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Inherited and acquired immunodeficiencies underlying tuberculosis in childhood

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Summary

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*M.tb*) and a few related mycobacteria, is a devastating disease, killing more than a million individuals per year worldwide. However, its pathogenesis remains largely elusive, as only a small proportion of infected individuals develop clinical disease either during primary infection or during reactivation from latency or secondary infection. Subacute, hematogenous, and extrapulmonary disease tends to be more frequent in infants, children, and teenagers than in adults. Life-threatening primary TB of childhood can result from known acquired or inherited immunodeficiencies, although the vast majority of cases remain unexplained. We review here the conditions conferring a predisposition to childhood clinical diseases caused by mycobacteria, including not only *M.tb* but also weakly virulent mycobacteria, such as BCG vaccines and environmental mycobacteria. Infections with weakly virulent mycobacteria are much rarer than TB, but the inherited and acquired immunodeficiencies underlying these infections are much better known. Their study has also provided genetic and immunological insights into childhood TB, as illustrated by the discovery of single-gene inborn errors of IFN-γ immunity underlying severe cases of TB. Novel findings are expected from ongoing and future human genetic studies of childhood TB in countries that combine a high proportion of consanguineous marriages, a high incidence of TB, and an excellent clinical care, such as Iran, Morocco, and Turkey.

Keywords

primary immunodeficiency; human genetics; IFN-γ; children; Mendelian susceptibility to mycobacterial diseases (MSMD)

Introduction

Tuberculosis: an ancient, deadly disease

Mycobacterium tuberculosis (*M.tb*) is the bacterium responsible for most cases of human tuberculosis (TB). Other rare causes include *M. bovis*, *M. africanum* and *M. canettii* (1, 2). *M.tb* has been causing death and disease in human populations since the Classical era (3). In

1882, Robert Koch discovered a staining technique that made it possible to identify *M.tb* (Fig. 1) (4). Bacilli are transmitted by the inhalation of aerosolized droplets generated by the coughing of a patient with active TB. This disease remains a major public health problem. One-third of the world population is thought to be infected with *M.tb*, with about 8.6 million new cases and 1.3 million deaths worldwide in 2012 (5). About 6–10% of these new cases are children, and children account for up to 40% of all new TB cases in the countries with the highest incidence of TB (5, 6). BCG vaccination provides some protection against severe disseminated TB in childhood, but this protection is incomplete (6). The development of antibiotics has greatly decreased childhood mortality due to TB, but more than 80 000 children still die from TB each year (7). The advent of multidrug-resistant TB, fueled by the HIV epidemic, has made it necessary to develop new therapeutic strategies (8). However, only a small fraction of the individuals exposed to *M.tb* develop clinical TB. This is particularly true for children, and the reasons for this remain unclear. Major research efforts are therefore being needed on elucidating the pathogenesis of childhood TB.

Childhood tuberculosis

A substantial proportion of subjects do not become infected despite sustained high levels of exposure to *M.tb* (9). About 5% of infected individuals develop clinical TB within 2 years of infection, either without latency or after a very short latent phase (10, 11). This ‘primary’ TB is particularly common in children, running a subacute course and often associated with extrapulmonary disease due to dissemination of the bacillus in the bloodstream (12, 13). However, most infected individuals develop latent TB infection with an absence of overt clinical signs; approximately 90–95% of these individuals never develop clinical disease (10, 14, 15). The remaining 5–10% develop chronic pulmonary TB later in life, typically due to reactivation from latency. Severe primary TB was, by far, the most frequent form in children in endemic areas before BCG and antibiotics became available, resulting in high rates of mortality in children under the age of 2 years (3, 16, 17). The risk of severe primary TB is still dependent on age at primary infection, decreasing from 10% to 20% for children under the age of 1 year to less than 0.5% for children over the age of 5 years (12, 13). These severe forms are mostly either miliary (Fig. 2) or affect the central nervous system (causing meningitis, in particular), and they remain life-threatening (12, 13). One of the key unanswered questions in the field of childhood TB concerns the nature of predisposition to the development of severe clinical forms in only a minority of infected children. HIV infection predisposes subjects to severe forms of childhood TB, but such infection is observed in only a small fraction of TB affected children (18). The last decade has provided a new clue to help us solve this riddle, by showing that at least some cases of severe TB, in HIV-seronegative children, can be explained by single-gene inborn errors of immunity (19, 20).

The human genetic theory of tuberculosis

The variability in the reaction of children to primary infection with *M.tb* was dramatically illustrated by the Lübeck accident in 1929 and 1930: 251 children were vaccinated with a strain of BCG contaminated with *M.tb*. “Only” 72 babies died within the year from TB, 135 got TB but spontaneously recovered, and 44 managed to fend off infection, for at least 12 years (3). Epidemiological surveys and familial aggregation studies have provided strong

evidence that this considerable interindividual variability in the development of both childhood and adult TB can be accounted for, at least in part, by host genetic factors (3, 9, 21, 22). In parallel, a long series of experimental studies in various animals, beginning in the 1930s, also established the importance of host genetic background for determining the outcome of primary infection with *M.tb* (reviewed in 14, 15, 22–29). However, without an appropriate laboratory animal model for the disease, it has been a long and difficult struggle to unravel the genetic basis of TB resistance/ susceptibility. The human genetic components of pulmonary TB in adults and of *M.tb* infection *per se* have been reviewed elsewhere (9, 16, 30–35). This review focuses on childhood TB. Evidence is emerging that severe TB in children may result from inborn errors of immunity (16, 31). The first evidence to support this view came from the identification of acquired immunodeficiencies and primary immunodeficiencies (PIDs), both of which are associated with a broader infectious phenotype, including mycobacterial diseases (Table 1). Subsequent progress came mostly from the study of clinical diseases caused by weakly virulent mycobacteria, such as BCG vaccines and non-tuberculous mycobacteria (NTM), in otherwise healthy individuals. This condition, Mendelian susceptibility to mycobacterial disease (MSMD) (OMIM209950), underlies a much narrower range of infections, and its study led to the identification of the first cases of Mendelian predisposition to TB.

