IMMUNOGENETICS

Tracking immune activity across the genome

Genome-wide association studies (GWASs) have been successful in linking genetic variants with certain immune diseases, but the precise functional consequences of these variants are poorly understood. Now, two studies published in *Science* have mapped how human genetic variation influences gene expression in resting and activated innate immune cell subsets.

GWASs have identified genetic variants that are associated with common diseases, such as inflammatory bowel disease and rheumatoid arthritis, and most of these variants are found in non-coding regions that are proposed to regulate the expression of immune genes. The two studies compared gene expression across the whole genome in monocytes and dendritic cells (DCs) that were exposed to inflammatory stimuli with that in unstimulated cells. Whereas a subset of genetic variants affected gene expression levels in unstimulated cells, many variants only affected gene expression in those that had been stimulated by an inflammatory signal. Thus, many variants that had not previously been associated with changes in gene expression were identified. Furthermore, these studies showed that genetic variants can influence the expression of genes that are in close proximity and also those that are on different chromosomes.

Fairfax *et al.* collected human CD14⁺ monocytes from 432 healthy Europeans and investigated changes in gene expression in these cells before and after exposure to bacterial

lipopolysaccharide (LPS) or to the pro-inflammatory cytokine interferon- γ (IFN γ). They found that a diverse set of immune-related genes showed changes in their expression levels after stimulation, including genes that encode transcription factors, cytokines and cytokine receptors. Furthermore, the authors found that some genetic variants — such as one that is located near *IFNB1* (which encodes IFN β) — were associated with early changes in gene expression following LPS stimulation (after 2 hours), but they could also detect different downstream effects of these same variants on gene expression at later stages (24 hours after LPS stimulation).

The authors compared their expression data with disease loci in the GWAS variant catalogue and found that 467 of the genetic variants that affected gene expression in monocytes were located in disease-associated gene regions. Specifically, these were regions that had previously been associated with inflammatory, autoimmune and gastroenterological diseases, whereas variants associated with cancer, reproductive conditions or cardiovascular disease were under-represented. Interestingly, 248 variants only affected gene expression in stimulated cells, suggesting that the functional effects of some disease-associated genetic variants may only be detectable in a context-specific manner.

The study by Lee *et al.* used DCs from >500 healthy individuals from different ethnic backgrounds to map genetic variants that influence gene

expression in cells stimulated with LPS, IFN β or influenza virus. The authors demonstrated how CRISPR (clustered regularly interspaced short palindromic repeats) technology can be used to modify the genome and validate an association between a genetic variant and gene expression. Similarly to Fairfax *et al.*, they identified hundreds of loci containing genetic variants that are associated with gene expression in a context-specific manner in DCs. For example, the authors identified a variant that affects the expression of *IRF7* (which encodes interferon regulatory factor 7, a protein that mediates antiviral responses) as well as the targets of this transcription factor. Such genetic variants may contribute to the diverse immune responses to influenza virus infection that are seen in humans.

Based on the approach taken by these two studies, further investigation of other immune cell types, and also of samples from patients with immune-related diseases, will improve our understanding of how human genetic variation affects the immune response. In addition, such work will provide an insight into the mechanisms underpinning the association of particular genetic variants with disease.

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ORIGINAL RESEARCH PAPERS Fairfax, B. P. *et al.* Innate immune activity conditions the effect of regulatory variants upon monocyte gene expression. *Science* <http://dx.doi.org/10.1126/science.1246949> (2014) | Lee, M. N. *et al.* Common genetic variants modulate pathogen-sensing responses in human dendritic cells. *Science* <http://dx.doi.org/10.1126/science.1246980> (2014)

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