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REVIEW

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Mendelian susceptibility to mycobacterial disease: an overview

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Abstract

Background Mycobacteria include ubiquitous species of varying virulence. However, environmental and individual-specific factors, particularly host genetics, play a crucial role in the outcome of exposure to mycobacteria. The first molecular evidence of a monogenic predisposition to mycobacteria came from the study of Mendelian susceptibility to mycobacterial disease (MSMD), a rare inborn error of IFN-γ immunity conferring a selective susceptibility to infections even with low virulent mycobacteria, in patients, mostly children, without recognizable immune defects in routine tests. This article provides a global and updated description of the most important molecular, cellular, and clinical features of all known monogenic defects of MSMD.

Results Over the last 20 years, 19 genes were found to be mutated in MSMD patients (*IFNGR1, IFNGR2, IFNG, IL12RB1, IL12RB2, IL23R, IL12B, ISG15, USP18, ZNFX1, TBX21, STAT1, TYK2, IRF8, CYBB, JAK1, RORC, NEMO*, and *SPPL2A*), and the allelic heterogeneity at these loci has led to the definition of 35 different genetic defects. Despite the clinical and genetic heterogeneity, almost all genetic etiologies of MSMD alter the interferon gamma (IFN-γ)-mediated immunity, by impairing or abolishing IFN-γ production or the response to this cytokine or both. It was proven that the human IFN-γ level is a quantitative trait that defines the outcome of mycobacterial infection.

Conclusion The study of these monogenic defects contributes to understanding the molecular mechanism of mycobacterial infections in humans and to the development of new diagnostic and therapeutic approaches to improve care and prognosis. These discoveries also bridge the gap between the simple Mendelian inheritance and complex human genetics.

Keywords Mycobacterial diseases, Monogenic, Inborn errors of immunity, Mendelian susceptibility, IFN-γ

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Background

The genus *Mycobacterium* includes over 190 recognized species, of which the most pathogenic are *Mycobacterium tuberculosis* (*M. tb*), *M. leprae*, and *M. ulcerans* [1]. Humans are constantly exposed to environmental mycobacteria (EM) which are isolated in soil, water, and aerosols. In addition, most children worldwide are vaccinated with Mycobacterium bovis Bacille Calmette-Guérin (BCG) vaccines. These pathogens can cause localized or disseminated clinical disease in rare cases. Indeed, environmental and individual-specific factors, particularly host genetics, play a crucial role in the outcome of exposure to mycobacteria and the heterogeneity of clinical manifestations [2–5]. Although genome-wide association studies have identified loci associated with host predisposition or resistance to infections with the more virulent *M. tb*, their results were not consistent or reproducible [6–8].

The understanding of the pathogenesis of mycobacterial diseases has been improved by studies of the rare syndrome of Mendelian susceptibility to mycobacterial disease (MSMD), an inborn error of immunity (IEI) or primary immunodeficiency (PID) classified by the International Union of Immunology Societies (IUIS) as a defect in intrinsic and innate immunity [9, 10]. This condition is characterized by selective susceptibility to infections with weakly virulent mycobacteria, including the *M. bovis* Bacille Calmette-Guérin (BCG) vaccines and various environmental mycobacteria in patients without classical immune defects [4, 11]. These patients may also present severe forms of primary tuberculosis caused by *M. tb* [8, 11, 12]. In addition, about half of patients develop non-typhoidal salmonellosis of varying severity [11, 13, 14]. In some cases, patients also suffer from chronic mucocutaneous candidiasis (CMC) [11, 13, 15, 16]. Other severe infections have more rarely been reported, including viral diseases (caused by cytomegalovirus, human herpesvirus 8, parainfluenza virus type 3, respiratory syncytial virus, and varicella zoster virus), parasitic diseases (leishmaniasis, toxoplasmosis), fungal diseases (histoplasmosis, paracoccidioidomycosis, coccidioidomycosis), and bacterial diseases (listeriosis, nocardiosis, klebsiellosis) [11, 17–22]. Severe forms of MSMD can lead to life-threatening infections at an early age, while mild forms may appear late or remain asymptomatic [11].

Since 1996, mutations causing MSMD have been identified in 19 genes (IFNGR1, IFNGR2, IFNG, IL12RB1, IL12RB2, IL23R, IL12B, ISG15, USP18, ZNFX1, TBX21, STAT1, TYK2, IRF8, CYBB, JAK1, RORC, NEMO, and SPPL2A). Allelic heterogeneity at these loci has led to the definition of 35 different genetic defects, based on the impact of the mutation (null or hypomorphic), the mode of transmission (dominant or recessive, autosomal or X-linked), the expression of the mutant allele (normal, low or absent), and the function affected (e.g., phosphorylation, binding to DNA or both) (Table 1) [15, 23–29]. Except for ZNFX1 deficiency, all genetic disorders have in common the alteration of the production or response to interferon-gamma (IFN-γ) or both. IFN-γ is a macrophage activation factor that plays a crucial,

Table 1 List of 19 known genes and their defects associated with Mendelian susceptibility to mycobacterial infections

