Inborn errors of immunity to infection: the rule rather than the exception

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The immune system’s function is to protect against microorganisms, but infection is nonetheless the most frequent cause of death in human history. Until the last century, life expectancy was only ~25 years. Recent increases in human life span primarily reflect the development of hygiene, vaccines, and anti-infectious drugs, rather than the adjustment of our immune system to coevolving microbes by natural selection. We argue here that most individuals retain a natural vulnerability to infectious diseases, reflecting a great diversity of inborn errors of immunity.

The burden of infection in human history

Humans are prone to a multitude of endemic and epidemic infectious diseases (1), which have been the leading cause of death throughout history (2). In mid–19th century England, ~60% of deaths were due to infectious diseases and this proportion was even higher in previous centuries, especially during epidemics. Mortality curves demonstrate that the burden of infectious diseases was high, with life expectancy averaging ~25 years from the Palaeolithic period until the Industrial Revolution (Fig. 1). Even in Europe, only 35% of people reached the age of 40 at the end of the 19th century. Life expectancy has now reached 80 years in these regions. The current high mortality rates in the poorest countries, such as Mozambique, may be seen as an unfortunate testimony to our common past (Fig. 1). On a historical scale, the increase in life expectancy is recent and is a major contributor to the ongoing population explosion. Increased life expectancy primarily reflects progress in the control of infectious diseases based on three factors: the development of hygiene, beginning in the mid–19th century (preventing the transmission of infection); the development of vaccines, beginning in the late 19th century (preventing disease in infected individuals); and the development of anti-infectious drugs, beginning in the early 20th century (preventing death in patients with clinical disease). The relative contributions of these three factors depend on the disease in question.

Inherited predisposition to infection

A complex interplay between environmental (microbial and nonmicrobial) and human (genetic and nongenetic) factors determines immunity to infection and the resulting clinical outcome of infection. By definition, humans dying of infection have impaired immunity to infection (immunodeficiency). Accumulating evidence suggests that human genetic factors play a particularly important role in immunodeficiency and susceptibility to infectious diseases (3, 4). The increase in life expectancy observed in the 20th century occurred despite the retention of poor immunity to particular infectious agents in most individuals (Fig. 1). There has been no sudden natural selection of high-quality immune system genes worldwide: this persistent immunodeficiency has simply been masked by medical progress. Investigations into natural host variability in the development of infectious diseases began in the early 20th century with the discovery by Charles Nicolle of the coexistence of symptomatic and asymptomatic infections in naive populations (5). The first evidence supporting the hypothesis that host variability and immunodeficiency were hereditary originated from observations of the ethnic or familial aggregation of both rare and common infections, which in some kindreds even followed a Mendelian (monogenic) pattern of inheritance (6, 7). Epidemiological studies of adopted individuals also showed that predisposition to infectious diseases was largely inherited, paradoxically more so than in diseases associated with less well-known environmental risk factors, such as cancer (8). Finally, studies comparing the concordance rate of infectious diseases between monozygotic and dizygotic twins have also implicated host genetic background in susceptibility to disease (3, 6).

Conventional primary immunodeficiencies

There have been three independent lines of molecular and cellular investigation in human genetics of infectious diseases: the study of rare primary immunodeficiencies (Mendelian predisposition to infectious diseases), that of complex (multigenic, non-Mendelian) predisposition or resistance to common infectious diseases, and that of common Mendelian resistance to infection. Compelling evidence for the heritable nature of impaired immunity was first provided by primary immunodeficiencies (9). The first primary immunodeficiency was described in 1952, but it was not until 1954 that this disease, Bruton’s agammaglobulinemia, was found to be...
X-linked and recessive (10). The classification of primary immunodeficiencies is currently based on immunological phenotype and mode of inheritance (7, 11). At least 200 primary immunodeficiencies are known, most of which have a prevalence of less than 1 per 50,000 births. Conventional primary immunodeficiencies are typically rare, recessive Mendelian disorders that directly affect leukocytes. They present during childhood as a vulnerability to multiple, recurrent, life-threatening infections by both weakly virulent opportunistic microorganisms and more virulent pathogens. Conventional primary immunodeficiencies are suspected on infectious grounds but were historically diagnosed on immunological grounds. Reticular dysgenesis is the most striking and severe form of primary immunodeficiency known (12). This exceedingly rare autosomal recessive disease, of unknown genetic etiology, is characterized by a total lack of granulocytes and lymphocytes. Patients with reticular dysgenesis are vulnerable to almost all microorganisms and die within a few weeks or months of birth in the absence of hematopoietic stem cell transplantation.

