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Nontuberculous mycobacterial infections in children with inborn errors of the immune system

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Summary Severe mycobacterial disease is mostly confined to patients who are immunocompromized either by acquired or inherited causes. One such genetic disorder is Mendelian Susceptibility to Mycobacterial Disease (MSMD), a hot topic within the field of primary immunodeficiency. This single gene disorder is characterized by isolated infection with mycobacteria or *Salmonella* due to a defect in the type-1 cytokine response. In the last two decades, ten genes have been labeled as causing MSMD when they harbor germline mutations, namely *IL12B*, *IL12RB1*, *IFNGR1*, *IFNGR2*, *STAT1*, *IKBKG*, *CYBB*, *TYK2*, *IRF8* and *ISG15*. The mutations lead to either insufficient production of IFN-γ, or to an insufficient response to the cytokine. Current treatment options include recombinant IFN-γ and hematologic stem cell transplantation (HSCT). In the future, gene therapy, antisense-mediated exon skipping and chemical intervention in glycosylation problems may become successful alternatives. Furthermore, it is likely that many new candidate genes and pathways crucial for mycobacterial immunity will be identified.

Introduction

In the last two decades, a great deal of research on monogenic disorders of immunity has focused on patients with severe non-tuberculous mycobacteria (NTM) or *Mycobacterium bovis*-Bacille Calmette—Guérin (BCG) infections. These predominantly pediatric disorders have been termed Mendelian Susceptibility to Mycobacterial Disease (MSMD, OMIM 209950). Almost every human encounters NTM during childhood and adolescence, and worldwide vaccination policies of newborns have ensured they have also been extensively exposed to BCG. However, these diseases manifest

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themselves in only a few individuals. Severe and disseminated mycobacterial disease is mostly confined either to patients who are immunocompromized by acquired or external causes such as HIV infection, hematological malignancy or immunosuppressive treatments, or to patients with inherited disorders such as severe combined immunodeficiency (SCID), MSMD, and chronic granulomatous disease (CGD). In countries where infection with *Mycobacterium. tuberculosis* is endemic and exposure widespread, these same groups may suffer from clinical tuberculosis (TB), but severe morbidity and early death due to virulent *M. tuberculosis* likely precludes the diagnosis of these underlying defects. Indeed, the incidence of TB in MSMD patients is relatively low.[1] In addition to mycobacterial infections, a subgroup of MSMD patients is highly susceptible to systemic nontyphoidal salmonellosis. Other infections may be present, but are not a hallmark of MSMD.[2–5]

The first report of genetic defects in MSMD patients was published in 1996 and concerned four Maltese children with fever, weight loss, hepatosplenomegaly, bone lesions and an intense acute-phase response. They had disseminated NTM infection due to a mutation in the interferon-γ receptor 1 (IFN-γR1), and three of them succumbed to it.[6] This report spawned a wealth of research on this type of primary immune disease (PID), identifying just under two dozen genetic disorders (Table 1)[7] and reporting over 300 patients world-wide. Ten genes, namely *IL12B*, *IL12RB1*, *IFNGR1*, *IFNGR2*, *STAT1*, *IKBKG*, *CYBB*, *TYK2*, *IRF8* and *ISG15*, have been labeled as causing MSMD when they exhibit germline mutations. *TYK2*, *IRF8* and *ISG15* were categorized as such only recently.[8–11] *IKBKG* and *CYBB* are located on the X-chromosome, while the others are on autosomes.[7] Most patients have either autosomal recessive mutations in IL-12Rβ1 or autosomal dominant mutations in IFN-γR1.[12] The latter group widely shares one mutation, namely c.819_822del (often referred to as 818del4).[12] For many MSMD patients, the genetic defects are still unknown. However, new and increasingly efficient gene-scanning techniques such as whole-exome and whole-genome sequencing may help bridge that gap in the near future.

Disseminated mycobacterial infections have also been associated with *GATA2* deficiency (MonoMAC syndrome) and autoantibodies to IFN-γ. However, these two ailments only present in adulthood. Furthermore, *GATA2* deficiency correlates with hematological problems and autoantibodies are acquired instead of inherited.[13,14] Accordingly, these diseases are omitted from this review.

IL-12 and IL-23

IL-12/IL-23 signaling

IL-12 and IL-23 are part of the IL-12 cytokine family that also includes IL-27 and IL-35. These molecules and their receptors are heterodimers, and some share the same

Table 1 Genetic etiologies of MSMD.

Gene	Number of patients reported[27]	Inheritance	Defect	Protein
IL12B	19	AR	Complete	E−
IL12RB1	198	AR	Complete	E−
		AR	Complete	E+
		AR	*Partial–severe*	*E−*[a]
IFNGR1	109	AR	Complete	E−
		AR	Complete	E+
		AR	Partial	E+
		AD	Partial	E++
IFNGR2	12	AR	Complete	E−
		AR	Complete	E+
		AR	Partial	E+
		AD	Partial	E+
STAT1	18 (of which 9 AR)	AR	Complete	E−P−B−[b]
		AR	Partial	E+P+B+[b]
		AD	Partial	E+P−B+
		AD	Partial	E+P+B−
NEMO	6	XR	Partial	E+
CYBB	7	XR	Partial	E+
TYK2	1[c] (or 2)	AR	Partial	E−
IRF8	2	AD	Partial	E+
ISG15	2	AR	Complete	E−

AR: autosomal recessive; AD: autosomal dominant; XR: X-linked recessive; E+: protein expression; E−: no protein expression; P+: protein phosphorylation; P−: no protein phosphorylation; B+: DNA-binding; B−: no DNA-binding.

[a] Severe, partial defect based on *in vitro* data (see text), severe defect based on clinical data.

[b] Autosomal recessive STAT1 mutations have been placed outside the realm of classical MSMD because these patients suffer also from significant viral infections.

[c] The detailed immunologic investigation of this patient is still to be reported.