Gene	Transmission	Defect	Protein
IL12B	AR	C	E−
IL12RB1	AR	C	E−
	AR	C	E+
IL12RB2	AR	C	E−
IL23R	AR	C	E + or E−
TYK2	AR	C	E + or E−
TYK2 P1104A	AR	P	E+
RORC	AR	C	E−
IFNGR1	AR	C	E−
	AR	C	E+
	AD	P	E+ + +
	AR	P	E+of mutant protein
	AR	P	E+
IFNGR2	AR	C	E+
	AR	C	E−
	AR	P	E+m
	AR	P	E+wt
	AD	P	E+
IFNG	AR	C	E−
JAK1	AR	P	E−
STAT1	AD	P	E+P−
	AD	P	E+B−
	AD	P	E+P−B−
	AR	C	E−
	AR	P	E+
IRF8	AD	P	E+
	AR	C	E+or E−
SPPL2A	AR	C	E+or E−
CYBB	XR	P	E+
IKBKG (NEMO)	XR	P	E+
ISG15	AR	C	E−
	AR	P	E+
USP18	AR	P	E+
ZNFX1	AR	C	E+or E−
TBX21	AR	C	E+

Table summarizing the genetic disorders causing isolated or syndromic MSMD. *AD* autosomal recessive, *AR* autosomal recessive, *XR* X-linked recessive, *C* complete, (*P* partial. Mutant protein is (E +) expressed, (E −) not expressed or (E + + +) increased, (P −) not phosphorylated or (B −) unable to bind DNA, (wt) wild type

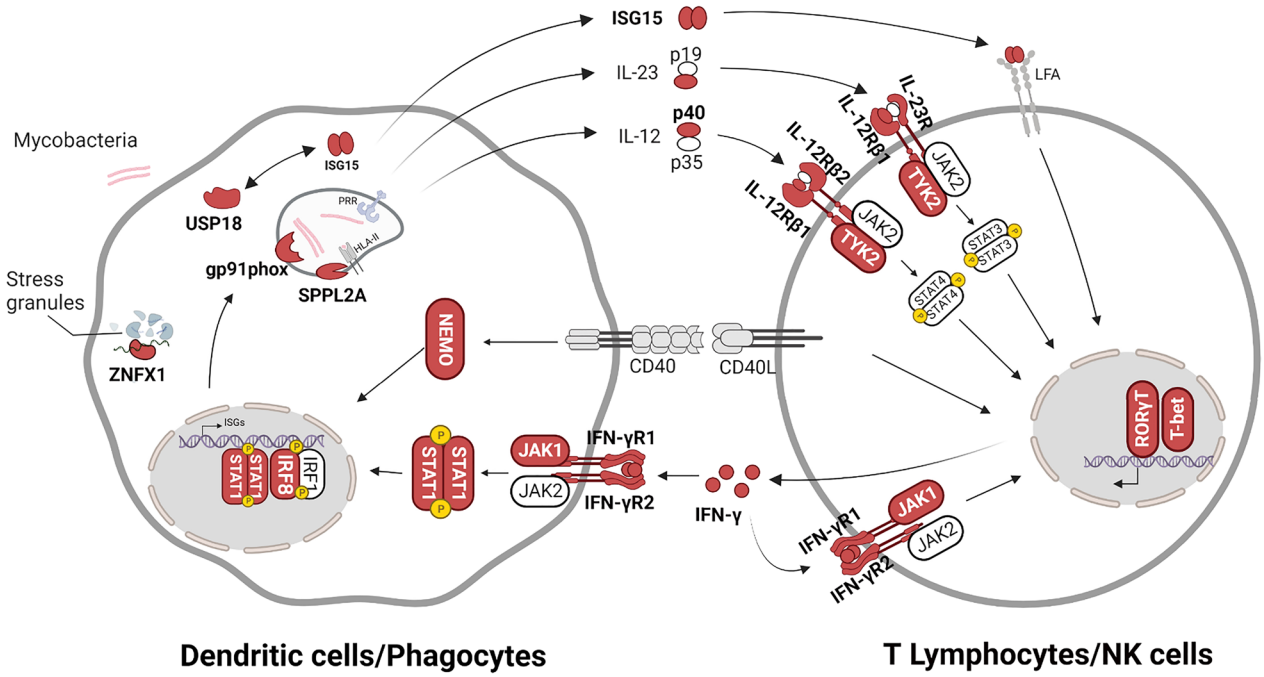

Fig. 1 Schematic diagram of the cooperation between phagocytes/dendritic cells and T/NK cells during mycobacterial infection. Proteins for which mutations in the corresponding genes have been associated with MSMD are indicated in red. Following phagocytosis of mycobacteria, pattern recognition receptors (PRRs) activate and induce the production and release of IL-12, IL-23, and ISG15. These cytokines bind to their receptors (IL-12R, IL-23R, and LFA-1) on T-helper and NK cells, inducing the production of IFN-γ via TYK2/JAK2-dependent pathways, using STAT4 and STAT3 dimers, as well as the transcription factors RORC and T-bet. In turn, secreted IFN-γ binds to its receptor (IFNγR) on the surface of macrophages and dendritic cells leading to the activation of JAK1/JAK2-dependent pathway involving STAT1, IRF8, and IRF1 transcription factors, which enhances the production of IL-12, IL-23, and ISG15 and promotes expression of interferon-stimulated genes (ISGs). USP18 liberates ISG15 from other bound proteins and ISG15 protects USP18 from degradation. Besides, the interaction of CD40 with its ligand leads to the activation of NEMO, which activates and releases the NF-kB transcription factors. This enhances the ability of phagocytes to eliminate intracellular microorganisms

non-redundant role in antimycobacterial immunity [12, 30]. The severity and penetrance of MSMD depend on the genetic etiology and are inversely correlated with residual production of or response to IFN-γ [30]. More profound IFN-γ deficiency is associated with a greater vulnerability to weakly virulent mycobacteria, whereas more selective IFN-γ deficiency is associated with a more selective predisposition to mycobacterial disease [12].

