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Mendelian susceptibility to mycobacterial disease: 2014–2018 update

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Abstract

Mendelian susceptibility to mycobacterial disease (MSMD) is caused by inborn errors of IFN-γ immunity. Since 1996, disease-causing mutations have been found in 11 genes, which, through allelic heterogeneity, underlie 21 different genetic disorders. We briefly review here progress in the study of molecular, cellular and clinical aspects of MSMD since the last comprehensive review published in 2014. Highlights include the discoveries of (i) a new genetic etiology, autosomal recessive SPPL2a deficiency, (ii) TYK2-deficient patients with a clinical phenotype of MSMD, (iii) an allelic form of partial recessive IFN-γR2 deficiency, and (iv) two forms of syndromic MSMD: RORγ/RORγT and JAK1 deficiencies. These recent findings illustrate how genetic and immunological studies of MSMD can shed a unique light onto the mechanisms of protective immunity to mycobacteria in humans.

Graphical Abstract

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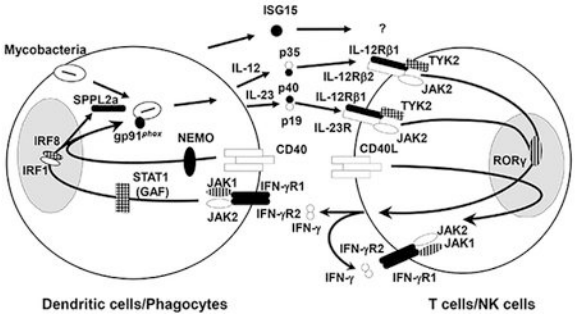
Mendelian susceptibility to mycobacterial disease (MSMD) is caused by inborn errors of IFN-? immunity. Since 1996, disease-causing mutations have been found in 11 genes, which, through allelic heterogeneity, underlie 21 different genetic disorders. We briefly review here progress in the study of molecular, cellular and clinical aspects of MSMD since the last comprehensive review published in 2014.



Keywords

Mycobacterium; IFN-γ; primary immunodeficiency; next-generation sequencing

Introduction

Mendelian susceptibility to mycobacterial disease (MSMD) is a rare inherited condition defined by selective susceptibility to weakly virulent mycobacteria, including Bacille Calmette-Guérin (BCG) vaccine substrains and various environmental mycobacteria (EM), in otherwise healthy patients without overt immunological abnormalities.[1] Patients with MSMD may also suffer from *bona fide* tuberculosis, caused by *Mycobacterium tuberculosis*.[2] A sizeable proportion of patients with MSMD also display invasive infections due to other intra-macrophagic microorganisms, such as *Salmonella*, or mucocutaneous infections caused by *Candida* species.[1,3,4] Other infectious diseases have also been reported, albeit more rarely.[1,4–7] Acquired and inherited immunodeficiencies conferring a predisposition to mycobacterial diseases in the context of other infections must first be excluded, before a diagnosis of MSMD can be reached.[1,2,8] The most severe forms of MSMD lead to early-onset, disseminated, persistent, life-threatening mycobacterial disease, whereas the least severe forms can have a late onset, be relatively circumscribed, spontaneously improve with age, or even remain clinically silent due to incomplete penetrance.[1] Clinical manifestations are, therefore, highly variable. Macrophage activation syndrome[9–11] or vasculitis[1,6,12–16] may occur in rare cases, probably as a consequence of uncontrolled infection. Since the discovery of its first genetic etiology in 1996, MSMD has been reported and a causal genetic lesion described in 501 individuals from 356 kindreds originating from 57 countries on five continents (Figure 1a). Over this period, the genetic dissection of MSMD in these patients has revealed this condition to be caused by inborn errors of IFN-γ immunity.[1,3–7, 9–409,40–53] These findings confirm that IFN-γ, first described in 1965 as an antiviral IFN,[54] is actually the macrophage-activating factor (MAF), as shown in 1983.[55] Mutations of 11 different genes (*IL12B*, *IL12RB1*, *ISG15*, *TYK2*, *IRF8*, *SPPL2A*, *CYBB*, *IFNGR1*, *IFNGR2*, *STAT1*, *NEMO*) have been shown to cause MSMD (Table 1).[1,17,39]

