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Interferon Gamma in Sickness Predisposing to *Mycobacterial* Infectious Diseases

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In recent decades, the prevalence of inborn errors of immunity has increased, necessitating the development of more effective treatment and care options for these highly morbid conditions. Due to these "experiments of nature," the complicated nature of the immune system is being revealed. Based on the functional and molecular tests, targeted therapies are now being developed which offer a more effective approach and reduce damage. This study aimed to investigate a key cytokine of the cellular immune response, interferon-gamma (IFN-γ), which is linked to Mendelian susceptibility to Mycobacterial disease, and its potential as a therapeutic option for IFN-γ deficiency.

INTERFERON GAMMA (IFN-γ) AND ITS FUNCTION

Cytokines are essential components of the immune system secreted by diverse cells to promote cell-to-cell communication, and can exert several functions. Cytokine immune responses are characterized by pleiotropy and redundancy.[1] Interferons (IFN) are cytokines that are secreted by the host cells during infection and are classified as follows: type I [IFN-alpha (α), IFN-beta (β), and IFN-omega (ω)], type II [(IFN-gamma (γ)], and type III (IFN-λ1, IFN-λ2, and IFN-λ3) IFNs. Each IFN type interacts with a specific receptor; however, IFN signaling pathways exhibit crosstalk.[2] IFN-γ is produced predominantly by primary T and natural killer (NK) cells.[3-5] It is the primary macrophage activating cytokine that performs a pivotal role in defense against intracellular pathogens such as mycobacteria, listeria, leishmania, and toxoplasma.[6] STAT4 signaling and interleukin-12 (IL-12), IL-23, and IL-18 induce IFN-γ expression in NK cells[7]. Both NK cells and T cells are activated by this interaction.[8] IFN-γ signaling occurs through the IFN-γ receptor (IFN-γR), a heterodimer composed of high affinity receptor IFN-γR1 associated with Janus kinase 1 (JAK1) and low affinity receptor IFN-γ R2 linked to JAK2.[9] The IFN-γR has two subunits: IFN-γR1, which consists of two ligand binding chains, and IFN-γR2, which consists of two signal transduction chains. IFN-γR1 is the primary molecule responsible for downstream signal transmission. IFN-γR2 is essential in the event that IFN-γR1 is absent, as it cannot bind to IFN-γ and initiate signal transmission.[10,11] However, the IFN-γ response is dependent upon the surface expression of IFN-γR2 for each cell type.[12] Following the binding of IFN-γ to its receptors, STAT1 is phosphorylated through the activation of JAK molecules, which then translocate to the nucleus, where it initiates the expression of interferon-stimulated genes (ISG), including interferon regulatory factors 1 and 5 [(IRF1) and IRF5, respectively].[13] The secretion and effects of IFN-γ are strictly regulated by mRNA instability, and T cells cease secretion upon the conclusion of their interaction with the target cell.[14]

THE ROLE OF IFN-γ IN MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASE

Mendelian susceptibility to Mycobacterial disease (MSMD) is a rare genetic condition that is classified as part of the intrinsic and innate defects of immunity. It is characterized by susceptibility to infections with weakly virulent mycobacteria, including *Mycobacterium bovis,* bacillus Calmette-Guérin (BCG), and environmental mycobacteria.[15-17] Mycobacterial diseases can exhibit diverse manifestations, ranging from localized infection to disseminated infectious disease, from