Acquired immunodeficiencies conferring a predisposition to mycobacterial diseases in childhood

Immunosuppressive treatments for a number of severe childhood conditions increase the risk of mycobacterial diseases. In particular, childhood leukemia is associated with a higher risk of developing BCG (36), and NTM infections (37–40) or TB (41–44) during chemotherapy or following bone marrow transplantation (BMT). NTM, *M.tb* and, more rarely, BCG infections have also been observed in children treated with immunosuppressive drugs for solid organ transplantation (45–47) or BMT (48–52) for other conditions, such as severe aplastic anemia, myeloma, familial hemophagocytic lymphohistiocytosis or malignant infantile osteopetrosis. However, worldwide, TB is the most common infection affecting patients seropositive for human immunodeficiency virus (HIV), and it remains the most common cause of death in patients with acquired immunodeficiency syndrome (AIDS) (53). Overall, 1.1 million of the 9 million individuals infected annually with *M.tb* are also infected with HIV. Data for children are scarce, with estimates varying widely as a function of the location of the study. The percentage of children infected with HIV and treated for TB ranges from 2% in the USA to 26% in South Africa (18). BCG vaccination is contra-indicated in HIV-infected individuals, and it has been suggested that vaccination should be delayed (to 8 weeks of age rather than at birth), to make it possible to identify HIV-positive children before vaccination takes place (54). NTM infections have also been reported in HIV-positive children (55–57). By causing a progressive decline in CD4 T-cell immunity, HIV infection strongly influences the pathogenesis of TB, resulting in a higher risk of clinical TB, with more frequent extrapulmonary involvement, atypical radiographic signs and paucibacillary disease, potentially hindering timely diagnosis. Globally, TB kills one-third of the patients co-infected with HIV (7), and this deadly association between TB and

HIV infection provides strong support for the hypothesis that CD4 T cells play a critical role in anti-TB immunity.

Inherited conditions affecting the lungs and conferring a predisposition to mycobacterial disease

Congenital lung disorders observed in the first few years of life, such as primary ciliary dyskinesia or pulmonary alveolar proteinosis (PAP), lead to airway clearance defects. In particular, PAP is associated with defects of pulmonary surfactant homoeostasis and alveolar macrophages. These defects result in impaired lung function and are probably responsible for secondary infections with mycobacteria, including *M.tb* in particular, which have only ever been reported in adults (58–60). Cystic fibrosis (CF) is another heritable condition leading to airway clearance defects (61). CF is caused by mutations in the cystic fibrosis transmembrane regulator (*CFTR*) gene, resulting in thick mucus secretions and a failure to clear these secretions. Patients suffer from chronic respiratory infections caused by common bacteria (e.g. *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Burkholderia cepacia* and *Haemophilus influenzae*), filamentous fungi and/or yeasts. NTM infections are increasingly being reported in adults with CF (62–64), but children are also vulnerable (65, 66). The frequency of NTM infections in CF children from the UK has been estimated at 3.3% (67). BCG infection has never been reported in these patients, even in countries with mandatory BCG vaccination policies and a relatively high prevalence of CF, such as France. Infections with *M.tb* have been reported, mostly in adults (68, 69) but also, more rarely, in children (70, 71). Overall, changes in the integrity of the lung may increase susceptibility to mycobacterial infections, including TB. The fine molecular and cellular basis of mycobacterial disease in the context of CF remains unclear.

Primary immunodeficiencies with T-cell deficiency

Most PIDs are associated with broad susceptibility to pathogens, but a few are associated with a narrower susceptibility to mycobacterial disease (72). These PIDs, include, in particular, those involving T-cell deficiency. Severe combined immunodeficiency diseases (SCID) are a group of genetic conditions characterized by very low levels of autologous T lymphocytes, with or without an associated lack of B cells (B^- or B^+) (72). Six and eight morbid genes have been identified for T^-B^- and T^-B^+ SCID, respectively (72). Affected patients are extremely vulnerable to various infectious diseases (viral, bacterial, fungal, or parasitic) in the first few months of life. They are also susceptible to infections with mycobacterial species, particularly BCG, which is typically administered as a vaccine in the first few months of life (73, 74). Most patients present disseminated BCG infection, described as BCG-osis, but local infections (BCG-itis) have also been described (73, 75). Three patients with SCID and TB have been reported (76, 77), and three others with NTM infections have been described [two with *M. avium* (78) and the other with *M. marinum* (79)]. However, these patients would probably be highly susceptible to NTM and *M.tb*, if exposed. Hypomorphic mutations of SCID genes underlie a less severe clinical and immunological phenotype, known as combined immunodeficiency (CID), in which NTM infections have been reported (80). CID may also be caused by a number of other genetic defects (72), some of which are associated with mycobacterial diseases in a small proportion

of patients, implying a more modest susceptibility to mycobacterial infection. Two patients with ZAP70 deficiency were found to display BCG-itis (81). One patient with major histocompatibility complex class II deficiency had *M. avium* complex infection (82), and one patient had BCG-osis (73). Two patients with purine nucleoside deficiency (PNP) developed BCG-osis (83, 84). One patient with Schimke immune-osseous dysplasia (SMARCAL1 deficiency) had NTM infection (85). Finally, five patients with Nijmegen breakage syndrome (NBS) and TB have been described (86–88). The T-cell defects in SCID and CID patients are probably responsible for their susceptibility to mycobacteria, which appears to be correlated with the severity of the T-cell defect. This observation further highlights the role of human T cells in anti-mycobacterial immunity.

Autosomal dominant GATA2 deficiency

GATA2 encodes a transcription factor involved in the homeostasis of hematopoietic stem cells. Heterozygous mutations of *GATA2* have been identified as the cause of eight diseases: monocytopenia and mycobacterial infection syndrome (89, 90); dendritic cell, monocyte, B, and natural killer (NK) lymphoid deficiency (91, 92); familial myelodysplastic syndromes (MDS)/acute myeloid leukemia (AML) (93); Emberger syndrome (primary lymphedema with MDS) (94, 95); pediatric neutropenia (96), aplastic anemia (97); hypo-gammaglobulinemia with impaired antibody response (98); and the original case report of human NK cell deficiency (99, 100). *GATA2* mutations are loss-of-function (LOF) and seem to act by haploinsufficiency (101). The clinical hallmarks of GATA2 deficiency include immunodeficiency with marked susceptibility to human papillomaviruses (HPVs) and mycobacteria (non-tuberculous and tuberculous) (102), predisposition to MDS/AML, PAP, and congenital lymphedema (103). Patients have normal numbers of T cells, but very few circulating monocytes; they also display B and NK lymphocytopenia and have no detectable peripheral blood myeloid or plasmacytoid dendritic cells (DCs). There is variability in the timing of the onset of clinical signs: the proportion of patients without symptoms is 50% at the age of 20 years, 25% at 30 years, and 16% at 40 years (102). However, one quarter of the patients display environmental mycobacterial infections during childhood. One young adult also suffered from TB (102). To our knowledge, no patient with GATA2 deficiency and isolated mycobacterial disease has ever been reported. The identification of such patients might improve our understanding of mycobacterial susceptibility in GATA2-deficient patients, although it has already been suggested that this susceptibility may be due to a lack of DC (see also IRF8 deficiency).

