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EDITORIAL

The human genetic determinism of life-threatening infectious diseases: genetic heterogeneity and physiological homogeneity?

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Abstract

Multicellular eukaryotes emerged late in evolution from an ocean of viruses, bacteria, archaea, and unicellular eukaryotes. These macroorganisms are exposed to and infected by a tremendous diversity of microorganisms. Those that are large enough can even be infected by multicellular fungi and parasites. Each interaction is unique, if only because it operates between two unique living organisms, in an infinite diversity of circumstances. This is neatly illustrated by the extraordinarily high level of interindividual clinical variability in human infections, even for a given pathogen, ranging from a total absence of clinical manifestations to death. We discuss here the idea that the determinism of human life-threatening infectious diseases can be governed by single-gene inborn errors of immunity, which are rarely Mendelian and frequently display incomplete penetrance. We briefly review the evidence in support of this notion obtained over the last two decades, referring to a number of focused and thorough reviews published by eminent colleagues in this issue of *Human Genetics*. It seems that almost any life-threatening infectious disease can be driven by at least one, and, perhaps, a great many diverse monogenic inborn errors, which may nonetheless be immunologically related. While the proportions of monogenic cases remain unknown, a picture in which genetic heterogeneity is combined with physiological homogeneity is emerging from these studies. A preliminary sketch of the human genetic architecture of severe infectious diseases is perhaps in sight.

Introduction

The proportions of infections that are benign and life-threatening in human populations vary enormously from microbe to microbe. This phenomenon of intermicrobial variability is relatively well known and understood, as it seems, at least at first glance, to be determined largely by microbial virulence, almost independently of the human population considered. Admittedly, the notion of virulence is no more than a paraphrase, a term coined to quantify the impact of the microbe in the general population. Its molecular basis remains elusive for the vast majority of microbial isolates. Nevertheless, it has some general value, almost regardless of the microbe and population considered. For example, Ebola virus can be said to be more virulent than herpes simplex virus, because it kills ~ 60% of those it infects versus less than 0.01% for herpes simplex virus, during primary infections in natural conditions (Garske et al. 2017; Khandaker et al. 2014). However, these proportions undoubtedly vary over time. Ebola, which emerged in 1976 (WHO 1978), will probably gradually lose virulence after hundreds or thousands of years of co-evolution between Ebola viruses and humans. Likewise, the ancestors of herpes simplex virus may have been more virulent and/or ancient humans more susceptible to this virus in the distant past. These proportions also clearly vary over space, as a given microbe may be more harmful in some populations than others, reflecting the influence of specific ecosystems and evolutionary events. This notion will later bring us to the contribution of human genetics, the theme of this issue of the journal. Nevertheless, beyond Ebola and herpes simplex virus, comparisons can be made between all viruses, bacteria, fungi, and parasites, and all microbes can

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be ranked, at least tentatively and provisionally, on a scale of virulence extending from innocuity to lethality.

Individual microbes and individual humans

This observation of intermicrobial variability gave rise to the binary notion of virulent vs. opportunistic infectious agents, a naive and questionable dichotomy that attempts to separate microbes into two groups: those that are sufficiently virulent to cause severe disease in "immunocompetent" individuals, and those that cause severe disease only in "immunocompromised" humans. Reality is evidently more complex, because of the almost continuous variation of the proportions of casualties between microbes, making it virtually impossible to separate them into two distinct groups. This concept is also logically inadequate, because any particular human with a life-threatening infectious disease is immunocompromised (i.e., not immunocompetent) with respect to the particular, invading microbe causing the disease concerned. It is inappropriate to restrict "immunodeficiency" to the detection of immunological anomalies, as both the methods of detection and the definition of anomalies evolve continuously. These approximate and simplistic notions have been of some practical medical utility, and have also provided a basis for the scientific field of immunity to infection. However, they do not come close to describing the reality of human infections in an accurate manner, as they do not even attempt to describe the outcomes of populations of humans confronted with populations of microbes. They are inspired by typology and essentialism, as though there really were one generic human "host", infected by one generic "pathogen". In the real world, there is no such thing as a host and a pathogen. There are only populations of individual humans and populations of individual microbes.