Two types of MSMD have been defined: isolated MSMD, in which patients are sensitive only to mycobacterial infections, and syndromic MSMD, in which patients suffer from mycobacterial infection in the context of one or a few other diseases [8, 11, 13, 15]. The study of these monogenic defects contributes to understanding the molecular mechanism of mycobacterial infections in humans and allows the development of new diagnostic and therapeutic approaches to improve care and prognosis. For example, MSMD patients with impaired production of IFN-γ may benefit from injections of human recombinant IFN-γ, while for patients with abolished response to this cytokine, hematopoietic stem cell transplantation (HSCT) and promising gene therapy are the only current therapeutic options [31–34]. In this review, we describe the most important molecular, cellular and clinical features of all monogenic defects of MSMD discovered over the last 25 years.

Main text

IL12RB1

In response to activation signals induced by pattern recognition receptors (PRRs), interleukin-12 (IL-12) is produced by dendritic cells, macrophages, and neutrophils. This cytokine stimulates the production of IFN-γ and TNF-α by T and NK cells and promotes the differentiation of naïve T cells into Th1 cells [35–38]. The IL-12 receptor is a heterodimer formed by two chains, IL-12Rβ1 and IL-12Rβ2 [39]. The IL-12Rβ1 chain also binds with the IL-23R subunit to form the IL-23 receptor [40] (Fig. 1). Autosomal recessive (AR) complete IL-12Rβ1 deficiency, or Immunodeficiency 30 (OMIM #614891), therefore alters signaling by IL-12 and IL-23. It is the most common genetic defect of MSMD, found in about 60% of diagnosed MSMD patients [13, 15]. All mutant alleles are loss of function (LOF) and their

transmission is AR, without expression of IL-12Rβ1 or, more rarely, with the expression of a non-functional protein on the cell surface (Table 1) [11, 13, 41–44]. Cells from these patients do not respond to stimulation by either IL-12 or IL-23, resulting in impaired production of IFN-γ by T and NK cells [41, 45]. The clinical phenotype associated with this defect is very heterogeneous, the affected patients are likely to be infected with BCG, EM, *M. tb*, and/or *Salmonella* sp. [16, 41, 43, 44, 46]. Leukocytoclastic vasculitis is also reported in some patients with IL-12Rβ1 deficiency, probably related to salmonellosis. CMC is observed in a third of these patients and is attributed to impaired development of Th17 cells caused by the absence of IL-23 [16, 41, 45]. Even rarer, other fungal infectious diseases, such as coccidioidomycosis, paracoccidioidomycosis, or histoplasmosis, have been diagnosed in IL-12Rβ1-deficient patients [20, 42, 47, 48]. Visceral leishmaniasis is also associated with this group of patients [19, 22]. Asymptomatic individuals have been reported, attesting to an incomplete clinical penetrance for this type of genetic disease in MSMD, with only 50–70% of adults being symptomatic by the age of 40 years [15, 41].

IL12RB2

An AR complete IL-12Rβ2 deficiency has been identified in a consanguineous Turkish family [45]. Two of the three patients who carried the homozygous loss-of-function (LOF) variant had clinical manifestations of mycobacterial infections. The first developed a disseminated BCG infection one year after vaccination. The second patient had pulmonary tuberculosis at the age of 5 years. They have never had salmonellosis or fungal infections. The third patient is asymptomatic [45]. No candidiasis was reported in all three patients as IL-17 immunity is maintained. These patients have low numbers of Th1 cells, while their Th17 cells are slightly low or normal [15, 45]. Indeed, the penetrance for MSMD is incomplete, probably as low as 0.5%, because IL-23 can largely compensate for the loss of IL-12 signaling [15].

IL23R

A new AR deficiency caused by a homozygous LOF mutation in the extracellular domain of the IL-23R subunit has been identified in a consanguineous Iranian family with two MSMD-affected children [45]. The first girl was vaccinated by BCG, after which she developed persistent lymphadenopathy for one year, with spontaneous recovery. Her brother was also vaccinated at birth by BCG, he developed axillary lymphadenopathy, hepatosplenomegaly, and mediastinal adenopathy. He died of disseminated BCG infection despite treatment with antibiotics for a year and a half and then with recombinant IFN-γ [45]. Another patient has been reported as having disseminated BCG disease [43]. The last reported patient is a 48-year-old man of Turkish origin carrying a homozygous LOF mutation in the intracellular domain of the IL23R subunit [29]. He suffered from disseminated multi-mycobacterial infection, with pulmonary (MAC), bone marrow, and gastrointestinal (*Mycobacterium tilburgii*) manifestations [29]. These patients had normal frequencies of various leukocyte subsets, but low levels of MAIT cells (mucosal-associated invariant T cells), an abnormal decrease in Th1 lymphocytes and a slight decrease in Th17 and Th2 cells. Cells from these patients may express, or not, the IL-23R protein, but they present abolished phosphorylation of STAT3 in response to IL-23, resulting in impaired production of IFN-γ in vitro [29, 45].

