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REVIEW ARTICLE

Immune defects in active mycobacterial diseases in patients with primary immunodeficiency diseases (PIDs)

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Mendelian susceptibility to

Natural human immunity to the mycobacteria group, including *Mycobacterium tuberculosis*, Bacille Calmette-Guérin (BCG) or nontuberculous mycobacteria (NTM), and/or *Salmonella* species, relies on the functional IL-12/23-IFN-γ integrity of macrophages (monocyte/dendritic cell) connecting to T lymphocyte/NK cells. Patients with severe forms of primary immunodeficiency diseases (PIDs) have more profound immune defects involving this impaired circuit in patients with severe combined immunodeficiencies (SCID) including complete DiGeorge syndrome, X-linked hyper IgM syndrome (HIGM) (CD40L mutation), CD40 deficiency, immunodeficiency with or without anhidrotic ectodermal dysplasia (NEMO and IKBA mutations), chronic granulomatous disease (CGD) and hyper IgE recurrent infection syndromes (HIES). The patients with severe PIDs have broader diverse infections rather than mycobacterial infections. In contrast, patients with an isolated inborn error of the IL-12/23-IFN-γ pathway are exclusively prone to low-virulence mycobacterial infections and nontyphoid salmonella infections, known as Mendelian susceptibility to the mycobacterial disease (MSMD) phenotype. Restricted defective molecules in the circuit, including IFN-γR1, IFN-γR2,

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mycobacterial disease (MSMD); primary immunodeficiency diseases (PIDs)

IL-12p40, IL-12R-β1, STAT-1, NEMO, IKBA and the recently discovered CYBB responsible for autophagocytic vacuole and proteolysis, and interferon regulatory factor 8 (IRF8) for dendritic cell immunodeficiency, have been identified in around 60% of patients with the MSMD phenotype. Among all of the patients with PIDs referred for investigation since 1985, we have identified four cases with the specific defect (IFNRG1 for three and IL12RB for one), presenting as both BCG-induced diseases and NTM infections, in addition to some patients with SCID, HIGM, CGD and HIES. Furthermore, manifestations in patients with autoantibodies to IFN-γ (autoAbs-IFN-γ), which is categorized as an anticytokine autoantibody syndrome, can resemble the relatively persistent MSMD phenotype lacking BCG-induced diseases.

Introduction

Human natural defense to the mycobacteria group, including *Mycobacterium tuberculosis*, Bacille Calmette-Guerin (BCG) or the nontuberculosis mycobacteria (NTM) relies on the functional IL-12/23-IFN-γ integrity of macrophage (monocyte/dendritic cell) connecting T lymphocyte/NK cells.[1] An intact IL-12/23-IFN-γ circuit phosphorylates macrophage intracytoplasmic signal transducers and activators of transcription-1 (STAT1) to upregulate specific genes to kill mycobacteria.[2,3] Augmenting the circuit, costimulator CD40 signaling enhances macrophage IL-12 production through the phosphorylation of IκB by the activated IKK complex, which consists of Ikk-α, Ikk-β and Ikk-γ (also called NF-kB essential modulator; NEMO), thereby releasing NF-κB for a further effective response.[4–9] Impaired immunity for HIV-uninfected human susceptibility to mycobacterial infection is mainly orchestrated by a defective IL-12/23-IFN-γ circuit.[10] IFN-γ is critical and irreplaceable in this circuit to induce the killing of mycobacteria.[1,10]

The clinical description of primary immunodeficiency diseases (PIDs) contains over 206 diseases for which more than 110 genetic etiologies have been described, and provides opportunities for diagnosis and genetic counseling.[11,12] An understanding of the pathogenesis of PIDs has an even greater biological impact on the definition of host gene function in nature (i.e., in the setting of a natural ecosystem), a unique added value of studying the human model.[13] Through such knout-out genetic human systems in nature, we reviewed the effect of impairment of the IL-12/23-IFN-γ circuit on human PIDs in this article, with the aim of reminding physicians to consider the possible diagnosis of PIDs in patients with refractory or/and recurrent to mycobacterial infections.

