IMMUNOGENOMICS

Impact of genetic ancestry on viral infection response

Pathogens impose selection pressures on human genomes. Depending on local environments, over time this pressure may lead to population-specific genetic variation that differentially affects infectious disease susceptibility. Randolph et al. sought to characterize the genetic determinants of differences in immune responses to viral infection between individuals of European and African ancestries.

Previous work investigating the effects of genetic ancestry on the response to viral infection focused on isolated cell types and was thus unable to discern interactions between different immune cells or distinguish between cell-type-specific and general effects. The authors infected peripheral blood mononuclear cells (PBMCs), obtained from 90 men of European or African ancestries, with influenza A virus (IAV) or mock treatment and obtained single-cell RNA sequencing (scRNA-seq) profiles after 6 h. Whole-genome sequencing was performed to estimate the proportion of African and European ancestries for each individual.

Differential gene expression analysis of the major PBMC cell types allowed the dissection of cell-type-specific versus shared responses and confirmed previous findings that monocytes exhibit the strongest response to IAV infection. While some responses correlated across cell types, opposing responses were also observed, for example, between monocytes and natural killer cells, despite these cell types sharing several differentially expressed genes.

Next, the team identified 1,949 genes whose expression levels correlated with the proportion of estimated ancestry. These population differentially expressed genes were highly cell type-specific and were enriched for transcriptional and translational functions. Gene-set enrichment analysis revealed differences in type I and II interferon pathways associated with genetic ancestry, with further experiments indicating that genetic ancestry may predict the magnitude of response to IAV infection. Indeed, increased degrees of European ancestries were associated with higher type I interferon activity during the early response to infection, which was able to predict a reduction in viral titres occurring at later stages. Mapping expression quantitative trait loci (eQTLs) in the IAV-infected and control samples revealed that *cis* eQTLs explain >50% of population differences in response to viral infection.

Finally, ancestry-related differentially expressed genes were enriched for genes associated with COVID-19 disease severity. While it remains to be seen whether this translates to differences in COVID-19 outcomes, it will be important to ensure that host genetic variation in the immune response does not exacerbate existing health disparities driven by external circumstances.

Linda Koch

ORIGINAL ARTICLE Randolph, H. E. et al. Genetic ancestry effects on the response to viral infection are pervasive but cell type specific. *Science* **374**, 1127–1133 (2021)
RELATED ARTICLE Kwok, A. J., Mentzer, A. & Knight, J. C. Host genetics and infectious disease: new tools, insights and translational opportunities. *Nat. Rev. Genet.* **22**, 137–153 (2021)

GENOME EDITING

CRISPR editing within microbial communities

The majority of microorganisms live within microbial communities, but functional genomics approaches that look at phenotypic outcomes upon perturbation are often applied to isolated, cultured species. Now, Rubin et al. report the development of a programmable organism- and locus-specific genome editing approach that can target microorganisms in their native community context, without the need for isolation.

Credit: Dimitris Skordopoulos/Panther Media GmbH/Alamy

To identify those microbial species in a community that are amenable to nucleic acid delivery and genome editing, the authors first developed environmental transformation sequencing (ET-seq). In this method, exposure of a complex microbial community to a randomly integrating *mariner* transposon and subsequent sequencing for insertion events and relative abundances forms the basis of a metric that integrates information on delivery approaches (conjugation, electroporation or natural transformation), insertion efficiency and mutant survival after delivery. Bioinformatic quantification of insertions and normalization based on an internal standard and metagenomic abundances yields a species-specific measure of genetic accessibility, that is, "the percentage of each member of a given microbiome that acquires a transposon insertion". The team validated their approach by adding a known amount of edited *Klebsiella michiganensis* to a synthetic soil community comprising nine members. This experiment showed that ET-seq was able to quantify genetic insertions that occurred in just 0.001% of cells.

ET-seq identified conjugation and electroporation as efficient delivery approaches in the synthetic soil community. The authors built a DNA-editing all-in-one RNA-guided CRISPR–Cas transposase (DART) system that is compatible with the delivery approaches as well as ET-seq. The transposons contain barcodes, so that the efficacy of CRISPR–Cas-guided transposition into the genome of an amenable microorganism (as determined by ET-seq) can be assessed without the need for selection. The team designed guide RNAs against two genomic regions specific to *K. michiganensis*, then delivered the DART system to a microbial community by conjugation; ET-seq revealed insertions of the barcoded transposon at the correct loci. Moreover, tracking of genome edits in the synthetic soil community enabled the team to quantify the fitness effects of mutations of interest.

Applying ET-seq and DART to infant gut microbiota cultivated ex vivo, the authors performed species- and site-specific editing in several strains. Furthermore, by using the DART system to deliver antibiotic markers into the microbial community using a strain-specific guide RNA, then selecting for the transposon cargo, the authors were able to isolate target organisms.

Going forwards, genome editing approaches that target individual organisms within microbial communities will help to characterize the complex interplay between members of the microbiome.

Linda Koch

ORIGINAL ARTICLE Rubin, B. E. et al. Species- and site-specific genome editing in complex bacterial communities. *Nat. Microbiol.* https://doi.org/10.1038/s41564-021-01014-7 (2021)