Nonconventional primary immunodeficiencies

Inborn errors of immunity are not limited to conventional primary immunodeficiencies, which are associated with overt immunological phenotypes and multiple infectious phenotypes. About a dozen intriguing Mendelian clinical syndromes marked by a predisposition to a single type of infection are known (4). These nonconventional primary immunodeficiencies may be recessive or dominant and may or may not affect cells derived from the hematopoietic lineage. Typically, no immunological abnormality is detected before the disease-causing gene is identified. Predispositions to viruses include the syndrome of epidermodysplasia verruciformis, characterized by disseminated cutaneous warts caused by oncogenic papillomaviruses. The discovery that mutations in EVER1 and EVER2, two genes of unknown function that are normally expressed in keratinocytes, were the cause of epidermodysplasia verruciformis, opened a promising field of research (13). Predispositions to bacteria include the syndrome of Mendelian susceptibility to mycobacterial diseases (MSMD) in patients with mutations in the interleukin-12–interferon-γ cytokine circuit and infections caused by weakly virulent mycobacteria (14–16). Studies of patients with MSMD led to the discovery that infectious diseases caused by more virulent pathogens can also be specifically favored by a Mendelian predisposition. In three unrelated families, patients with interleukin-12 receptor β1 (IL-12Rβ1) deficiency, a genetic cause of MSMD, were found to suffer from severe tuberculosis in the absence of prior infection by weakly virulent mycobacteria (17). These three families are the first examples of a truly Mendelian predisposition to bona fide human tuberculosis. They provide proof of principle that common infectious diseases in otherwise healthy individuals may reflect Mendelian predisposition.

Major susceptibility genes

The proportion of patients suffering from infectious diseases due to Mendelian predisposition is unknown. Recent years have seen the emergence of the related concept of major genes, defined as genes whose common mutations (polymorphisms) exert an effect strong enough to be detected in complex segregation studies, genome-wide linkage scans, or both. Some of these genes may even correspond to solitary loci, exerting a nearly Mendelian impact (6). The first identified major gene predisposing to infectious diseases in humans controls susceptibility to leprosy, a disease caused by the bacterium Mycobacterium leprae. A complex segregation study performed in 1988 showed that human genetic predisposition to leprosy depends on a major gene (18), which was localized to a candidate region on 6q25 using a genome-wide
scan. In 2004, the major gene was found to correspond to the regulatory region shared by PARKIN and PACRG (Parkin coregulated gene), genes that are normally coexpressed in mononuclear phagocytes and Schwann cells (19). PARKIN encodes an E3-ubiquitin ligase, revealing the involvement of an unexpected immunological pathway in immunity to M. leprae—an invaluable finding in the absence of an animal model of leprosy. Many other infectious diseases are controlled by major genes, which affect susceptibility to disease at different points, including during the initial infection and during the development of clinical disease. For example, levels of infection by Schistosoma mansoni are controlled by a major gene on chromosome 5q (20) and the development of liver disease is controlled by another major gene on chromosome 6q (21). Both genes remain to be identified.

Other susceptibility genes
The term minor gene may be inappropriate for other susceptibility genes that are not found by linkage studies, as some may have a strong impact on the development of infectious diseases, possibly even equal to that of major genes in terms of relative and attributable risks at the individual and population levels, respectively (Fig. 2). This is best illustrated by the discovery that heterozygous carriers of the sickle cell trait are more resistant to severe forms of malaria than individuals homozygous for the wild-type hemoglobin allele (22). This observation, made by Anthony C. Allison in 1954 from an association study based on epidemiological surveys, marked the birth of the field of complex genetic susceptibility and resistance to common human infectious diseases (23). It indicated that infectious diseases have a profound impact on the natural selection of our genome, with the sickle cell trait reaching a frequency of up to 15% in endemic areas. However, in general, candidate genes selected on immunological grounds have since failed to reveal associations of a similar level of importance.

Countless association studies have generated weak and/or irreproducible results, with little or no biological validation of the findings. Despite scarce molecular evidence, the polygenic hypothesis of human predisposition to infectious diseases has continued to predominate. According to this view, genetic susceptibility to infectious diseases results in each individual from the sum of common mutations in multiple genes, each mutation having a modest impact. Nevertheless, truly polygenic inheritance may be mimicked at the population level by numerous Mendelian traits or major genes, each affecting a small number of individuals and/or specific groups of individuals (24).

