Review

Mendelian susceptibility to mycobacterial disease


The host response to mycobacterial infection is mediated by the type I cytokine pathway (cell-mediated immunity). Deficiencies in this response result in susceptibility to poorly pathogenic mycobacterial species such as bacille Calmette-Guérin and environmental mycobacteria. In recent years a number of mutations in the genes encoding major components in the type I cytokine axis have been described which predispose to disseminated infection with these weakly virulent mycobacterial species. Affected individuals are also prone to extra-intestinal disease caused by non-typhoidal Salmonella. The genes involved display a high level of allelic heterogeneity, accounting for a number of distinct genetic disorders which vary in their mode of inheritance and clinical presentation. These disorders have been termed Mendelian susceptibility to mycobacterial disease and are discussed in this review article.

Conflict of interest

No conflict of interest.

Vaccination with attenuated Mycobacterium bovis BCG (bacille Calmette-Guérin) is practised worldwide and only rarely leads to disseminated infection, referred to as ‘BCG-osis’, usually indicating the presence of an underlying immune deficiency. Similarly, exposure to environmental non-tuberculous mycobacteria is almost universal by early childhood and disseminated infection with these ubiquitous pathogens suggests an immune defect, which may be primary or acquired (1, 2). The host response to mycobacterial infection depends on the integrity of the type I cytokine pathway. In recent years a series of inherited disorders of this pathway have been described which convey an almost isolated predisposition to disseminated infection with mycobacteria. These genetic defects have been grouped under the umbrella term ‘Mendelian susceptibility to mycobacterial disease’ (MSMD) (3). In addition to their vulnerability to poorly pathogenic mycobacterial species, individuals with MSMD are prone to invasive extra-intestinal disease caused by weakly virulent non-typhoidal Salmonella (4).

The type I cytokine pathway

Mycobacteria are intracellular pathogens and the host defence requires an effective cell-mediated immune response. Both dendritic cells and macrophages act as antigen-presenting cells (APCs). They recognize invading mycobacteria through pattern recognition receptors which include members of the Toll-like receptor (TLR) family, C-type lectins such as DC-SIGN (CD209 antigen) and mannose receptors (5). Signal transduction cascades lead to activation of the infected APC and production of interleukin-12 (IL-12) and interleukin-23 (IL-23) (Fig. 1) (6). These cytokines bind to their respective receptors (IL-12R and IL-23R) on T-helper and natural killer (NK) cells, inducing the production of interferon (IFN)-γ, IL-17 and tumour necrosis factor-α (6).
Uncommitted T-helper cells start to differentiate towards an antigen-specific T-helper type 1 (Th1) phenotype and become a major source of IFN-γ during the adaptive immune response (5). Optimal production of IL-12 requires binding of mycobacterial cell wall components to TLR2 and TLR4 on the surface of APCs (7).

Secretion of IL-12 and IFN-γ is enhanced by two major pathways: firstly, a T-cell-dependent pathway mediated through the interaction of CD40 expressed on APCs with CD40 ligand on activated T cells; secondly, co-stimulation occurs via receptors of the interleukin-1 receptor family such as the IL-18R (7). IL-18 is produced by APCs and induces Th1 cell maturation, migration and activation. It acts in synergy with IL-12 and IL-23 to enhance production of IFN-γ (8, 9).

Secreted IFN-γ binds to its receptor (IFN-γR) expressed on the surface of dendritic cells and macrophages. The IFN-γR is composed of two chains, IFN-γR1 which is a ligand-binding chain, and IFN-γR2 which is required for signal transduction via Janus kinases and signal transducer and activator of transcription-1 (Stat-1) (5, 7, 10). Stat-1 is critical in signal transduction upon IFN-γR ligand binding (10). IFN-γ upregulates production of IL-12 by the macrophage and facilitates mycobacterial killing by enhancing receptor-mediated phagocytosis, phagolysosomal fusion and expression of inducible nitric oxide synthase and NADPH-oxidase components (5–7, 10).