Broad predisposition to multiple and mycobacterial infections

Severe combined immunodeficiency (SCID)

Despite the huge heterogeneity on the molecular level,[14] the clinical manifestations of the different SCID forms are characterized, often before the 3rd month of life,[15,16] by recurrent infections with a protracted course and unexpected complications. Before the age of 6 months, patients with SCIDs develop chronic diarrhea, interstitial pneumonia and/or therapy-resistant mucocutaneous candidiasis. Infections with opportunistic pathogens, such as *Pneumocystis jiroveci* (previously classified as *Pneumocystis carinii*) are often present as well as various other opportunistic pathogens, such as *Listeria* sp., *Salmonella typhi*, *Toxoplasma*, *Mycobacterium sp.*, *Aspergillus* spp, adenovirus, respiratory syncytial virus (RSV), cytomegalovirus (CMV), herpes simplex virus (HSV) and Epstein-Barr Virus (EBV). Of note, the BCG vaccination causes disseminated infections that may be lethal in SCID patients. Infiltrating and ulcerating lesions at the site of the BCG vaccination and in the regional lymph nodes, and even systemic propagation with papular cutaneous lesions, osteolytic lesions and organ impairment of liver, spleen, lymph-node and lung, may occur.[15,16] As the BCG vaccination is no longer generally recommended in many countries, patients should be checked for exposure to the BCG vaccination, and if patients have been exposed, adequate antimycobacterial treatment should be initiated even in the absence of any clinical manifestations.[15–19] We have evaluated T cell receptor excision circle (TREC) quantification using neonatal Guthrie cards to detect patients with severe T cell deficiency who have extremely low TRECs and increased BCG infection in Taiwan since June 2009.[20–22] For neonates with undetectable TRECs including those with SCIDs, attenuated vaccination is exhibited until adequate management rescues the profound T cell defects. In the case of oral live polio vaccine or upon contact with recently vaccinated persons, central nervous poliomyelitis-infections and carditis may occur.[23]

The suspicion of SCID is always to be considered as a "pediatric emergency" with the risk of a rapidly fatal evolution and a higher transplant engraftment rate close to 95% if an adequate donor is available before 3 months of age.[15,16,24] In half of the SCID patients without genetic identification, a "classical" SCID-phenotype that contains a hypoplasia of the lymphatic tissues (lymph nodes, tonsils, thymic shadow), lymphopenia, hypogammaglobulinemia, and recurrent opportunistic infections that are refractory to treatment and requires further immunological investigations until SCID can be excluded.[15–22] Around 5% of patients with DiGeorge syndrome have thymic aplasia present as the SCID-phenotype, termed the complete form of DiGeorge syndrome, and requires transplantation from hematopoietic stem cells or thymus.[25,26]

Chronic granulomatous diseases (CGD, gp91phox, gp22phox, gp47phox, gp67phox)

Patients with CGD with the mutant components of nicotinamide dinucleotide phosphate (NADP) oxidase, including membrane-bound gh91- and p22-phox, and cytoplasmic p47- and p67-phox, experience inhibited reactive oxygen species (ROS) production leaving engulfed pathogens alive.[27] Patients with CGD have a broader susceptibility to multiple pathogens, often presenting as mucocutaneous infections and pneumonia caused by *Staphylococcus aureus*, *Candida albicans*, and *Aspergillus* spp.[22,28] In a report of 73 predominantly nonChinese CGD patients with a focus on mycobacterial infections,[29] there were BCG-induced diseases in 38 patients, tuberculosis in 16, both tuberculosis and BCG-induced disease in seven, mycobacterium species in seven, and environmental or non-tuberculosis mycobacteria (NTM) in four. Among them, nine patients were otherwise healthy and had isolated mycobacterial diseases, including tuberculosis in six patients (disseminated in three and pulmonary in three) and BCG-induced disease in three (two BCGosis and one BCGitis). Another study with a series of 17 Chinese CGD patients found pulmonary tuberculosis and BCG-induced disease in three patients (one local, one regional, and one disseminated), pulmonary tuberculosis in three, and BCG-induced disease in four (one local, one regional, one distant, and one disseminated).[30] Furthermore, the *Salmonella* species has been found to contribute from 5% to 10% of infecting organisms in CGD patients in nonChinese countries,[31] and approximately 35% in Chinese patients in Hong Kong.[30] From these observations in areas endemic for mycobacteria and salmonella, CGD patients may resemble or have overlapping infectious pathogens as patients with an isolated defective IL-12/23-IFN-γ circuit, both belonging to congenital phagocyte defects[32] and similarly treated with antibacterial regimes and IFN-γ.

