FH tightly controls AP activity in a manner that differs from FHL-1.

## Increasing Yield and Function of Tissue-Resident Lymphocytes




The release of NAD and ATP during tissue processing can lead to ARTC2.2-mediated ribosylation of P2RX7 in invariant NKT cells (iNKT) and CD8$^+$ tissue-resident memory T cells ($T_{RM}$). When P2RX7 is ribosylated by ARTC2.2, it leads to irreversible pore formation and ultimately, cell death. Borges da Silva et al. (p. 2153) have shown that processing tissue in the presence of antagonist nanoparticles against ARTC2.2 can increase the yield, viability, and function of tissue-resident iNKT and CD8$^+$ $T_{RM}$. The ex vivo recovery of iNKT and CD8$^+$ $T_{RM}$ treated with anti-ARTC2.2 nanoparticles was significantly increased in nonlymphoid tissues. Additionally, treating animals with anti-ARTC2.2 nanoparticles prior to tissue recovery increased cell recovery and function of both iNKT and CD8$^+$ $T_{RM}$. Blockade of ARTC2.2 also promoted an increase in CD103$^-$ CD8$^+$ $T_{RM}$ recovered from the small intestine, suggesting that these cells are more susceptible to P2RX7-mediated cell death and are underrepresented in traditional analysis. Taken together, these data show that significant cell death from the ARTC2.2/P2RX7 pathway may skew leukocyte analysis from tissue.

## Macaque MAITs

Innate-like T cells found in the gut—MR1-restricted mucosal-associated invariant T (MAIT) cells—respond to bacterial and viral infections and have been shown to be depleted during HIV infection. MAIT cells have been characterized in humans but are not as well defined in nonhuman primate models. In this issue, Juno et al. (p. 2105) use a pigtail macaque (PTM) model to characterize MAIT cells before and during SIV/simian HIV (SHIV) infection. They develop a PTM-specific MR1 tetramer to track MAIT cells and observe many transcriptional and phenotypic similarities shared by human and PTM MAIT cells. Unlike human MAIT cells, PTM counterparts express low levels of the gut-homing integrin α4β7 in naive animals and show less enrichment in the gut and rectum. Acute SIV/SHIV infection induced proliferation and upregulation of α4β7 in PTM MAIT cells and recruitment to rectal mucosa. During chronic infection, peripheral PTM MAIT cells exhibit an activated phenotype, lack Tbet, and are not significantly depleted in mucosal tissues. These data indicate that differential expression of α4β7 in PTM and human MAIT cells impacts mucosal homing prior to infection and can influence proliferation and mucosal depletion during chronic infection.



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