The IL-12 receptor is a complex of IL-12 receptor β1 (IL-12Rβ1) and IL-12 receptor β2 (IL-12Rβ2), expressed on the surface of T-helper and NK cells (5). IL-12 is a heterodimer consisting of p40 and p35 subunits; IL-12p40 binds primarily to IL-12Rβ1, while IL-12p35 binds to IL-12Rβ2 (5). IL-23 also has the p40 subunit, coupled to a different chain, p19 (11). The IL-23 receptor is a complex of IL-12Rβ1 and another subunit IL-23R (12). IL-12 and IL-23 act in a similar way, but IL-23 appears to be less effective at inducing IFN-γ production and more important in promoting the proliferation of memory T cells (11). Signal transduction through the IL-12R and IL-23R induces tyrosine phosphorylation of Janus kinases (Jak2 and Tyk2) and subsequent activation of Stat molecules (6, 7).

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Mutations have been identified in the following autosomal genes involved in the IL-12/IL-23/IFN-γ axis: **IFNGR1** and **IFNGR2** (encoding IFN-γR1 and IFN-γR2, respectively), **STAT1** (encoding Stat-1), **IL12P40** (encoding the IL-12p40 subunit), **IL12RB1** (encoding the IL-12Rβ1 chain) and **TYK2** (encoding tyrosine kinase 2) (7, 9, 13). In addition an X-linked genetic trait has been identified affecting **NEMO**, encoding nuclear factor-κB-essential modulator (NEMO) (14). These genes display a high level of allelic heterogeneity accounting for a number of distinct genetic disorders which vary in their mode of inheritance and clinical presentation. Mutations may be dominant.
or recessive and associated with a partial or complete deficiency of the gene product.

IFN-γR1 deficiency (OMIM 107470)

Recessive mutations in IFNGRI may be partial or complete. Recessive complete IFN-γR1 deficiency was the first category of MSMD to be identified in 1996 (15, 16). There are two forms of autosomal recessive complete IFN-γR1 deficiency: most mutations prevent the expression of IFN-γR1 on the cell surface, while a minority of mutations result in cell surface expression of dysfunctional molecules which do not recognize IFN-γ (13, 17, 18). There is no cellular response to IFN-γ in vitro and patients’ plasma usually contains large amounts of IFN-γ (13, 19). Recessive complete IFN-γR1 deficiency is associated with severe, often fatal infection with BCG and environmental mycobacteria (EM) in early childhood (13). The mean age at onset of the first EM infection is 3.1 years (SD 2.5) (20). Infections commonly disseminate to involve the soft tissues, lymph nodes, bone marrow, lung, skin and bones, leading to fever, weight loss, lymphadenopathy and hepatosplenomegaly (7). The prognosis is poor and treatment with IFN-γ is ineffective due to the absence of functional receptors. Haematopoietic stem cell transplantation (HSCT) has been curative in a small number of patients (21, 22). Optimal suppression of mycobacterial infection before HSCT and the use of a non-T-cell-depleted graft from an HLA-identical sibling after a fully myeloablative conditioning regimen are recommended (21, 22).

Other infections reported in patients with recessive complete IFN-γR1 deficiency are Salmonella spp., Listeria monocytogenes and viruses, including human herpes virus 8, cytomegalovirus, varicella zoster, and herpes simplex virus (7, 13).

Recessive partial IFN-γR1 deficiency diminishes the cellular response to IFN-γ, with in vitro signal transduction produced by high IFN-γ concentrations (23). Patients have a milder clinical phenotype compared to those with recessive complete IFN-γR1 deficiency, presenting with infection due to BCG or EM which may be disseminated but generally responds to antimicrobial drugs and, if needed, recombinant IFN-γ (23, 24). HSCT is not indicated. Infection with Mycobacterium tuberculosis has also been reported in a child with this deficiency and was curable with antituberculous therapy (23).

Dominant mutations in IFNGRI result in truncation of the intracellular domain of the IFN-γR1 chain, which lacks the cytoplasmic motifs required for Jak1 and Stat-1 binding as well as receptor recycling (7, 25). Non-functional truncated IFN-γ receptors accumulate on the cell surface, predominating over residual normal receptors. A partial deficiency results, with a weak cellular response to IFN-γ which can be overcome in vitro by stimulating with high IFN-γ concentrations (7, 17). The condition is associated with recurrent, moderately severe infection with BCG and EM, often with bone involvement (20). Children present with mycobacterial infection later than those with recessive complete IFN-γR1 deficiency [mean age at onset of first EM infection 13.4 years (SD 14.3)] (20). Unifocal or multifocal osteomyelitis caused by Mycobacterium avium has been repeatedly associated with dominant IFN-γR1 deficiency (20). In some patients skeletal lesions and histopathological findings may mimic Langerhans’ cell histiocytosis (26). Salmonellosis has been described in 5% of cases (20). Outcome is generally good with prolonged antimicrobial treatment and, if needed, recombinant IFN-γ (17).