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acute to chronic infection, and from poorly differentiated to well-differentiated granuloma.[18-20] Common clinical findings include localized or diffuse lymphadenopathy, cutaneous manifestations, pulmonary involvement, osteomyelitis, and hepatosplenomegaly.[21,22] Certain patients demonstrate findings resembling macrophage activation syndrome.[23] Although the definition of MSMD indicates a predisposition to *Mycobacterial* infections, some bacterial, viral, and fungal infections may cooccur in addition to various clinical phenotypes of mycobacteria. Additionally, a few patients are susceptible to tuberculosis. MSMD is believed to affect approximately 1 in 50,000 individuals worldwide.[21,24] Since the initial identification of IFN-γR1 deficiency as the first MSMD in 1996, numerous other MSMDs have been discovered to be inherited in both autosomal and X-linked manners. These include the following: *CCR2, CYBB, IFNG, IFNGR1, IFNGR2, IL12B, IL12RB1, IL12RB2, IL23R, IRF1, IRF8, ISG15, JAK1, MCTS1, NEMO, RORC, SPPL2A, STAT1, TBX21, TYK2,* and *ZNFX1* (Table 1).[25,26] These genes encode two distinct types of proteins associated with the IFN-γ-mediated immune response: i) proteins playing a role in the production of IFN-γ: *IFNG, IL12B, IL12RB1, IL12RB2, IL23R, ISG15, MCTS1, RORC, TBX21, TYK2*; ii) proteins that are expressed in response to IFN-γ: *CYBB, JAK1, IFNGR1, IFNGR2, IRF1, STAT1, USP18*; or iii) those performing both functions: *IRF8, NEMO, SPPL2A* (Figure 1). The exception is that the effect of *ZNFX1* in combination with MSMD is unclear.[27] A reduced number of macrophages in tissues is indicative of CCR2 involvement. The immune response to mycobacteria depends on the residual activity of IFN-γ. The most severe variants of MSMD are autosomal recessive (AR) complete deficiency of IFN-γR1, IFN-γR2, STAT1, IRF1, and IFN-γ. Most patients succumb to severe and disseminated *Mycobacterial* infections before the age of ten. The disease course and therapeutic implications are contingent upon the genetic etiology [multiple antibiotics against mycobacteria, hematopoietic stem cell transplant (HSCT), resection of lymph nodes, and IFN-γ].

AR COMPLETE IFN-γ DEFICIENCY WITH ABSENCE OF PRODUCTION AND SECRETION

Although the role of impaired IFN-γ production in MSMD development has been widely recognized, it was not until 2020 that Kerner et al.[23] first described inherited IFN-γ deficiency. The paper presented two AR IFN-γ deficiency patients from two related consanguineous families in Lebanon. The first child experienced prolonged fever three weeks after the BCG vaccination, which was administered at the age of three months. Hepatosplenomegaly, maculopapular rashes, and failure to thrive were documented in addition to an axillary mass on the left side. BCG-osis was diagnosed subsequent to the discovery of acid-fast bacilli (AFB) during a lymph node biopsy. Initially, the patient was administered multiple antibiotics. Subsequently, recombinant human[28] IFN-γ was initiated at a dose of 50 μg/m^2, thrice a week. Hemophagocytic lymphohistiocytosis (HLH) was suspected fourteen months after the diagnosis of BCG-osis, despite the absence of hemophagocytosis in the bone marrow examination. Due to the HLH relapse, the patient underwent HSCT from a matched sibling donor in accordance with the HLH-04 protocol. However, the patient succumbed nine days following the HSCT. The cousin of this first patient presented

TABLE 1. Mendelian Susceptibility to Mycobacterial Disease.

Affected gene	Inheritance pattern	Defect	Protein response
CCR2	AR	C	E-
IFNG	AR	C	E-
IFNGR1	AR	C	E+ or E-
	AD	P	↑ E+
	AR	P	E+
	AR	P	↓ E+
IFNGR2	AR	C	E+ or E-
	AR	P	E+
	AR	P	↓ E+
	AD	P	↓ E+
IL12B	AR	C	E-
IL12RB1	AR	C	E- or E+
IL12RB2	AR	C	E-
IL23R	AR	C	E- or E+
IRF1	AR	C	E- or E+
IRF8	AR	C	E- or E+
	AD	P	E+
ISG15	AR	C	E-
JAK1	AR	P	E+
RORC	AR	C	E-
SPPL2A	AR	C	E- or E+
STAT1	AR	C	E-
	AR	P	E+
	AD	P	E+, Phos-
	AD	P	E+, B-
	AD	P	E+, Phos-, B-
TBX21	AR	C	E-
TYK2	AR	C	E- or E+
	AR	P	E+
	AR	P	E+, IL-23-
	AR P1104A[#]	P	E+, IL-23-
USP18	AR	P	E+
ZNFX1	AR	?	E- or E+
CYBB	XR	P	E+
MCTS1	XR	C	E-
NEMO (IKBKG)	XR	P	E+

The inheritance pattern of MSMD may be autosomal recessive (AR), autosomal dominant (AD), or X-linked-recessive (XR). Defects are complete (C), partial (P), or not determined (?). The impact of variants on protein expression is as follows: protein not expressed, protein expressed (E+); decreased expression of functional protein (↓ E+); increased expression of functional protein (↑ E+); decreased binding to DNA (B-); decreased phosphorylation (Phos-); decreased responsiveness to IL-23. Amorphic variants in CYBB are responsible for chronic granulomatous disease (CGD); NEMO mutations underlie incontinentia pigmentii development; and USP18 mutations underlie interferonopathy development. #TYK2 P1104A is a common allele.