The products of all these genes are involved in IFN-γ production (IL-12p40, IL-12Rβ1, TYK2, SPPL2a, ISG15), the response to IFN-γ (IFN-γR1, IFN-γR2, STAT1, gp91^{phox}), or both (IRF8 and NEMO) (Figure 1b).[1,17,39] MSMD can be inherited in an autosomal recessive (AR) (*IL12RB1*, *IL12B*, *TYK2*, *IFNGR1*, *IFNGR2, ISG15, SPPL2A*), autosomal dominant (AD) (*IFNGR1*, *IFNGR2*, *STAT1*, *IRF8*), or X-linked recessive (XR) manner (*CYBB*, *NEMO*).[1,17,39] Allelic heterogeneity at the 11 loci underlies 21 different genetic forms of MSMD[1,17,39], defined on the basis of (i) the functional deficiency being partial or complete, (ii) the protein being produced or not, and (iii) the mechanism underlying the dysfunction of expressed proteins (Table 1). The causal genetic lesions include single nucleotide variations, small deletions, duplications, insertions, or indels, and copy number variations (CNV; large deletions, insertions, or duplications).[6, 42] Since the last comprehensive review on MSMD in 2014,[1] three new genetic disorders have been reported, caused by mutations of *TYK2*[17] and *SPPL2A,*[39] (two novel genetic etiologies) and *IFNGR2*[56] (a novel allelic form). Moreover, new mutations associated with the other 18 disorders have also been reported.[5–7,10,12,18,22,25,30,32,34,36,42,43,45–49,57] We also discuss here two recently reported syndromic forms of MSMD: AR RORγ/RORγT and JAK1 deficiencies.[58,59] Like three previously reported etiologies of syndromic MSMD, AR STAT1 and IRF8 deficiencies,[1] and AD GATA2 deficiency,[60] RORγ/RORγT and JAK1 deficiencies underlie mycobacterial diseases in the context of other infections.[58,59] Unlike TYK2 deficiency, which also typically underlies mycobacterial disease and other infections,[17] these five genetic etiologies of syndromic MSMD have not been diagnosed in patients with a pure form of MSMD limited to mycobacterial disease.

A new genetic etiology: AR SPPL2a deficiency

A new genetic etiology of MSMD has recently been described in three patients from two kindreds originating from Morocco and Turkey presenting BCG disease a few months after vaccination. Whole exome-sequencing (WES) and whole-genome linkage (WGL) analyses identified two different homozygous splice site mutations in *SPPL2A*, c.733+1G>A or c. 1328–1G>A, in patients from these two kindreds.[39] These splice site mutations disrupt the mRNA, creating aberrant transcripts without any leakiness, and, in overexpression systems, they result in a lack of protein production, or the production of a truncated protein. *SPPL2A* encodes signal peptide peptidase-like 2 A (SPPL2a), a protease with multiple substrates, including, in particular, the amino-terminal fragment of the HLA invariant chain (CD74)[39], which is expressed by HLA-class II^{+} antigen-presenting cells. SPPL2a deficiency results in a deficit of conventional type 2 dendritic cells (cDC2), probably through accumulation of the toxic uncleaved CD74 amino-terminal fragment in these cells.[39] This has been demonstrated for Sppl2a$^{-/-}$ mice, the equivalent DC phenotype of which is rescued by the genetic ablation of CD74.[61] However, human SPPL2a deficiency does not significantly affect B-cell immunity,[39] by contrast to what has been observed in mice with the corresponding defect.[61–63] The immunological phenotype of SPPL2a-deficient patients is reminiscent of that of patients with AD IRF8 deficiency, who display a somewhat broader depletion of cDC.[1] A binding site for IRF8 has been identified in the *Sppl2a* promoter in mouse macrophages, suggesting that the cDC2 deficit in AD-IRF8 deficiency may reflect an impairment of *SPPL2A* induction.[39] Both AD IRF8 and AR SPPL2a deficiencies are also associated with a

defect of IFN-γ production by mycobacterium-specific Th1* cells, a subset of $CD4^+$ T cells secreting both IFN-γ and IL-17A/F.[39] This suggests that cDC2 may be essential for the priming of Th1* cells through the presentation of mycobacterial antigen.[39] SPPL2a deficiency thus causes MSMD through a quantitative defect of IL-12- and IL-23-producing cDC2s and through the impairment of IFN-γ production by mycobacterium-specific memory Th1* cells (Figure 1b and Table 1).[39]