Chronic granulomatous disease (CGD)

CGD is a life-threatening PID affecting phagocytes. It is caused by a mutation of any of the genes encoding one of the components of the nicotinamide adenine dinucleotide phosphatase (NADPH) oxidase complex, which is active particularly in the phagocytes, including granulocytes, monocytes and macrophages (104–106). Mutations may affect *CYBB* (located on the X chromosome) encoding gp91phox (in 70% of cases), *CYBA* encoding p22phox (5%), *NCF1* encoding p47phox (20%), *NCF2* encoding p67phox (5%), and *NCF4* encoding p40phox, this last defect having been found in only one patient to date (107). These mutations result in an inability to produce NADPH-oxidase-dependent reactive

oxygen species, which are required for the phagocytic killing of microorganisms. Interestingly, some specific *CYBB* mutations have been shown to confer a selective predisposition to tuberculous mycobacteria, but not CGD (see paragraph below). Overall, CGD patients are highly susceptible to pyogenic bacterial and fungal infections, caused by *Staphylococcus aureus* and *Aspergillus fumigatus* in particular, but also to mycobacterial infections. One recent study of 71 CGD patients focused on mycobacterial infections: 53 patients (75%) presented adverse effects of BCG vaccination (mostly BCG-itis) and 31 (44%) had TB (including 13 who also had BCG infection); none of the patients had NTM disease (F. Conti, JL. Casanova, J. Bustamante, unpublished data). Worldwide, 296 CGD patients with mycobacterial infections had been reported by 2013 (F. Conti, JL. Casanova, J. Bustamante, unpublished data) and the CGD database (http://www.uta.fi/imt/bioinfo/CYBB-base/ for patients with CYBB deficiency) recorded 1150 CGD patients with known genetic defects in 2010 (108, 109). The proportion of CGD patients with mycobacterial infections therefore may be up to 25% (104, 108–111). Only four patients with NTM infections have been reported (112–115) which appeared to be extremely rare in CGD patients as compared to TB and BCG infections. Overall, mycobacterial diseases are relatively common in patients with CGD living in countries in which TB is endemic and BCG vaccination is mandatory. This suggests that phagocytes and the NADPH-oxidase complex are crucial for human immunity to tuberculous mycobacteria.

Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID)

X-linked EDA-ID (116–118) is caused by hypomorphic mutations in the gene encoding NF-κB essential modulator (NEMO), a protein essential for activation of the ubiquitous transcription factor NF-κB. Clinically, the syndrome involves hypohidrosis, widely spaced cone- or peg-shaped teeth, and hypotrichosis (119, 120). These features result from defective signaling via the ectodysplasin receptor (EDA-R) signaling pathway. No consistent T- or B-cell abnormality has been identified in addition to the impaired Ab response to polysaccharides in all cases, and high serum levels of IgM, and low serum levels of IgG, IgA or IgG2 in several cases. The broad and profound immunological phenotypes of patients with NEMO deficiencies are responsible for the broad susceptibility of these patients to infections with invasive pyogenic bacteria, NTM, and, to a lesser extent, parasites, viruses, and fungi (120). The first patient with EDA-ID described died of miliary TB at the age of 20 months (121). Up to 100 male patients with hypomorphic mutations of *NEMO* have been reported, and mycobacterial infections were found in about 40% of them (117, 122–128). Some missense mutations confer a predisposition to mycobacterial disease only, with no signs of EDA (see paragraph below). An autosomal dominant (AD) form of EDA-ID was also reported in eight patients (129–136). This form is caused by a hypermorphic heterozygous mutation of *NFKBIA/IKBA*, impairing the degradation of IκBα and resulting in the partial retention of NF-κB dimers in the cytoplasm (129). IκBα deficiency results in a severe impairment of TCR signaling (129). One patients displayed mycobacterial diseases (134). Homozygous LOF mutations in *IKBKB*, encoding IKK2, a component of the IKK complex, have also been reported (137–139). Patients display hypogamma-globulinemia, an excess of naïve T and B cells and they suffer from bacterial, viral, and fungal infections with (137) or without (138, 139) the clinical signs of EDA. Interestingly, five of the nine patients

described had mycobacterial disease, including one patient with TB (138). Not all patients with EDA-ID present mycobacterial disease, but NEMO-IKK2-IκBα-dependent NF-κB activation nevertheless appears to be essential for human anti-mycobacterial immunity.

X-linked recessive CD40L deficiency

CD40 ligand (CD40L) deficiency is a rare genetic disorder of T cells, leading to X-linked hyper IgM syndrome (X-HIGM). CD40L is normally expressed on activated T cells, and, following binding to CD40, it is expressed on macrophages, DC and B cells (antigen-presenting cells, APC). It signals partly through NEMO-NF-κB, to induce IL-12 production (140, 141). Mutations of the gene encoding CD40L result in impaired T/APC interaction, leading to a failure of B-cell immunoglobulin isotype switching and impaired macrophage activation. Patients with X-HIGM display recurrent bacterial infections in association with markedly low serum IgG, IgA, and IgE levels, but normal to high serum IgM levels (142). In addition to bacterial infections associated with an impaired antibody response, a prominent clinical feature of patients with X-HIGM is a high frequency of opportunistic infections with *Pneumocystis jirovecii* and *Cryptosporidium parvum*. X-HIGM patients have also been reported to suffer from localized and disseminated BCG disease (87, 143, 144), NTM disease (145), and, more frequently, TB (87, 144–148). Given that most patients with X-HIGM have been exposed to NTM for long periods and most were vaccinated with BCG, X-HIGM seems to result in a moderate impairment of anti-mycobacterial immunity. Nevertheless, severe TB appears to be a serious threat in patients living in areas endemic for TB, probably due to impaired CD40-dependent IL-12 production during infection.

