CellPress

Review

Primary Immunodeficiencies and Inflammatory Disease: A Growing Genetic Intersection

Nassima Fodil,[1,‡] David Langlais,[1,‡] and Philippe Gros[1,*]

Recent advances in genome analysis have provided important insights into the genetic architecture of infectious and inflammatory diseases. The combined analysis of loci detected by genome-wide association studies (GWAS) in 22 inflammatory diseases has revealed a shared genetic core and associated biochemical pathways that play a central role in pathological inflammation. Parallel whole-exome sequencing studies have identified 265 genes mutated in primary immunodeficiencies (PID). Here, we examine the overlap between these two data sets, and find that it consists of genes essential for protection against infections and in which persistent activation causes pathological inflammation. Based on this intersection, we propose that, although strong or inactivating mutations (rare variants) in these genes may cause severe disease (PIDs), their more subtle modulation potentially by common regulatory/coding variants may contribute to chronic inflammation.

Genomics Meet Human Infectious and Inflammatory Diseases

The 'disease state' results from interactions between intrinsic genetic risks from the host and extrinsic environmental triggers. The genetic component may be simple, involving powerful mutations that inactivate key physiological pathways, or may be complex and heterogeneous, involving combinations of weak genetic lesions whose accumulation phenotypically mimics the effect of a strong mutation. On the other hand, environmental triggers of disease are often complex, heterogeneous, and generally poorly understood. Genetic analysis of susceptibility to infections has proven particularly successful to study how the interface between host and environment causes clinical disease [1–3]. In infectious diseases, exposure to the environmental trigger (e.g., microbial pathogens) is absolutely required to reveal the host genetic diversity and associated risk. In most extreme cases, selective pressure by lethal microbes has impacted the human genome and has left identifiable genetic fingerprints in areas of endemic disease and following epidemics. Striking examples include the protective role of hemoglobin (Hb) and ACKR1 (DARC) variants against malaria [4], and of CCR5 deletion against HIV [5]. Dramatic increases in performance and affordability of DNA sequencing now permits genome and whole-exome sequencing (WES) of unique human patients or families that display unusual susceptibility to infections, including pure or syndromic **PIDs** (see Glossary) [6–8]. The analysis of such patients has generated a rich genetic data set on the association of rare variants with this group of diseases.

On the other hand, burns, trauma, and environmental insults may disrupt protective tissue barriers and lead to acute or chronic exposure to microbes present at mucosal surfaces and/or

Trends

Alterations in numbers and activity of immune cells and associated responses result in infectious and inflammatory diseases, which are two of the most common disease areas in humans.

Complex genomic data sets involving hundreds of genes are emerging from genome-wide association studies of susceptibility to common inflammatory diseases, and from whole-exome sequencing of patients suffering from primary immunodeficiencies.

Combined analysis of risk loci for 22 common human inflammatory diseases, and of all primary immunodeficiencies with a known genetic lesion identifies a highly significant genetic overlap between the two groups of diseases.

The cellular and molecular pathways anchored around these genes are therefore required for protection against infections, but their persistent or dysregulated engagement for pathological inflammation in humans.

[1]Department of Biochemistry, Complex Traits Group, McGill University, Montreal, QC, Canada
[‡]These authors contributed equally to this article

*Correspondence:
philippe.gros@mcgill.ca (P. Gros).

 http://dx.doi.org/10.1016/j.it.2015.12.006

to appetizing self-antigens. This triggers an inflammatory response in the host, a normal physiological process that involves initial recognition of tissue damage, elimination of the causative lesion, and restoration of tissue homeostasis. Tight regulation of this response is critical: in the presence of persistent tissue injury or sustained microbial insult, overexpression of proinflammatory mediators or insufficient production of anti-inflammatory signals results in immunopathology, including inflammatory or autoimmune disease or allergy. Genetic analysis of susceptibility to acute (sepsis, encephalitis) or chronic inflammatory diseases with possible microbial, autoimmune, and/or autoinflammatory etiologies (inflammatory bowel disease, rheumatoid arthritis, psoriasis to name only a few) has offered additional opportunities to identify important elements of host response to microbial and autoimmune stimuli [9]. Population and family studies have long established a strong genetic component to susceptibility to inflammatory diseases. The recent availability of high-density arrays of polymorphic variants genome-wide (**SNP chips**) or clustered around 'immune' loci (**immunochips**) has facilitated the search for genetic determinants (common variants) of susceptibility to inflammatory diseases in humans. Such **GWAS** in very large cohorts of human patients (>50 000) from different populations, and subsequent **meta-analyses** of multiple published GWAS of the same disease, have mapped hundreds of genetic loci, each with small effect size, but that together define a rich genetic architecture for several of these complex disorders [10–18].

