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Recent Insights into the Pathobiology of Innate Immune Deficiencies

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Abstract

Primary immunodeficiencies are a heterogeneous group of genetically inherited diseases affecting the innate and adaptive immune systems that confer susceptibility to infection, autoimmunity, and cancer. Innate immunity includes neutrophils, macrophages, dendritic cells, natural killer cells, and natural killer T cells in conjunction with natural barriers (mostly skin and gastrointestinal and respiratory mucosa), as well as antimicrobial agents, opsonins (e.g., complement), and cytokines. Although somewhat primitive, innate immune cells can orchestrate discrete immune responses through the recognition of diverse pathogens by different pattern-recognition receptors. In this review, we discuss the most recent discoveries as well as the already established pathophysiologic mechanisms underlying innate immunity defects associated with primary immunodeficiencies.

Keywords

Primary immunodeficiencies; Innate immunity; Neutrophils; Macrophages; Dendritic cells; Natural killer cells; NK cells; NKT cells; Opsonins; Complement; Pattern-recognition receptors

Introduction

Scientists have used different standards to classify the human immune system. One of these practical but arbitrary approaches divides host defense into two complementary compartments: innate and adaptive. These work together to efficiently prevent, control, and when necessary destroy the wide range of pathogens that challenge vertebrates. While T- and B-cell-mediated adaptive immunity requires DNA rearrangement and amplifies its response upon re-exposure to the same antigen, resulting in long-lasting specific immunity, the innate system is preformed in the germline. Innate immunity includes epithelial and mucosal barriers, natural antimicrobial products, pattern-recognition receptors, and cytokines (Table 1). It precedes adaptive immunity phylogenetically and is present in all multicellular organisms, including plants, insects, and animals. Although somewhat primitive, innate immune cells orchestrate discrete immune responses through the recognition of diverse pathogens by pattern-recognition receptors [1–3•]. Neutrophils, macrophages, dendritic cells, natural killer (NK) cells, and NKT cells in conjunction with natural barriers (mostly skin, and gastrointestinal and respiratory mucosa), antimicrobial

agents, opsonins (e.g., complement), and cytokines are critical innate components. We review recent developments in innate immunity and immunodeficiency.

Mononuclear Phagocytes

Mononuclear phagocytes are crucial for antigen presentation and protection against intracellular infections. They are also necessary for lymphocyte stimulation, proliferation, and cytokine production and response. Macrophages are irreplaceable in controlling mycobacterial infections (Fig. 1). Macrophages phagocytose mycobacteria, leading to the production of interleukin (IL)-12 p70, a heterodimer of IL-12 p40 and IL-12 p35, as well as IL-23, a heterodimer of IL-12 p40 and IL-12 p19. IL-12 and IL-23 stimulate T and NK cells through their cognate receptors to phosphorylate signal transducer and activator of transcription (STAT)4, leading to the production of interferon (IFN)- γ . IFN- γ acts through its heterodimeric receptor to phosphorylate primarily *STAT1* and turn on IFN-responsive genes, which promote mycobacterial clearance. Innate immunodeficiencies with increased susceptibility to both tuberculosis and nontuberculous mycobacteria are collectively referred to as *mendelian susceptibility to mycobacterial diseases* (MSMD) [4, 5].

In recent years, seven different genes have been found to be mutated in patients with MSMD: *IFNGR1*, *IFNGR2*, *STAT1*, *IL12B* (IL-12p40), *IL12RB1*, *TYK2*, and *IKBK* (*NEMO*), all of which are involved in IL-12/23-dependent, IFN- γ -mediated immunity. More recently, mutations in *IRF8* were also associated with MSMD. Specific mutations at these loci account for the different inheritance patterns of disorders (autosomal recessive, autosomal dominant, or X-linked), the presence or absence of protein expression (missense or nonsense mutations), the severity of the phenotype (complete or partial deficiency), and the specific function affected. These syndromes are clinically heterogeneous, ranging from locally limited to life-threatening, disseminated mycobacterial diseases. In addition to mycobacteria, other intracellular bacteria (e.g., salmonella), viruses (e.g., varicella zoster virus), and fungi (e.g., histoplasmosis, coccidioidomycosis, paracoccidioidomycosis) have been reported in patients with MSMD [6, 7]. Therefore, although the term MSMD provides a convenient shorthand for discussion of these disorders, it is more appropriate to recognize them as showing mendelian susceptibility to a spectrum of intracellular infections that are heavily dependent on IFN- γ signaling.

