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Human inborn errors of immunity to infection affecting cells other than leukocytes: from the immune system to the whole organism

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Abstract

Studies of vertebrate immunity have traditionally focused on professional cells, including circulating and tissue-resident leukocytes. However, evidence to suggest that non-professional cells are also essential for protective immunity in natural conditions of infection has emerged from three lines of research in human genetics. First, studies of Mendelian resistance to infection have revealed an essential role of DARC-expressing erythrocytes in protection against *Plasmodium vivax* infection, and an essential role of FUT2-expressing intestinal epithelial cells for protection against norovirus and rotavirus infections. Second, studies of inborn errors of non-hematopoietic cell-extrinsic immunity have shown that APOL1 and complement cascade components secreted by hepatocytes are essential for protective immunity to trypanosome and pyogenic bacteria, respectively. Third, studies of inborn errors of non-hematopoietic cell-intrinsic immunity have suggested that keratinocytes, pulmonary epithelial cells, and cortical neurons are essential for tissue-specific protective immunity to human papillomaviruses, influenza virus, and herpes simplex virus, respectively. Various other types of genetic resistance or predisposition to infection in human populations are not readily explained by inborn variants of genes operating in leukocytes and may therefore involve defects in other cells. The probing of this unchartered territory by human genetics is reshaping immunology, by scaling immunity to infection up from the immune system to the whole organism.

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Introduction

The human body comprises more than 400 discernable cell types [1]. All cell types are thought to contribute to host defense, because (i) their presence ensures the physical delineation and integrity of tissues and organs, (ii) they interact with professional leukocytes via soluble and membrane-bound molecules, and (iii) they are targets of microbes and their products. However, host defense in vertebrates has traditionally been attributed to the immune system, which was largely seen as restricted to immunoglobulins (Ig) and complement during the “immunochemistry” period in the history of immunology. This definition was expanded to include leukocytes during the more recent “immunobiology” period, which began in the 1960s [2]. This is understandable, as immunology has, as a discipline, mostly focused on antigens rather than pathogens, as a direct consequence of Pasteur’s discovery of the principle of specific vaccination in 1881 [3]. reinforced by Landsteiner’s discovery of specific antibody responses to haptens in 1917 [4]. Phagocytes have been known to contribute to protective immunity since Metchnikoff s work, but their role in host defense was rarely studied by immunologists, due to a lack of antigen specificity [5]. Only since the 1990s have immunologists turned their attention to the contributions of innate immunity to host defense at large, as illustrated by their rediscovery of granulocytes, which had traditionally been studied by hematologists [6]. Nevertheless, it is generally thought that immunity is ensured exclusively by the circulating and tissue-resident professional leukocytes, including myeloid and lymphoid cells, mostly of hematopoietic origin, together with certain tissue macrophages generated earlier in embryonic development [7,8].

Other cells, not included in this definition of the immune system, are rarely considered to play a role in host defense in humans or other vertebrates. The classic dichotomies of cellular and humoral immunity, and innate and adaptive immunity, typically refer to leukocytes [9,10]. Nevertheless, the development or function of certain leukocyte subsets can be strongly affected by deficiencies of non-hematopoietic cells that prevent the development of certain lymphoid organs. Indeed, a phenocopy of severe combined immunodeficiency can result from thymic stromal cell-intrinsic defects of thymus development in patients with autosomal recessive (AR) FOXN1 deficiency or autosomal dominant (AD) Di George syndrome due to the 22q11.2 deletion or mutations of the *CHD7* gene [11,12]. Likewise, AD RPSA deficiency results in isolated congenital asplenia, abolishing the filtering function of splenic macrophages [13]. Moreover, sickle-cell disease (SCD) and cystic fibrosis (CF) are well-known AR disorders of cells other than leukocytes with life-threatening infectious phenotypes [14–19]. The *HBB* gene is expressed in erythrocytes, whereas *CFTR* is expressed in various cell types and organs, including, in particular, the ionocytes of the pulmonary epithelium [20]. Patients with SCD are prone to invasive bacterial infections because of functional asplenia [15,21]. Patients with CF are probably prone to respiratory infections because of abnormal fluid composition within the airway [16–19]. Variants of *DCTN4* act as modifiers of chronic *Pseudomonas aeruginosa* infection in CF patients [22]. Both SCD and CF are inborn errors conferring a predisposition to infection, but the cellular basis of the infections associated with them remains incompletely understood. We review here the human genetic studies that have provided

evidence for an essential role of specific cells other than leukocytes in host defense under natural conditions of infection, a hallmark of human studies [23–25].