Each human × microbe interaction is unique

Indeed, infection occurs when real individual human beings, not virtual hosts representative of the human species, encounter real microbial isolates, not virtual microbes representative of their own species. Incidentally, while the definition of the human species is difficult from an evolutionary but not from a physiological standpoint, that of any microbial species is difficult from both evolutionary and physiological standpoints. Moreover, human life and death are notions fundamentally and exclusively attached to individuals, not populations. The same is true for the life and death of microbes and, indeed, any other living organism. Like evolution, physiology and pathology operate at the individual level, and not at the population level. All living organisms are unique in space and time. This revolutionary insight was at the heart of the theories of evolution and physiology put forward by Charles Darwin and Claude Bernard. It is also this notion that makes life sciences so fundamentally different from physical sciences, and sometimes difficult for physicists and mathematicians to understand (Bernard 1865; Darwin 1993). All printed copies of this paper are identical, and will remain so for a long time; whereas, all readers of this paper are different from each other. They will also continue to differ as they age. Ernst Mayr's "population thinking" and Archibald Garrod's "chemical individuality" later made reference to this seminal notion of biology, again from the complementary perspectives of evolution and physiology (Bearn 1993; Mayr 1988). Each interaction between a human and a microbe is, therefore, unique in space and time. Moreover, a single human, made of cells that inevitably diverge from each other genetically and epigenetically, is almost never infected by a single microbial organism. Instead, this single, heterogeneous human is infected by many members of the same microbial family, which can evolve, mutating and further diverging within this individual, adding another level of diversity and complexity to the interaction.

Gigantic inter-individual variability

In this context, it is not surprising that there is tremendous interindividual variability in the clinical outcomes of almost all primary infections with a given microbe, ranging from a total lack of symptoms and signs to death, as dramatically illustrated with the current pandemics of SARS-CoV-2 infection (Casanova et al. 2020). The most virulent microbes can be innocuous in rare individuals; whereas, the least virulent microbes can kill others, albeit rarely. This is, in a nutshell, what we like to refer to as the "infection enigma" (Casanova 2015a; Casanova and Abel 2013). In principle, the interindividual variability of clinical outcome during infection can be accounted for by the variability of the microbes themselves (inherited or acquired, including after selection by anti-infectious agents), and/or by the variability of the hosts (inherited or acquired, including after infection with other microbes), and/or by factors with no effect on the intrinsic capacities of the host and microbe, such as the numbers of invading microbes and their route of infection. The contribution of these last two factors has been amply documented in both clinical studies and experimental models. The route of infection is critical, as demonstrated by staphylococcal diseases following breaches of the skin (Thomer et al. 2016). Other examples include pneumococcal meningitis after congenital or traumatic cerebrospinal fluid fistulas (Henaff et al. 2017). The microbial inoculum is also critical, as extensively documented in experimental infections in animal models (Vidal et al. 2008). An unfortunate example of an experimental infection in humans is

the Lübeck disaster, when infants were given a live BCG vaccine contaminated with *M. tuberculosis*. It was shown that the inoculated dose of *M. tuberculosis* was strongly correlated with the subsequent risk of tuberculosis (Fox et al. 2016). The size of the microbial inoculum is probably also important in natural infections (Casanova 2015a; Vidal et al. 2008).

Role of microbial virulence

Microbial variability within a species (with the caveat that microbial species cannot be defined as rigorously as species of multicellular eukaryotes that reproduce sexually) has occasionally been shown to account for the emergence of more virulent microbial strains (Geoghegan and Holmes 2018; Vouga and Greub 2016). A good example is the difference between seasonal influenza viruses, which arise by genetic drift and strike each year with modest variations of virulence, and pandemic influenza viruses, which arise by genetic shift and strike only a few times per century, with much greater virulence (Ciancanelli et al. 2016; Kash and Taubenberger 2015; Krammer et al. 2018; Taubenberger and Morens 2006). However, these elegant studies of microbial virulence diversity were interpreted under the false premise that the infected human population was homogeneous. For reasons pertaining to both practicality and prejudice, microbes were only rarely, if ever, studied for their particular impact in different individuals. Humans resistant to pandemic influenza, and those vulnerable to seasonal influenza, were ignored, neglected, or, at most, considered to be enigmatic outliers of little interest (Ciancanelli et al. 2016). It remains unclear if such interindividual variability in the course of an endemic or epidemic infection results, at least in part, from intermicrobial variability. Although unlikely, resistance to pandemic influenza might result from infection with a defective virus; whereas, death from seasonal influenza might result from infection with a more virulent virus. This general hypothesis probably deserves more attention from virologists and microbiologists.