Mutations in *IFNGR1* were the first to be identified as conferring innate mycobacterial susceptibility. This gene can be mutated in ways that lead to recessive or dominant transmission. The dominant form is most frequently characterized by nontuberculous mycobacterial osteomyelitis [8]. While recessive complete mutations typically permit no protein expression, dominant mutations are characterized by surface overaccumulation of a mutated receptor that still binds IFN- γ but dominantly inhibits intracellular signaling. Dominant mutations such as 818del4 (a hotspot for *IFNGR1* mutations) introduce stop codons upstream of three critical IFN- γ R1 protein motifs: the endocytosis/recycling domain, the Janus kinase (Jak)1 binding site, and the STAT1 binding site. The lack of the endocytosis/recycling domain permits plasma membrane overaccumulation of a receptor devoid of its signaling capacity that interferes with assembly of the normal competent receptor.

With more than 140 patients identified worldwide, *IL12RB1* deficiency is the most common form of innate mycobacterial susceptibility but appears to be very environment sensitive. Individuals carrying biallelic mutations can display very little or no mycobacterial, salmonella, or fungal susceptibility, which is consistent with partial penetrance and variable expressivity for this deficiency [9•]. This is clearly demonstrated by the paucity of cases of

IL12RB1 deficiency in North America despite similar genetics to parts of Europe and South America, where it is more common.

Male patients with mutations in *NEMO* show broad clinical heterogeneity. *NEMO* encodes the nuclear factor- κ B essential modulator, also known as I κ B kinase (*IKBK*) γ , the critical scaffold component of the IKK complex. Mutations in this gene are responsible for various diseases: amorphic alleles resulting in null mutations lead to incontinentia pigmenti in females but are incompatible with life in male fetuses. On the other hand, hypomorphic alleles can also result in incontinentia pigmenti in females but present in males as various combinations of the syndrome of X-linked anhidrotic ectodermal dysplasia and immunodeficiency. X-linked anhidrotic ectodermal dysplasia with immunodeficiency is probably the most common phenotype, but tremendous heterogeneity exists in this syndrome. Genotype–phenotype associations have been surprisingly elusive in this disease, but mutations at the very C-terminus involving the stop codon have been associated with osteopetrosis and/or lymphedema [10•]. The range of infections in these patients is broad and includes viral (e.g., cytomegalovirus), fungal (e.g., pneumocystis pneumonia), pneumococcal, *Pseudomonas* spp, and mycobacterial infections.

Thus far, only two patients with complete *TYK2* deficiency have been described [11]. Tyk2 is a member of the Jak/STAT signaling family and constitutively associated with receptors for type 1 IFNs (IFN- α and IFN- β), IL-6, IL-10, IL-12, and IL-23 signaling. One patient carried a homozygous 4-bp deletion resulting in an early stop codon. He showed a complex clinical phenotype characterized by viral (molluscum contagiosum, herpes simplex), fungal (oral candidiasis), bacterial (*Staphylococcus aureus*, non-typhi *Salmonella*), and mycobacterial (localized bacille Calmette-Guérin–itis) susceptibility, as well as atopic dermatitis, mild eosinophilia, and elevated serum IgE. A second case was recently reported in which the patient did not have the allergic phenomena. Therefore, Tyk2 deficiency impairs type 1 IFN signaling (viral susceptibility), IL-12/IL-23 signaling (mycobacterial and superficial fungal susceptibility) [9•], and IL-6 signaling (*S. aureus* susceptibility) [12•]. The role of Tyk2 in atopic dermatitis and elevated IgE appears to be redundant (Casanova, unpublished data).