Monogenic resistance to infections: erythrocytes and the intestinal epithelium

The study of monogenic resistance to human infections has provided compelling evidence that non-professional cells play an essential role in protective immunity. Protection against infection with *Plasmodium vivax* is conferred by a lack of expression of the Duffy antigen receptor for chemokines (DARC), a coreceptor for the parasite on the surface of erythrocytes [26]. Duffy-negative erythrocytes were shown to resist invasion by *P. vivax* [27] and its simian homolog *P. knowlesi* [28] *in vitro*. The resistance trait is AR and the causal single-nucleotide mutation, also known as FY*O (Duffy null), disrupts a binding site for the GATA1 erythroid transcription factor in the *DARC* promoter, thereby selectively preventing gene transcription in erythroid cells [29]. The relevance of this erythrocyte-intrinsic mechanism of host defense is illustrated by evolutionary studies of the *DARC* locus. Indeed, natural selection in areas of endemic disease has increased the proportion of resistant individuals. The Duffy null mutation is not found in European populations, but has become fixed in some African populations in which *P. vivax* infection has been endemic [30]. A recent study confirmed the positive selection of an FY*O null mutation, by showing that this mutation swept to fixation in Africa from a very low initial frequency (0.1%), with a very strong selection coefficient [31]. This gene displays “beneficial redundancy” [32], although the protection it confers is not absolute, with rare observations of *P. vivax* infection in Duffy-negative subjects [33,34]. Understandably, the deficiency of this chemokine receptor does not seem to have deleterious effects on any other physiological pathways. Indeed, the expression defect is erythrocyte-specific, as the DARC chemokine receptor is expressed normally on other cell types [29].

Resistance to certain enteric viruses is provided by biallelic loss-of-function (LOF) mutations of the fucosyltransferase 2 (*FUT2*) gene [35], which encodes a protein that regulates the expression of histoblood group antigens (HBGAs) on the surface of mucosal epithelial cells of the gastrointestinal, genitourinary, and respiratory tracts, and is responsible for the “secretor” phenotype [36,37]. Several LOF *FUT2* mutations underlie the “non-secretor” phenotype, which confers resistance to norovirus [38,39] and rotavirus [40,41] infections. Common strains of norovirus (particularly genogroups I and II) and rotavirus (particularly the P[4] and P[8] genotypes) bind to HBGA [37,42–44]. LOF mutations affecting HBGA expression therefore lead to resistance to these strains [35,45]. However, a recent study showed that the binding of rotavirus to HBGA was not essential for the *in vitro* infection of transformed cells [46]. This finding requires confirmation in more relevant cellular models, such as human intestinal organoids [47], but it suggests that HBGAs may enhance viral replication and disease development without actually being essential for infection *per se* [46]. The *FUT2* gene also displays “beneficial redundancy” [32], although protection against enteric viral diseases is not absolute [45]. Moreover, *FUT2* non-secretor status has been associated with predisposition to Crohn’s disease [48], Behçet’s disease [49], and various bacterial infections [35] including otitis media [50]. Consistently, a complex

pattern of natural selection has been described for *FUT2*, with most variants displaying a long history of balancing selection in Eurasian and African populations [51]. Overall, *FUT2* may be considered an important genetic factor influencing epithelial-intrinsic mucosal immunity to various pathogens in the intestinal tract [50,52]. Thus, humans can develop protective immunity to life-threatening infections through the natural selection of genotypes at the *DARC* and *FUT2* loci that block the infection of nonprofessional target cells by parasites and viruses, respectively. Allelic variants of genes expressed in erythrocytes and the intestinal epithelium can therefore be life-saving.

