A Genomic Road Map for Complex Human Disease

Peter K. Gregersen

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approach (*12*) to calculating reconnection rates in plasmas explicitly allows for quantification of this plasmasphere effect. In the Cassak-Shay formulation, the reconnection rate is sensitive to the mass density of each of the two plasmas coming into contact—the solar wind and the magnetosphere. Previous work reported a critical statistical analysis of measurements of the mass density of this cold magnetospheric plasma entering the boundary reconnection site (*13*). Now, Walsh *et al*. put together observations of the complete flow of this cold plasma from the near-Earth regions to the sunward boundary of the magnetosphere and supply satellite measurements that show that the plasma indeed mass loads the rate of reconnection.

The plasmasphere effect is indicative of a new level of sophistication in the understanding of how the magnetospheric system operates. The effect can be particularly important for reducing solar-wind/magnetosphere coupling during geomagnetic storms. Instead of unchallenged solar-wind control of the rate of solar-wind/magnetosphere coupling, we see that the magnetosphere, with the help of the ionosphere, fights back.

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GENETICS

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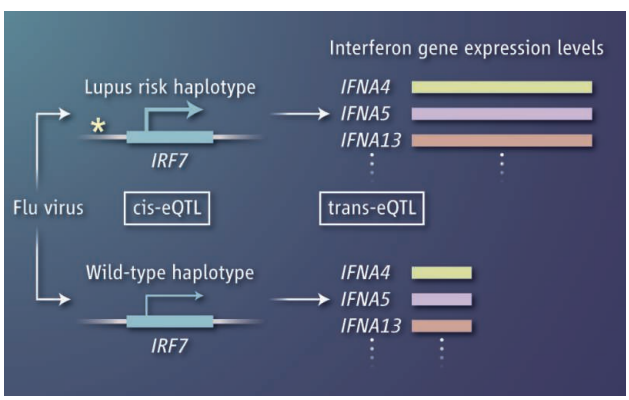
Consideration of cell type- and disease-associated environmental conditions is critical to connecting specific genetic variants to immune disorders.

Peter K. Gregersen

Despite the successes of genome-wide association studies (GWAS) in identifying genetic connections with human disease, it has become clear that interpreting these data requires a clear understanding of how these new risk genes are regulated. On pages 1118 and 1119 of this issue, Fairfax *et al*. (*1*) and Lee *et al*. (*2*), respectively, elucidate networks of genetic regulation in the context of the human innate immune system and show how this information can be directly applied to understanding the genetics of autoimmune disorders.



Variation and response. eQTL information can be integrated with GWAS information to better understand how genetic variants are linked to innate immune responses to infection. Shown is the locus of the *IRF7* gene in dendritic cells from two individuals. The top locus has a SNP (asterisk) that is associated with susceptibility to the autoimmune condition lupus. This locus is also an eQTL for the dendritic cell response (interferon production) to infection with influenza virus. Elevated production of interferon is also often observed in lupus, a disease that has been associated with abnormalities in dendritic cells (*8*).

The human immune system can be broadly divided into the innate and adaptive immune systems. The latter enables the formation of immune memory through T cell responses and the production of antibodies by B cells. Although many genetic variants control these processes, the human major histocompatibility complex [(MHC); cell surface molecules that mediate interactions with immune cells] has a predominant role in determining specificity of the adaptive immune response.

Robert S. Boas Center for Genomics and Human Genetics, The Feinstein Institute for Medical Research, North Shore LIJ Health System, 350 Community Drive, Manhasset, NY 110430, USA. E-mail: peterg@nshs.edu

By contrast, the innate immune system comprises phylogenetically older mechanisms of immediate immune defense with various cellular components, many of which interact with the adaptive immune system. Two innate immune cells, monocytes and dendritic cells, are the focus of studies by Fairfax *et al*. and Lee *et al*., respectively.

Gene expression can be quantified according to the amount of messenger RNA (mRNA) in cells and is therefore a quantitative trait. Genetic variants that regulate mRNA expression are one form of quantitative trait locus (QTL), or eQTL. Early investigations of eQTLs often examined cell lines or peripheral blood. However, the message that emerges from Fairfax *et al*. and Lee *et al*. is that the patterns of eQTLs are highly dependent on the specific cell type examined, and even more strikingly, on the in vitro environmental conditions to which a cell is exposed. Both groups focused on immune activators, including viruses, cytokines (interferon), and bacterial products such as lipopolysaccharide (LPS). These exposures are directly relevant to disease-related phenotypic differences among individuals.