Role of acquired immunodeficiency

Paradoxically, while the impact of individual microbes in individual patients has not been systematically studied, predisposition to particular infections has been studied in individual patients in a given population, and even across populations. Acquired immunodeficiency in individual patients has been attributed to previous infections, the best known example being viral infections, and to medicines, such as immunosuppressive drugs in particular. The viruses known to cause immunosuppression include measles virus and human immunodeficiency virus (HIV) (McChesney and Oldstone 1989; Mina et al. 2019; Naniche and Oldstone 2000; Petrova et al. 2019). There are countless immunosuppressive drugs that cause predisposition to severe infections (Koo et al. 2011; Winthrop et al. 2008). There are also probably many currently unknown forms of acquired immunodeficiency, beyond microbes and medicines, including some caused by somatic genetic mutations and epigenetic modifications, which probably contribute to aging-associated immunodeficiency (Brodin et al. 2015; Casanova 2015a; Casanova et al. 2020). However, aging probably preferentially affects immunity to secondary infection or latent microbes (Laemmle et al. 2019), if only because the proportion of primary infections decreases with age; whereas, the proportions of latent and secondary infections increase (Alcais et al. 2010; Feigin and Cherry 1998; Mandell et al. 2004). This is neatly illustrated by zoster, which results from reactivation of varicella zoster virus (VZV). Its incidence rises after 50 years of life and can be prevented by vaccination of VZV-infected individuals in this age group (Lal et al. 2015). Latency is easy to define, but it is more difficult to define secondary infections, because the two (or more) microbes concerned may not differ significantly, despite there being years or decades between the primary and secondary infections. Reactivation from latency can be difficult to differentiate from a new infection (Cardona 2016; Stewart et al. 2003). In addition, each microbe is related to many others, that are nonetheless different from it, making a rigorous definition of primary and secondary infections difficult, if not impossible.

Major impact of primary infections

Nevertheless, we will not discuss the human genetic control of secondary or reactivation infections here, for two main reasons. First, the outcome of secondary or latent infections is probably heavily influenced by the adaptive immune system (Brodin et al. 2015; Casanova 2015b; Casanova et al. 2020; Paul 2008), which emerged twice in evolutionary history, through convergent evolution (Cooper 2010; Guo et al. 2009; Hirano et al. 2013; Pancer et al. 2004). Although genetically controlled, this system and the immunity it confers are separated from the germline through the generation of somatically rearranged clonal receptors for antigens. In the course of secondary infection, the adaptive immune system confers enhanced immunity through the memory of past infections, in what is quintessentially a somatic process. Again, we do not mean by this that the process is not under germline genetic control, but we think that it is much more difficult to disentangle the germline and somatic variations influencing outcome for secondary than for primary infections. Second, from both physiological and evolutionary

angles, the fundamental challenge posed to humans and other species by microbial threats results more from primary than from secondary infections. This is well documented in humans, in which life expectancy at birth in natural conditions, with little or no medical care, remained at 20–25 years for at least 10,000 years worldwide, until about the end of the nineteenth century (Cairns 1997; Casanova and Abel 2005). Half of all children died before the age of 15 years, in the vast majority of cases from primary infection rather than from predation, war, or famine. The very recent increase in human life span results mostly from the conquests of hygiene, aseptic surgery, serotherapy, vaccines, and anti-infectious medicines, which followed the germ theory (Casanova and Abel 2005). The tendency of the adaptive immune responses of modern-day humans to become gradually less effective against VZV over time, from the age of 50 years onward, is certainly a major medical problem in 2020, but a minor biological problem, at least from an evolutionary perspective, because of both its very recent occurrence and its negligible impact on reproduction.

The human genetic hypothesis

One of the fundamental evolutionary and physiological problems of mankind is, therefore, that of childhood deaths from infection: what is its root cause, given that most children, including the relatives of those who die, survive infections with the same or related microbes, with no major consequences? The human genetic hypothesis was proposed as a response to this question and documented by means of classical genetics during the first half of the twentieth century. We have reviewed the history of this field elsewhere (Casanova 2015a, b; Casanova and Abel 2013, 2020). Briefly, proof-of-principle that severe infections could have a genetic origin was provided in 1905 for plants, in 1923 for animals, and between 1909 and 1943 for humans, by both biometricians and geneticists (Casanova 2015a, b). Plant biologists provided the first compelling evidence that severe infections can be genetic, and even Mendelian, through their studies of fungal infections of wheat. However, it is interesting to note that Pasteur himself established that one of the two infections of silk worm, flacherie, was also "inherited", not in the sense that the microbe was transmitted from the parents to the offspring, but that the offspring inherited their parents' predisposition to infection (Pasteur 1926). Pasteur was not aware of Mendel's laws of genetics and did not pursue this route of research. The genetic component of plant infections became Flor's general model, as proposed in 1942 (Flor 1942). Multiple studies documented the importance of the genetic background for the outcome of infection in various animals, including mice, rats, rabbits, and guinea pigs (Casanova 2015a; Lurie 1941; Vidal et al. 2008; Webster 1939). In humans, various epidemiological and clinical genetic approaches were followed from 1909 to the 1940s, the most remarkable and convincing investigations being twin studies comparing monozygotic and dizygotic twins for concordance for a particular phenotype (Casanova and Abel 2013; Casanova et al. 2020; Kallmann and Reisner 1943). Adoptive studies, which are equally powerful, were conducted later (Sorensen et al. 1988).