Inborn errors of complement and APOL1: hepatocytes

Since 1966, inherited defects of various components of the complement cascade have been shown to underlie one or more infections [53–59]. About 50 proteins contribute to the three branches of complement and their fine regulation [60,61]. Most of these proteins are synthesized in the liver, principally by hepatocytes [62–66], but a few are produced predominantly by other cells [67]. The classical complement pathway component C1q can be produced *in vitro* by epithelial cells, fibroblasts, and monocytes/macrophages [68,69]. The alternative pathway component factor D is produced mostly by adipocytes [70,71] and, to a lesser extent, by monocytes/macrophages, whereas properdin is produced principally by monocytes/macrophages [72] and, to a lesser extent, by granulocytes and lymphocytes [72]. The main sources of terminal component C7 are monocytes and tissue-resident macrophages, including Kupffer cells [73]. Nevertheless, at least 90% of the total amount of complement proteins in the plasma is synthesized by liver hepatocytes [74], as demonstrated by the infectious diseases occurring as a result of acquired complement deficiency in patients with liver failure [74]. Defects in the early components (C1, C4, C2) of the classical pathway (C1-C9)[75] usually underlie invasive childhood infections with encapsulated pyogenic bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae* [54–59,75–84]. Defects of C3, affecting both the classical and alternative pathways, and of factor H or factor I from the alternative pathway also underlie recurrent and severe pyogenic infections [84–92]. By contrast, defects of the terminal components (C5-C9) of the membrane-attack complex, or of the activating proteins properdin or factor D of the alternative pathway underlie selective susceptibility to life-threatening, invasive *Neisseria* diseases, typically meningococcal meningitis, which frequently recur [56,93–110], Numerous mutations of the corresponding genes have been described since 1966 [55,56,58,76,78–80,83,84,86,87,89–102,107–110]. Overall, these findings demonstrate that immunity mediated by hepatocytes can be life-saving, through the secretion of complement components into the bloodstream.

Apolipoprotein LI (APOL1), encoded by the *APOL1* gene, which is found exclusively in primates, is a component of serum high-density lipoproteins that is also produced mostly in the liver by hepatocytes, and, to a lesser extent, in other tissues such as the lung, placenta, spleen, and kidney [111–113]. Surprisingly, it has been shown to play a key role in host defense against trypanosomes. *Trypanosoma evansi* (*T. evansi*) is a weakly virulent parasite unable to cause disease in the vast majority of humans. However, it was found to be the cause of disease in an Indian patient whose serum displayed no lytic activity with *T. evansi* [114]. This patient has been diagnosed with AR, complete APOL1 deficiency [114]. The

addition of recombinant APOL1 to the patient' serum rescued its trypanolytic activity [114]. Human APOL1 is, therefore, essential for protective immunity to *T. evansi in vivo*. APOL1 also plays a role in immunity to infection with the more virulent *T. brucei in vitro* [115,116]. Following its endocytosis by trypanosomes, the secreted APOL1 forms anion-selective pores in the lysosomal membrane of the trypanosome, inducing uncontrolled osmotic swelling of the lysosome, leading to lysis of the trypanosome [117,118]. This mechanism explains the natural resistance of humans to infection with weakly virulent strains of trypanosomes, such as *T. evansi*. By contrast, *T. brucei rhodesiense* and *T. brucei gambiense*, which are endemic in Eastern and Western Africa, respectively, are resistant to APOL1, and are therefore able to cause sleeping sickness (also known as human African trypanosomiasis, HAT) in most infected individuals [119–121]. The serum resistance-associated (SRA) protein of *T. brucei rhodesiense* and the serum resistance glycoprotein of *T. brucei gambiense* (TgsGP) interact specifically with APOL1, and this interaction renders the trypanosome resistant [122,123]. Interestingly, two variants encoding APOL1 of enhanced trypanolytic activity against *T. brucei rhodesiense* are only present in African populations where they harbor signatures of positive selection while increasing the risk of kidney disease [124], and were found to protect against *T. brucei rhodesiense* infection in an Ugandan population [125]. Liver-produced APOL1 is thus essential for host defense against trypanosomes, providing another example of the life-saving role of hepatocytes in immunity to infection through their secretion of particular products.