IL12B

IL-12 is a heterodimeric cytokine composed of two subunits encoded by 2 distinct genes, p35 subunit (*IL12A*) and p40 subunit (*IL12B*) [36]. The p40 subunit also heterodimerizes with the p19 subunit of IL-23 *(IL23A)* to form IL-23 [38]. IL-23 is important for the expansion and survival of Th17 cells [49]. Defect of the *IL12B* gene (p40 subunit) causes immunodeficiency 29 (OMIM #614890), a frequently reported cause of MSMD with AR transmission. Patients usually develop BCG and/or salmonellosis infections [11, 25, 50–53]. Cases of tuberculosis and EM infection have also been reported [50]. These patients also suffer from CMC due to disruption of IL-17 secretion induced by IL-23 [11, 50, 54]. Other infectious diseases, such as nocardiosis, klebsiellosis, or leishmaniasis, have been also associated with this group of MSMD [22, 50]. The prognosis of this defect is generally good, with a strong similarity to IL-12Rβ1 deficiency [41, 50].

TYK2

TYK2 is a Janus kinase (JAK) involved in various signaling pathways, including responses to IL-12, IL-23, IFN-α/β, and IL-10. Once activated, TYK2 phosphorylates the intracellular part of the receptor and the recruited STATs. AR complete TYK2 deficiency, or immunodeficiency 35 (#611,521), was first described in 2006 in a Japanese patient with the hyper-IgE syndrome (HIES) and BCG infection [55]. He had a history of infections with viruses, fungi, mycobacteria, and *Salmonella sp.* [55]. Then, other patients from Argentina, Iran, Saudi Arabia, Turkey, Pakistan, Malaysia, and China had been reported [28, 56–61]. Overall, out of 25 reported patients with AR complete TYK2 deficiency, eight patients had a history of BCG infections (localized or regional or disseminated)

five had *M. tb* infection, and one patient had EM disease [28, 55–60], including two patients with salmonellosis [55, 58]. Fifteen patients suffered from viral diseases, which is consistent with their poor cellular response to IFN-α/β [28, 55, 56, 61]. Six patients had fungal diseases caused by *C. albicans*, including one case of CMC. Interestingly, only 36% (8/22) of BCG-vaccinated patients with AR complete TYK2 deficiency have suffered from BCG disease, which indicates an incomplete penetrance of this defect for MSMD. This incomplete penetrance for mycobacterial and viral diseases results from impaired, but not abolished, responses to IL-12, IL-23, and IFN-α/IFN-β due to residual TYK2-independent responses implying other molecules, such as other JAK kinases [56]. Only one patient suffered from HIES [55] and another had elevated IgE level without HIES [57]. The HIES phenotype in this patient was attributed to impaired fibroblastic responses to IL-6, which was not rescued by wild-type TYK2 [56]. Thus, HIES and high serum IgE levels may be caused by genetic variants at loci other than TYK2 [28, 56]. Except for one, all identified variants/mutations altered the expression of the TYK2 protein [28, 55–61].

In this context, ten other homozygous patients for a common variant of TYK2, P1104A, have recently been reported [62]. Three patients from Iran, Sweden, and the USA have BCG and *M. avium* complex (MAC) infections, while the other seven patients from Algeria, Brazil, Chile, Morocco, and Turkey have *M. tb* infections (6 pulmonary and 1 miliary tuberculosis) [62]. Patients' leukocytes respond poorly to IL-23 in terms of IFN-γ production. Homozygosity for P1104A selectively affects IL-23 signaling, as cellular responses to IL-12, IFN-α/β and IL-10 are intact in these patients [62]. Patients had normal development of IL-17 + CD4 + T cells ex vivo, which corresponds to the absence of CMC in these individuals. These patients are also normally resistant to other infectious diseases [62]. The homozygosity of P1104A is present in 1/600 humans of European origin, but the penetrance of this variant is much lower for MSMD (less than 0.5%) than for tuberculosis (greater than 50% in areas of endemic tuberculosis) [62, 63]. Furthermore, the frequency of the variant significantly decreased in Europe over the last 2000 years, by negative selection probably reflecting endemicity for TB [64].

RORC

The *RORC* gene can encode two nuclear receptor isoforms that act as transcription factors: RORγ which is ubiquitously expressed, and ROR-γT, which is restricted to leukocytes. The RORγT isoform promotes the differentiation of thymocytes into Th17 cells [65]. Three homozygous mutations of *RORC* were discovered in seven patients from three unrelated consanguineous families [66]. Mutant alleles are LOF with AR segregation and cause immunodeficiency 42 (OMIM: #616622). The patients suffered from early childhood from mycobacterial infections (BCG or *M. tb*) or CMC, impaired lymphoid development, and a small thymus [66]. The cells of these patients have impaired production of IL-17A, IL-17F, and IL-22 and an apparent defect in IFN-γ production in response to stimulation by BCG and IL-12 [66]. The impaired secretion of IL-17A /F by patients' T cells justifies CMC in these patients [66]. IFN-γ secretion was normal in naïve or memory $CD4^+$ T, but was strongly impaired in γδ and Th_1 T cells, which explains mycobacterial infections [66].

