IMMUNOGENETICS

Proving the central hypothesis

Nat. Genet. **54**, 393–402 (2022)

Although not mutually exclusive, the 'central hypothesis' and 'peripheral hypothesis' are alternative theories to explain autoimmune risk associated with *HLA* alleles. New work published in *Nature Genetics* shows how *HLA* genes can contribute to the TCR repertoire in autoimmune diseases and hence provides genetic evidence to support the central hypothesis. The authors analyzed TCRβ sequences from a large number of healthy donors and treated CDR3 amino acid sequences as a quantitative trait. CDR3 variance was most associated with *HLA-DRB1* site 13, an *HLA* position known to be highly associated with rheumatoid arthritis. The authors then designed CDR3 risk scores to quantify the enrichment of *HLA* autoimmune risk patterns and used TCR sequence datasets from patients with rheumatoid arthritis or celiac disease to show that TCRs specific for known pathogenic antigens had higher risk scores than control TCRs. *NJB*

https://doi.org/10.1038/s41590-022-01204-3

COVID-19

Monocytes as targets

Nature https://doi.org/10.1038/s41586-022-04702-4 (2022)

Monocytes do not express ACE, the receptor for SARS-CoV-2. In *Nature*, Lieberman and colleagues show that a small percentage of monocytes in patients with COVID-19 are infected with SARS-CoV-2 by Fcγ receptor-mediated uptake of antibody-opsonized virus and undergo inflammatory cell death. Markers of pyroptosis (GSDMD, LDH, IL-1RA and IL-18) are increased in the plasma of patients with severe compared with mild or moderate disease, and 4–6% of monocytes in patients with severe disease show the formation of ASC specks (colocalized with NLRP3 and AIM2 specks) and undergo pyroptosis. Around 10% of blood monocytes and 8–15% of lung macrophages from patients with COVID-19 stain for nucleocapsid (N) protein. ASC specks are detected in N^+ macrophages, but not in N^+ epithelial and endothelial cells in the lung. Detection of subgenomic RNA indicates viral replication, but infectious virus is not detected in the culture supernatants of infected monocytes. This indicates that infected monocytes do not support viral replication, but undergo pyroptosis and can contribute to systemic inflammation. *IV*

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TUMOR IMMUNOLOGY

Antigen-presenting CAFs

J. Exp. Med. **219**, e20210815 (2022)

Cancer-associated fibroblasts (CAFs) have been previously shown to suppress immune responses in the tumor microenvironment. In the *Journal of Experimental Medicine*, Kerdidani et al. report that fibroblasts that express MHC class II (MHCII) are abundant in lung tumors from humans and mice. In contrast to other tumor types, lung tumor-associated $MHCII^+$ fibroblasts promote $CD4^+$ T cell-dependent anti-tumor responses. Such fibroblasts seem to be derived from alveolar type II epithelial cells. IFN-γ signaling induces the upregulation of MHCII expression as well as complement protein C1q and complement factor D. In addition, tumor-infiltrating $CD4^+$ T cells express C1qbp at the cell surface, where it provides a pro-survival signal upon C1q binding. Conditional deletion of *H2-Ab1* (which encodes $I\text{-}A^b$ molecules) or blocking the interaction of C1q with C1qbp impairs tumor control. Hence, these findings suggest that in situ MHCII antigen presentation within the tumor environment by a specialized subset of CAFs contributes to tumor immunity. *LAD*

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PERIPHERAL TOLERANCE

Human regulatory $CD8^+$ T cells

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MHC class I-restricted $CD8^+$ T cells are known for their cytotoxic activity against pathogen-infected cells and tumor cells; however, a subset of regulatory $CD8^+$ T cells that express Ly49 have been described in mice. In *Science*, Li et al. report an analogous regulatory $CD8^+$ T cell subset that express inhibitory killer cell immunoglobulin-like receptors (KIRs) in humans. These cells are more abundant in patients with autoimmune disease than in healthy donors. Increased frequencies of KIR^+CD8^+ T cells were also found to correlate with the severity of vasculitis disease in patients with COVID. The expression profiles of KIR^+CD8^+ T cells are similar to mouse $Ly49^+CD8^+$ T cells, including the transcription factor Helios and CX3CR1. TCR-sequencing analysis showed that the repertoire of KIR^+CD8^+ T cells is less diverse than KIR^-CD8^+ T cells. In vitro assays showed that KIR^+CD8^+ T cells can kill autoreactive $CD4^+$ T cells via recognition of antigens presented by classical HLA molecules and by HLA-E. Although it remains unclear what promotes KIR expression in this subset of $CD8^+$ T cells, these findings point to regulatory mechanisms at play to limit potentially autoreactive $CD4^+$ T cells that can arise after viral infection. *LAD*

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