Ectodermal dysplasia with hyper IgM syndromes (NEMO, IκBα)

CD40 signaling initiates class switch recombination (CSR) and somatic hypermutation (SHM) to augment the adaptive immune response.[33] CD40 is expressed on B cells, macrophages/monocytes and dendritic cells, and a lack of signaling to such cells results in impaired handling of opportunistic pathogens including mycobacteria. In practice, tuberculosis is relatively uncommon, being reported in only one case in two large series[34,35] and occasionally in case reports.[36] Histoplasmosis was reported in one case in the North American series.[35] Disseminated atypical mycobacterial or BCG infection has not been reported in patients with CD40 ligand deficiency. However, atypical mycobacterial disease is a relatively common manifestation in defects of intracellular downstream NFκB signaling, including NEMO and IκBα mutations.[37]

Boys with X-linked anhidrotic ectodermal dysplasia and immunodeficiency have hypomorphic mutations in the IKBKG gene, which codes for the protein IKK-γ part of a kinase complex involved in releasing NFκB from its association with the inhibitory complex IκB allowing translocation to the nucleus.[38,39] An overlapping clinical syndrome with autosomal dominant inheritance causing ectodermal dysplasia and immunodeficiency is caused by mutations in NFKBIA encoding IκBα, part of the inhibitory complex.[40] Both of these syndromes are very variable both in immunological and nonimmunological features, and an HIGM pattern of immunodeficiency can be seen with some mutations.[41,42] Given that NFκB is involved in a number of T cell and Toll receptor signaling pathways, the immunodeficiency is more extensive than simply CSR and HSM, and therefore prone to a variety of bacterial and opportunistic infections, more common in mycobacterial infections.

Hyper IgE recurrent infection syndromes (TYK2)

Almost all patients with HIES suffer from recurrent staphylococcal infections, beginning in infancy and predominantly involving the skin and lungs.[43–48] This situation contrasts starkly with that in patients with CGD, in which recurrent staphylococcal infections occur in a wide variety of organs, including the lungs, lymph nodes, skin, liver, bones, gastrointestinal tract, kidney, and brain.[49] *Staphylococcus aureus* is the bacterium most frequently isolated from HIES patients, however *Streptococcus pneumoniae*, *Haemophilus influenzae*, and enteric Gram-negative bacteria are occasionally isolated from HIES patients during episodes of infection. Fungal infections including mucocutaneous candidiasis and pulmonary aspergillosis are also common in HIES. Eczema usually begins during the neonatal period, before the onset of atopic dermatitis. Patients with HIES suffer from atopic dermatitis associated with extremely high serum IgE levels and eosinophilia, but are usually free from other allergic manifestations, such as allergic rhinitis, asthma, urticaria, and anaphylaxis.