TBX21

T-bet or T-box protein 21 (TBX21) is a transcription factor that governs the development or function of several IFN-γ-producing lymphocytes, including T helper 1 (TH1) cells, NK and invariant NKT (iNKT) cells in particular. Recently, a patient from a consanguineous family from Morocco has been identified with AR complete T-bet deficiency (immunodeficiency 88 (OMIM #619630)) [24, 67]. The patient suffered from BCG disease following vaccination and persistent reactive airway disease associated with increased production of Th2 cytokines [24, 67]. T-bet-deficient mice are highly vulnerable to mycobacteria. Thus, mycobacterial disease and T-bet deficiency in this patient are consistent with the data in mice. Cellular immunophenotyping showed a strong diminution of circulating NK, invariant NKT, and Th1 cells in vivo. The frequency of Vδ2+$\gamma\delta$ T and MAIT cells was also impaired. HVS-T cells from the patient express normal volumes of *TBX21* RNA but protein expression is diminished [24]. The discovery of inherited T-bet deficiency provides a unique opportunity to analyze the role of this fundamental transcription factor in human leukocyte subsets, especially Th cells.

IFNGR1

The receptor of IFN-γ is a heterodimer formed by two chains IFN-γR1 (binding to IFN-γ) and IFN-γR2 (signal transduction). IFN-γR1 or IFN-γR2 deficiency may be AR or AD, complete or partial, with or without expression of the protein on the cell surface [11, 13]. The AR complete IFN-γR1 deficiency (immunodeficiency 27A (OMIM #209950) was identified in 1996 as the first genetic etiology of MSMD [68, 69]. This defect is characterized by severe and early infections by BCG and/or EM, often resulting in the death of patients in the absence of hematopoietic stem cell transplantation (HSTC) [68–70]. Tuberculosis has been identified in two patients, one of

whom died of disseminated infection [70, 71]. Salmonellosis has also been reported in three patients [68–70]. The plasma of patients contains high levels of IFN-γ [70, 72]. The cellular phenotype of AR complete IFN-γR1 deficiency is characterized by the absence of response to IFN-γ in vitro, resulting in an abolished activation of gamma-activating factor (GAF: STAT1 homodimers) and production of IL-12p70 by leukocytes [68, 70, 73].

AR partial IFN-γR1 deficiency is characterized by a less severe clinical phenotype than that of AR complete IFN-γR1 deficiency [74–77]. Patients' cells express the receptor on their surface but show an altered response to stimulation by high concentrations of IFN-γ [75]. These patients suffer from mycobacterial infections with BCG and/or EM, causing osteomyelitis in more than half of them [70, 77]. *M. tb* infection has been reported in a child who had not been vaccinated with BCG [74]. IFN-γ was detectable in the plasma of these patients [75].

Autosomal dominant (AD) IFN-γR1 deficiency (immunodeficiency 27B (OMIM #615978)) results in detectable activation of GAF with less severe and late mycobacterial infections [78]. Bone disease and MAC osteomyelitis are more common in this AD form [70, 79]. All variants confer a similar cellular phenotype, characterized by the impaired response to IFN-γ *in vitro*. Large amounts of IFN-γR1 are detected on the surface of cells, due to the accumulation of truncated IFN-γR1 receptors lacking the recycling domain or STAT1 and JAK1 docking sites, altering the normal signaling of IFN-γ by negative dominance, despite the presence of receptors encoded by the wild-type allele [70, 78].

IFNGR2

AR defects in IFN-γR2 (immunodeficiency 28 (OMIM #614889) also lead to severe and early mycobacterial infections. Two complete and two partial forms of AR IFN-γR2 deficiency have been reported, which differ in the absence or expression of the mutant or wild-type IFN-γR2 on the cell surface. The two forms of AR complete IFNγR2 deficiency (with or without expression of the protein on the cell surface) are manifested in early childhood by severe and often fatal infections with BCG, *M. abscessus*, *M. avium*, *M. fortuitum*, *M. porcium*, and *M. simiae* [80–85]. In both forms, the cellular response to IFN-γ is abolished [80–85].

The AR partial IFN-γR2 deficiency with the expression of functionally impaired protein has been described in six patients with mycobacterial infections caused by BCG, *M. abscessus*, *M. bovis*, *M. elephantis*, *M. fortuitum*, and *M. simiae* [82, 86, 87]. Among them, two patients (33%) died [82, 87]. A particular form of AR partial IFN-γR2 deficiency, with the expression of a small amount of normal IFN-γR2 (wild type), was described in three patients having BCG infection, one of whom died of infection with *M. chelonei* at the age of five [88]. The alteration of the cellular response to IFN-γ was more severe than that caused by the previously reported form of AR partial IFN-γR2 deficiency, but less severe than that of the AR complete deficiency [88].

Finally, an AD form of partial IFN-γR2 deficiency was found in a Polish patient with mild BCG infection [89]. The patient and other heterozygous individuals for the mutation showed low levels of IFN-γR2 expression at the cell surface and an impaired response to IFN-γ [89]. The clinical penetrance of this deficit for MSMD is very low, as only one case among the 18 heterozygous individuals was found to be affected [89, 90]. The mechanism underlying the incomplete penetrance remains unknown [90].