This flurry of technology development has produced very detailed genetic maps for susceptibility to infections and to inflammation, and those have been reviewed elsewhere [19–21]. Although these are briefly cited herein, the specific focus of this review is on the nature and extent of shared genetic risks across both groups of diseases. Specifically, we discuss how this genetic intersection points to specific genes and pathways that are required for protection against infections but whose sustained engagement in the presence of persistent insult leads to pathological inflammation. We also review how this intersection may provide information on the etiology of certain inflammatory conditions and, conversely, how the two parallel data sets may help identify and validate morbid genes at candidate loci. Finally, this intersection lends support to the hypothesis that strong but rare mutations at specific genes of this overlap may independently cause severe diseases (PIDs), while more subtle modulation by common coding or regulatory variants may contribute to chronic inflammation in the presence of a persistent tissue insult.

Primary Immunodeficiencies

In addition to classical genetic approaches (linkage mapping, immune phenotype-driven candidate gene sequencing, and studies from animal models), WES has dramatically increased the pace at which causative genes are being discovered for PIDs. WES has been most effective in identifying 'morbid' genes in groups of PID patients (Mendelian disorders) where the presence of homozygosity for deleterious mutations is likely to be high, including: (i) familial cases, consanguinity, or cases from isolated populations; (ii) patients presenting with particularly severe pathological form of an otherwise more benign condition (unusual pathogenesis); and (iii) rare early-onset pediatric cases. To date, mutations in 265 genes have been shown to cause PIDs, providing a rich data set for the systematic characterization of cellular and molecular networks involved in the development, activity, and regulation of immune cells during response to infectious or to inflammatory stimuli (see Table S1 in the supplemental information online) [22–24]. A clinical classification has recently been provided for PIDs where the genetic etiology is known [25]. It includes: (i) combined immunodeficiencies (T and/or B cells); (ii) combined immunodeficiencies with syndromic features; (iii) humoral deficiencies; (iv) diseases of immune dysregulation; (v) defects in phagocytes numbers or function; (vi) defects in innate immunity; (vii) autoinflammatory disorders; and (viii) deficiencies of the complement system. While the majority of mutations affect the development and function of leukocytes, others are inborn errors of metabolisms (in so-called 'house-keeping' proteins) with or without syndromic features [23]. The

Glossary

Complex disorders: diseases that are likely associated with the effects of multiple genes in combination with lifestyle and environmental factors.
Expression quantitative trait loci (eQTL): loci that affect mRNA expression levels of a specific gene or group of genes.
Genome-wide association study (GWAS): aims to associate disease phenotypes with specific genetic markers or loci (SNPs), and is generally conducted in large populations.
Immunochip: custom genotyping array containing genetic markers associated with immune-related gene(s).
Linkage disequilibrium (LD): situation when multiple physically linked genetic markers (and associated genes) associated with disease are inherited together as 'haplotype blocks', due to absence of recombination events between them in the population studied. The disease-causing genetic lesion may map within the boundaries of the haplotype block or may be physically linked outside the limits of the haplotype block.
Mendelian disorders: genetic diseases that follow simple Mendelian patterns of inheritance.
Meta-analysis: a combined analysis of multiple published GWAS to provide additional statistical power to identify disease loci.
Polygenic disease: a disease with a genetic component that involves several genes.
Primary immunodeficiency (PID): disorders resulting from inherited defects of the immune system characterized by an increased susceptibility to infections and, in some cases, increased incidence of autoimmunity and malignancies.
Quantitative trait loci (QTL): part of the genome (locus) that modulates a quantitative phenotype.
Single nucleotide polymorphism (SNP): single-nucleotide difference in the DNA sequence of individual members of a given species.
SNP chips (SNP arrays): an array of SNPs that allows genome-wide assignment and is used for association studies.