Complete AR TYK2 deficiency and MSMD

Human TYK2 is a Janus kinase (JAK) involved in the pathways of response to IL-10, IL-12, IL-23 and IFN-α/β. The first patient with inherited complete AR TYK2 deficiency was reported in Japan in 2006.[2,17] He suffered from typical signs of hyper-immunoglobulin E (IgE) syndrome (HIES): atopic dermatitis, high IgE levels, and recurrent cutaneous staphylococcal infections.[2,17] He also had nontyphi *Salmonella* infections, lymphadenitis after BCG vaccination and a history of viral infections. In 2015, seven other patients from five unrelated families from Argentina, Iran, Morocco, and Turkey were reported, with homozygous nonsense or frameshift *TYK2* mutations responsible for complete AR TYK2 deficiency.[17] These patients displayed intracellular bacterial and/or viral infections, and none had the classic features of HIES.[17] These seven patients had all been vaccinated with BCG. Four suffered from adverse reactions to BCG (either localized or regional (BCG-itis) or disseminated (BCG-osis)), another from abdominal tuberculosis, another from miliary tuberculosis, and only one had no history of mycobacterial disease.[17] It is probable that their susceptibility to mycobacterial disease results from impaired (but not abolished) IL-12 and IL-23 responses, resulting in defective IFN-γ production by T cells and NK cells (Figure 1b and Table 1).[17] Four of the seven patients also suffered from viral disease, consistent with their poor cellular responses to type I IFNs.[17] However, one patient had a pure clinical phenotype of MSMD, and two had a phenotype of isolated tuberculosis.[17] There is, thus, incomplete penetrance for both mycobacterial and viral infections in complete AR TYK2 deficiency. Intriguingly, a ninth patient was reported to suffer from HIES.[57] Overall, among the nine patients with complete AR TYK2 deficiency, five had a history of BCG disease, and thus displayed phenotype of MSMD, due to poor cellular responses to IL-12 and IL-23.[17,57] Two patients from one Japanese kindred with compound heterozygous frameshift and missense *TYK2* mutations causing partial TYK2 deficiency were recently reported.[64] Both displayed EBV-driven lymphoproliferative diseases but no MSMD.[64]

A new allelic form of AR partial IFN-γR2 deficiency

A new form of partial IFN-γR2 deficiency was recently described in three patients from two kindreds from Turkey and India.[56] The three patients developed BCG disease following vaccination. One of the patients died from *M. chelonei* infection at the age of five years.[56] WES identified homozygous mutations in the first or second codon of *IFNGR2* (c.1A>G and c.4delC).[56] In an overexpression system, the two mutant proteins were produced, albeit in small amounts, and their function was impaired, as demonstrated by the cellular response to IFN-γ.[56] Similar results were obtained for patients' SV40-fibroblasts, Epstein-Barr transformed B lymphocytes (EBV-B cells), primary $CD4^+$ T cells, and monocyte derived-macrophages (MDM) (homozygous for c.1A>G).[56] The three patients had high plasma IFN-

γ concentrations, as reported for patients with other forms of IFN-γR1 or IFN-γR2 deficiency.[56] The impairment of the cellular response to IFN-γ was more severe than that in patients with previously reported forms of AR partial IFN-γR2 deficiency, but less severe than that in patients with AR complete IFN-γR2 deficiency.[56] Interestingly, the two mutations led to a re-initiation of translation at proximal non-canonical codons located within the signal peptide, rather than at more distal AUG codons.[56] The shorter signal peptide generated was sufficient for entry into and trafficking through the secretory pathway.[56] These patients therefore had low levels of wild-type, full-length IFN-γR2 molecules on the surface of their cells. By contrast, the missense mutations underlying previously reported forms of partial AR IFN-γR2 deficiency result in the expression at the cell surface of abnormal and dysfunctional proteins. The mutations in the first or second codon result in the production of very low levels of normal IFN-γR2 proteins, *i.e.* a purely quantitative form of partial IFN-γR2 deficiency (Table 1).[56]

