VACCINES

Immune epigenome

Reporting in *Cell*, Bali Pulendran and colleagues describe the epigenetic and transcriptional changes, occurring at a single-cell level, in humans in response to influenza virus vaccination. They showed that the trivalent inactivated seasonal influenza vaccine (TIV) induced global changes to the chromatin state — including acetylation, methylation and phosphorylation — in multiple immune cell subsets. The changes persisted for up to 6 months and were most pronounced in myeloid cells. Notably, in classical monocytes and myeloid dendritic cells, acetylation of multiple histones was repressed 30 days after vaccination and returned to baseline levels at day 180. Transcriptomics revealed this repression coincided with downregulation of histone acetyltransferases and the arginine deiminase PADI4 and upregulation of histone deacetylases. Moreover, hypoacetylation was associated with diminished cytokine responses following Toll-like receptor (TLR) stimulation of peripheral blood mononuclear cells at day 30 after vaccination.

Analysis of chromatin accessibility using ATAC-seq of purified immune cell subsets post vaccination revealed thousands of regions of reduced chromatin accessibility in myeloid cells, including genes for cytokines, chemokines, pattern recognition receptors and adhesion molecules, indicating reduced gene activity. A subcluster of monocytes showed reduced chromatin accessibility at regions targeted by AP-1 family transcription factors, which are responsible for production of pro-inflammatory cytokines and TLR signalling molecules.

The finding of immune refractoriness following TIV is at odds with previous studies describing enhanced and persistent innate responses — termed trained immunity — following live attenuated BCG vaccination, leading the authors to hypothesize that lack of adjuvant signals in TIV may explain the induction of a form of trained tolerance. Addition of the adjuvant AS03 to H5N1 pandemic influenza vaccine led to a similar repressive state — hypoacetylation of histones, reduced AP-1 accessibility and diminished cytokine and chemokine production — as observed with TIV. However, the adjuvanted vaccine also induced increased chromatin accessibility for interferon-response factors and STAT family members, leading to increased expression of antiviral genes such as interferons. This was associated with enhanced resistance to unrelated Zika and dengue viruses in vitro.

So, the authors suggest that the coexistence of immune refractoriness and antiviral vigilance — within the same cell — allows for the avoidance of immunopathology while maintaining viral immunity.

Lucy Bird

ORIGINAL ARTICLE Wimmers, F. et al. The single-cell epigenomic and transcriptional landscape of immunity to influenza vaccination. *Cell* https://doi.org/10.1016/j.cell.2021.05.039 (2021)

IMMUNOMETABOLISM

Steroid response to malaria

During blood-stage malaria, infection of red blood cells with *Plasmodium falciparum* leads to global metabolic changes in the host as a result of both the pathogen hijacking host metabolism for its own survival and proliferation, and host adaptation to the metabolic demands of an immune response to infection. However, the extent to which metabolic changes are associated with variation in host susceptibility to malaria is unknown. This study reports serum metabolome profiling of children naturally infected with *P. falciparum* in Burkina Faso, West Africa, revealing major changes in endogenous steroid levels with effects on adaptive immunity.

Healthy children of the Gouin ethnic group were sampled before and during seasonal infection with *P. falciparum* to generate 200 serum metabolome profiles. Six hundred and sixty-seven metabolites were identified for downstream analysis. As expected, principal component analysis showed a strong effect of infection on the serum metabolome; the abundance of 195 metabolites was associated with infection status, and 53 of these were also strongly associated with parasitaemia.

The most highly represented class among these 53 metabolites was endogenous steroids. The authors showed a statistically significant negative correlation between 13 steroids and the lymphocyte count during infection, which suggests that these steroids might have an inhibitory effect on the immune response. To investigate further, they generated 72 RNA-sequencing profiles from

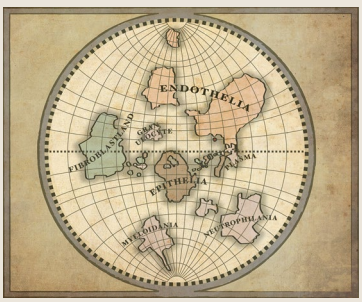
STROMAL IMMUNOLOGY

Oral mucosa atlas

Researchers reporting in *Cell* provide an atlas of the human oral mucosa, identifying a complex cellular landscape with an array of stromal cell populations that support antimicrobial defences and neutrophil recruitment. As well as being a valuable community resource, the atlas reveals new insights into stromal–immune responsiveness in the healthy oral mucosa and during periodontitis.

The authors carried out single-cell RNA sequencing of biopsy samples of buccal (inside cheek lining) and gingival (gum) mucosa from healthy volunteers. In both mucosal sites, four major cell compartments were defined according to classic cell type-specific markers for endothelial, epithelial, fibroblast and immune cells. Within the endothelial compartment, four further subpopulations were defined, revealing three that were specialized for immune functions, such as antigen presentation and immune cell recruitment.

Several epithelial cell subpopulations were also identified, with one subset confined to the gingival mucosa that had a gene expression profile consistent with inflammatory responses, including antimicrobial and inflammatory factors and neutrophil-recruiting chemokines. Of the five fibroblast subpopulations, three expressed genes consistent with inflammatory responses. This suggests that stromal cells, even in healthy oral mucosa, have a unique immunological wiring and enhanced inflammatory responsiveness.



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