IFNG

The first mutation in IFN-γR1 has been identified in 1996 [68, 69]. Surprisingly, only one deleterious mutation has been reported in the IFN-γ cytokine [91]. Two Lebanese distant cousins living in Kuwait were both homozygous for the frameshift c.354_357del mutation in the *IFNG* gene. Both children suffered from severe and disseminated BCG disease. The patients had no other severe infections. The development of myeloid and lymphoid cells is intact in IFN-γ-deficient patients. Their lymphocytes failed to express and secrete detectable IFN-γ, and the secretion of TNF was very impaired [91]. An early diagnosis of patients with this deficiency should be useful to indicate recombinant IFN-γ as treatment.

JAK1

The signal from the IFN-γ receptor, as well as that of the IFN type I receptor, is transduced via a JAK/STAT pathway using JAK1 [92]. AR partial JAK1 deficiency has been reported in a 22-year-old Pakistani patient from consanguineous parents [93]. The patient presented with an infection by EM and a history of viral, fungal, and parasitic skin infections. He died of urothelial carcinoma at the age of 22 [93, 94]. Cellular responses to IFN-γ and IFN-α were altered but not suppressed by this mutant allele [93]. Altered responses to IL-2, IL-4, IL-10, and IL-27 have also been observed in leukocytes [93]. Probably, this defect can also be the cause of early susceptibility to cancer [93]. AR partial JAK1 deficiency, therefore, results in susceptibility to mycobacteria due to an altered IFN-γ signaling pathway and to other infections due to defective responses to other cytokines, including IFN-α.

STAT1

STAT1 (signal transducer and activator of transcription) is a transcription factor involved in the response to type I

(IFN-α/β), type II (IFN-γ), and type III (IFN-λ) IFNs [92, 95, 96]. The defect may segregate as AD (immunodeficiency 31A (OMIM #614892)) or AR (immunodeficiency 31B (OMIM #613796)). AR STAT1 deficiency is characterized by the absence or impaired protein expression and the abolition or impaired cellular responses to IFN-γ, IFN-α/β, and IFN-λ, leading to severe and potentially fatal mycobacterial and viral infections [95, 97–101]. Cells from patients with complete or partial AR STAT1 deficiencies show an abolished or impaired response to STAT1-dependent cytokines [98, 99]. AD STAT1 deficiency is caused by LOF or hypomorphic monoallelic mutations affecting phosphorylation or DNA binding, or both (Table 1) [102–106]. This AD form produces relatively mild infections due to BCG and *M. avium*. Multifocal osteomyelitis occurs frequently in these patients [102, 103]. Clinical penetrance for MSMD is incomplete, as five people known to be genetically affected have not developed the disease [102, 106]. Cells from heterozygous patients show a defect only for activation of GAF after stimulation with IFN-γ (or IFN-α), with no detectable defect for activation of ISGF3 in response to stimulation with IFN-α [102]. Therefore, these patients are normally resistant to viral infections and likely to have mycobacterial infections [102, 106].

IRF8

Interferon regulatory factor 8 (IRF8) is part of a family of transcription factors regulating the expression of IFN type I genes and is involved in the development of the myeloid lineage [107, 108]. IRF8 deficiency can present as AD or AR forms [11, 13]. AD form of IRF8 deficiency (immunodeficiency 32A (OMIM #614893)) was found in two patients originating from Chile and Brazil suffering from recurrent episodes of disseminated BCG infections [109]. They carry the same de novo heterozygous mutation as they were absent from parents and siblings [109]. This variant, affecting the DNA binding domain of IRF8, causes poor transactivation of target genes, such as *IL12B* or *NOS2* [109, 110]. Both patients had no decline in circulating lymphocytes and granulocytes. However, they exhibited the loss of one type of circulating dendritic cells (CD11c + CD1c +). These cells are potent producers of IL-12, suggesting that the depletion of these IL-12-producing cells contributes to the susceptibility to mycobacterial infection in these patients [109].

The AR IRF8 deficiency (immunodeficiency 32B (OMIM #226990) causes severe monocytopenia and a deficiency in dendritic cells, resulting in severe and recurrent infections, including disseminated BCG infections and candidiasis [109, 111]. Peripheral mononuclear blood cells (PBMC) from patients did not produce IL-12 in response to stimulations by BCG, phytohemagglutinin (PHA), and lipopolysaccharide (LPS), causing very low production of IFN-γ [109, 111]. AR complete IRF8 deficiency combines mycobacterial and fungal infections, myeloproliferation, and absence of circulating monocytes and dendritic cells [109, 111]. A recent patient with AR complete IRF8 deficiency has been described as having pulmonary alveolar proteinosis (PAP) with neutrophilia and absence of circulating monocytes and DCs [112].