Mendelian resistance to infection
Interestingly, molecular evidence that most humans are genetically predisposed to infectious diseases has been provided by three studies disclosing the genetic basis of Mendelian resistance to virulent infectious agents. These studies showed that inborn errors of immunity do not necessarily correspond to mutations, as wild-type alleles may themselves be highly deleterious if they encode ports of entry for microbes. Furthermore, bona fide mutant alleles

![Figure 2. Variations in protective immunity to infection can be described at the genetic, cellular, individual, and population levels. Typically, rare susceptibility alleles are loss-of-function or hypomorphic, and are associated with a complete or partial cellular defect and a Mendelian disorder. Common susceptibility alleles may be hypomorphic or even wild type and associated with a subtle or normal cellular phenotype and a complex disease. The effects of rare and common alleles on individuals are generally specified in terms of clinical penetrance and relative risk, respectively. Denoting d as the wild-type allele and D as the deleterious allele, there are three penetrances, f_ddd, f_Dd, and f_DD, defined as the probability of clinical disease for individuals with dd, Dd, and DD genotypes, respectively. There are two relative risks (RR), defined as the variation in the risk of clinical disease for Dd and DD individuals, compared with dd individuals, that can be computed from penetrances as RR_dd = f_Dd/f_dd and RR_DD = f_DD/f_dd.](image-url)
that are intrinsically deleterious at the cellular level may be beneficial at the individual and population levels upon microbial exposure. Autosomal recessive deleterious mutations in DARC (25, 26), CCR5 (27–29), and FUT2 (30) are associated with protective immunity to Plasmodium vivax, HIV, and noroviruses, respectively. These genes encode key cell surface receptors for the corresponding pathogens on erythrocytes, CD4 T cells, and intestinal epithelial cells, respectively. These mutations prevent the entry of pathogens into their principal target cell, thereby preventing replicative host infection. These mutant alleles do not seem to decrease the overall fitness of people who are homozygous or compound heterozygous, and their expansion in human populations may have been favored by the selective advantage they confer in terms of protection against the corresponding organism (DARC) or other, as yet unknown, infections (CCR5 and perhaps FUT2). It is clear that individuals homozygous for the wild-type DARC, CCR5, and FUT2 alleles are intrinsically immunodeficient with regard to particular pathogens, whereas mutant individuals display greater immunity to these pathogens, with no apparent fitness cost. However, some of the patients with these mutations may, perhaps, be vulnerable to other, as yet unknown pathogens. In any event, there are probably many other similar human mutations, which have been or are being selected because they confer Mendelian resistance to virulent pathogens.

**Multiple errors of immunity**

There are thus multiple forms of genetic predisposition to infection in humans (Fig. 2; reference 4). The fields of primary immunodeficiencies and of host susceptibility to infection have followed parallel paths since the early 1950s. Work on susceptibility to infection converged with Mendelian genetics in 1996, with the first successful identification of a major locus for schistosomiasis by genome-wide scan (20). In the same year, research on primary immunodeficiencies converged with studies on host susceptibility to infection, with the identification of interferon-γ receptor 1 (IFNγR1) mutations in patients with MSMD, a nonconventional primary immunodeficiency (14, 15). There has since been considerable cross talk between these fields, and it is expected that they will eventually merge, as they tackle the same question from the complementary angles of individuals and populations: which inborn errors make us vulnerable to infection? The more recent field of Mendelian resistance to infection, founded by Louis H. Miller in 1976 with the discovery of Mendelian resistance to P. vivax (25), has also blossomed since 1996 (26–29). It is now clear that many genotypes and cellular phenotypes are associated with predisposition to clinical infectious diseases at the individual and population levels (Fig. 2). Human predisposition to infection reflects highly diverse situations, ranging from exceedingly rare mutations with high penetrance in individuals to common mutations accounting for high attributable risk in populations. Moreover, a variety of genes are involved, mirroring the diversity of the microorganisms representing a threat.

**Immunity at individual and population levels**

The human immune system is efficient at the species level, having allowed reproduction for ~200,000 years despite the tremendous abundance and diversity of environmental, commensal, and parasitic microbes. Overall, our species is immunocompetent but it is most unlikely that there has ever been a truly immunocompetent individual who was resistant to all pathogens. The immune system does well at the population level but poorly at the individual level because it faces a living, rapidly dividing, highly diverse, and coevolving parasitic environment. At the individual level it fails much more frequently than other physiological systems. Each novel microorganism poses a new challenge, and such microorganisms are arising much more rapidly than resistant hosts. Inborn errors of immunity are therefore—unfortunately but inevitably—the rule rather than the exception. Despite a gradual evolutionary adjustment of our immune genes, most individuals remain intrinsically vulnerable to present and, to an even greater extent, future infectious diseases. The recent increase in human life expectancy reflects the intellectual conquests of hygiene, vaccines, and antibiotics. These discoveries were based on our understanding of general principles of microbiology and immunology. Deciphering the genetic basis of impaired immunity to specific infections is a new frontier that should drive further progress in human health. Understanding the failures of the immune system should make it possible to devise novel ways of making it succeed.

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