Epidermodysplasia verruciformis: keratinocytes

Human papillomaviruses (HPVs) display strict tropism for keratinocytes, the major component of stratifying epithelia [126,127]. This tropism is dependent on the lifecycle of HPV, which is built around epithelial stratification. HPVs target self-renewing stem cells in the basal layer of the epidermis and the bulge of the hair follicles. HPV infections are widespread, usually asymptomatic and cleared up after a few months by the T-cell response. Epidermodysplasia verruciformis (EV) is a genetic vulnerability to specific HPVs and was the first of the five known "Mendelian infections" (OMIM 226400) to be described [128–130]. Indeed, EV was first clinically described in 1922 as a congenital dermatosis characterized by lifelong disseminated and persistent flat warts and pityriasis versicolor-like (PV-like) lesions [131]. An AR mode of inheritance was documented in 1933 and a viral etiology in 1946 [132,133]. EV is associated with a higher risk of non-melanoma skin carcinomas (NMSC) [134,135], but there are no other clinical signs in most patients with typical "isolated EV", which is apparently due to inborn errors of keratinocytes [136]. Other patients suffering from EV and other infectious or tumoral manifestations display atypical, "syndromic EV", due to inborn errors of T cells [137,138]. In 1978, Orth et al. showed that EV skin lesions are caused by a very specific group of weakly virulent, E5- and E8-deficient skin- and keratinocyte-tropic human HP Vs from the β genus [139]. β-HPVs are very common and cause asymptomatic infections of the skin in the general population [140,141]. In 2002, Orth et al. identified the first two EV-causing genes through genome-wide linkage (GWL) analysis, with the discovery of homozygous null mutations in *EVER1* (*TMC6*) or *EVER2* (*TMC8*) in patients with isolated EV [142–147]. These patients have no detectable

leukocyte phenotype [148,149], suggesting that EVER proteins govern keratinocyte-intrinsic immunity to β-HPVs [143].

In 2004, the observation that patients with severe combined immunodeficiency due to mutations of the related genes *IL2RG* and *JAK3*, normally expressed in both leukocytes and keratinocytes, often developed isolated EV years after successful hematopoietic stem cell transplantation [150,151], further suggested an essential role for keratinocytes in immunity to β-HPVs [150]. Biochemical studies of EVER proteins proved very difficult, at least partly because no specific antibody could be raised against these proteins. The recent discovery of AR complete CIB1 deficiency in other patients with isolated EV has provided new insight into the pathogenesis of EV [152,153]. In mice, the CIB1 protein is ubiquitous and functionally pleiotropic [154]. CIB1-deficient mice have phenotypes relating to the heart, vasculature, hemostasis, and fertility [155–158]. None of these phenotypes has been found in CIB1-deficient patients presenting with isolated EV, even in late adulthood [152,153]. In fact, human CIB1 is strongly expressed in keratinocytes, in which it forms a complex with the EVER1 and EVER2 proteins [152]. CIB1 levels are very low in keratinocytes with deficiencies of EVER1 or EVER2 [152]. The requirement of EVER1 and EVER2 for CIB1 expression in keratinocytes accounts for EVER1, EVER2 and CIB1 deficiencies being clinical and virological phenocopies. These findings also suggest that this complex governs keratinocyte-intrinsic immunity to β-HPVs. However, the previously reported functions of EVER proteins, such as their interaction with the zinc transporter ZnT-1 [159], their control of the activity of the transcription factor AP-1 [159,160], and their involvement in cellular responses to TNF-α [160,161], were shown not to require CIB1 [152,153]. The disruption of these functions is not, therefore, the core mechanism of typical EV. By contrast, CIB1 does interact with E5 and E8, the viral proteins not expressed by β-HPVs, suggesting that the EVER-CIB1 complex acts as a restriction factor for HPVs in human keratinocytes [152]. Interestingly, the EVER-CIB1 complex is apparently not induced by anti-viral IFNs, unlike many other mechanisms of cell-intrinsic immunity [162–165]. Overall, studies of EV suggest that keratinocyte-intrinsic immunity to β-HPVs is governed by the EVER-CIB1 complex.