Recently, HIES has been classified into two categories, type 1 and type 2, regardless of the mode of inheritance. Patients with autosomal dominant STAT3 mutations belonging to type 1 HIES have abnormalities in multiple systems of the body, including the skeletal and dental systems. Autosomal recessive TYK2 deficiency has been identified as a molecular cause of type 2 HIES based on the finding that a type 2 HIES patient was susceptible to intracellular bacterial infection and had a defect in signal transduction for IL-12 and IFNα.[50] TYK2 is one of the founding members of the Janus kinase family (Jaks), transducing a signal downstream from a number of cytokines.[51–54] The aforementioned patient with type 2 HIES had a homozygous four-base pair deletion in the coding region of the TYK2 gene, resulting in a premature stop codon and the absence of TYK2 protein. This disorder was named AR-HIES with mycobacterial and viral infections due to severe defects in response to a number of cytokines, including type 1 IFN, IL-12, IL-23, IL-10, and IL-6.[32,50] In addition, patients with STAT1 mutations impairing both IFN-γ and INFα/β signaling have been found to suffer from both mycobacterial disease and disseminated HSV-1 infection.[55] The absence of TYK2 resulted in defective IL-12 signaling, leading to impaired TH1 differentiation and IFN-γ production and susceptibility to intracellular bacterial infections. This is consistent with the observation that patients with

IL-12β and IL-12RB1 deficiencies are susceptible to intracellular mycobacterial infections.[2]

Narrow predisposition to mycobacterial diseases

Mendelian Susceptibility to Mycobacteria Disease (MSMD)

MSMD (MIM 209950)[56] is a rare congenital syndrome that was probably first described in 1951 in an otherwise healthy child with disseminated disease caused by BCG vaccine.[57] It is defined by severe clinical disease, either disseminated or localized and recurrent, caused by weakly virulent mycobacterial species, such as BCG vaccines and nontuberculous, environmental mycobacteria (EM) in otherwise healthy individuals.[2,3,58–60] Understandably, patients with MSMD are also susceptible to the more virulent species, *Mycobacterium tuberculosis*.[5,61–64] Severe disease caused by nontyphoidal and, to a lesser extent, typhoidal *Salmonella* serotypes is also common, observed in nearly half of the reported cases, including patients who did not have any mycobacterial disease before the diagnosis of salmonellosis, or even at last follow-up.[2,3,65] The title "Mendelian susceptibility to mycobacteria disease" is therefore misleading, and it may be more accurate to refer to the underlying genetic defects, namely inborn errors of the IL-12/23-IFN-γ circuit. Other infectious diseases have rarely been reported in these patients, and have mostly involved pathogens phylogenetically (e.g., *Nocardia*) or pathologically (e.g., *Paracoccidioidomyces*) related to mycobacteria, suggesting that these infections were not coincidental.

Based on the genetic analysis from a large cohort of 220 MSMD patients with a defective IL-12/23-IFN-γ circuit by Casanova et al,[59] the genetic mutations were ranked as IL12RB1 (40%), IFNRG1 (39%), IL12p40 (9%), Stat-1 (5%), IFNRG2 (4%), and NEMO (3%). Applying this new concept to people of Chinese descent living in areas endemic for mycobacteria and salmonella in mainland China, Hong Kong, and Taiwan, two more siblings from two unrelated Hong Kong families were each identified with IL12RB1 Arg285stop and 1791+2T>G mutations, respectively. In one family, one died of disseminated BCGosis at around 2 years of age, while his sibling who did not receive a BCG vaccination died of disseminated mycobacterial tuberculosis at the age of 6 years. In the other family, one died of disseminated BCGosis at 1 year of age, while his sibling had cervical and axillary lymphadenopathy after a BCG vaccination, which was well controlled by antimycobacterial drugs.[66]

Using such a genetic approach in Taiwan 3 years ago, the heterozygous 818del4 dominant partial IFN-γ receptor 1 was identified in three of our four patients and was the hotspot dominant IFNGR1 mutation (approximately 87% among known dominant IFNGR1 mutations).[67] The onset age of BCG-induced diseases in all of our patients with partial IFNRG1 mutations was below 1 year, which is lower than that in a study of nonChinese patients, mainly including American, Irish, and German patients, whose mean age was 13.4 years (range 1.5–57 years).[4] BCG-induced disease in these Taiwanese cases initially occurred in the lymphoadenitis (regional phenotype) and gradually extended to the skin and bones (distant or disseminated phenotype). Some nonChinese patients with the same IFNRG1 mutations were able to resist BCG-induced diseases after receiving the BCG vaccine.[4] The discrepancy in BCG vaccine infections may vary by BCG strain type, such as the Pasteur, Glaxo, Copenhagen, Russia, or Tokyo 172 strains (our BCG strain). Alternatively, patients with partial IFNRG1 deficiency who did not develop BCG-induced disease might not have been recognized and consequently treated as refractory, recurrent, or reactive mycobacterial infection (tuberculosis or nontuberculosis), especially in endemic areas such as Taiwan.