Autosomal recessive STAT1 deficiency

Signal transducer and activator of transcription 1 (STAT1) is a component of the JAK/STAT signaling pathways involved in the responses to various cytokines and growth factor stimuli. In both mice and humans, STAT1 has been implicated in the response to IFNs (IFN-α/β, IFN-λ, and IFN-γ) and IL-27. Autosomal recessive (AR) complete and partial STAT1 deficiencies were first described in 2003 (149) and 2009 (150), respectively. Patients with complete STAT1 deficiency display a clinical phenotype of severe and life-threatening mycobacterial and viral disease. Partial STAT1 deficiency is associated with milder disease (149–156). The corresponding mutant alleles were shown to be amorphic and hypomorphic, respectively. The mycobacterial species identified were BCG, *M. kansasii*, *M. avium*, and *M. szulgai*. Cells from patients with complete and partial STAT1 deficiencies display an abolished or impaired response to the STAT1- dependent cytokines, IFN-γ, IFN-α, IL-29, and IL-27 (149, 151, 152). The susceptibility to viral infections may be explained by an impaired STAT1-dependent response to IFN-α/β. By contrast, abolished or impaired IFN-γ signaling probably accounts for the mycobacterial infections of the patients (19). However, a role for IL-27 cannot be excluded (157). None of these patients has been reported to suffer from TB, probably due to a lack of exposure. An AD form of STAT1 deficiency has been described, in which patients present only mycobacterial disease. This form will be described below.

Autosomal recessive IRF8 deficiency

Interferon regulatory factor 8 (IRF8) is a transcription factor involved in the development of myeloid subsets. AR complete IRF8 deficiency was described in a single patient in 2011 (158). This patient carries a homozygous missense mutation of *IRF8* (K108E) and presents a phenotype very similar to that of Bxh2 mice carrying a hypomorphic mutation of *IRF8* (159). The patient suffered from BCG-osis and oral candidiasis. He has normal levels of B cells and NK cells, but abnormal white blood cell counts, with an absence of monocytes and an excessive number of neutrophils. An analysis of peripheral blood mononuclear cells (PBMCs) by flow cytometry revealed a severe depletion of the non-lymphoid HLA-DR$^+$ compartment, with a total absence of both CD14$^+$ and CD16$^+$ monocytes in particular. In addition, no DC were detectable in the blood. The cells absent included both CD11c myeloid (CD1c$^+$ and CD141$^+$) and plasmacytoid (CD123$^+$) cells. In addition, a bone marrow biopsy showed myeloid hyperplasia (158). A recent study dedicated to the functional characterization of this allele showed that the mutation caused a loss of nuclear localization and a loss of transcriptional activity, accompanied by a decrease in protein stability, and increases in ubiquitination, sumoylation, and proteosomal degradation (160). The patient had normal numbers of T cells (CD4$^+$ and CD8$^+$), but they appeared to be anergic, probably due to the absence of myeloid APC. Whole blood cells failed to produce IL-12 in response to BCG, phytohemagglutinin (PHA), and lipopolysaccaride (LPS), and levels of IFN-γ production were very low (as were TNF-α, IL-10, and IL-6 levels). AR complete IRF8 deficiency is a life-threatening disorder combining fungal and mycobacterial infections, myeloproliferation and an absence of monocytes and dendritic cells. An AD form of IRF8 deficiency associated exclusively with mycobacterial diseases will be discussed below.

Autosomal recessive TYK2 deficiency

TYK2 is a Janus kinase (JAK). The JAKs bind to the intracellular part of some receptors and become activated following ligand binding and changes in the conformation of the receptors. They autophosphorylate and *trans*-phosphorylate each other on tyrosine residues, and they also phosphorylate the intracellular part of the receptor and the STATs recruited to the docking site. TYK2 is involved in various signaling pathways, including the responses to IL-12, IFN-α/β, IL-10, and IL-6 (161). TYK2 deficiency was first described in a single patient in 2006 (161). This patient comes from Japan and was diagnosed with hyper IgE syndrome (HIES) in conjunction with disseminated mycobacterial and viral diseases. The patient displays a homozygous deletion of four base pairs at the beginning of *TYK2*, resulting in a premature stop codon terminating the protein early in its translation (position 90 of the 1187 amino acids of the WT TYK2). Another patient from Turkey was subsequently diagnosed with TYK2 deficiency. Surprisingly, he displayed mycobacterial, *Brucella*, and viral infections, but no signs of HIES (162). He is homozygous for a nine-base pair deletion, introducing to a premature stop codon at position 767. Both patients have no WT TYK2 protein. Three other patients with complete TYK2 deficiency have since been identified with a sole clinical phenotype of BCG-osis, severe abdominal TB, and miliary TB, respectively (Kreins *et al.*, submitted). More patients with inherited TYK2 deficiency are required for the collective ascertainment and precise definition of the core clinical

phenotype of this disorder. TYK2 is involved in the IL-12 signaling pathway, and abolition of the response to IL-12 was reported in the first TYK2-deficient patient (161). An impaired response to IL-12 has been shown to confer high levels of susceptibility to mycobacteria in MSMD patients with mutations of *IL12B* and *IL12RB1* (see below) (163–166). It therefore seems likely that the susceptibility of TYK2-deficient patients to mycobacteria results from impaired IL-12 signaling, leading to defective IFN-γ production.