Inborn errors underlying influenza pneumonitis: pulmonary epithelial cells

Influenza viruses, especially the influenza A virus (IAV), cause yearly seasonal and, more rarely, pandemic infections [166]. However, even during the worst ever pandemic, the 1918 “Spanish Flu” pandemic, only a minority (fewer than 10%) of symptomatic patients died. The proportion of lethal infections in the course of seasonal influenza is smaller still, with case-fatality ratios of only about 0.04-0.4% [167,168]. IAV is a single-stranded, segmented RNA virus from the Orthomyxoviridae family of viruses [166]. It is a respiratory virus that infects the lung epithelial cells, including both type 1 and 2 pneumocytes *in vitro*, with different preferences according to the strain concerned. Severe infections can cause acute respiratory distress syndrome (ARDS), which is characterized by damage to the epithelial-endothelial barrier, fluid leakage into the alveolar lumen, and respiratory insufficiency, often leading to multiple organ failure and associated with mortality rates of up to 60% [169]. In children, unlike adults, most cases of influenza ARDS cannot be accounted for by pre-existing cardiac or pulmonary lesions [168]. Influenza has an incubation period of only

about 1-2 days and no viremia is detected before ARDS [170], suggesting that infection is initially confined to the lung, where pulmonary epithelial cell-intrinsic and resident alveolar macrophages probably play an important role in controlling the infection before leukocyte extravasation. Indeed, influenza ARDS has not been reported in children with any of the more than 200 primary immunodeficiencies affecting T and B cells, including severe combined immunodeficiencies and agammaglobulinemia [167,171]. Adaptive immunity is required for protective responses to influenza vaccination, but does not seem to be required for host defense against influenza virus. Collectively, these findings suggested that influenza ARDS in otherwise healthy, unvaccinated children might be due to single-gene inborn errors of cell-intrinsic or innate immunity.

Consistent with the genetic hypothesis, forward genetics approaches identified inherited Mxl deficiency as a strong determinant of vulnerability to influenza in mice [167,172]. Mx1 is an IFN-stimulated gene (ISG) product [172], so this observation also indicated the involvement of type I and III anti-viral IFNs. Human GATA2 deficiency, a primary immunodeficiency in which counts of dendritic cells, monocytes, NK cells, and B cells are low, underlying multiple infections, was recently reported to underlie influenza ARDS in adult patients, suggesting that IFN-producing plasmacytoid dendritic cells (pDCs) are crucial for immunity to influenza virus [173,174]. In 2015, AR IRF7 deficiency was identified as the first monogenic etiology of isolated influenza ARDS, in an otherwise healthy child [175]. IRF7 is a transcription factor that amplifies the expression of type I (13 IFNA, IFNB, IFNE, IFNK, IFNW) and type III (IL29, IL28A, IL28B) IFN genes. IRF7 deficiency is an inborn error of innate immunity, as the patient's pDCs do not amplify the production of type I and III IFNs [175]. It is also an inborn error of cell-intrinsic immunity, as pulmonary epithelial cells (PECs) do not control viral growth [175]. These findings were corroborated by the subsequent discovery of an AR deficiency of IRF9, which normally forms ISGF3 with STAT1 and STAT2 upon stimulation with type I and III IFNs, in another child [176]. The patient's fibroblasts did not activate ISGF3-dependent ISGs in response to type I IFNs and did not control viral growth [176]. The patient's pDCs and PECs were not tested, but would not be predicted to form ISGF3 either. These newly identified inborn errors highlighted the importance of type I and III IFNs in the control of IAV infection. The relative contributions of PECs and pDCs (and other cell types) to the pathogenesis of influenza ARDS in IRF7- and IRF9-deficient patients are unknown. Interestingly, human patients with other inborn errors of type I and III IFN immunity have not been reported to suffer from severe influenza, suggesting that penetrance may be incomplete, due to a lack of infection or other mechanisms [177–184]. Although the cellular basis of viral infections other than influenza seen in these patients is unclear, it may involve cells other than leukocytes. At any rate, the search for new genetic etiologies of influenza ARDS should clarify the molecular and cellular basis of this disease, including the potential contribution of IFN-dependent mechanisms in PECs.