New mutations at known MSMD loci

Since 2014,[1] 34 new disease-causing mutations have been reported at six MSMD loci already discovered before this date, including *IFNGR1*,[10,40,42,43,45,46,48,49] *IFNGR2*,[5,10,47] *IL12RB1*,[6,12,22,25,30] *IL12B*,[7] *STAT1*,[32–34] and *NEMO*.[18,36–38] Interestingly, the two new hypomorphic *NEMO* mutations underlie mycobacterial diseases without anhidrotic ectodermal dysplasia (EDA).[18,36–38] One of these mutations (c.1–16G>C) is located in the non-coding exon 1B of *NEMO*.[36–38] Three patients harboring this mutation presented adulthood-onset disseminated mycobacterial disease.[36] Another patient with the same phenotype carried the previously described[65] c.1–16+1G>T *NEMO* mutation.[36] A founder effect was described for the known p.W60* mutation, which is responsible for IL-12p40 deficiency in Saudi patients.[19] By contrast, fewer CNVs have been reported, but those identified include an entire deletion of the *IFNGR1* gene.[42] Four large deletions and the first large duplication at the *IL12RB1* locus were identified by targeted next-generation sequencing (NGS).[6] Up to 7% of *IL12RB1* mutations are CNVs, and the genetic structure of this locus leaves it prone to various *Alu*-mediated CNVs.[6] There are probably many undetected CNVs at other MSMD loci.[6] Finally, new mutations underlying complete AR IFN-γR2 deficiency[5] and AD STAT1 deficiency[32, 66] have been reported in two patients with a phenotype broader than the expected MSMD. Interestingly, both these patients actually suffered from two different primary immunodeficiencies (PIDS).[5, 32, 66] The first also had IFN-αR1 deficiency,[5] accounting for viral diseases, and the second had p40^{phox} deficiency,[32, 66] accounting for pyogenic bacterial diseases. This situation is reminiscent of that previously reported for patients with both ataxia-telangiectasia and IL-12Rβ1 deficiency.[1] These findings highlight the importance of testing patients with a phenotype broader than expected, including the canonical MSMD phenotype, for other genetic diseases.

RORγ/RORγT and JAK1 deficiencies: new genetic etiologies of syndromic MSMD

Syndromic MSMD is typically defined as a combination of both mycobacterial disease and other infections associated with a more complex cellular phenotype. Known examples include AR STAT1 and TYK2 deficiencies, underlying mycobacterial and viral diseases,[1,17] and AD GATA2 deficiency, underlying mycobacterial and viral diseases in the context of multiple myeloid and lymphoid abnormalities.[1, 60] Two new disorders belonging to this group were recently discovered.[58,59] A combination of WES and WGL identified homozygous *RORC* mutations in seven patients from three kindreds living in Chile, Israel, and Saudi Arabia, respectively.[58] The patients had BCG-osis and chronic mucocutaneous candidiasis (CMC).[58] The *RORC* gene can encode two protein isoforms that act as transcription factors: nuclear orphan receptor γ (RORγ), which is ubiquitously expressed, and RORγT, the expression of which is restricted to leukocytes. The mutations identified in the three kindreds were p.S38L, p.Q329*, p.Q441* for the RORγ isoform and p.S17L, p.Q308*, p.Q420* for the RORγT isoform. The mutant *RORC* alleles are loss-of-function.[58] The patients displayed impaired lymphoid development with a small thymus, mild T lymphopenia, and small number of ILC3, MAIT cells and NKT cells.[58] IL-17A/F secretion was impaired in T cells from the patients, accounting for CMC.[58] IFN-γ secretion was normal in naïve or memory $CD4^+$ T cells but strongly impaired in γδ T cells and Th1* cells, accounting for mycobacterial disease.[58] Bi-allelic *RORC* mutations thus impair IL-17 and IFN-γ immunity, underlying candidiasis and mycobacteriosis, respectively.[58] In addition, two homozygous variants (p.P733L, p.P832S) of the pseudokinase domain of JAK1 were recently identified by WES in a patient from Pakistan with atypical mycobacterial disease and a history of viral, fungal, and parasitic skin infections.[59] This patient died from urothelial carcinoma at the age of 22 years.[59] JAK1 is a tyrosine kinase involved in the intracellular signaling of many cytokines, including IFN-α/β and IFN-γ. Cellular responses to IFN-γ and IFN-α were impaired but not abolished by this mutant allele in an overexpression system (U4A cells), in primary fibroblasts, and in leukocytes from the patient.[59] The p.P733L mutation was found to be hypomorphic and responsible for this cellular phenotype, whereas the p.P832S mutation was neutral. Impaired responses to IL-2, IL-4, IL-10 and IL-27 were also documented in leukocytes.[59] AR partial JAK1 deficiency thus causes susceptibility to mycobacteria due to the impairment of IFN-γ signaling, and susceptibility to other infections due to defective responses to other cytokines, including IFN-α. This condition may also cause susceptibility to early-onset cancer.[59]