IFN-γR2 deficiency (OMIM 147569)

IFN-γR2 deficiency is a rare aetiology of MSMD. Autosomal recessive mutations in IFNGR2 can be associated with partial or complete IFN-γR2 deficiency depending on whether the cellular response to IFN-γ is residual or undetectable, respectively (13). Complete recessive IFN-γR2 deficiency may be associated with either undetectable expression of IFN-γR2 on the cell surface or with surface expression of non-functional receptors (27–29). Complete IFN-γR2 deficiency, like complete IFN-γR1 deficiency, presents with severe, often fatal infection with BCG and EM in early childhood (13). The prognosis is poor and HSCT offers the only possible cure (13).

Partial recessive IFN-γR2 deficiency has been reported in a child who presented with relatively mild M. bovis BCG and Mycobacterium abscessus infection (30). The cellular response to IFN-γ was impaired but not abolished.

Partial dominant IFN-γR2 deficiency has been described in one family, characterized by a dominant negative in vitro phenotype with impaired signalling in response to IFN-γ (31). Two siblings were homozygous for the mutation and lacked all IFN-γR activity. One presented with multifocal M. abscessus osteomyelitis, the other with disseminated cytomegalovirus and M. avium infection. Their heterozygous parents showed partial IFN-γR activity and have not developed clinical disease.
Stat-1 deficiency (OMIM 600555)

Stat-1 is a critical downstream signalling molecule for both IFN-γ and IFN-α/β, which stimulate different transcriptional activators (32). IFN-γ induces the formation of gamma activating factor (GAF; Stat-1 homodimers), while IFN-α/β induces IFN-stimulated γ factor 3 (ISGF-3; heterotrimers composed of Stat-1, Stat-2 and IFN regulatory factor 9) (32). Autosomal recessive Stat-1 deficiency impairs activation of both GAF and ISGF-3, conferring susceptibility to both mycobacteria (IFN-γ-mediated immunity) and viruses (IFN-α/β-mediated immunity), and is therefore not classified as an aetiology of MSMD (13, 33, 34). Autosomal dominant Stat-1 deficiency, however, is recognized within the spectrum of MSMD. Autosomal dominant STAT1 mutations are dominant for IFN-γ-induced GAF activation and recessive for IFN-α/β-induced ISGF-3 activation, selectively impairing antimycobacterial immunity while antiviral immunity remains intact (35, 36). A partial deficiency results.

Autosomal dominant Stat-1 deficiency has a low clinical penetrance and a mild clinical phenotype which resembles partial deficiencies of IFN-γR1 and IFN-γR2 (13). Treatment comprises antibiotics and recombinant IFN-γ.

IL-12p40 deficiency (OMIM 151561)

IL12B encodes the IL-12p40 subunit, shared by both IL-12 and IL-23. Autosomal recessive mutations in IL12B have been described, resulting in a complete deficiency with undetectable IL-12p40 secretion (13, 37, 38). Patients often present with BCG disease following vaccination and approximately half have Salmonella infection (17, 37). The prognosis is generally good for patients who receive antimicrobial treatment and recombinant IFN-γ (13).

IL-12Rβ1 deficiency (OMIM 601604)

This is the most common form of MSMD, first described in 1998 (17, 39). Numerous autosomal recessive mutations in the IL12RB1 gene have been found, resulting in complete IL-12Rβ1 deficiency (17). In most cases there is no expression of IL-12Rβ1 at the surface of activated T-lymphocytes and NK cells, eliminating the cellular response to IL-12 and IL-23 (40). In a rare form of autosomal recessive complete IL-12Rβ1 deficiency non-functional IL-12Rβ1 is expressed on the cell surface (41). The clinical phenotype is similar to that for IL-12p40 deficiency: BCG and (often recurrent) Salmonella are the most common infections and usually respond to prolonged antimicrobials and recombinant IFN-γ (13, 40). IL-12Rβ1 deficiency has low penetrance for case definition phenotypes and genetically affected siblings of index cases may be asymptomatic (40). Infections usually occur before the age of 12 years in patients with symptomatic disease (17).