Inborn errors underlying viral encephalitis: neurons and oligodendrocytes

At least twenty viruses can cause devastating encephalitis in humans, reaching the brain by crossing the blood-brain barrier (e.g. cytomegalovirus), via the peripheral nervous system (PNS) (e.g. herpes simplex virus 1 (HSV-1)), or both (e.g. influenza virus (IV)) [185].

Typically, viral encephalitis is not followed by dissemination of the virus to other organs, suggesting that its pathogenesis may involve an impairment of central nervous system (CNS)-specific immunity to viruses. Human genetic studies of isolated HSV-1 encephalitis (HSE) of the forebrain led to the discovery of single-gene inborn errors of the Toll-like receptor 3 (TLR3)-interferon (IFN)-α/β and -λ pathway, due to mono- or biallelic mutations of six TLR3 pathway genes (*TLR3*, *UNC93B1*, *TRIF*, *TRAF3*, *TBK1* or *IRF3*) [186–196]. Moreover, AR complete STAT1 deficiency [178,197,198] and X-linked partial NEMO deficiency [199–201] were observed in children with mycobacterial disease who died of HSE. These findings suggested that TLR3-dependent IFN-α/β and -λ immunity is critical for host defense against HSV-1 in the CNS. TLR3-mediated antiviral immunity seems to be redundant in most TLR3-expressing cell types, including leukocytes in particular, accounting for the lack of viral dissemination during the course of HSE [188,192]. The hypothesis that CNS-specific cell-intrinsic immunity rather than leukocyte-mediated immunity is critical for host defense against neurotropic viral infection was then tested experimentally, initially with dermal fibroblasts and induced pluripotent stem cell (iPSC)-derived CNS- and PNS-resident cells from patients with forebrain HSE and mutations of TLR3 pathway genes. TLR3 pathway-deficient fibroblasts [187–193] and iPSC-derived cortical neurons and oligodendrocytes [194] were much more susceptible to HSV-1 infection than control cells, probably due to the lack of TLR3-dependent IFN-β and IFN-λ responses. By contrast, *in vitro*-differentiated UNC-93B-deficient astrocytes or neural stem cells, and TLR3-deficient peripheral trigeminal neurons had a susceptibility to infection similar to that of control cells [202]. Microglial cells, the CNS resident macrophages, were not tested. TLR3-dependent, IFN-mediated cortical neuron- and oligodendrocyte-autonomous anti-HSV-1 immunity thus seems to be critical for host defense against HSV-1 infection of the human forebrain. These data provided a plausible mechanism for the pathogenesis of forebrain HSE [187,192].

Children with brainstem infections caused by HSV-1 or other viruses, including influenza B virus (IBV) and norovirus, have recently been studied. These children present inborn errors of RNA lariat metabolism, due to biallelic hypomorphic mutations of *DBR1*, which encodes the only known RNA lariat-debranching enzyme [203,204]. The antiviral responses of leukocytes from DBR1-deficient patients have not been studied, because of the unusual expression profile of *DBR1*. Indeed, DBR1 protein levels are highest in the brainstem and spinal cord, strongly suggesting that DBR1 deficiency disrupts immunity in brainstem-resident cells [203]. Inherited DBR1 deficiency probably underlies viral infection of the brainstem through the disruption of brainstem-specific and cell-intrinsic immunity to viruses. DBR1-deficient fibroblasts from patients, whose TLR3 and IFN-α/β responsive pathways were intact, have been studied as a proxy. They were found to be highly susceptible to HSV-1 and VSV, like TLR3- and STAT1-deficient fibroblasts [203]. The cellular basis of brainstem infection in patients with *DBR1* mutations remains unknown, as iPSC-derived brainstem cells have not been tested. The molecular mechanism also remains elusive. DBR1-deficient fibroblasts have higher RNA lariat levels than control cells. This accumulation of RNA lariats may impair virus recognition by host cells, thereby damaging cell-intrinsic defenses against viral invasion. DBR1 may also regulate the processing of some host protein-coding RNAs, noncoding RNAs (ncRNAs) [205–209], or viral RNA