Mendelian susceptibility to mycobacterial diseases (MSMD)

In addition to these various PIDs, studies in the early 1990s identified a new PID consisting exclusively of susceptibility to mycobacterial diseases due to weakly virulent mycobacterial species, either NTM or the BCG vaccine, in otherwise healthy children; this condition was named MSMD (19). Since the identification of the first morbid gene (167, 168), a total of nine genes (*IFNGR1*, *IFNGR2*, *STAT1*, *IRF8*, *CYBB*, *IL12B*, *IL12RB1*, *NEMO*, and *ISG15*) (158, 167–181) have been implicated in this condition (Fig. 3), and 18 different genetic etiologies based on the mode of inheritance, the expression of the mutant allele and the function abolished, have been characterized as responsible for MSMD (182). The MSMD genes are described below, and it is interesting to note that defects in some of these genes (described above) lead to a broader phenotype, due to a different mode of inheritance (*STAT1*, *IRF8*) or different mutations (*NEMO*, *CYBB*). All the mutated MSMD genes are involved in the IFN-γ signaling pathway, highlighting the crucial role of this molecule in anti-mycobacterial immunity (Fig. 3). The corresponding genetic defects lead to an impairment of either the response to or the production of IFN-γ [first identified as macrophage-activating factor (183)], and some have also been shown to be responsible for childhood TB.

IFN-γR deficiencies

IFN-γR1 and IFN-γR2 are the ligand-binding and transducing receptor chains of the IFN-γ receptor, respectively. AR and AD, complete and partial deficiencies, with or without expression of the molecule at the cell surface, of both IFN-γR1 and IFN-γR2 have been described (167–173, 184–186). Complete IFN-γR deficiency is associated with abolished gamma-activating factor (GAF) activation and is clinically very severe, often leading to the death of the patients in the absence of hematopoietic stem cell transplantation, whereas partial deficiency, resulting in some detectable GAF activation, has a more favorable outcome (187, 188). Patients suffered from diseases caused by BCG and NTM. Other rare pathogens have also been described, but each only in a very small number of patients (182). Patients are also susceptible to *M.tb*. Indeed, during the investigation of MSMD, several siblings of MSMD patients carrying the same genetic defect as the index case were found to display severe TB. Two patients with complete IFN-γR1 deficiency had TB in addition to *M. avium* and *M. fortuitum* infections in one (189) and to *M. fortuitum* infection in the other (171, 188). Two patients with partial dominant IFN-γR1 deficiency had TB only (due to *M. bovis*) (190) and TB associated with *M. avium* infection (188). Finally a child with partial recessive IFN-γR1 deficiency was found to suffer from TB only (170). Two other cases (siblings of probands with partial recessive IFN-γR1 deficiency) were found to have TB, but the mutations could not be demonstrated genetically, due to a lack of material (169, 191).

This highlights the crucial role of the IFN-γ response in anti-mycobacterial immunity in general and in anti-TB immunity in particular.

Autosomal dominant STAT1 deficiency

Patients with mycobacterial diseases only have been shown to carry heterozygous mutations of *STAT1*. Since 2001, 12 patients with AD LOF STAT1 mutations have been reported (175, 192–195). These patients have suffered from BCG-osis (*n* = 6), *M. avium* (*n* = 3), and *M.tb* (*n* = 1) infections, and mycobacterial disease due to an unspecified mycobacterium in two patients. Two grandparents of two patients had had TB, but the genetic diagnosis could not be confirmed (192). The patients were successfully treated, and no death due to mycobacteria was observed. Clinical penetrance is incomplete, because five individuals known to be genetically affected have not developed the disease. The mutations are heterozygous missense mutations affecting phosphorylation or DNA-binding, or both. *In vitro* studies on STAT1-deficient cells showed that the mutations were LOF (amorphic or hypomorphic) for GAF and interferon-stimulated gene factor 3 (ISGF3) in response to IFN-γ and IFN-α, respectively (175, 192). However, heterozygous cells from patients display a defect only for GAF activation upon IFN-γ (and IFN-α) stimulation, with no detectable defect for ISGF3 activation in response to IFN-α stimulation. These *STAT1* mutations are, therefore, recessive for ISGF3 activation in response to IFN-α and dominant negative for GAF activation in response to IFNγ (and IFN-α) stimulation (175). Similarly, ISGF3-dependent responses to IL-29 are normal in patients, whereas GAFdependent responses to IL-27 are impaired (192). Consequently, patients are normally resistant to viral infections due to normal ISGF3 activation after IFN-α signaling (and IL-29 signaling) and susceptible to mycobacterial disease due to impaired IFN-γ signaling (and perhaps IL-27 signaling). This experiment of nature highlights the role of the STAT1-dependent IFN-γ response in anti-mycobacterial immunity, including *M.tb*.

X-linked recessive gp91phox deficiency

Seven male patients with X-linked CYBB deficiency from two unrelated families developed infections due to tuberculous mycobacteria only, without the other signs previously described for CGD. They were shown to carry specific hemizygous missense mutations of *CYBB*, encoding gp91phox (Q231P and T178P). Six had BCG infections and the seventh, who was not vaccinated with BCG, developed a disseminated form of *bona fide* TB. An obligate carrier developed tuberculous salpingitis (105, 176). These particular mutations were shown to abolish the respiratory burst function in monocyte-derived macrophages (MDMs), when these cells were activated with BCG, PPD (purified protein derived from *M.tb*), or IFN-γ. By contrast to what had been observed for CGD patients, neutrophils, monocytes, and monocyte-derived dendritic cells (MDDCs) from these patients had a normal respiratory burst, as estimated by measurements of superoxide and hydrogen peroxide production (176, 196). Interestingly, the impaired function of NADPH in MDM was found to be correlated with the impaired expression of $gp91^{phox}$ in these cells (176). This provides a good illustration of the power of human genetics to dissect the role of molecules in different tissues. It also suggested that CGD patients suffered from mycobacterial diseases due to impairment of the respiratory burst specifically in

macrophages, highlighting the critical role of these cells and this pathway in anti-mycobacterial immunity (111). Overall, these studies demonstrate that the respiratory burst in macrophages is essential to contain infections due to BCG and *M.tb*, but, surprisingly, not those caused by NTM.