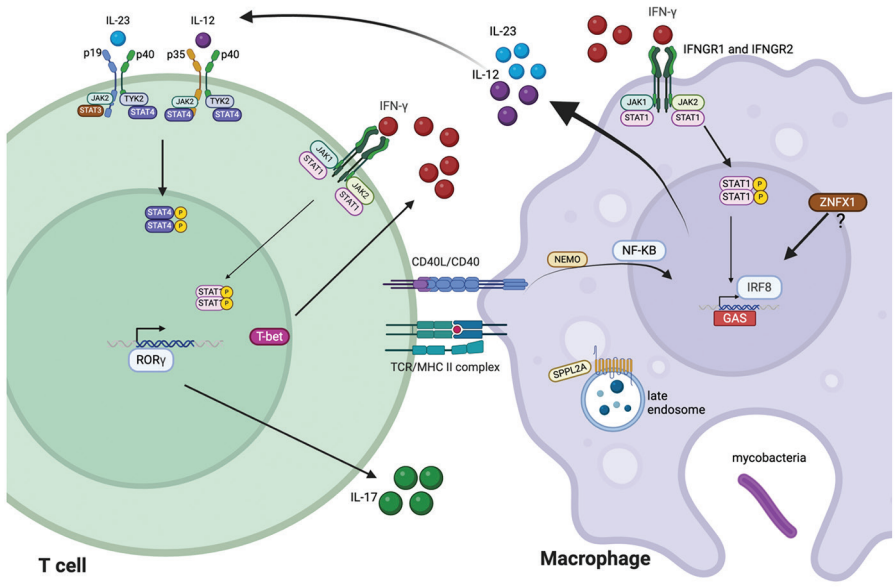

FIG. 1. Molecular pathways underlying Mendelian susceptibility to Mycobacterial disease. "Created with BioRender.com."

TABLE 2. Summary of Clinical Features of MSMD Patients Who were Treated with rhIFN-γ.

Condition	Indication and dosage	Outcome	Adverse events	Ref
NEMO or IKBKG (X-linked recessive partial deficiency)	*Mycobacterium avium* complex infections (n = 4) 50 mcg/m^2, 3 times/week	Clinical improvement within 8 weeks	Fatigue, malaise, myalgia (n = 2)	45,46
IL-12Rß1 (AR complete deficiency)	Refractory BCG-osis (n = 1) The initial dose was 50 µg/m^2 three times per week for three months, then increased to 100 µg/m^2, and eventually increased to 200 µg/m^2 six months later due to poor response.	Positive clinical effect only after 200 µg/m^2 3 times/week	-	44
	Refractory BCG-osis (n = 1) 25 µg/m^2 twice a week over 18 months	Clinical remission after nine months	N/A	47
	Refractory BCG-osis (n = 1) Initiated as 25 µ/m^2 twice a week over 18 months, continuously increased 150 µg/m^2	No response; succumbed due to dissemination of the infection.	N/A	
	Disseminated BCG-osis 25 µg/m^2, 3 times/week increased to 100 µg/m^2 (n = 1)	Clinical improvement after two months	N/A	48
	50 µg/m^2, 3 times/week (n = 16/22 patients) during infection and as prophylaxis afterward	Lower mortality in patients treated with rhIFN-γ	Fever	49
	50 µg/m^2, 3 times/week during infection (n = 6/10 patients)	Improvement in some patients	N/A	50
	BCG-osis, salmonellosis, leukocytoclastic vasculitis (n = 3)	Resolution of major symptoms	N/A	51
	Salmonella enteritidis (n = 1) 50 µg/m^2, 3 times/week	Clinical improvement	N/A	52
	M. intracellulare infection (n = 1) 50 µg/m^2, 3 times/week	Clinical improvement	N/A	28