The respective contributions of microbiologists, immunologists, and geneticists

Interestingly enough, the problem of interindividual clinical variability in the course of primary infection was not tackled by immunologists and microbiologists. This merits a brief word. Microbiologists fundamentally see the microbe as causal and, therefore, consider interindividual clinical variability to be also due to some form of microbial variability, whether qualitative or quantitative. Even though the vast majority of present-day pathogens kill less than 1% of the individuals they infect, microbiologists generally attribute disease and death to the microbe as a matter of principle, although they generally do not document any particular variation accounting for disease or death in specific patients. Immunologists are the heirs of another historical doctrine. Most are reluctant to admit that their legitimately cherished center of interest, the immune system, even if scaled up or upgraded to the whole organism, can be efficient at the population level, but not at the individual level. The idea that most humans are immunodeficient with respect to at least some microbes is still not admitted by most immunologists, although compelling from a logical point of view. This state of affairs may perhaps be accounted for, at least in part, by the desertion of the field of immunity to infection by many immunologists, in 1917, in response to Landsteiner's stunning discovery of antibody responses to haptens, i.e., synthetic molecules that do not exist in nature. Immunologists have ever focused on the "antibody enigma" of Kindt and Capra, which differs from the infection enigma described above (Kindt and Capra 1984). The little interest of microbiologists and immunologists in resolving this question may explain why a third group of scholars, plant, animal and human geneticists, decided to tackle the infection enigma.

Clinical and population genetics

If we fast-forward a little, and narrow our focus down to humans, there was a shift in the field of human genetics of infectious diseases from classic to molecular genetics in the early 1950s. Over the next 60 years, the field remained

divided into two branches, with clinical and population geneticists tackling the problem from different angles (Casanova and Abel 2013). They addressed the same problem, but formulated different hypotheses and used different methods, both to describe the phenotypes of patients and to analyze their genotypes. Population geneticists conducted population-based studies and paid little attention to detailed clinical phenotypes, family histories, and the underlying mechanisms of disease (Casanova and Abel 2007a). In addition, they genotyped the observed human genetic variation and analyzed it as markers, rather than as candidate genetic lesions. By contrast, clinical geneticists conducted patient- or family-based studies and, given the higher granularity of their approach, undertook detailed clinical studies, with direct searches for candidate disease-causing mutations, and attempted to decipher the mechanisms of disease (Casanova and Abel 2007a). With the benefit of hindsight, there is little doubt that clinical genetics was much more informative than population genetics during the period extending from 1950 to 2010. The greatest achievement in the population genetics of infectious diseases remains the discovery in 1954 of the HbS trait conferring tenfold resistance to severe *Plasmodium falciparum* malaria, which marked the birth of the field (Allison 1954, 2009). Subsequent population studies did not detect such high levels of genetic protection or predisposition (Casanova and Abel 2013), even those leading to the identification of *IL28B* variants strongly influencing the clearance of hepatitis C virus infection (Ge et al. 2009; Suppiah et al. 2009; Tanaka et al. 2009; Thomas et al. 2009). In addition, the tenfold resistance to severe malaria told us more about the impact of severe infections on the distribution of human variants (the HbS allele being selected by malaria), than about the causality between human genotypes and severe infections (HbS heterozygotes being incompletely protected from malaria).

"Mendelian" basis of susceptibility/resistance to infections

By contrast, at least 200 inborn errors of immunity and three Mendelian resistances to infection were reported by 2010 (Casanova 2015b; Casanova and Abel 2007b). This field was actually born in 1946 with the discovery of autosomal recessive epidermodysplasia verruciformis, although its birth was long attributed to the discovery of X-linked agammaglobulinemia in 1952, or of autosomal recessive neutropenia in 1950 (Casanova and Abel 2013, 2020). This field has provided countless examples of inborn errors of immunity underlying one or more infectious diseases (Meyts et al. 2016; Tangye et al. 2020). Key to this discipline is Claude Bernard's notion of determinism, which differs from that of predisposition commonly adopted by population geneticists. The year of 1996 marked a watershed moment, with the discovery of the first molecular genetic basis of both Mendelian resistance and the first Mendelian predisposition to a specific infectious disease: resistance to HIV infection (Dean et al. 1996; Liu et al. 1996; Samson et al. 1996) and predisposition to weakly virulent mycobacteria (Jouanguy et al. 1996; Newport et al. 1996), respectively. The discovery of the resistance of CCR5-deficient $CD4^+$ T cells to HIV was inspired by elegant studies dating back to 1976 on the lack of Duffy antigens on the erythrocytes of individuals resistant to *Plasmodium vivax* (Miller et al. 1976). However, the molecular genetic basis of this phenotype was not determined until 1995, with the identification of a subtle mutation in the DARC promoter (Tournamille et al. 1995). The Mendelian basis of a specific, hitherto "idiopathic" mycobacterial infection in otherwise healthy patients was particularly surprising, as it was at odds with findings for other primary immunodeficiencies described from the 1950s onward, these immunodeficiencies being associated with both immunological abnormalities and multiple infections. Mendelian susceptibility to mycobacterial disease (MSMD) was shown to be caused by inborn errors of IFN-γ immunity (Bustamante et al. 2014; Casanova and Abel 2002). The search for the molecular basis of a "Mendelian infection" was inspired by the discoveries of the first monogenic lesions of *Mx* (Staeheli et al. 1986) and *Nramp1* (Skamene et al. 1982; Vidal et al. 1993) in 1986 and 1993, respectively, underlying specific infections in mice (caused by influenza virus and mycobacteria, respectively), and the superb work on monogenic infections in plants (Dangl and Jones 2001; Jones et al. 2016).