SPPL2A

SPPL2a (signal peptide peptidase-like 2A) is an intracellular transmembrane protease with several substrates [113], including, in particular, the N-terminal fragment (NTF) of the HLA invariant chain (CD74) expressed by HLA-II$^+$ antigen-presenting cells [114]. The SPPL2A-deficient mice display impaired CD74 degradation in B lymphocytes and dendritic cells. The description of a new genetic etiology of MSMD was recently illustrated in three patients from two Moroccan and Turkish families [114]. Patients develop BCG infections a few months after vaccination [114]. SPPL2a deficiency leads to a decrease in the number of conventional type 2 dendritic cells (cDC2), such as the AD IRF8 deficiency which also causes a somewhat greater depletion of the cDC [109]. Thus, IRF8 connects with SPPL2A via IL-12-producing myeloid dendritic cells. In mouse macrophages, a binding site for IRF8 was identified in the SPPL2a promoter, suggesting that the decrease in cDC2 in AD IRF8 deficiency might reflect an altered induction of SPPL2A [114]. Memory T cells from donors deficient in SSPL2a and IRF8 exhibited altered IFN-γ production in response to BCG and *M. tb* antigens [114].

CYBB

NADPH oxidase (NOX) is a membrane enzyme complex. It is the key enzyme of the oxidative burst that occurs in phagocytes and contributes to the degradation of internalized particles and bacteria. NADPH oxidase is assembled from seven subunits, including cytochrome b (− 245), which is a heterodimer composed of a beta subunit (CYBB or gp91$^{phox)}$ and an alpha subunit (CYBA or p22$^{phox)}$. Mutations in one gene of the NADPH oxidase complex can cause chronic granulomatosis disease (CGD) [115]. In contrast, seven male patients with X-linked (XR) gp91^{phox} deficiency (immunodeficiency 34 (OMIM #300645)) from two unrelated families developed mycobacterial infections without further signs of CGD [115, 116]. Six patients had BCG infections (BCG-itis or BCG-osis) and the seventh, who had not been vaccinated with BCG, developed disseminated tuberculosis [115, 116]. Contrary to what had been observed in patients with CGD, circulating phagocytic cells (neutrophils, monocytes) and dendritic cells of these patients

exhibited normal NADPH oxidase activity with very impaired NADPH oxidase activity in monocyte-derived macrophages (MDMs) and EBV-B cells [115, 116].

NEMO (IKBKG)

NEMO (NF-kB essential modulator) is a protein encoded in humans by the *IKBKG* gene. NEMO (or IKK*γ)* is a subunit of the IKK kinase complex. This complex consists of two catalytic kinases, IKK*α* and IKK*β*, and a regulatory subunit IKK*γ*. Once the complex is activated, it activates and releases NF-KB [117]. NF-kB is a transcription factor regulating the activity of several genes involved in ontogeny, homeostasis, activation, and maintenance of self-tolerance in lymphocytes [117, 118].

NEMO mutations may exhibit various characteristics, including immunodeficiency 33 (OMIM #300636), which manifests as XR susceptibility to mycobacterial infections. Two variants, p.E315A and p.R319Q have been identified as responsible for XR-linked MSMD. Patients presented with *M. avium, or M. tb* infections without any other severe infections and little dental abnormalities (conical teeth) [119, 120]. Low levels of IFN-*γ* and IL-12 secretion by the peripheral mononuclear blood cells (PBMCs) of the patients in response to PHA or CD3-specific antibodies were observed in these patients. The mechanism underlying this susceptibility involves the impairment of CD40-dependent IL-12 production. These hypomorphic recessive mutations of NEMO selectively impair the T cell-dependent, CD40- dependent, c-Rel-mediated NF-κB pathway in the myeloid cells of these patients [120].

ISG15

ISG15 encodes a ubiquitin-like protein that is attached to substrates in a process called ISGylation, which closely resembles ubiquitination [86]. Moreover, ISG15 is secreted by neutrophils and other myeloid cells (e.g. monocytes) upon bacterial challenge and acts as a very potent IFN-*γ* inducing cytokine in lymphocytes (particularly NK cells), in synergy with IL-12 [86]. In the absence of the ISG15, the amount of IFN-*γ* production is reduced, which may explain the increased susceptibility to mycobacterial infections in the AR complete ISG15 deficiency (immunodeficiency 38 (OMIM #616126). The first description of this IEI reported three patients with severe BCG and mycobacterial infections [121]. Intracranial calcification is also reported, attributed to the role of ISG15 stabilization of USP18, a potent negative regulator of IFN-I-mediated inflammation [122]. Other new ISG15-deficient patients were reported presenting mycobacterial diseases in the context of severe skin inflammation, as a third clinical phenotype of AR complete ISG15 deficiency [123, 124]. Stimulation of T and NK cells, by IL-12, IL-23, and ISG15, to produce IFN-γ is therefore essential for effective immunity against mycobacteria.

USP18

Ubiquitin-specific protease 18 (USP18) belongs to a family of deubiquitinating enzymes that cleave the bond between ubiquitin and a lysine residue of a ubiquitin-modified protein. USP18 specifically removes covalently linked ISG15 from other proteins, in a process called deISGylation. In turn, ISG15 prevents USP18 from being degraded by the proteasome [122]. The expression of USP18 is strongly induced by type I and type III interferons and PRRs after viral or bacterial infection. USP18 downregulates the IFN-I response by blocking JAK1 interaction with the subunit 2 (IFNAR2) of the IFN-I receptor independently of its protease activity [125]. Complete USP18 deficiency is responsible for the most severe interferonopathy (to overt type I IFN inflammation) with no complications of the BCG vaccine [126, 127]. Recently, three patients from a Moroccan consanguineous family have been identified with AR partial USP18 deficiency [26]. All patients suffered from disseminated BCG disease associated with intracranial calcifications. The homozygous variant, c.179T > A (p.I60N) is situated in exon 3 of USP18 and does not affect the protein expression in an overexpression system [26]. The secretion of IFN-*γ* or IL-12 in whole blood activation is intact in these patients. However, the persistent IFN-I signaling impairs the ability of myeloid cells to produce IL-12 and IL-23 and contributes to MSMD [26].