Cases of severe tuberculosis infection have been reported in three children with IL-12Rβ1 deficiency (42–45). These children were from unrelated kindreds and had no personal history of infection with BCG, EM or Salmonella (42). One child in Morocco developed abdominal tuberculosis having been vaccinated three times with BCG with no adverse effects, although her brother who was also IL-12Rβ1-deficient developed BCG disease after immunization (43). In another family from Spain one child developed disseminated tuberculosis and underwent investigation because her sister had a history of extra-intestinal non-typhoidal Salmonella adenitis in early childhood (44). Both had IL-12Rβ1 deficiency. Finally, a girl from Turkey with disseminated tuberculosis was found to have IL-12Rβ1 deficiency, although she had no familial history of mycobacteriosis or salmonellosis (45). These cases raise the possibility that a significant proportion of children worldwide with disseminated tuberculosis have a Mendelian predisposition to the disease (42).

Invasive Salmonella infection affects approximately half of patients with an impaired IL-12/IL-23 pathway. The incidence in patients with an impaired IFN-γ pathway is much lower, implying a particular role for IL-12 and IL-23 in Salmonella immunity (13, 46).

Tyrosine kinase 2 deficiency (OMIM 611521)

Signal transduction through the IL-12R results in tyrosine phosphorylation of the associated kinases Jak2 and Tyk2 and consequent activation of Stat-4 (7). Phosphorylated Stat-4 dimers translocate to the nucleus to activate transcription of their target genes (6). This process is essential for the efficient production of IFN-γ (7). Tyk2 deficiency has been described in an individual who showed susceptibility to a variety of infections (viral, fungal, bacterial and mycobacterial) including BCG at 22 months and non-typhoidal Salmonella gastroenteritis at 15 years of age (47). The patient also suffered from atopic dermatitis with elevated serum IgE. A homozygous mutation in TYK2 was identified and the patient’s cells displayed defects in multiple cytokine signalling pathways including the IL-12 and IL-23 pathways.
Mutations in NEMO (OMIM 300248) account for an X-linked recessive form of MSMD (14). NEMO is a regulatory subunit of the nuclear factor-kB (NFkB) inhibitor kinase complex, which controls activation of the ubiquitous transcription factor NFkB, implicated in various developmental and immunological pathways (48). CD40 ligand-expressing T cells enhance IL-12 production in monocytes and dendritic cells by engaging with CD40, expressed on APCs, leading to activation of NFkB-c-Rel signalling pathways and enhanced IL-12 production (14). Two mutations have been identified in the leucine zipper domain of the NEMO gene, both of which impair this T-cell-dependent, CD40-triggered, NFkB/c-Rel-mediated induction of IL-12 (14). Insufficient production of IL-12 after T-cell stimulation results in suboptimal IFN-γ production, predisposing individuals to mycobacterial disease. Infections in all but one of the six patients with X-linked recessive MSMD were limited to mycobacterial disease, most commonly M. avium (14). One patient had concomitant M. avium and M. tuberculosis. Prognosis is variable and IFN-γ may be beneficial (17).

There may be other X-linked recessive forms of MSMD, unrelated to NEMO. Bustamante et al. (49) described recurrent mycobacterial disease in four male maternal relatives. Three had recurrent BCG infection and the fourth had recurrent tuberculosis. Known mutations in autosomal genes and NEMO were excluded, suggesting a novel X-linked recessive form of MSMD. Two candidate regions on the X-chromosome were identified by genetic linkage analysis.

**Conclusion**

Individuals who present with disseminated or recurrent infection due to BCG or EM, or with extra-intestinal infection caused by non-typhoidal Salmonella, should be investigated for a defect in cell-mediated immunity, including MSMD after exclusion of HIV, particularly if family members are asymptomatic. MSMD displays a high degree of genetic heterogeneity, with numerous mutations in several genes identified so far. Ascertaining a genetic diagnosis for patients with disseminated mycobacterial disease is important as it bears implications for prognosis and treatment. Approximately half of all patients with MSMD still lack a defined genetic aetiology (17). Novel mechanisms of mutation and pathogenesis remain to be discovered and will provide new insights into the host response to intracellular infection with mycobacteria and Salmonella.

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**References**