Autosomal dominant IRF8 deficiency

Two patients from two independent families with MSMD as their sole clinical phenotype were identified as carrying a heterozygous (T80A) *IRF8* mutation (158). Both patients suffered from recurrent episodes of mycobacterial disease caused by BCG. The T80A allele is expressed at normal levels in the cells of the patients, and was shown to be hypomorphic for the induction of IRF8-dependent target genes (such as *NOS2* and *IL12B*). The mutation appears to affect the DNA-binding ability of IRF8 and was shown to be dominant negative in mouse macrophages. Immunophenotyping of PBMCs from the patients showed that there was no deficiency of circulating lymphocytes and granulocytes, monocyte subgroups or $CD123^+$ plasmacytoid DCs. However, within the $CD11c^+$ subgroup of DCs, which are normally divided into minor $CD141^+$ and major $CD1c^+$ subgroups, there was a marked loss of $CD1c^+$ DCs, whereas the total number of $CD11c^+$ and $CD141^+$ cells was normal. The $CD1c^+$ DCs produce huge amounts of IL-12 when stimulated by the TLR7/8 ligand (R848). However, the level of IL-12 production mediated by the mutant T80A protein is only one-third that for the wildtype. In addition, the defect in IL-12 production is not general, as no defect was observed in whole blood assays or in EBV-immortalized B cells stimulated with phorbol 12,13-dibutyrate (PDBu). Once again, AD IRF8 deficiency highlights that the specific loss of $CD11c^+$ $CD1c^+$ cells results in predisposition to mycobacterial disease. However, the precise role of these cells in susceptibility to mycobacteria remains unclear, although it seems likely that the loss of these cells may lead to an impaired response to IFN-γ and impaired IL-12 production.

X-linked recessive NEMO deficiency

Seven male patients with two specific NEMO mutations (E315A and R319Q) have been identified (180). These patients suffered from mycobacterial diseases (BCG and NTM); one patient had proven TB, and another had probable TB. No other severe infections have been reported in these patients, with the exception of invasive *Haemophilus influenzae* type b infection in one patient. Only one of the patients has conical decidual incisors. The PBMCs of the patients displayed low levels of IFN-γ and IL-12 production, after stimulation by PHA or CD3-specific antibodies (180, 197–200). Co-culture experiments showed that monocytes from some of these patients had selective, intrinsic defects of T cell-dependent IL-12 production, resulting in impaired IFN-γ production (180). Unlike other known *NEMO* mutations, these two specific mutations selectively impair the T cell-dependent, CD40-mediated activation of c-Rel, which leads to the production of IL-12 (180). In addition, pull-down assays have revealed a milder defect in ubiquitin binding than for the mutations associated with EDA-ID (127, 201). Thus, these hypomorphic recessive mutations of *NEMO* selectively impair the T cell-dependent, CD40-dependent, c-Rel-mediated NF-κB pathway of IL-12 activation in myeloid cells. This alternative pathway of IL-12 production is therefore essential for human immunity against BCG and *M.tb*. The prognosis of the patients

is variable, and they might benefit from treatment with antibiotics and IFNγ (197, 202). This again highlights the power of human genetics to decipher the individual roles of molecules and pathways *in natura*.

Autosomal recessive ISG15 deficiency

A recent report has highlighted the role of a potent inducer of IFN-γ, interferon-stimulated gene 15 (ISG15) (181). *ISG15* encodes a ubiquitin-like protein that is attached to substrates in a process called ISGylation, which closely resembles ubiquitination (203). ISG15 is present in neutrophils and myeloid cells and can be released upon bacterial challenge, inducing IFN-γ secretion in synergy with IL-12 (203). AR complete ISG15 deficiency has been found in patients with MSMD suffering from BCG disease. The alleles are loss-of-expression and LOF, and the cells of the patients display an impairment of IFNγ production in response to stimulation with BCG and IL-12, as in IL-12Rβ1-deficient patients (see the next paragraph). This defect can be rescued by the addition of free extracellular recombinant human ISG15, clearly demonstrating the critical role of extracellular ISG15 in IFN-γ induction. Another intriguing clinical phenotype, intracranial calcifications, was subsequently observed in these patients and in three others (204). Enhanced IFN-α/β immunity due to the absence of intracellular ISG15, preventing the stabilization of USP18, a critical negative regulator of IFN-α/β, is observed in all ISG15-deficient patients, reminiscent of the Mendelian autoinflammatory interferonopathies Aicardi-Goutiéres syndrome and spondyloenchondrodysplasia, which are also associated with intracranial calcifications (204). IFN-γ induction and secretion by T and NK cells, stimulated by IL-12 and ISG15, is thus required for efficient antimycobacterial immunity.

Autosomal recessive IL-12p40 and IL-12Rβ1 deficiencies

IL-12 consisting of two subunits, IL-12p40 (also common to IL-23) and IL-12p35, is secreted by myeloid cells and is a strong inducer of IFN-γ production. Similarly, the IL-12 receptor (IL-12R) comprises IL-12Rβ1 (also common to IL-23R) the ligand-binding chain and IL-12Rβ2, the signal-transducing chain (205), and is expressed at the surface of T and NK cells. AR complete IL-12p40 and IL-12Rβ1 deficiencies were first described in 1998 (177–179), and account for more than 50% of the cases of MSMD for which a genetic cause has been identified (182). Both defects have been reviewed in detail (165, 166, 182, 206) and will be summarized in brief here. All mutant alleles are LOF and their transmission is AR. The cells of patients do not produce or do not respond to IL-12 and IL-23, resulting in impaired IFN-γ production by T and NK cells. The development of IL-17 T cells is also impaired, due to the absence of IL-23, probably accounting for he candidiasis observed in one-third of the patients (207). The clinical phenotype of these patients is highly heterogeneous, ranging from death in early infancy to an asymptomatic course throughout adulthood (165, 166, 182). Most patients suffered from infections caused by BCG and NTM (slow or fast growing), and about half were also found to be susceptible to salmonellosis. Three patients with complete IL-12p40 deficiency also suffered from TB, one as the only infectious disease observed (166), and the other two together with other infections (BCG and *Salmonella*) (208, 209). In this context, 13 patients with IL-12Rβ1 deficiency have been found to have TB in addition to (n = 7) or without (n = 6) other mycobacterial diseases (165,

207, 210–218). IL-12Rβ1 deficiency is the most frequently reported Mendelian cause of childhood TB to date (see the subsequent paragraph on childhood TB).