Mutations in *STAT1* come in recessive and dominant forms, leading to profound broad infection susceptibility in infancy (recessive complete deficiency) or milder mycobacterial susceptibility presenting later in childhood (partial dominant deficiency) [13].

Neutrophils

Neutrophils develop from myeloid stem cells in the bone marrow over about 14 days, when fully mature cells with their load of primary, secondary, and tertiary granules are released into the bloodstream. Neutrophils typically last about 6 to 10 h in the circulation before exiting into the parenchyma via diapedesis. In the tissues, they may be primarily phagocytic, bactericidal, fungicidal, or they may remove damaged tissue. Neutropenia usually is caused by decreased production, increased destruction, or a combination of the two [14•].

Disorders of Bone Marrow Egress

Myelokathexis (from the Greek meaning “retained in the bone marrow”) is a congenital disorder associated with severe chronic neutropenia that is associated with a defect in the process of neutrophil emigration from the bone marrow. Bone marrow aspirates from patients with myelokathexis show myeloid hypercellularity with increased numbers of granulocytes at all stages of differentiation, including excessive numbers of neutrophils progressing to apoptosis. The acronym WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) refers to the syndrome caused by heterozygous mutations of the

intracellular C-terminus of the chemokine receptor CXCR4. These mutations cause a dominant disorder characterized by enhanced responses to CXCL12 (stromal cell–derived factor-1), the cognate ligand of CXCR4 expressed on bone marrow stromal cells. Enhanced activity of CXCR4 delays release of mature neutrophils from bone marrow, resulting in peripheral neutropenia. These mature neutrophils are retained in the marrow past their normal release and progress to apoptosis. CXCR4 hyperfunction also appears to be responsible for B-cell lymphopenia and hypogammaglobulinemia, with severe reduction in circulating CD27⁺ memory B cells affecting both unswitched (IgD-positive) and switched (IgD-negative) B lymphocytes. The cause of excessive warts in WHIM syndrome is not completely understood, but CXCR4 is expressed on keratinocytes, and its hyperfunction may play a role in facilitating persistence of infection with human papilloma virus [15]. However, not every patient with WHIM syndrome has mutations in CXCR4, indicating genetic heterogeneity. GPCR kinase-3 (GRK3), which regulates CXCL12-promoted internalization and desensitization of CXCR4, was profoundly decreased in at least one CXCR4 mutation–negative WHIM patient [16•].

Defects of Adhesion

Leukocyte movement from the bloodstream toward inflamed sites is crucial in fighting infections. Adhesion to the endothelium, other leukocytes, and bacteria is critical for leukocytes to travel, communicate, inflame, and fight. The integrin and selectin adhesion molecules mediate these processes.

Leukocyte Adhesion Deficiency Type 1—Leukocyte adhesion deficiency type 1 (LAD1) is an autosomal recessive disorder produced by mutations in the common $\beta 2$ chain (CD18) of the $\beta 2$ integrin family (*ITGB2*, 21q22.3). Each of the $\beta 2$ integrins is a heterodimer composed of one α chain (CD11a, CD11b, or CD11c) noncovalently linked to the common $\beta 2$ subunit (CD18). The α – β heterodimers of the $\beta 2$ integrin family include CD11a/CD18 (lymphocyte function–associated antigen-1), CD11b/CD18 (macrophage antigen-1 or complement receptor-3), and CD11c/CD18 (p150.95 or complement receptor-4). CD18 is required for normal expression of the α – β heterodimers. Therefore, mutations resulting in failure to produce a functional $\beta 2$ subunit lead to very low or no expression of CD11a, CD11b, and/or CD11c, causing LAD1. The severe phenotype of LAD1 is caused by less than 1% of normal expression of CD18 on neutrophils, whereas the moderate phenotype shows 1% to 30% of normal expression. However, rare missense mutations in CD18 allow normal protein expression with impaired activity, indicating that CD18 detection alone is insufficient to exclude the diagnosis of LAD1 [17].

