Genome **Medicine**

COMMENTARY

Shared pathways to infectious disease susceptibility?

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Abstract

The recent advent of genomic approaches for association testing is starting to enable a more comprehensive understanding of the role of human immune response in determining infectious disease outcomes. Progressing from traditional linkage approaches using microsatellite markers to high-resolution genome-wide association scans, these new approaches are leading to the robust discovery of a large number of disease susceptibility genes and the beginnings of an appreciation of their connections. In this commentary, we discuss how this technology development has led to increasingly complex and common infectious diseases being unraveled, and how this is starting to dissect pathogen-specific human responses. Intriguingly, these still preliminary findings suggest that pathogen innate detection mechanisms may not be as shared among diseases as immune response mechanisms.

Introduction

Many severe diseases resulting from infections, such as meningitis, dengue, or leprosy, are relatively rare within the human population when compared with the often ubiquitous nature of the causative infectious agent in specific world regions. While antibody responses to these organisms can be measured in large percentages of these populations, disease leading to hospitalization affects a small minority. This has led to the realization that the type of host response made to an infectious encounter may play a large role in determining the outcome. Understanding how most people successfully contain these infectious challenges may lead to the development of novel therapeutics for those individuals at risk of severe disease.

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This application of human genetics has proven insightful in those rare humans who are broadly susceptible to infections, where Mendelian genetic linkage approaches have revealed highly penetrant mutations that cause disease. With the advent of genome-wide association study (GWAS) technology, the field has been looking to see if the lessons learnt can be carried over to more common infectious diseases.

Severe combined immune deficiency and partial immune deficiency

The first studies of immune response defects and infectious disease outcomes strongly suggested that infectious diseases would have shared pathways to disease. Severe combined immune deficiency (SCID) - a genetic disorder that affects the adaptive immune system - demonstrates the importance of the immune system in protection against infection, as patients with SCID quickly succumb to life-threatening sepsis from a very wide range of infectious agents. The gene responsible for the majority of SCID cases, *CD132* (the common γ-chain), was identified using the traditional linkage approach [1-3]. Because the common γ-chain is shared by many cytokine receptors (receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21), mutations that result in a non-functional common γ-chain cause widespread defects in IL signaling and failure of B and T cells to develop and mature. This is a rather profound example, and knowledge of the responsible gene has opened avenues for therapeutic intervention in cases of X-linked SCID, where gene transfer of the normal *CD132* appears to be a promising, even curative, treatment modality [4,5]. Similar observations and clinical conclusions have been made with another form of SCID caused by defects in the variable, diversity, joining recombination process [6].

Partial immune deficiency, referring to the inactivation of a single immune pathway due to genetic mutations in one or more members of the network, was initially suspected to act in a similar way to the SCID mutations, with patients having a predisposition to a wide variety of infections. As these mutations are highly penetrant, traditional genetic linkage studies have been able to isolate the responsible genes and pathways for some of

these conditions, many of which have severe or even fatal clinical presentations. Notable examples include the IFN-γ receptor (*IFNGR1*) in cases of severe mycobacterial infections [7], the lysosomal trafficking regulator (*LYST*) for Chediak-Higashi syndrome [8], and Bruton's tyrosine kinase for X-linked agammaglobulinemia [9,10].

While the immune system has multiple pathways, each is thought to be active against a wide range of micro-organisms. Thus, it is perhaps surprising that the spectrum of infection susceptibility for these three genes appears to be fairly constrained. For example, *IFNGR1* mutations mainly predispose to mycobacterial infections, and *LYST* and Bruton's tyrosine kinase mutations mainly predispose to predominantly pyogenic bacterial infections (for example, *Streptococcus pyogenes*, pneumococcus, and *Haemophilus influenzae*). This surprising finding echoes another example: that of complement deficiency and its observed confinement to increased susceptibility towards encapsulated bacteria, particularly *Neisseria* spp., despite consistent documentation on the importance of the complement pathway in common blood pathogen clearance [11,12].

Subtle changes to immune genes as a result of genetic polymorphism

In the last 5 years, advances in genomic research have enabled the use of the GWAS design, permitting the robust identification of host susceptibility genes for infectious pathogens in increased detail. Although the advent of GWAS in infectious diseases has been slow compared with GWAS in many other complex disease phenotypes [13,14], this approach has nonetheless allowed unprecedented identification (or confirmation) of genes associated with susceptibility to the infectious diseases studied so far [15-18].

Infectious disease genes identified via the GWAS approach have thus far been relatively 'pathogen specific', with cross-pathogen sharing being the exception rather than the rule.

The greatest surprise has related to observations within the human leukocyte antigen (HLA) locus, where broad-based sharing between pathogen groups could be expected, given the central role played by HLA in immune recognition of pathogens and the initiation of immune responses. However, recent GWAS have found that while different HLA alleles appear to be shared between various auto-immune phenotypes (such as psoriasis [19], vitiligo [20], or systemic lupus erythematosus [21]), there appears to be little evidence of substantial susceptibility sharing for HLA between different infectious diseases. This disparity is striking even among supposedly 'similar' pathogen groups: a very strong contribution of the HLA locus has been observed for leprosy (*Mycobacterium leprae*) [15,22], but not for tuberculosis (*Mycobacterium tuberculosis*) susceptibility [23,24], highlighting the vast complexity of the immune response to diverse pathogens. This complexity is further shown in two genetic studies of vaccine response: while the HLA is crucial for success (or otherwise) for hepatitis B virus vaccination [25], it is not the case for *H. influenzae* type b vaccination [26].