In contrast, the homozygous missense mutation of Arg211Pro in the IL12RB1 gene is loss-of-function and causes recessive complete IL12RB1 deficiency, unrecognized by the monoclonal antibody, and without affinity to IL-12. About half of IL12RB1-deficient patients are infected by nontyphoid salmonella and may present as isolated and recurrent salmonella infection.[7,68] In an extreme case, six recurrent episodes of *Salmonella enteritidis* bacteremia occurred in a Turkish patient with an Arg175Trp IL12RB1 mutation. It was finally eradicated with one month of quinolone (ciprofloxacin) therapy plus trimethoprim-sulfamethoxazole prophylaxis after a series of failed treatments with 7-day cefixime, 10-day ceftriaxone, and 14-day cefotaxime, respectively.[69] Aggressive treatment strategies in our Arg211Pro IL12RB1 patient failed to eradicate the salmonella infection, and *Salmonella enteritidis* D became localized in the pulmonary parenchyma, causing necrosis, cavitation, and pneumatocele formation, which had a poor response to antibiotics and was not even cleared after surgical drainage. IFN-γ finally led to the efficient eradication of salmonella in this case.

The treatment strategy in IL12RB1 deficiency is similar to that of partial IFNRG1 deficiency. Stem cell transplantation is not indicated, different from those patients with complete IFNRG1 deficiency who are obligated to receive transplantation because they always develop disseminated BCG-induced diseases, fail to form well-circumscribed granuloma, and die at an early age despite IFN-γ treatment.[70,71] Our IL12RB1-deficient patient did not develop BCG-induced disease after receiving the BCG vaccine which seemed to confer resistance to environmental mycobacteria, as noted previously by Fieschi et al.[7] This reflects that IL-12 signaling is critical for protective immunity to salmonella, although not necessarily for mycobacterium.

X-linked ectodermal dysplasia with hyper IgM syndromes (NEMO)

Among the IL-12/23-IFN-γ pathways, patients with defective candidates of IFN-γR1, IFN-γR2, IL-12p40, IL-12R-β1, STAT-1, NEMO and IKBA have increased susceptibility to mycobacterial infections as well as a broader range of pathogens in those with STAT-1, NEMO and IKBA mutations. However, six patients from three unrelated kindreds with NEMO mutations in the leucine zipper (LZ) domain of E315A and R319Q were first identified to present as

Table 1 Six patients with NEMO mutations from three unrelated families presenting as X-linked MSMD phenotype.

Patient (ethnics)	Infection events in three families with X-linked MSMD-NEMO mutations
P1(French)	Receive BCG vaccine. Erosive granulomatous cutaneous MAC infection in face & arm (13 y, Tx: INH, RIF, EMB, clofazimine, streoptomycin for 2.5 y; well response to IFN-γ). Intermittent mycobacterial infections in the last 10 years.
PII-1	Miliary TB (6 y). Disseminated MAC (40 y, not eradicated). Enterobacter sepsis (48 y).
PIII-7	Disseminated MAC (5 y). Died of motorcycle accident (10 y).
PIII-8	Recurrent H. influenza (6 y). Disseminated abdominal MAC. Ectodermal dysplasia: conical teeth, hypodonia, hypotrichosis, abnormal hair whorl (14 y, Tx: poor response despite IFN-γ), normal response to polysaccharide antigens.
P2, II-1 (Italian, Serbian)	Receive BCG vaccine. Persistent low grade fever, night sweats, cough, cervical & inguinal lymphoadenopethy, positive PPD (2 y, Tx: INH, RIF for 6 m). Cervical lymphoadenopethy & prolonged fever, salmonella colitis (3 y). Concial decidual incisors (7 y).
P3, II-2(German)	Not-BCG vaccine, H. influenza b cervical lymphoadenitis (1 y). Fever of unknown origin, splenomegaly, hypergammaglobulinemia, granulocytosis (9 y). PPD positive, pulmonary infiltration (10 y, Tx: INH for 3 m, replaced by cefodoxime)