Patients with the moderate phenotype tend to be diagnosed later in life, have normal umbilical separation, have fewer life-threatening infections, and live longer. Somatic reversion of CD18 mutations has been reported in LAD1 [18•]. These mutations were identified in older children or adults and involved cytotoxic T lymphocytes, but not phagocytes. These patients had less severe phenotypes at the time that the reversion was identified, but whether these are causally related to disease modification is still unclear. Bone marrow transplantation is the definitive treatment and is effective in LAD1 but is still complicated by graft rejection for unclear reasons. Laboratory and animal gene therapy studies in LAD1 are provocative but still not clinically available [19–21].

Leukocyte Adhesion Deficiency Type 2 or Congenital Disorder of Glycosylation Type IIc—Leukocyte adhesion deficiency type 2, or congenital disorder of glycosylation type IIc is a very rare autosomal recessive inherited disease in which fucose metabolism is primarily affected because of mutations in the GDP fucose transporter causing a lack of expression of sialyl-LewisX (CD15s) and other fucosylated proteins.

CD15s mediates the leukocyte interaction with selectins, permitting rolling of leukocytes along the endothelium in search of sites of activation. These patients have infections, leukocytosis with impaired inflammation, mental retardation, short stature, distinctive facies, and the Bombay (hh) blood phenotype. The frequency and severity of infections tend to decline over time, and fucose supplementation has been variable in its efficacy [22].

Leukocyte Adhesion Deficiency Type 3—Leukocyte adhesion deficiency type 3 deficiency (previously known as LAD1 variant) resembles LAD1 because of leukocytosis and infections but also has a component like Glanzmann thrombasthenia (a $\beta 3$ integrin-related bleeding disorder). Leukocyte adhesion deficiency type 3 is caused by mutations in *KINDLIN3*, a molecule responsible for $\beta 1$, $\beta 2$, and $\beta 3$ integrin activation in leukocytes and platelets [22, 23].

Rac2 Deficiency—Rac2 deficiency was first reported in a male patient with an autosomal dominant mutation in the Rho guanosine triphosphatase *RAC2* who presented with delayed umbilical cord separation, perirectal abscesses, failure to heal surgical wounds, and absent pus despite neutrophilia. Rac2 is critical to the regulation of the actin cytoskeleton and superoxide production. The patient underwent a matched-related bone marrow transplantation that functionally and clinically corrected his deficiency. Interestingly, another Rac2-deficient patient was recently diagnosed and successfully transplanted after being detected through a neonatal screening test program analyzing T-cell excision circles [24, 25•].

Defects of Microorganism Killing

Chronic Granulomatous Disease—Chronic granulomatous disease (CGD) is a rare genetic disease that predisposes individuals to recurrent life-threatening infections mostly caused by catalase-positive bacteria and fungi, and exuberant granuloma formation due to defects in the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [26]. The NADPH oxidase is assembled from six proteins in the secondary granule wall (p22phox and gp91phox), the cytosol (p40phox, p47phox, p67phox), and the plasma membrane (Rac2). The complex delivers an electron to molecular oxygen, leading to the formation of superoxide and its downstream metabolites, hydrogen peroxide, and hypohalous acid (bleach if the halide is chlorine). Interestingly, patients with CGD and modest residual production of those reactive oxygen intermediates (ROIs) have significantly less severe illness and a greater likelihood of long-term survival than patients with little residual ROI production [27•].

Recently, mutations in p40 were reported in a compound heterozygous patient with inflammatory bowel disease and impaired phagocytosis-induced intracellular superoxide production, whereas extracellular release of superoxide elicited by phorbol ester or formyl-methionyl-leucylphenylalanine was unaffected [28•].

