T CELLS

Memory T cells and where to find them

Cell https://doi.org/10.1016/j.cell.2020.11.019 (2020)

Studying lymphocyte migration and functional differentiation in humans under steady-state conditions is technically very challenging due to limited access to tissues. In *Cell*, Buggert et al. take advantage of a large cohort of patients undergoing thoracic duct cannulation to study lymph immune cell populations and to compare these to the populations in the vasculature and lymphoid and non-lymphoid tissues (decidua, liver and colon). Leukocytes in the lymph are overwhelmingly T cells, but there are also some B cells and NK cells and small numbers of innate cell populations. This is in contrast with the blood, where innate immune populations — especially neutrophils — predominate. $CD8^+$ T cells in the two compartments are also distinct, with cytotoxic effector memory and virus-specific populations common in the blood, whereas the lymph contains naive, early memory cells with stem cell–like features. Furthermore, not all memory cells migrated through tissues, and cytolytically active cells were rarely present in tissues. These data suggest that cytolytic effector cells are largely absent from tissues at steady-state to avoid collateral damage, but they can rapidly move from the blood into tissues during infection. *ZF*

https://doi.org/10.1038/s41590-021-00863-y

COVID-19

Antihypertensives in immunity

Nat. Biotechnol. https://doi.org/10.1038/s41587-020-00796-1 (2020)

Patients with hypertension and cardiovascular disease face greater risk of developing more severe disease upon SARS-CoV-2 infection. In *Nature Biotechnology*, Trump et al. utilize single-cell RNA-seq expression to examine differences in the immune responses of patients with COVID-19 who have underlying hypertension. Their study cohort compares patients who are taking angiotensin-converting enzyme inhibitors (ACEIs) with those taking angiotensin receptor blockers (ARBs) or neither antihypertensive therapy, and they also compare non-hypertensive patients with COVID-19 and non-infected individuals with hypertension. While neither treatment increased the expression of the host receptor ACE2, utilized for cell entry by SARS-CoV-2, a higher proportion of patients on ARB therapy experienced severe disease, and these patients had delayed viral clearance as compared to those on ACEI therapy. ACEI versus ARB therapies elicit multiple differences in innate immune responses in both stromal cells lining the nasopharynx and immune cells recruited upon infection. ACEI promoted high antiviral gene expression, whereas ARB treatment had higher proinflammatory gene expression, including high expression of the chemokines CCL3 and CCL4, which were both associated with more severe COVID-19. These differences begin to unravel why some patients differ in their antiviral responses, but further follow-up studies are needed to validate these findings and for mechanistic understanding. *LAD*

https://doi.org/10.1038/s41590-021-00864-x

ANTIMICROBIAL PEPTIDES

Protecting the CNS

Proc. Natl Acad. Sci. USA https://doi.org/10.1073/pnas.1917623117 (2020)

The brain and central nervous system (CNS) pose challenges for immune defense against microbial infections, as substantial collateral tissue damage can ensue following immune cell infiltration and activation. In the *Proceedings of the National Academy of Sciences*, Lee et al. identify pituitary adenylate cyclase–activating polypeptide (PACAP) as a highly conserved endogenous antimicrobial peptide that is rapidly induced in the CNS upon bacterial or fungal infection. PACAP induces pores and other membrane-disrupting activity in *Staphylococcus aureus* and *Candida albicans*, causing microbial cell death in a manner similar to that of a structurally related but non-homologous antimicrobial peptide LL37. Importantly, upregulation of PACAP expression in the brain did not lead to overt neutrophilic or immune cell infiltration, suggesting that it might serve an endogenous antimicrobial function while preserving tissue integrity and function. *LAD*

https://doi.org/10.1038/s41590-021-00865-w

SARS-COV-2 SEROLOGY

A shifty target

Elife https://doi.org/10.7554/eLife.61312 (2020)

A major outstanding question in the biology of SARS-CoV-2 is the extent to which the virus will adapt to pressure from the immune system. In *eLife*, Bieniasz and colleagues use a recombinant chimeric reporter virus that expresses the SARS-CoV-2 spike (S) protein (VSV-SARS-CoV-2) to assess adaptation in the face of neutralizing antibodies — both monoclonal and those found in convalescent plasma. VSV-SARS-CoV-2 lacks a genetic proof reading function, so it is subject to higher mutation rates and therefore allows viral evolution to be tracked in vitro. Under such selective pressure, escape mutations readily appear in the S protein receptor binding domain and confer resistance to antibody neutralization, yet these mutations do not impair ACE2 receptor binding. By interrogating public SARS-CoV-2 databases, the authors found that similar S protein mutations are already circulating in the human population. While the findings have potentially concerning implications for the efficacy of monoclonal antibodies, there was no evidence for complete evasion of convalescent plasma. Therefore, antibody combinations to multiple viral epitopes may limit the impact of SARS-CoV-2 adaptation. *ZF*

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