EMB = ethambutol; IFN-γ = interferon-gamma; INH = isoniazid; MAC = mycobacterium avium complex; PPD = purified protein derivative; RIF = rifampicin; TB = tuberculosis; Tx = treatment.

XR-MSMD (Table 1). The mutant proteins were produced in normal amounts in blood and fibroblastic cells, however the patients' monocytes presented with an intrinsic defect in T cell-dependent IL-12 production, resulting in defective IFN-γ secretion by T cells. IL-12 production was also impaired as the result of a specific defect in NEMO- and NF-κB/c-Rel-mediated CD40 signaling after the stimulation of monocytes and dendritic cells by CD40L-expressing T cells and fibroblasts, respectively. However, there were no significant findings in the CD40-dependent upregulation of costimulatory molecules of the dendritic cells, the proliferation and immunoglobulin class switch of B cells, and other NF-κB activators in the patients' blood and fibroblastic cells.[72] The authors first demonstrate the importance of the T cell- and CD40L-triggered, CD40-, and NEMO/NF-κB/c-Rel-mediated induction of IL-12 by monocyte-derived cells for protective immunity to mycobacteria in humans.

X-linked chronic granulomatous diseases (gp91phox)

The mutant human gene encoding the gp91phox (CYBB) subunit of the phagocyte NADPH oxidase, causing X-linked chronic granulomatous disease (CGD), impairs the respiratory burst of all types of phagocytes. Patients with CYBB

Table 2 Seven French patients from two unrelated families with CYBB mutations presenting as X-linked MSMD phenotype.

Patient (birth year)	Infection events in two families with X-linked MSMD-CYBB mutations
P1 (1953)	No BCG vaccine, pulmonary TB (10 y and INH for 10 m). Multiple mediastinal lymph nodes (34 y, fever, lymphoadenopathy, hepatomegaly, fatigue and anorexia, Px: rare epithelioid and giant cells, Tx: INH, RIF, EMB, PNA for 23 m).
P2 (1950)	BCGitis, regional axillary adenitis (self-limited), local ulcer and fistula (12 y, surgery), cervical lymph MAC adenitis (INH, RIF, EMB for 18 m). Ophthalmic zoster (21 y).
P3 (1955)	BCGitis, regional axillary adenitis (surgery). Abdominal zoster and self-limit warts (21 y).
P4 (1974)	BCGitis (2 y received), regional axillary adenitis (Px: epithelioid granuloma and giant cells, surgery). Intestinal volvulus due to multiple enlarged lymph node (21 y). Left supraclavicular lymphoadenopathy (24 y, TB, INH, RIF, EMB for 12 m plus IFN-γ), cervical adenitis (27 y, surgery, Px: epithelioid granuloma and giant cells growing from BCG).
Female carrier 1 (1920)	Tuberculous salpingitis and pulmonary open cavity TB (29 y, Streptomycin, INH). Intercostal zoster.
P5 (1969)	BCGitis, regional axillary adenitis, BCGosis (6 m, anti-mycobacterial Tx for 2 y). Lymphoadenitis (4 y, anti-mycobacterial Tx, surgery), BCG ititis (10 y), multiple cervical & abdominal lymphoadenopathy (38 y, INH, RIF, EMB, PZA over 1 y, partial response).
P6 (1969)	BCGitis (2 y received), regional axillary adenitis self-limit (2 y & 13 y), multiple cervical, axillary, crural lymphoadenopathy (29 y, INH, RIF, EMB, ofloxacin).
P7 (1974)	BCGitis, regional axillary adenitis (3 m, surgery).