The gastrointestinal and genitourinary tracts are frequently affected by inflammatory and granulomatous manifestations in CGD patients; the retina and lungs also can be affected. Autoimmune disorders are also more common in CGD patients than in the general population. Discoid and systemic lupus erythematosus occur in CGD and in X-linked CGD female carriers. Idiopathic thrombocytopenic purpura and juvenile rheumatoid arthritis also occur more frequently in CGD than in the general population [29].

The X-linked carriers of gp91phox have one population of phagocytes that produces superoxide and one that does not, giving carriers a characteristic mosaic pattern on oxidative testing. Infections are not usually seen in these female carriers unless the normal neutrophils are below 10%, in which case these carriers are at risk of CGD-type infections [30].

Careful work in CGD mice proved that IL-17 production was exuberant and actually blocked fungal killing, greatly contributing to the susceptibility of CGD mice to *Aspergillus* spp [31]. However, this phenomenon is apparently restricted to mice, as human studies have failed to show any excess IL-17 production [32].

Study of peripheral blood markers has shown several innate inflammatory components to be reduced in CGD and apparently dependent on the level of superoxide production. These include Toll-like receptor 5, Toll-like receptor 9, CD11b, CD18, CD35, and CXCR1 [33]. However, other investigators have shown evidence for overactivation of innate immune responses at baseline in CGD patients, making their cells look similar to lipopolysaccharide-stimulated cells [34]. Harmonization of the hyper- and hypoinflammatory aspects of CGD will require careful study.

Natural Killer and Natural Killer T Cells

NK cells mediate recognition and killing of target cells and the production of immunoregulatory cytokines, particularly IFN- γ , enhancing the innate immune response and helping shape the adaptive immune response. Unlike adaptive T- and B-cell lymphocytes, NK cells do not rearrange their receptor genes but rely on a fixed number of inhibitory and activating NK-cell receptors (NKR) that are capable of recognizing major histocompatibility complex (MHC) class I molecules. The tolerance of NK cells to self is achieved through mechanisms that require the engagement of inhibitory NKRs with self-MHC before attaining functional competence, a process termed *licensing*. NK-cell effector functions can be triggered by the engagement of activating NKRs with cell surface ligands—which can be encoded by the host or by pathogens—some of which are upregulated in infected cells or tumors. NK cells also respond to cytokines from antigen-presenting cells, allowing early response against pathogens [35, 36]. NK-cell deficiencies have been described in many primary immunodeficiencies (PIDs) as sequelae of the underlying mutation, indicating that many PIDs are likely confounded with NK deficiency as well [37].

NKT cells constitute a distinctive subpopulation of mature lymphocytes that co-express NK (CD56) and T (CD3) antigens and are involved in innate immunity. NKT cells exhibit unique features with regard to antigen specificity, effector functions, and tissue distribution. They are abundant in the liver, bone marrow, and thymus but are relatively rare in the lymph nodes and spleen. Most human NKT cells are invariant (iNKT, or type I NKT cells) and express a T-cell antigen receptor (TCR) composed of a single TCR- α chain (V α 24-J α 18) and a highly skewed TCR- β chain (V β 11). Functionally, iNKT cells are defined by their response to glycolipid α -galactosylceramide (α GalCer) presented by the MHC-I-type molecule CD1d. In addition to iNKT cells, a second category of NKT cells have more diverse TCRs without using the invariant V α and V β combination and not responding to α GalCer. Unlike iNKT cells, these noninvariant, or type II NKT cells respond to other glycolipids presented by CD1d molecules, to which they are restricted [38•].