Although this general message may be straightforward, and even expected, obtaining supporting data is not trivial; the scientific treasures are to be found in the complexity of the experimental details. There are many potential sources of variation in gene expression, and providing robust evidence for genetic variation interacting with environmental exposures requires the study of hundreds of subjects with defined genotypes, comprehensive and reproducible gene

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expression analysis, careful isolation of the proper cell subsets, and controlled in vitro stimulations with respect to dose and timing.

eQTLs may act in cis (regulatory variants located near the gene under regulation), or in trans (regulation by variants at great distance, including on different chromosomes). There are many examples of cis regulation, but trans regulation has been more difficult to sort out due to its complexity and the large number of potential variants to investigate. It is therefore gratifying that both studies show an integrated network of cis and trans regulation. Fairfax *et al*. identify, within the Toll-like receptor (TLR) pathway (which responds to bacterial LPS), the transcription factor interferon regulatory factor 2 (IRF2) as an eQTL in monocytes. Lee *et al*. demonstrate trans-eQTLs of IRF7 in dendritic cells under several conditions. Adding to this complexity, it is apparent that trans-eQTLs can also be time dependent, mediated indirectly through intervening signaling pathways. For example, interferon B1 (IFNB1) is among the cis-eQTLs in monocytes that is induced by LPS at 2 hours after exposure. However, at 24 hours after exposure, this cis-eQTL is no longer observed, but multiple trans-eQTLs appear in pathways downstream of IFNB1. Although Lee *et al*. restricted their full analyses of LPS-triggered responses to an early time point (5 hours after exposure), it is clear from their exploratory time-course data that similarly connected time-dependent eQTL responses are likely to exist in dendritic cells. One example of an additional mechanistic twist involves a coding-region eQTL in the gene encoding cytochrome P450 1B1 that leads to shortened protein half-life and consequent compensatory feedback on transcription of its own mRNA. Clearly, the experimental details are critical for eQTL discovery and mechanistic understanding.

Such information can be applied to understanding GWAS data. For example, the haplotype bearing the IRF7 trans-eQTL contains a single-nucleotide polymorphism that is associated with systemic lupus and is also an eQTL for induction of a robust interferon response to viral exposure (see the figure), a finding consistent with abnormal regulation of interferon in this disease (*3*). Similarly, Fairfax *et al*. show that an interferon-dependent eQTL in the gene encoding caspase recruitment domain–containing protein 9 (CARD9), a protein associated with the inflammatory bowel disorder Crohn's disease (*4*), is actually a secondary independent disease-associated variant in the *CARD9* locus. Indeed, the studies of Fairfax *et al*. and Lee *et al*. reveal a great deal of overlap between eQLT loci and a variety of immune-related disorders. Furthermore, Lee *et al*. show that many eQTL loci have multiple variants with distinct effects, emphasizing the complexity of interpreting associations identified by GWAS, even at a single locus.

An intriguing observation by Fairfax *et al*. is that interferon acts through the MHC to induce many trans-eQTL effects in isolated monocytes. The MHC is one of the most gene-dense and highly polymorphic regions in the genome, so it can be difficult to pinpoint exactly which genetic variants are responsible for these trans-eQTL effects. The MHC is the predominant genetic locus controlling adaptive immunity and many autoimmune diseases, primarily through interactions with T cell receptors. For these eQTL effects on monocytes, however, T cells are not present in the system. Nevertheless, eQTL effects are correlated with the cis-eQTL effects on class II MHC expression, suggesting that the class II molecules themselves may be mechanistically involved. This is consistent with studies showing intracellular signaling by MHC class molecules (*5*), as well as their ability to modify signaling, through TLR pathways (*6*).

eQTLs for gene expression that are cell type– and context-specific will be reflective of quantitative immune traits at the system and organismal levels (*7*, *8*), which in turn constitute phenotypes that are likely to determine disease susceptibility (*9*). Elucidating these relationships is a major challenge, and will require extensive collaboration among clinical and basic investigators, as well as scientists with advanced computational expertise.

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MEDICINE

Combating Evolution to Fight Disease

Susan M. Rosenberg[1] and Christine Queitsch[2]

Molecular mechanisms that generate biological diversity are rewriting ideas about how evolution proceeds, with implications for treating disease.

Molecular biology and evolutionary biology have been separate disciplines and scientific cultures: The former is mechanistic and focused on molecules; the latter is theoretical and focused on populations. However, these domains are beginning to converge in laboratories addressing molecular mechanisms that explain how evolutionary processes work, and bring these processes to bear on medical problems such as cancer and infectious disease. Each discipline can be viewed as a missing link in the other's description of biology, and in medicine.

[1]Departments of Molecular and Human Genetics, Biochemistry and Molecular Biology, Molecular Virology and Microbiology, and Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, TX 77030, USA. [2]Department of Genome Sciences, University of Washington, Seattle, WA 98195, USA. E-mail: smr@bcm.edu

Traditional evolutionary biology began in the 1930s with the "modern synthesis," which fused Darwin's theses on phenotypic variation and selection with Mendel's concepts of genetic inheritance to explain the source of biological diversity. This synthesis predated knowledge that genes were made of DNA and of the structure of DNA and how it replicates. Thus, molecular mechanisms could not be integrated into concepts about how phenotypic variation is generated. Instead, assumptions had to be made about the origins of the variation that drives evolution. Among the cornerstone assumptions were that mutations are the sole drivers of evolution; mutations occur randomly, constantly, and gradually; and the transmission of genetic information is vertical from parent to offspring, rather than horizontal (infectious) between individuals and species (as is now apparent throughout the tree