EMB = ethambutol; IFN-γ = interferon-gamma; INH = isoniazid; MAC = mycobacterium avium complex; PPD = purified protein derivative; Px: pathology; PZA = pyrazinamide; RIF = rifampicin; TB = tuberculosis; Tx = treatment.

Table 3 Three patients increase susceptibility to mycobacterial infections, especially BCG.

Patient (birth year, ethnics)	Infection events in families with AR MSMD-IR8 mutation
K108E/female (Irish)	Intracranial calcification (*in utero*). Failure to thrive, marked hepatosplenomegaly, pleural effusion, ascites, oral candidiasis, discharging BCG scar, suppurative axillary lymphadenitis (10 wk). Monocytopenia (0), anemia (Hb = 4.6), lymphocytosis (125,000/mm^3), hypoalbuminemia. Florid myeloproliferation. Loss IL12 production and poor IFN-γ response. Delayed neutrophil oxidase burst. Rhinovirus deterioration and respiratory failure. Suspicious HLH development (HLH-2004: corticosteroids, etoposide and cyclosporine). CBHSCT, condition: treosulfan & fludarabine; GvHD: alemtuzumab, cyclosporine & mycophenolate mofetil (9 m).
	Infection events in families with AD MSMD-IR8 mutations.
T80A/male (1970; Italian Brazil)	Disseminated BCG lymphoadenopathies (15 m, RIF, INH & PZA for 6 m); abdominal lymphoadenopathies (20 y, RIF, INH & PZA for 6 m); peripheral & abdominal lymphoadenopathies (30 y, poor response to [RIF, INH & PZA] for 6 m and [ciprofloxacin, clarithromycin & ethambutol] for 36 m; good response to [amikin, rifabutin, clofazimine, ofloxacin, cycloserine & ethambutol]).
T80A/female(1996; Italian Chile)	Left axillary lymphoadenopathy (1 y; surgery). Fever and axillary, cervical, retroperitoneal & celiac lymphoadenopathies (2 y; RIF, NIH & PZA for 12 m).

CBHSCT = cord blood hematopoietic stem cell transplantation; EMB = ethambutol; HLH = hemophagocytic lymphocystic histiocytosis; IFN-γ = interferon-gamma; PZA = pyrazinamide; RIF = rifampicin.

mutations have an increased susceptibility to various catalase-positive pathogens infecting mainly respiratory and mucocutaneous systems. However, two kindreds in otherwise healthy male adults with T178P (in 3 patients) and Q231P (in 5 patients) developed unexpectedly X-linked MSMD syndromes (the clinical features are summarized in Table 2). These eight patients had previously unknown mutations in *CYBB* that resulted in an impaired respiratory burst in monocyte-derived macrophages, but not in monocytes or granulocytes. The macrophage-specific functional consequences of the germline mutation resulted from selective cell-specific impairment in the assembly of the NADPH oxidase.[73,74] This "experiment of nature" indicates that *CYBB* is associated with MSMD and demonstrates that respiratory burst in human macrophages is a crucial mechanism for protective immunity to tuberculous mycobacteria.

Autosomal dominant interferon regulatory factor 8 (IRF8) for dendritic cell immunodeficiency

In 2011, three patients with IRF8 mutations were recognized to have recurrent infections related to the BCG vaccine. Two Italians with the same autosomal dominant (AD, heterozygous) mutation of T80A IRF8 were healthy but had isolated and recurrent BCG infections because of a selection depletion of CD11c+CD1c+ circulating dendritic cells. In contrast, one Irish person with an autosomal recessive (AR, homozygous) mutation of K108E IRF8 had the SCID-phenotype at 6 weeks, presenting as discharging BCG scar, suppurative axillary lymphadenitis and oral candidiasis (Table 3). An successful unrelated cord blood hematopoietic stem cell transplantation restored his complete lack of circulating monocytes and dendritic cells at 9 months of age. These findings suggest that IRF8 is also critical for the development of monocytes and dendritic cells and for antimycobacterial immunity.[75]