NKT cells can make both the T-helper type 1 cytokine IFN- γ and the T-helper type 2 cytokines IL-4 and IL-13. They appear to play an important role in allergy (e.g., asthma), autoimmunity (e.g., hepatitis), and tumor control. iNKT cells exhibit perforin- and/or FasL-mediated cytotoxicity, especially when activated by α GalCer or IL-12, resulting in potent antitumor activity as well as antiviral effect, even though viruses do not express glycolipids. We recently found that iNKT cells may be involved in fulminant hepatic failure during hepatitis A virus (HAV) infection. The CD8 lymphocytes that infiltrate the liver were previously thought to be responsible for hepatocyte damage following HAV infection. However, these cells are not natural liver residents, and their presence in the liver occurs 2 to 3 weeks after the onset of clinical manifestations. On the other hand, iNKT cells are

resident lymphocytes in the liver; express the HAV cellular receptor 1 (HAVcr1, also known as TIM1) on their cell surface; recognize HAV antigens in the hepatocyte cell membrane; and generate liver damage by means of increased perforin, granzyme B, and IFN- γ generation in a HAVcr1-dependent manner. Interestingly, a particular variant of HAVcr1 (157ins6) is overrepresented among patients with HAV-induced fulminant hepatic failure [39••].

NKT cells play important roles in viral control. Patients with increased susceptibility to Epstein-Barr virus (EBV) and other herpes virus infections have diminished or dysfunctional NKT cells. Patients with X-linked lymphoproliferative disease lack iNKT cells and are particularly susceptible to EBV. Patients with a similar syndrome due to mutations in X-linked inhibitor of apoptosis also show a selective reduction in iNKT-cell numbers without T, B, or NK lymphopenia. A similar disease was described in patients with homozygous mutations in IL-2-inducible tyrosine kinase who had life-threatening EBV infections with almost no iNKT cells detected in the peripheral blood [40••]. Interestingly, Wiskott-Aldrich syndrome (WAS) was also recently shown to have iNKT-cell deficiency, and WAS patients are also prone to EBV lymphomas [41•].

Complement

The complement system is composed of more than 30 different and interacting serum- and membrane-bound proteins. All vertebrates show some evidence of serum complement activity. As activated complement is strongly proinflammatory, it is not surprising that almost half of complement components serve to downregulate its activity. Therefore, different deficiencies within the complement system can lead to enhanced infection susceptibility or inappropriate inflammation. Because complement also helps remove immune complexes, certain deficiencies cause impaired immune complex clearance, which can lead to vasculitis and macular degeneration [42, 43].

The complement system involves three activation pathways: the classical pathway, the alternative pathway, and the lectin pathway, all of which converge at C3 and activate a common final pathway (Fig. 2). The classical pathway depends on antibody or C-reactive protein for initiation. The lectin (or mannan-binding pathway) is activated upon binding to certain carbohydrates. Mannose-binding protein, which is like C1q, ficolin, and other related lectins, binds to monosaccharides, including mannose, N-acetylglucosamine, N-acetylmannosamine, and L-fucose on microbial surfaces. These in turn activate different mannose-binding, lectin-associated proteases that cleave C4 and C2. The alternative pathway is antibody independent and relies on minimal spontaneous hydrolytic changes on C3.

Properdin, factor H, and factor I play critical regulatory roles in alternative pathway activation. Properdin stabilizes the C3bBb complex, prolonging the life of the enzyme, while factor H inhibits the formation and also degrades C3bBb, and factor I inactivates C3b. Therefore, it follows from the biologic effort put into complement inactivation that mutations that inhibit the inactivation of complement activity are deleterious, leading to complications such as thrombotic microangiopathies; atypical hemolytic uremic syndrome; and possibly the syndrome of hemolytic anemia, elevated liver enzymes, and low platelets (HELLP) [43].

While most complement deficiencies are autosomal recessive, deficiency of C1 inhibitor is autosomal dominant, and properdin deficiency is X-linked recessive. Null mutations are usually responsible for complement deficiencies, and heterozygous individuals produce one half of the normal plasma level of a specific complement protein. Interestingly, individuals who are heterozygous for a null allele usually present with normal total complement activity

in assays as complement hemolytic 50 or alternative pathway 50. Activating defects related to the microangiopathic disorders show haploinsufficiency [42].