Monogenic basis of infectious diseases

Since 1946, only five severe human infectious diseases have been shown to be often familial, and in such cases, to segregate as Mendelian traits (Table 1). They were confirmed to be Mendelian when their molecular genetic basis was discovered, from 1996 onward (Casanova and Abel 2020). Needless to say, the vast majority of infectious diseases are not Mendelian. However, all infections studied to date have turned out to be monogenic, at least in one child. More than 15 human infections fall into this category, including viral, bacterial, fungal, and parasitic diseases (Table 1). Genetic heterogeneity, including both locus and allelic heterogeneity, is a hallmark of the infections most studied genetically. In contrast, these infections also seem to display physiological homogeneity. For example, MSMD is caused by inborn errors of IFN-γ immunity (Casanova and Abel 2002; Martinez-Barricarte et al. 2018; Rosain et al. 2019), with mutations of 15 genes and 30 allelic forms already reported; whereas, chronic mucocutaneous candidiasis (CMC) is

Table 1 Mendelian and monogenic susceptibility/resistance to infection[a]

Infectious agent	Clinical phenotype	Immunological phenotype	Gene	Inheritance
BCG vaccines and environmental mycobacteria	MSMD	IFN-γ deficiency	*IFNGR1, IFNGR2, IL12RB1, IL12B, NEMO, STAT1, CYBB, IRF8, ISG15, TYK2, RORC, IL12RB2, IL23R, SPPL2A, JAK1*	Mendelian or monogenic AR, AD, XR[b]
Mycobacterium tuberculosis	Tuberculosis (TB)	IFN-γ deficiency	*IL12RB1, TYK2*[c]	Monogenic AR
Neisseria	Invasive disease	Complement deficiency	*C5*, *C6*, *C7*, *C8A*, *C8B*, *C9*, *CFB, CFD, CFP*	Monogenic AR, XR
Encapsulated pyogenic bacteria	Invasive disease	Complement deficiency	*C1QA, C1QB, C1QC, C1S, C2, C3, C4A, C4B, CFH, CFI*	Monogenic AR
Streptococcus pneumoniae	Invasive disease	TIR response deficiency	*IRAK4, MYD88, NEMO, HOIL1, HOIP, RPSA* [d]	Monogenic AR, AD
Staphylococcus aureus	Recurrent disease	TLR2 response deficiency or IL-6 deficiency	*TIRAP, IL6RA, ZNF341, STAT3, IL6ST* [e]	Mendelian or monogenic AR, AD
Tropheryma whipplei	Whipple's disease	IRF4 deficiency	*IRF4*	Monogenic AD
Epstein–Barr virus	X-linked lymphoproliferative disease; severe infection; B-cell lymphoma	Cytotoxic T/NK cell deficiency	*SH2D1A, XIAP, CD27, CD70, ITK, TNFRSF9, MAGT1*	Mendelian or monogenic AR, XR
Human papillomavirus	Epidermodysplasia verruciformis Recurrent respiratory papillomatosis	EVER-CIB1 deficiency NLRP1 gain of function (GOF)	*EVER1*, *EVER2, CIB1* *NLRP1*	Mendelian AR Monogenic AR
Herpes simplex virus (HSV)	Forebrain encephalitis	TLR3-IFN-α/β deficiency	*UNC93B, TLR3, TRAF3, TRIF, TBK1, IRF3*	Monogenic AR, AD
		snoRNA31 deficiency	*SNORA31*	Monogenic AD
HSV, influenza, etc.	Brainstem encephalitis	DBR1 deficiency	*DBR1*	Mendelian AR
Influenza	Severe influenza	Type I and III IFN deficiency	*IRF7, IRF9, TLR3*	Monogenic AR, AD
Cytomegalovirus (CMV)	Lethal infection	NOS2 deficiency	*NOS2*	Mendelian AR
Rhinovirus, Respiratory syncitial virus (RSV)	Recurrent/severe infections	MDA5 deficiency	*IFIH1*	Monogenic AR, AD
Human herpes virus 8	Kaposi sarcoma	OX40 deficiency	*OX40*	Monogenic AR
Hepatitis A virus	Fulminant hepatitis	IL18BP deficiency	*IL18BP*	Monogenic AR
Live measles and yellow fever vaccines	Severe infections	IFN-α/β response deficiency	*IFNAR1, IFNAR2, STAT1, STAT2*	Monogenic AR
Candida	CMC	IL-17 deficiency	*IL17F, IL17RA, IL17RC, TRAP3IP2, STAT1, JNK1*	Mendelian AR, AD
Dermatophytes	Invasive dermatophytosis	CARD9 deficiency	*CARD9*	Mendelian AR
Trypanosoma evansi	Trypanosomiasis	APOL1 deficiency	*APOL1*	Monogenic AR
Plasmodium vivax	Resistance to infection	Lack of receptor for pathogen in erythrocytes	*DARC*	Mendelian AR
Human immunodeficiency virus-1	Resistance to infection	Lack of receptor for pathogen in $CD4^+$ T cells	*CCR5*	Mendelian AR
Norovirus	Resistance to infection	Lack of receptor for pathogen in intestinal epithelium	*FUT2*	Mendelian AR