Autoantibodies to interferon γ (antiIFN-γ Abs)

Although the first cases of immunodeficiency caused by autoantibodies to interferon γ were described in 2004,[76,77] Madariaga and coworkers had identified antiinterferon γ autoantibodies in otherwise normal individuals infected with *Mycobacterium tuberculosis* in 1998.[78] The highest titers of autoantibodies to interferon γ in tuberculous patients were in those with recent latent tuberculosis infections, followed by patients with severe active *M. tuberculosis* infection. Susceptibility to tuberculous and NTM infection as well as listeriosis, salmonellosis, histoplasmosis, melioidosis, and penicilliosis has been shown in patients with interferon γ receptor deficiency.[3]

Reviewing the literature regarding patients with antiIFN-γ Abs, 14 HIV-negative adults were reported with severe opportunistic infections and high titers of neutralizing autoantibodies to interferon γ.[76–82] *In vitro*, antiIFN-γ Abs block downstream mediators of interferon γ, including STAT1 phosphorylation, TNF, and interleukin-12 production, suggesting that these autoantibodies may interfere with the natural inflammatory response to infections with mycobacteria. Clinically, all patients had at least one NTM infection and five were infected with multiple mycobacterial species. The most common organisms were *M. avium* complex (11 infections) followed by rapid-growing mycobacteria (six infections). Of the 14 reported cases, 11 were Asian, suggesting possible genetic associations. Outcomes ranged from fatal infections to complete recovery.[76–82]

Conclusion

Patients with SCID including complete DiGeorge syndrome[83,84] have an en bloc absence of IL-12/23 effector T lymphocyte/NK cells. Patients with X-linked hyper IgM syndrome (CD40L mutation), CD40 deficiency and

immunodeficiency with/without anhidrotic ectodermal dysplasia (IκBα and NEMO mutation)[29,85] could not augment the CD40 pathway to IL-12/23-IFN-γ signaling. Moreover, patients with CGD and hyper IgE syndrome (HIES) had insufficient macrophage-producing ROS and defective IL-6 and IL-10 response to kill intracellular mycobacterial pathogens.[27,30,31,49,50] These immunodeficiencies have a broader susceptibility to multiple pathogens as well as mycobacterial and/or salmonella infection. However, an inborn error of the IL-12/23-IFN-γ circuit is prone to poorly virulent mycobacterial and nontyphoid salmonella infections rather than anything else,[10] commonly known as MSMD.[56] X-linked MSMD caused by selectively defective NEMO and CYBB mutations has been incidentally identified from clinical observations in the presence of ectodermal dysplasia and whole exons sequencing in patients with normal respiratory bursts, respectively.[72,74] To predict the prognosis in BCG-induced infections, we are working on the AD-IRF8 mutation to evaluate Taiwanese patients with a benign course in contrast to the AR-IRF8 mutations with the SCID-phenotype, although ethnic variation may exist.[75] We have standardized the functional assessment of these antiIFN-γ Abs and identified some patients who are adult-onset and have a relatively more persistent MSMD phenotype lacking BCG-induced diseases (Lee & Ku submission).

We have already launched the website for the Primary Immunodeficiency Care And Research (PICAR) Institute (http://www.cgmh.org.tw/chldhos/intr/c4a80/06index003.htm) to provide clinical consultation, immune functional assessment and candidate genetic analysis for timely management strategies. Based on the clinical course, "infections with normally harmless tuberculosis-like bacteria" is one of 10 PIDs warning signs, especially in adult patients, as well as "recurring infections or infections requiring prolonged antibiotic therapy" and "infections with unusual localization or unusual pathogens" in two of six adult ESID (European Society of ImmunoDeficiencies) warning signs. Hopefully this will improve the recognition rate of adult-onset PIDs while elucidating the possible immune defects in the patients suffering from refractory, recurrent or unusual mycobacterial infections.

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