Complement is also involved in B-cell signaling, memory, and antibody generation through complement receptor 2 (CR2, or CD21). Engagement of C3d-coated antigen by mature cognate B cells ligates the co-receptor (i.e., CD19, CD21, and CD81) and the B-cell receptor, enhancing B-cell receptor signaling by several orders of magnitude. Distinctive subgroups of patients with rheumatoid arthritis and others with common variable immunodeficiency who have autoimmune manifestations show an abnormally increased number of CD21-negative or low B cells in the peripheral blood. These cells are characteristically unresponsive to different B-cell stimulants and express germline autoreactive antibodies that recognize nuclear and cytoplasmic structures [44•, 45, 46•].

Complex Disorders

Adult patients with disseminated mycobacterial disease have been described with high-titer–blocking, anti-IFN- γ autoantibodies. These patients have a clear B-cell disorder mimicking a monocyte disorder. Similar anticytokine autoantibody disorders have been described in several other conditions, including pulmonary alveolar proteinosis and pure red cell aplasia [47]. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), or autoimmune polyglandular syndrome type 1 patients have mutations in autoimmune regulator (*AIRE*). *AIRE* is mainly expressed by medullary thymic epithelial cells and regulates the expression of tissue antigens to maturing thymocytes. This in turn is key to achieving negative selection of autoreactive T cells within the thymus. Downstream B cells and their products (e.g., anti-parathyroid antibodies, anti-adrenal antibodies) produce the endocrinopathy and other APECED manifestations [48]. The pathophysiology of the chronic mucocutaneous candidiasis seen in APECED was recently elucidated. Neutralizing anti-IL-17A, IL-17F, and IL-22 autoantibodies are now thought to be responsible for these manifestations [49•, 50•]. In other words, a monogenic, primarily thymic defect eliciting T- and subsequently B-cell defects is the basis for a disease largely believed to be an innate immune defect.

More recently, mutations in IL-17RA and IL-17F were found in autosomal recessive and autosomal dominant familial forms, respectively, of chronic mucocutaneous candidiasis, reinforcing the central role of the IL-17 pathway in the control of *Candida* spp infections [51•].

Conclusions

PIDs are a heterogeneous group of genetically inherited diseases affecting the innate and adaptive immune systems that confer susceptibility to infection, autoimmunity, and cancer. Although we have a tendency to lump PIDs into subgroups based on cell types or compartments (T cells, B cells, NK cells, complement, phagocytes), these compartments synergistically interact, creating the complex and idiosyncratic entity known as the immune response.

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Fig. 1. Schematic representation of the interleukin (IL)-12/IL-23/interferon (IFN)- γ pathway and its role in mycobacterial disease control. Jak—Janus kinase; NK—natural killer; STAT—signal transducer and activator of transcription; TNF—tumor necrosis factor; TNFR—TNF receptor; Tyk—tyrosine kinase

Fig. 2. Schematic diagram of complement activation. CRP—C-reactive protein; MASP—mannose-binding lectin-associated protease

Table 1

Innate immune system components

Natural barriers	Cells	Pattern-recognition receptors	Cytokines	Natural antimicrobial products
Skin, mucosal epithelia	Neutrophils, macrophages/ dendritic cells, natural killer cells, natural killer T cells, $\gamma\delta$ T cells, B1 lymphocytes	Mannose-binding lectins, Toll-like receptors, ...	IL-1, IL-6, IL-8, IL-12, IL-15, IL-18, G-CSF, M-CSF, GM-CSF, TNF- α , IFN- γ , ...	Defensins, lactoferrin, lysozyme, natural antibodies, complement, reactive oxygen species

IFN interferon; IL interleukin; *G-CSF* granulocyte colony-stimulating factor; *GM-CSF* granulocyte-macrophage colony-stimulating factor; *M-CSF* macrophage colony-stimulating factor; *TNF* tumor necrosis factor