Concluding remarks

Over the last years, the genetic dissection of patients with isolated MSMD or syndromic MSMD has shed new light on the molecular and cellular bases of human immunity to mycobacteria (Figure 1b). An enigma not addressed here concerns the occurrence of mycobacterial disease in some patients with gain-of-function *STAT1* mutations.[67] This is paradoxical, as STAT1 deficiency underlies mycobacterial disease by decreasing cellular responses to IFN-γ.[1] One would have predicted patients with enhanced cellular responses to IFN-γ not to be expected to be prone to mycobacterial disease, and even perhaps being

protected from them. This mystery remains to be solved, but the last four years have clearly revealed four new molecular players in MSMD players at the molecular level: SPPL2a, TYK2, JAK1 and RORγ/RORγT. They have also revealed two new MSMD players at the cellular level, IFN-γ-producing Th1* and γδ T cells.[58] They have also collectively confirmed the importance of previously identified molecules, encoded by known MSMD loci. Finally, they have added weight to the previous suggestion that IL-12- and IL-23-producing cDC2s are essential for protective immunity to mycobacteria.[39] Admittedly, the contribution of these cells to this condition will be proven only if genetic defects exclusively preventing their development or function are discovered. The study of MSMD is far from complete. MSMD is the most studied of a handful of "Mendelian infections" that provided early support for a genetic theory of infectious diseases, paving the way for the study of monogenic but non-Mendelian infections.[68,69] Only about half the MSMD patients in our laboratory cohort have a known single-gene inborn error of IFN-γ immunity. A molecular diagnosis of MSMD makes it possible to offer families genetic counseling and paves the way for treatment options based on a better understanding of the pathogenesis of mycobacterial disease. For example, IFN-γ therapy should be considered as the natural treatment, in conjunction with antibiotics, in all patients who do not have a complete lack of cellular responses to this cytokine. Next-generation sequencing (NGS) techniques, including both WES and whole-genome sequencing (WGS) in particular, are now accelerating genetic dissection in the remaining MSMD patients without a genetic diagnosis. This work will lead to the discovery of new genetic etiologies[39,70] and will improve the screening of mutations not easily detectable by Sanger sequencing, such as CNV.[6] NGS is a powerful tool that will help to decipher the genetic and clinical heterogeneity of MSMD,[70] paving the way for similar studies on tuberculosis.[2,71]

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Figure 1 – . Genetic spectrum of MSMD (a) Geographic distribution of patients with MSMD. (b) Cells involved in the production of and response to IFN-γ.

Proteins for which a mutation of the corresponding gene has been recognized to cause solely MSMD (IFN-γR1, IFN-γR2, SPPL2a, NEMO, gp91^{phox}, IL-12p40, IL-12Rβ1, ISG15) are depicted in black, those responsible for syndromic MSMD (JAK1, RORγ) are depicted with vertical lines, those that can cause either MSMD or syndromic MSMD (IRF8, STAT1, TYK2) are depicted with crossed lines.

Table 1 –

Overview of diseases underlying MSMD

Gene	Inheritance	Defect	Protein
IL12RB1	AR	C	E−
	AR	C	E+
IL12B	AR	C	E−
ISG15	AR	C	E−
SPPL2A	AR	C	E− or E+
IRF8	AD	P	E+
TYK2	AR	C	E−
IFNGR1	AR	C	E+
	AR	C	E−
	AD	P	E+++
	AR	P	E+
IFNGR2	AR	C	E+
	AR	C	E−
	AR	P	E+ of mutant protein
	AR	P	E+ of WT protein
	AD	P	E+
STAT1	AD	P	E+P−
	AD	P	E+B−
	AD	P	E+P−B−
NEMO (*IKBKG*)	XR	P	E+
CYBB	XR	P	E+

MSMD genetic etiologies may display autosomal recessive (AR), autosomal dominant (AD), or X-linked recessive (XR) inheritance. Defects may be complete (C) or partial (P). Expression (E) of the mutant protein may be abolished (E−), decreased or normal (E+), or increased (E+++). The mutant protein may be phosphorylated normally, unable to undergo phosphorylation (P−) or unable to bind DNA (B−).