[a]We refer to monogenic disorders with complete clinical penetrance as Mendelian, and those with incomplete penetrance as monogenic

[b]*AR* autosomal recessive, *AD* autosomal dominant, *XR* X-linked recessive

[c]We list only genes found mutated in two or more patients with TB. Most MSMD-causing genes are also rare genetic etiologies of TB. We do not indicate any difference between allelic forms. This is particularly relevant for *TYK2*, as homozygosity for loss of function (LOF) variants is a rare etiology of TB, whereas homozygosity for the P1104A allele is common in the general population and may account for about 1% of TB cases in humans of European descent (Boisson-Dupuis et al. 2018; Kerner et al. 2019)

[d]Variants of *RPSA* underlie isolated congenital asplenia

[e]Variants of *STAT3*, *ZNF341* and *IL6ST* underlie staphylococcal disease and a few other infections

caused by inborn errors of IL-17A/F immunity (Li et al. 2017, 2019, Puel et al. 2012), with mutations of 10 genes and 11 allelic forms. The notions of genetic heterogeneity and physiological homogeneity have gained momentum from next-generation sequencing (NGS) studies. In this respect, 2010 marked another watershed moment, as NGS provided both clinical and population geneticists with the same genetic data. It is probably fair to say that NGS has brought clinical and population genetics closer than ever, with both fields now analyzing the same types of data. Thanks to this joint, synergistic approach, the search for monogenic lesions underlying severe infectious diseases has blossomed, as exemplified by the population-based discovery of homozygosity for the P1104A *TYK2* allele as a factor conferring predisposition to tuberculosis (Boisson-Dupuis et al. 2018; Kerner et al. 2019). We do not mean to imply that all new genetic etiologies can easily and immediately be connected physiologically with known etiologies. For example, *SNORA31* mutations have been found to underlie herpes simplex encephalitis, but appear to be unconnected to mutations in the TLR3 pathway (Lafaille et al. 2019). This work may take time, as it is much like a giant jigsaw puzzle. However, we are willing to predict that this hypothesis often applies and that there will probably be a single, final, assembled molecular puzzle corresponding to each severe infectious disease.

Human genetics of infectious diseases: quo vadis?

Three key questions, at the crossroads of clinical and population genetics, have emerged from these studies. First, does this model of monogenic lesions, typically with incomplete penetrance (complete penetrance observed more rarely), and with genetic heterogeneity and physiological homogeneity, apply to all severe infections? All infections studied to date have been found to be monogenic, in at least one patient, but does this apply to all infections, rare or common? Second, are there only rare genetic etiologies, accounting for only a small proportion of any common infection (and arguably a higher proportion of rare infections)? The recent identification of homozygosity for *TYK2* P1104A as a common recessive etiology of tuberculosis, suggests that monogenic (but not Mendelian) infections may be more common than previously thought (Boisson-Dupuis et al. 2018; Kerner et al. 2019). What is the proportion of monogenic forms, for any given infection, including common infections? Third, what are the determinants of incomplete penetrance? This is of importance, especially as different infections have been shown to be allelic, and even driven by the same allele in different patients, as illustrated by herpes simplex encephalitis and influenza pneumonitis, which seem to strike different patients with *TLR3* mutations (Lim et al. 2019; Zhang et al. 2007). Genetic modifiers may be involved, although other factors mentioned above, such as microbe numbers and the route of infection, probably also play a key role. There are probably also digenic and oligogenic forms of predisposition to infection. Large population-based studies should help us to tackle these three problems. For example, the pandemics of SARS-CoV-2 infection led to the COVID Human Genetic Effort (https://www.covidhge.com/), which is an international consortium that aims to analyze the human genetic basis of life-threatening COVID-19 in previously healthy and relatively young (< 50 years) patients. In this context, it is worth mentioning that monogenic resistance to infections has not grown, as a field, as quickly and broadly as studies of monogenic forms of predisposition. The three compelling cases of resistance were discovered in 1976, 1996, and 2003 for infections with *Plasmodium vivax* (Miller et al. 1976), HIV (Dean et al. 1996; Liu et al. 1996; Samson et al. 1996), and norovirus (Lindesmith et al. 2003), respectively, and the genetic lesion underlying resistance to *P. vivax* was not described until 1995 (Tournamille et al. 1995). It is surprising that this field has not taken off yet, particularly in light of the small but distinct proportion of humans completely resistant to infection with some very common pathogens, as attested by negative serological tests.