TABLE 2. Continued

Condition	Indication and dosage	Outcome	Adverse events	Ref
	M. tuberculosis complex 200 μg/m², 3 times/week (n = 1)	Improvement in general condition	N/A	53
	Pericarditis following *Salmonella enteritidis* infection 50 μg/m², 3 times/week (n = 1)	Clinical improvement	N/A	54
	BCG-itis, oral candidiasis, prophylaxis 50 μg/m², 3 times/week (n = 1)	Good clinical condition	N/A	55
	M. bovis, 25-150 μg/m², 3 times/week	Poor response	N/A	56
	Lymphadenitis due to *Salmonella* 50 μg/m², 3 times/week (n = 1)	Good response	N/A	57
	Leishmania tropica, *Leishmania* infantum (n = 1)	Multiple relapse	N/A	58
	BCG-osis, cutaneous tuberculosis (n = 7)	N/A	N/A	59
	Mycobacterial infections	Increase in treatment response	N/A	60
	M. bovis abscess, meningitis (n = 1) *Nocardia nova, Klebsiella pneumonia* (n = 1)	Poor response	N/A	61
		Good response	N/A	
IL-12p40 (AR complete deficiency)	Leukocytoclastic vasculitis, *M. bovis*-BCG 50 mcg/m², 3 times/week (n = 1)	Improvement	N/A	51
	During infection (n = 12)	N/A	N/A	62
IFN-γR1 (AD or AR partial deficiency)	*Mycobacterial* infection (n = 2)	Improvement	N/A	63
	Lung and cerebral lesions caused by multidrug resistant BCG (n = 1) Multidrug resistant *M. abscessus* (n = 1)	Modest improvement	N/A	38
	M. bovis infection (n = 2) *M. avium* infection (n = 1)	Improvement	N/A	
		N/A N/A		
	Disseminated *Mycobacterium avium* complex infection (n = 1) 50 μg/m², 3 times/week	Clinical improvement	-	39
	Coccidioidomycosis and disseminated *M. kansasii* 50 μg/m², 3 times/week (n = 1)	Clinical improvement	-	40
	Disseminated histoplasmosis 50 μg/m², 3 times/week (n = 1)	Clinical improvement	N/A	41
STAT1 (AD deficiency)	Multifocal osteomyelitis BCG (n = 2) 1.5 μg/kg, 3 times/week	Resolution of infection	N/A	42
IFN-γR2 (AR partial deficiency)	Osteomyelitis due to *M. bovis*-BCG (n = 1) BCG vaccination-related suppurative lymphadenitis (n = 1)	Clinical improvement	N/A	64
		Clinical improvement	N/A	
IFN-γ (AR complete deficiency)	BCG-osis 50 μg/m², 3 times/week (for infection and lifelong prophylaxis)	Clinical improvement	-	29

BCG, Bacillus Calmette-Guérin; N/A, not available; rhIFN-γ, human recombinant interferon-gamma.

similarly with left axillary mass six weeks after the BCG vaccination. Hepatosplenomegaly, leukocytosis, anemia and elevated liver enzymes were documented along with low erythrocyte sedimentation rate. Similar to first patient, the lymph node biopsy revealed AFB and a diagnosis of BCG-osis was made accordingly. After antibiotic treatment, this patient also underwent HSCT and is currently doing well. Whole exome sequencing and genome-wide linkage analysis were performed for both families. In both patients, a homozygous frameshift deletion c.354_357del was detected in exon 3 of *IFNG*, encoding IFN-γ protein. As demonstrated by the capacity of conditioned media to upregulate HLA-DR expression, transfection experiments in vitro result in a lack of protein expression and function. In contrast to the healthy controls, the patients' cells did not produce any detectable IFN-γ following stimulation with BCG and IL-12.[23] The development of all major lymphoid and myeloid subsets is largely unaffected, as previously demonstrated in other MSMD forms. Population genetic studies have indicated that the *IFNG* gene is under strong purifying selection, attributing for the rarity of this disorder in humans.