Anti-cytokine antibodies conferring a predisposition to mycobacterial diseases

In 2004 and 2005, the first reports of the existence of autoantibodies against IFN-γ in patients with disseminated mycobacterial diseases were published (219–221). This disorder has been found only in adults to date, but it is nevertheless of interest here as it constitutes an acquired phenocopy of inborn errors of IFN-γ. The mycobacterial species are mostly NTM, but *M.tb* has been identified in some cases (219, 222, 223). However, unlike IFN-γ, this condition is frequently associated with pathogens other than mycobacteria, such as *Salmonella*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Penicillium marneffei*, and varicella zoster virus. Since 2004, more than 150 adult patients with neutralizing autoantibodies against IFN-γ have been identified (219–244). Most are of Asian descent and it was recently and elegantly shown for the first time that the production of anti-IFN-γ autoantibodies is under tight genetic control in humans (242). The authors found that two linked HLA-II alleles defining a haplotype – DRB1*16:02 and DQB1*05:02 – were associated with disease, with an odds ratio of approximately 8.1. In other words, the relative risk of developing this illness was almost 10 times higher in individuals carrying at least one such haplotype (242). This further demonstrates the role of IFN-γ in anti-mycobacterial immunity. In addition, although rare in children, therapeutic TNFα-blocking antibodies have been shown to favor mycobacterial disease in juvenile idiopathic arthritis and pediatric inflammatory bowel disease (245). This observation is consistent with an abundance of laboratory data demonstrating a central role for TNF-α in TB immunity (22, 246). Blocking either of these two pathways (IFN-γ and TNF-α) results *in vivo* in an increase in susceptibility to clinical disease caused by mycobacterial species, including *M.tb*.

Inborn errors of immunity underlying childhood tuberculosis

We have reviewed above the genetic disorders underlying severe clinical disease caused by BCG/NTM or *M.tb* in childhood. The studies of diseases caused by weakly virulent mycobacteria were instrumental in the identification of the first genetic basis of TB. Both types of disease have been reported in some patients (165, 170, 180, 189, 190, 207–209, 211, 216–218, 247). In other patients, TB was the only ‘phenotype’ with (166, 176, 188, 191, 192, 210, 212–215, 248, 249) (Table 1) or without a family history of BCG/NTM disease (176, 188, 191, 192, 210, 213, 248). Overall, these observations provided the first proof-of-principle that TB is not only an infectious disease but can also be a Mendelian genetic disorder, at least in some rare cases. Other cases were suspected but not genetically proved (250, 251). The most common genetic defect identified in patients with severe TB to date is complete IL-12Rβ1 deficiency (165). In a more systematic search for *IL12RB1* mutations in 50 children with severe TB, two patients (4%) with complete IL-12Rβ1 deficiency were identified (20). One of these patients was from Morocco and displayed severe pulmonary TB at the age of 13 years, dying of this disease a few months later. The other patient was Iranian, developed TB at 7 months of age, and was treated, with TB recurring and again successfully treated at the age of 6 years. An older sibling with the same

mutation suffered from scrofuloderma of the neck at the age of 12 years, successfully treated with anti-mycobacterial therapy. Unfortunately, no pathological and microbiological investigations were carried out to check the probable *M.tb* etiology of scrofuloderma. These results raise the possibility that a substantial proportion of children with severe TB carry single-gene inborn errors of immunity. This proportion has been estimated at up to 45% by theoretical calculations (16). The advent of next-generation sequencing, with whole exome and whole genome sequencing in particular, should provide the necessary tools to determine this frequency experimentally. Overall, children and young adults with severe primary TB should be considered as potentially carrying a known or new monogenic PID, possibly but not necessarily affecting IFN-γ immunity. Much further work is required if we are to understand fully the pathogenesis of childhood TB, and its genetic component in particular. However, it has already been established that correct IFN-γ production and response are required for efficient anti-mycobacterial immunity, including against *M.tb*. Studies in countries that combine a high proportion of consanguineous marriages, a high incidence of TB, and an excellent medical care, such as Morocco, Turkey, and Iran, will probably play a key role in this endeavor. Some of the key discoveries in MSMD and childhood TB have already been made in patients from these three countries (20, 165, 166, 181, 182, 210, 214, 215).

Concluding remarks

Despite being an ancient and powerful serial killer, TB and its pathogenesis are still barely understood. The genetic investigation of the host has provided us with some clues. Some acquired or inherited PIDs are associated with an increase in the risk of mycobacterial diseases, including TB. A number of monogenic disorders impairing IFN-γ immunity lead to more specific vulnerability to mycobacterial infections. In addition, specific mutations in genes known to underlie classical PIDs, involving hypomorphism (in the cases of *STAT1* and *NEMO*) or cell-type specificity (like *CYBB*), have been shown to confer selective predisposition to mycobacterial infections, including TB. All these discoveries have provided the proof-of-principle for a monogenic predisposition to severe TB, which can now be investigated at a large scale by whole exome and whole genome sequencing. They also make it possible to decipher and quantify the roles of specific cells or molecules in natural conditions. At the immunological level, anti-mycobacterial immunity involves T cells (as illustrated by AIDS), dendritic cells (IRF8 and GATA2 deficiencies), and macrophages (CYBB deficiency), and requires IFN-γ immunity to be fully operational (MSMD). Studies of MSMD have clearly shown that human IFN-γ-mediated immunity is a genetically controlled continuous trait determining the outcome of mycobacterial infections (187). More pathways will perhaps be identified as involved in the near future, through detailed genetic investigations based on next-generation sequencing. These findings have important medical implications, as they pave the way for new treatments based on physiopathology. The best example is provided by patients with IL-12Rβ1 deficiency presenting TB due to impaired IFN-γ production, for whom treatment with recombinant human IFN-γ, in addition to anti-mycobacterial drugs, seems to be effective (197, 202, 252).