Clinical implications

The discovery that many severe infections can have a monogenic basis, with incomplete penetrance and genetic heterogeneity but physiological homogeneity, at least in some patients, has important clinical and biological implications. At the clinical level, these findings provide patients with a molecular diagnosis and open up possibilities for the genetic counseling of their families. An understanding of the pathogenesis of a disease is always useful clinically, in the long term, if not more rapidly. This, in turn, paves the way for preventive or therapeutic approaches aiming to restore immunity. For example, an infection caused by an inherited deficiency of a cytokine can best be prevented or treated with the corresponding recombinant cytokine, or a key product controlled by that cytokine. The best example of this to date is provided by recombinant IFN-γ treatment in patients with genetic defects impairing the production of IFN-γ (Alangari et al. 2011; Holland 2001). It is also worth mentioning that the elucidation of the pathogenesis of an infectious disease in rare monogenic cases can shed light onto the mechanisms at work in other, more common patients, such as those infected with HIV (Zhang et al. 2017). Finally, vaccine development will also benefit from this approach, as its aim is to protect genetically predisposed individuals; whereas, the vaccination of naturally resistant

individuals is not necessary and may be a major confounding factor in any trial (Glass et al. 2012). The biological implications of these studies are also important. An inherited deficiency defines the redundant and non-redundant roles of the corresponding gene, and its ecologically relevant and evolutionarily selected functions (Barreiro and Quintana-Murci 2010; Quintana-Murci 2019; Quintana-Murci and Clark 2013). These studies define immunity to infection *in natura* (Quintana-Murci et al. 2007). This contrasts with and complements the study of experimental infections in experimental conditions in animal models of disease (Casanova and Abel 2004; Fortin et al. 2007; Quintana-Murci et al. 2007). Such studies also define the levels of redundancy of human genes: genes with low levels of redundancy underlie multiple infections when mutated; whereas, highly redundant genes underlie one or a few infections; completely redundant genes underlie no infectious phenotype; and beneficially redundant genes underlie resistance to one or more infections when mutated (Casanova and Abel 2018).

Biological implications

The biological implications of the field are already apparent, perhaps more so than the clinical implications. Indeed, the human genetic approach that launched this description of immunity to infection in natural conditions has already overturned many immunological dogmas (Casanova et al. 2013). For example, TLRs other than TLR3 and IL-1Rs were thought to be crucial for host defense against various infectious agents. The discovery of IRAK4 and MyD88 deficiencies showed that they were, instead, collectively essential for host defense against pneumococcus and staphylococcus, but otherwise largely redundant (Casanova et al. 2011; Ku et al. 2007; Picard et al. 2003; von Bernuth et al. 2008, 2012). This approach has also revealed the role of cells other than leukocytes in immunity (Zhang et al. 2019). For example, mutations of *TLR3* were shown to underlie herpes simplex virus encephalitis and influenza pneumonitis, not by disrupting leukocytic immunity, but by impairing cortical neuron and pulmonary epithelial cell intrinsic immunity to viruses (Casanova et al. 2011; Casrouge et al. 2006; Lafaille et al. 2012; Lim et al. 2019; Zhang et al. 2007; Zimmer et al. 2018). The reasons why these and other studies are at odds with immunological studies and predictions is a topic of interest extending well beyond the scope of this chapter. Suffice it to say that immunity to infection in natural conditions, which can be best studied by human genetics, has been found to have a much higher level of redundancy than previously anticipated (Casanova and Abel 2018). The specificity of an inborn error of immunity for a particular infection is not the result of a specific molecular interaction, as for most forms of specificity in immunology. Instead, it reflects the broad redundancy of the genetic defect for host defense, with only a hole in protective immunity being clinically visible. These defects can be seen as lacunar inborn errors of immunity to infection.