AR IFN-γ DEFICIENCY WITH ABNORMAL CONFORMATION

A subsequent report by Rosain et al.[29] in 2024 included an additional Turkish patient from consanguineous parents. Axillary enlargement was observed on the left side six weeks following the BCG vaccination, without any accompanying symptoms. At six months of age, the patient presented with a high fever, hepatosplenomegaly, a generalized maculopapular rash, and lymphadenopathy on the left axillary side. Laboratory examination demonstrated hypofibrinogenemia, hypertriglyceridemia, hyperferritinemia, severe anemia, thrombocytopenia, and leukocytosis. Serological assays and blood cultures did not reveal any indications of an infectious agent. As HLH was suspected, etoposide, dexamethasone, and cyclosporine were administered, resulting in a favorable response. Antimycobacterial treatment was administered due to the suspicion of BCG-osis. A homozygous, single-nucleotide variant, c.224C>T or p.F75S, was identified in the *IFNG* gene through clinical WES, as confirmed by Sanger sequencing. This variant was anticipated to be deleterious, and the combined annotation dependent depletion score was higher. Despite the production of mutant IFN-γ within the cells, it was not effectively folded or secreted due to overexpression, constitutive expression in the patient's cells, or recipient cells. In contrast to the normal secretion of IFN-γ in PHA-activated blasts stimulated with IL-12, IL-23, or phorbol myristate acetate/ionomycin (PMA/ionomycin) in healthy controls, the patient was unable to generate detectable amounts of IFN-γ. Following a genetic diagnosis at 12 months of age, the patient was administered recombinant human[28] IFN-γ therapy at a dose of 50 μg/m^2 three times per week. During this treatment, the patient's triglyceride and ferritin levels were restored, and he remained in good health. The patient's samples were subsequently subjected to RNA sequencing before and ten hours after IFN-γ1b administration. The induction of GAS-dependent myeloid ISGs, including *IRF1*, *GBP4*, *APOL3,* and *CXCL10* proteins, was demonstrated. Neutralizing antibodies were not detected after six months of therapy. The treatment was well tolerated, and no recurrence of infectious disease was noted during this treatment. The patient is currently five years old and free of any HLH-like or Mycobacterial diseases. He continues to receive human recombinant IFN-γ 50 μg/m^2 three times per week without the need for any additional drugs. This was the first report of a patient with cytokine deficiency who was successfully treated with a recombinant cytokine.

RHIFN-γ AS TREATMENT IN IEIS

In addition to antimycobacterials, rhIFN-γ therapy has shown promising results in patients with acquired immune deficiency syndrome and *Mycobacterium avian* complex[30] infection.[31] Treatment using rhIFN-γ has been approved for controlling infections in chronic granulomatous disease (CGD) patients and for delaying disease progression in osteopetrosis.[32] A double-blind, placebo-controlled study conducted by the International CGD Cooperative Study Group demonstrated that rhIFN-γ administration three times per week was beneficial in reducing the frequency of infections in CGD patients.[33] There is no link between this effect and the type of CGD, patient age, or concurrent antibiotic use. The mechanism underlying this effect was first attributed to increased superoxide production and cytochrome b gene expression in neutrophils and monocytes.[34-37] Only a few adverse effects were reported, including erythema, fever, chills, and myalgia, and autoantibodies to IFN-γ were not detectable.[33] Furthermore, its effects on several other MSMD patients depend on the underlying genetic disorder. The treatment with rhIFN-γ was effective in patients with an impaired but abolished response to IFN-γ, as evidenced by the reports on AR partial IFN-γR1, AR partial IFN-γR2, autosomal dominant IFN-γR1,[42] deficiencies (Table 2). Additionally, the treatment was effective in patients exhibiting impaired IFN-γ production, such as those with AR IL-12 p40 and IL-12 Rβ1 deficiencies.[43] Nevertheless, in specific circumstances, such as in patients with IL-12Rβ1 deficiency that is complicated by BCG-osis that is resistant to anti-BCG antibiotics, larger doses (200 μg/m^2) may be necessary.[44]

Conditions related to impaired IFN-γ-mediated immunity have enhanced our understanding of the crucial role of this cytokine in inflammation, particularly in Mycobacterial diseases. In countries where the BCG vaccine is routinely administered, it is crucial to identify patients with susceptibility to BCG disease. Early diagnosis is essential to be able to treat these patients effectively. Targeted therapies are now commonly employed for IEI patients in cases where the molecular mechanism has been identified. Although HSCT may be the only definitive treatment for many of these IEIs, improving the patient's condition with the appropriate treatment can result in favorable outcomes.

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