lariats [210–213], thereby controlling cell-intrinsic defense against intracellular virus replication. Human genetic studies of viral encephalitis have thus shown that TLR3 governs cell-intrinsic immunity to HSV1 in the forebrain, whereas DBR1 governs cell-intrinsic immunity to various viruses in the brainstem. The genetic dissection of HSE and other types of viral encephalitis by forward genetics will pave the way for delineating the contribution of CNS-specific resident cells to protective immunity to viruses.

Conclusion

This review provides an overview of known examples of cell-intrinsic and cell-extrinsic mechanisms by which human non-professional, tissue-resident cells other than leukocytes contribute to protective immunity to infection in natural conditions (Table 1). These findings are probably no more than the tip of the iceberg. The range of cells and mechanisms involved in host defense is almost certainly much broader than previously appreciated. Most of the genetic etiologies of EV, influenza ARDS, and viral encephalitis, remain unknown. Future studies of these three infections will probably reveal novel mechanisms of organ- or tissue-specific, cell-intrinsic immunity to viruses. The pathogenesis of most other tissue- or organ-specific infections striking otherwise healthy patients remains unexplained. In addition, genetic resistance to infections other than *P. vivax* and norovirus infection, including, in particular, viral infections, which make use of only a few receptors to infect target cells, or microbial toxins that target a specific protein, will probably be discovered. Surprisingly, individuals seronegative for many common viruses can be identified in human populations. Finally, inborn errors of liver-produced complement and APOL1 may not be isolated examples of cell-extrinsic immunity by cells other than leukocytes. The forward genetic study of resistance and predisposition to various human infections, in terms of both microbial and anatomical diversity, may identify new components secreted by cells other than leukocytes as essential for certain types of host defense. Overall, it appears that protective immunity to the many microbes in our environment probably involves a much broader range of cells and molecules than initially thought based on the results of studies preferentially focusing on innate and adaptive leukocytes. Protective immunity requires many more cell types than are found in the classically defined immune system. It requires the whole organism.

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Highlights

- Cells other than leukocytes can be essential for protective immunity in humans.
- Human inborn errors of immunity to infection can affect non-professional cells, other than professional leukocytes.
- Immunity to infection is not restricted to the immune system and involves the whole organism.

Table 1.

Human inborn errors of immunity to infection affecting cells other than leukocytes[a]

Gene	Relevant cell type	Infectious phenotype	References
DARC	Erythrocytes	Resistance to *Plasmodium vivax*	26–31
FUT2	Intestinal epithelial cells	Resistance to norovirus, rotavirus	35, 38–41, 44–46
C1	Hepatocytes	Susceptibility to encapsulated pyogenic bacteria	54–59, 75–90, 91
C4			
C2			
C3			
CFH			
CFI			
C5	Hepatocytes	Susceptibility to invasive *Neisseria* infection	56, 93–110
C6			
C7			
C8			
C9			
CFD			
CFP			
APOL1	Hepatocytes	Susceptibility to *Trypanosoma evansi*	114
EVER1	Keratinocytes	Susceptibility to β-human papillomaviruses	142–144
EVER2			142–147
CIB1			152, 153
IRF7	Pulmonary epithelial cells	Susceptibility to influenza virus	175
IRF9			176
TLR3	Cortical neurons and oligodendrocytes	Susceptibility to herpes simplex virus 1	188, 192–194
UNC93B1			187, 194
TRIF			191
TRAF3			190
TBK1			189
IRF3			195
DBR1	Brainstem resident cells	Susceptibility to various viruses	203

[a] See text for explanations.