ZNFX1

The *ZNFX1* gene encodes the zinc finger NFX1-type containing 1 (ZNFX1) protein, a helicase of the superfamily 1 (SF1), important for the direct induction of IFN*α*/*β*-stimulated gene (ISG) with antiviral activities. ZNFX1 is highly expressed in myeloid cells and very few studies have investigated the structure and function of this protein. AR ZNFX1 deficiency (immunodeficiency 91 (OMIM #619644)) was reported in three patients from 2 unrelated consanguineous families from Iran and Morocco [23]. The first patient had BCG-osis following BCG vaccination at age of three months and later developed recurrent respiratory infections, including CMV infections, associated with pneumonia and interstitial lung disease. The Moroccan kindred is living in Belgium and none of the patients has received BCG vaccination, one developed disseminated tuberculosis at the age of 11 years and the other did not suffer from severe infectious diseases. The two patients also had recurrent and unexplained episodes of fever, thrombocytopenia, and organomegaly. A brother of these two patients died at 14 months of age from *M. tuberculosis* meningoencephalitis.

This patient was not genotyped. The two homozygous variants were predicted to be LOF [23]. Cells from patients produced IFN-γ and IL-12 similarly to cells of healthy controls [23]. Other patients with a more complex phenotype associating monocytosis, thrombocytopenia, hepatosplenomegaly, recurrent infections, and macrophagic activation were also reported [27, 128]. ZNFX1 protein is localized in stress granules of cells. Future studies are necessary to determine the connection of ZNFX1 with IFN-γ.

Conclusion

The constant progress of genomics and the establishment of new functional tests have paved the way for the identification of monogenic hereditary defects conferring a selective predisposition to infections by certain types of microbes, as a new type of IEIs [9]. Studies on these IEIs allow us to understand the molecular basis of the immune response against diverse types of pathogens. MSMD, which predisposes mainly to mycobacterial infections, is the most studied of these IEIs, with 35 different disorders found in 19 distinct genes. Despite the clinical and genetic heterogeneity of MSMD, functional studies have shown remarkable physiological homogeneity. Indeed, all genetic etiologies of MSMD alter IFN-γ-mediated immunity. The IL-12/IL-23/ISG15/IFN-γ axis is critical for human defense against mycobacterial infection [30]. The discovery of these genetic etiologies of MSMD has important diagnostic, therapeutic, and preventive implications. Indeed, the molecular diagnosis of MSMD allows for offering a better therapeutic approach and genetic counseling to affected families. Patients with defects in IFN-γ production may benefit from treatment with recombinant human IFN-γ, in addition to antibiotics. In contrast, HSCT is the only medical option to date for patients with a completely defective response to IFN-γ. In addition, gene therapy represents a promising therapeutic intervention for these defects after being successfully tested [33, 34]. In addition, BCG vaccine is contraindicated in patients with MSMD and newborn siblings until genetic assertion, as most patients are diagnosed after being vaccinated and developing BCG complications. However, suspending BCG vaccination can be detrimental to patients in tuberculosis-endemic regions. Early newborn screening, preemptive treatment with antimycobacterial therapy and the development of safer vaccine platforms for patients with genetic immune disorders may be alternative strategies. Thus, targeted genotyping or whole exome/genome sequencing has become a diagnostic necessity even in emerging countries. Despite these recent discoveries, the genetic puzzle of mycobacterial infections remains far from complete, as no genetic etiology has yet been identified for nearly half of all MSMD patients. Other pathways could be identified as being involved soon.

Abbreviations

AD	Autosomal dominant
AR	Autosomal recessive
BCG	Bacille Calmette-Guérin
cDC2	Conventional type 2 dendritic cells
CGD	Chronic granulomatosis disease
CMC	Chronic mucocutaneous candidiasis
DCs	Dendritic cells
EM	Environmental mycobacteria
GAF	Gamma-activating factor
HSCT	Hematopoietic stem cell transplantation
IEI	Inborn error of immunity
IFN-γ	Interferon gamma
IL-12	Interleukin 12
IRF8	Interferon regulatory factor 8
ISGF3	Interferon-stimulated gene factor 3
ISGs	Interferon-stimulated genes
IUIS	International Union of Immunology Societies
JAK	Janus kinase
LOF	Loss of function
LPS	Lipopolysaccharide
M. tb	*Mycobacterium tuberculosis*
MSMD	Mendelian susceptibility to mycobacterial disease
NEMO	NF-kB essential modulator
NOX	NADPH oxidase
OMIM	Online Mendelian inheritance in man
PBMC	Peripheral mononuclear blood cells
PHA	Phytohemagglutinin
PID	Primary immunodeficiency
PRRs	Pattern recognition receptors
STAT1	Signal transducer and activator of transcription 1
SF1	Superfamily 1
TBX21	T-box protein 21
USP18	Ubiquitin-specific protease 18
XR	X-linked recessive
ZNFX1	Zinc finger NFX1-type containing 1

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