Although findings thus far have suggested that the main pathways underlying susceptibility to pathogenic infection are pathogen specific, it is nonetheless relevant to understand similarities in the infection and invasion process for the very diverse pathogens that the human body encounters daily. For example, knowledge gleaned from the rare primary immune deficiencies has shown that defects in extremely central components of the immune system result in broad, general susceptibility to multiple infectious diseases. Elucidation of the responsible genes and pathways often yields considerable insight into disease mechanisms and pathogenesis, and can inform medical treatment (a good example being the case of X-linked agammaglobulinemia where common antibiotic treatments do not suffice, and immunoglobulin replacement is necessary). If some of these therapeutic findings could be extended to the commoner forms of infection that clinicians encounter on a daily basis, this could have an immediate public health impact.

Genomic approaches have played a supporting role in the identification of potential therapeutic targets. One of the virulent capabilities of *Neisseria meningitidis* is its ability to recruit human factor H (encoded by *CFH*) via molecular mimicry [27], thus avoiding complement-mediated killing of the bacterium. A recently completed GWAS on host susceptibility to meningococcal disease has shown that genetic polymorphisms within *CFH* as well as *CFH*-related genes are very strongly associated with susceptibility to meningococcal disease [18]. As the bacterial factor H-binding protein is now a strong meningococcal vaccine candidate [28], it is clear that genomic approaches can be used independently to discover or to confirm therapeutic targets identified by functional approaches.

Leprosy, tuberculosis, Crohn's disease, and ulcerative colitis have also been the subjects of recent investigations. Indeed, genomic approaches have underlined the importance of the nucleotide-binding oligomerization domain containing (NOD)2 signaling cascade in inflammatory and infectious diseases. Different members of the pathway (*NOD2*, *TNFSF15*, and *RIPK2*) have been strongly implicated ($P < 10^{-10}$) in susceptibility to leprosy [15,29], as well as Crohn's disease, which is an inflammatory bowel disease with substantial links to infectious agents [30,31]. However, observations by us and others [24] do not implicate NOD2 pathway members as strongly in tuberculosis susceptibility. The same has been observed for *CARD9* (a member of the extended NOD family of

genes), which has been strongly associated with ulcerative colitis susceptibility [32] and functionally implicated in tuberculosis [33], but not with leprosy [15].

Another gene observed to be a strong ($P < 10^{-10}$) susceptibility factor for leprosy is *TNFSF15* [15]. The exact same SNP (rs6478108) has also been found to be strongly associated ($P < 10^{-10}$) with Crohn's disease [34]. However, the minor allele has been found to be associated with increased risk of leprosy, but with decreased risk of Crohn's disease. This suggests that differential regulation of the immune response appears to be critical to reach a balance between protection from invading pathogens and susceptibility to inflammatory disorders, thus highlighting TNFSF15 as a potential therapeutic target in manipulation of the strength of the immune response.

Indeed, the disparity in susceptibility genes for Crohn's disease and ulcerative colitis (different members of the pathogen-sensing CARD family are involved: *NOD2* for Crohn's, and *CARD9* for ulcerative colitis) is likely to reflect different sites of pathology, different bacterial spectra, and therefore different mechanisms for microbial recognition. Strikingly, there is evidence suggesting that the downstream, cytokine-mediated pathogenesis pathways (for example, those involving IL-23) could be common across both diseases [32].

Missing 'shared susceptibility'?

The majority of evidence collected so far from genomic approaches appears to suggest that, barring specific exceptions, common host susceptibility to different invading pathogens appears to be controlled by discrete genes and pathways. As genomic approaches are still limited in resolution, there is a possibility that truly shared mechanisms governing susceptibility across multiple pathogen groups have yet to be found. This seems to be likely in view of the finite number of pathogen-recognizing receptors available at the first lines of defence, coupled with their convergent, downstream signaling pathways. An example for 'shared susceptibility' would be *TIRAP*, which encodes a common adaptor for two major pathogen-sensing receptors (TLR2 and TLR4); an inactivating mutation (S180L) within *TIRAP* appears to associate with susceptibility to invasive pneumococcus and *H. influenzae*, as well as *Trypanosoma cruzi* infections [26,35,36], with a yet unconfirmed association with tuberculosis [37,38].

Considering the evidence now available, there is reason to believe that host susceptibility to infection could be specific and 'mechanism dependent' in terms of pathogen recognition and the site of infection, with shared common signaling pathways playing an important role downstream of pathogen contact points.

A further benefit in the large-scale deployment of hypothesis-free genomic approaches is that they could

help in establishing the etiology of certain autoimmune diseases where infectious diseases have long been suspected - but not confirmed - to be a predisposing factor. For example, in the case of type 1 diabetes, GWAS have implicated an extraordinary number of immune-related genes, some of which overlap with infection pathways, thus lending credence to the above hypothesis.

Genomic approaches have resulted in improved treatment strategies for patients with severe and partial immune deficiencies by identifying the deficient protein component(s), but for many of the common infections, due to their complex nature, genomic approaches have not yet been as fruitful in informing medical treatment. Emerging antibiotic resistance is putting additional pressure on research efforts in host and pathogen genomics for further improvement of therapeutic strategy beyond antimicrobial treatment, but there is hope that this research will lead to novel human protein-based therapies.

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