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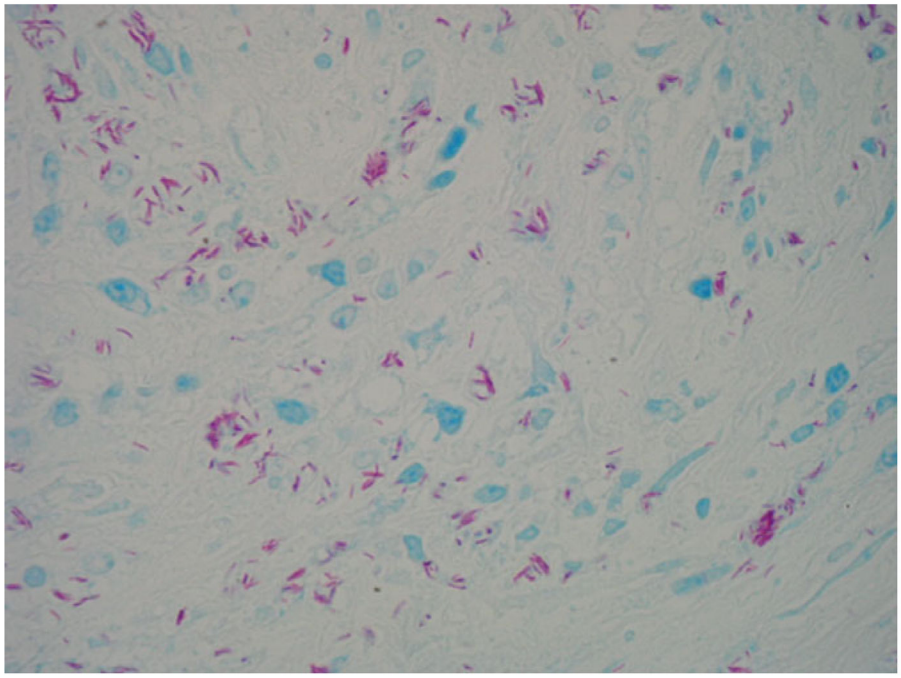

Fig. 1.
Ziehl–Neelsen staining of acid-fast mycobacteria in a mesenteric lymph node biopsy. Magnification ×630.

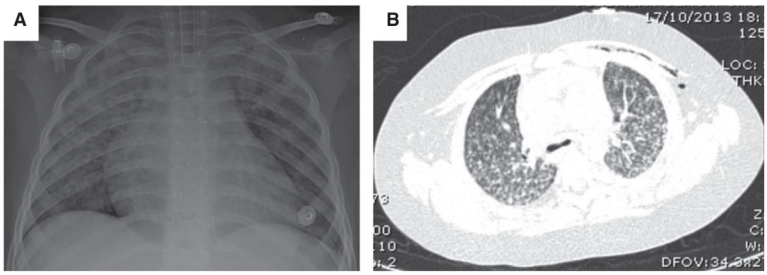

Fig. 2.

Infiltration of both lungs by multiple micronodules shown in chest X-ray (A) and thoracic computed tomography (B) in a 3 years old child with miliary TB.

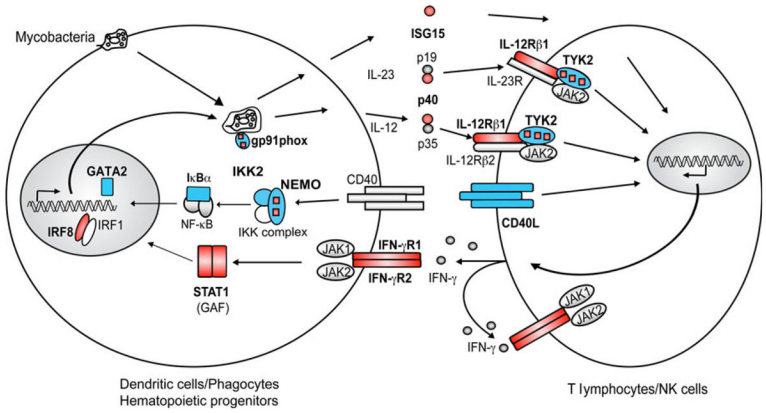

Fig. 3.

Schematic diagram of the cooperation between phagocytes/dendritic cells and T lymphocytes/NK cells during mycobacterial infection. Molecules in blue are mutated in patients with a broad infectious phenotype including mycobacterial diseases. Molecules in red are mutated in patients with isolated mycobacterial diseases (for IRF8 and STAT1, the AD forms by LOF only). Molecules in blue with red dots indicate that specific mutations in the corresponding genes are responsible for isolated mycobacterial diseases. As described in the review, patients with acquired or inherited profound T-cell deficiency are also susceptible to mycobacterial infections.

Table 1

Acquired and inherited conditions with mycobacterial susceptibility to BCG, NTM, or *Mycobacterium tuberculosis* (TB)

	NTM	BCG	TB	TB only*	Other infections†	Physiopathology
Acquired ID						
Immunosuppressive treatment/BMT	+	?	+	No	Yes	Impairment of immune cells
HIV	+	+	+	No	Yes	T-cell defect
Anti-IFN-γ antibodies	+	−	+	No	Yes	Impaired IFN-γ response
Anti-TNF-α antibodies	+/−	−	+	Yes	Yes	Impaired TNF-α response
Inherited ID						
Cystic fibrosis	+	−	+	No	Yes	Alteration of the lungs
PID						
SCID	−	+	+	No	Yes	T-cell defect
AD GATA2 deficiency	+	−	+	No	Yes	Quantitative defect of monocytes, DC, and PAP
CGD	+/−	+	+	No	Yes	Respiratory burst defect in all phagocytic cells
EDA-ID	+	+	+	No	Yes	Impaired CD40-dependent IL-12 production
XR CD40L deficiency	+	+	+	No	Yes	Impaired CD40-dependent IL-12 production
AR STAT1 deficiency	+	+	−	No	Yes	Impaired IFN-γ response
AR IRF8 deficiency	−	+	−	No	Yes	Absence of monocytes and DC
AR TYK2 deficiency	−	+	+	Yes	Yes	Impaired IFN-γ production
MSMD						
IFN-γR deficiencies	+	+	+	Yes	No	Impaired IFN-γ response
AD STAT1 deficiency	+	+	+	Yes	No	Impaired IFN-γ response
XR gp91phox deficiency	−	+	+	Yes	No	Respiratory burst defect in macrophages
AD IRF8 deficiency	−	+	−	No	No	Absence of $CD11C^+$ $CD1c^+$ DC
XR NEMO deficiency	+	+	+	No	No	Impaired CD40-dependent IL-12 production
IL-12 and IL-12R deficiencies	+	+	+	Yes	Yes	Impaired IFN-γ production
AR ISG15 deficiency	−	+	−	No	No	Impaired IFN-γ production

*Patients with only TB are also noted.

†The clinical phenotype of the patients may (yes) or may not or only rarely (no) include other infectious diseases. MSMD patients are typically vulnerable to other intra-macrophagic pathogens, such as Salmonella (182).