Topics covered in this special issue

We have assembled, in this special issue of *Human Genetics,* a collection of reviews covering specific aspects of this area of biomedical research. Some chapters review recent progress in related fields, such as human evolutionary genetics (Lluis Quintana-Murci and Luis Barreiro) (Barreiro and Quintana-Murci 2020), human immunology (Petter Brodin) (Brodin 2020), human non-protein coding variants (Amalio Telenti) (Telenti and di Iulio 2019), the question of penetrance (Dusan Bogunovic) (Gruber and Bogunovic 2020), and computational approaches in human genetics (Yuval Itan) (Bayrak and Itan 2020). Most chapters cover the human genetic basis of specific infections: (i) mycobacterial infections, including MSMD (Jacinta Bustamante) (Bustamante 2020), tuberculosis (Stéphanie Boisson-Dupuis) (Boisson-Dupuis 2020), leprosy (Erwin Schurr) (Fava et al. 2019), and Buruli ulcer (Jérémy Manry) (Manry 2020); (ii) other bacterial infections, including those caused by *Neisseria* (Vanessa Sancho-Shimizu and Mike Levin) (Hodeib et al. 2020), and pyogenic bacteria (Bertrand Boisson) (Boisson 2020); (iii) viral infections, including those caused by Epstein–Barr virus (Stuart Tangye) (Tangye 2020), human papilloma viruses (Vivien Béziat) (Beziat 2020), influenza virus (Qian Zhang) (Zhang 2020a), rhinovirus (Helen Su) (Lamborn and Su 2020), norovirus (Jacques Le Pendu) (Le Pendu and Ruvoen-Clouet 2019), human immunodeficiency virus (Paul McLaren) (Gingras et al. 2020), and viruses causing encephalitis (Shen-Ying Zhang) (Zhang 2020b), chronic hepatitis (Aurélie Cobat) (Nahon and Cobat 2020), and fulminant hepatitis (Emmanuelle Jouanguy) (Jouanguy 2020); (iv) peripheral and invasive candidiasis (Anne Puel) (Puel 2020); (v) parasitic infections, including malaria (Tom Williams) (Kariuki and Williams 2020), leishmaniasis (Jenefer Blackwell) (Blackwell et al. 2020), and schistosomiasis (Alain Dessein) (Dessein et al. 2020); and (vi) fetal and neonatal infections (Alessandro Borghesi) (Borghesi et al. 2020). Unfortunately, a few monogenic infectious diseases described in Table 1 are not reviewed here, including Whipple's disease (*Tropheryma whipplei*) due to IRF4 deficiency (Guerin et al. 2018), Kaposi sarcoma (human herpes virus 8) due to OX40 deficiency (Byun et al. 2013), lethal cytomegalovirus infection due to NOS2 deficiency (Drutman et al. 2020), and trypanosomiasis (*Trypanosoma evansi*) due to APOL1 deficiency (Vanhollebeke et al. 2006). One chapter addresses the timely question of interaction between the human genome and the viral genome (Jacques Fellay)

(Fellay and Pedergnana 2019); whereas, another reviews autoimmune phenocopies of monogenic infections due to autoantibodies against cytokines (Cheng-Lung Ku and Rainer Doffinger) (Ku et al. 2020). Finally, we have invited colleagues outside the field of the human genetics of infectious diseases to contribute to this issue with reviews about the genetic basis of infections in other species. In particular, Otto Haller reviews the Mx saga (Haller and Kochs 2019), concerning the first animal/human gene conferring predisposition to a specific infection to be identified (Staeheli et al. 1986), and Philippe Gros, who had discovered the molecular basis of the Bcg locus by performing the first positional cloning in mice (Vidal et al. 1993), reviews the complex role of IRF8 in mice and humans (Salem et al. 2020).

Concluding remarks

In assembling this collection of reviews, we intend to provide a broad overview of the vitality of this nascent field. We think the field has an enormous potential for growth, as the vast majority of human infections have not been studied from a human genetic and immunological angle. Moreover, for the infections that have been studied, no genetic defects have yet been identified for the vast majority of patients. This field is important medically, as most microbes will inevitably become resistant to current anti-infectious agents, and the development of novel anti-infectious agents is likely be slower than in the past. Restoring the immunity of immunodeficient patients with recombinant cytokines or other molecules will become an alternative and timely approach. Moreover, infections are the only conditions that can kill a sizeable proportion of humans in a short period of time, as dramatically reminded by the recent Ebola epidemics and the current SARS-CoV-2 pandemics. We will not be wiped out by malignant, metabolic, or neurodegenerative conditions. Emerging and re-emerging microbes, and microbes resistant to anti-infectious agents pose a fundamental threat to mankind, the magnitude of which is difficult to overestimate. Finally, the study of host defense in natural conditions is a fundamental biological problem. Indeed, bacteria and archaea inhabited the planet alone for about one billion years, before the arrival of unicellular eukaryotes, with which they cohabited for about another billion years. Phages and other viruses accompanied them. Understanding how multicellular eukaryotes, including plants and animals, and, of course humans, developed in this ocean of unicellular organisms and viruses is a fundamental biological problem (Futuyma 1998; Woese et al. 1990). The immunity of multicellular organisms to unicellular organisms and viruses, and even to other multicellular organisms, is both primordial and essential. It can be studied by means of genetics, and ideally by human genetics.

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