IMMUNE REGULATION

Mapping innate variation

> cytokines are under fewer constraints and can undergo rapid evolution to counteract rapidly evolving pathogens

A new study by Sarah Teichmann and colleagues has used transcriptomics to map variation in the innate immune response across species. They describe high variability in the expression of cytokine genes, both at the single-cell level and across species. By contrast, genes encoding transcription factors and kinases show less variability in expression and are more conserved.

Two notable features of the innate immune system are the rapid evolution of many of its genes and its highly heterogeneous response to pathogens. How, then, can innate responses still be tightly regulated to prevent immunopathology? To address this, Hagai et al. characterized transcriptional changes (both at bulk population level and at single-cell level) that occur in activated fibroblasts or bone marrow-derived mononuclear phagocytes. Specifically, they compared transcriptional changes in primary dermal fibroblasts from humans, macaques, mice and rats that were stimulated with the viral double-stranded RNA mimetic poly(I:C) and also examined lipopolysaccharide (LPS)-induced transcriptional changes in mononuclear phagocytes from mice, rats, rabbits and pigs.

Fibroblasts treated with poly(I:C) showed rapid upregulation of pro-inflammatory and antiviral genes, and correlation analyses indicated a similar transcriptional response across species. As expected, the transcriptional responses were more strongly correlated between closely related species. At the level of individual genes, some genes responded similarly across species, whereas others responded differently between rodents and primates. Analysis of LPS-stimulated phagocytes also indicated conserved and clade-specific transcriptional responses.

To quantify transcriptional divergence between species, the authors focused on the differentially expressed genes that had one-to-one orthologues across the species; they identified 955 such genes in poly(I:C)-stimulated human fibroblasts and 2,336 in LPS-stimulated mouse phagocytes. These genes were further subdivided based on whether they showed high, medium or low divergence. The authors examined the promoter architecture of diverging genes using chromatin immunoprecipitation sequencing. They found an increased density of transcription factor-binding motifs and higher conservation of core promoter regions in highly divergent genes; this appeared to be related to the enrichment of TATA boxes or CpG islands in the promoters of high- and low-divergence gene groups, respectively.

The authors next grouped genes according to function and showed that genes encoding cytokines and their receptors diverged significantly faster than genes involved in apoptosis or immune regulation. Moreover, cytokines showed larger transcriptional ranges across conditions. Cytokine gene promoters are enriched in TATA boxes, suggesting this architecture is associated with higher divergence across species and greater transcriptional range. Genes that were highly divergent across species also showed more variability of expression at the single-cell level, and, again, this was associated with the presence of TATA boxes in their promoters.

A comparison of three main gene groups (cytokines, transcription factors and kinases) showed that unlike cytokines, transcription factors and kinases showed relatively low levels of cell-to-cell variability in their expression. Notably, this pattern was conserved across species. Cytokines also tended to be co-expressed in the same cell with other cytokines and with positive and negative regulators of their function.

Finally, the authors examined how divergence in gene coding sequence relates to its transcriptional divergence. They found that genes showing high transcriptional divergence across species also evolve faster in their coding sequences. In addition, these rapidly evolving genes had higher rates of gene duplication and loss, and are often evolutionarily younger. These genes also encoded proteins that had fewer protein–protein interactions and that were less likely to interact with viral proteins.

In summary, innate immune genes that diverge rapidly across species show higher variability in expression at the single-cell level and have unique promoter architecture. Notably, these genes share key features with the stress-related genes found in yeast. The authors suggest that genes involved in immune regulation are under stronger functional and regulatory constraints and therefore less divergent. By contrast, cytokines are under fewer constraints and can undergo rapid evolution to counteract rapidly evolving pathogens. They propose that these unique gene-expression patterns enable effective, but balanced, innate immune responses.

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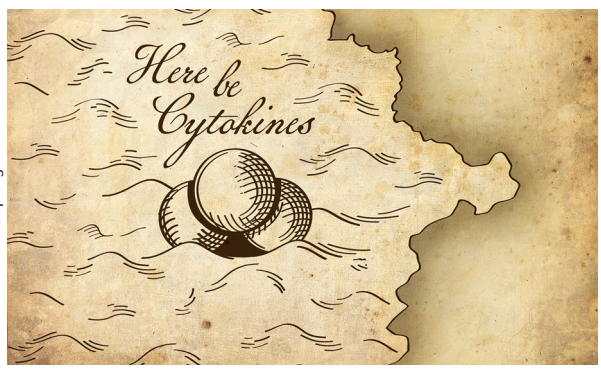

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