

Mutations in *IFNGR1* or *IFNGR2* and Interferon- γ Receptor Deficiency – an Overview

Introduction

Inherited susceptibility to mycobacterial infections, often referred to as Mendelian susceptibility to mycobacterial disease (MSMD) or Familial Atypical Mycobacteriosis, is a rare immunodeficiency caused by defects in the interferon- γ -mediated immune response, which plays a key role in activation of the microbicidal response of macrophages (for comprehensive reviews, refer to references 1-3). Depending on the underlying genetic defect, disease severity can range from a mild form, which is easily treatable with prophylactic antibiotics and interferon- γ therapy, to a severe form, for which stem-cell transplantation is recommended. Molecular diagnosis may allow prediction of phenotype, helping to guide the selection of the appropriate treatment (2).

To date, loss-of-function mutations in five different genes have been implicated in MSMD. Mutations that result in a complete loss of cellular responsiveness to interferon- γ (IFN- γ) signaling are associated with more severe disease, while mutations that allow residual IFN- γ signaling give rise to the milder form of the disease.

- Interferon- γ receptor (IFN- γ R) deficiency is the most common type of MSMD. It is caused by autosomal dominant or autosomal recessive loss-of-function mutations in *IFNGR1* (4-6) or, in rare cases, autosomal recessive loss-of-function mutations in *IFNGR2* (7, 8). Both genes encode subunits of IFN- γ R, and mutations in either gene can impair or abolish responsiveness to IFN- γ signaling.
- Interleukin-12 (IL-12) pathway defects result from autosomal recessive loss-of-function mutations in *IL12B*, which encodes the IL-12p40 subunit of both IL-12 and IL-23, and *IL12RB1*, which codes for the β 1 subunit of the IL-12 and IL-23 receptors (reviewed in 3). Mutations in

IL12B or *IL12RB1* disrupt signaling by IL-12 and IL-23, resulting in reduced IFN- γ production.

- STAT1 deficiency is a related disorder caused by autosomal recessive or autosomal dominant loss-of-function mutations in *STAT1*, the gene encoding the signal transducer and activator of transcription protein-1 (STAT1) (reviewed in 3). Mutations in *STAT1* cause impaired signaling from both type I (IFN α/β) and type II (IFN- γ) IFNs.

Molecular Pathophysiology

IFNGR1 and *IFNGR2* code for the two subunits of IFN- γ R, a member of the class II cytokine receptor family. The ligand for IFN- γ R, IFN- γ , is synthesized and released by T cells and NK cells in response to signals from IL-12 and IL-23, which are secreted by phagocytizing macrophages (reviewed in 9). Binding of IFN- γ to IFN- γ R activates the Jak-Stat signaling pathway, resulting in phosphorylation of STAT1, which induces transcription of IFN- γ -regulated genes necessary for the microbicidal response of macrophages (reviewed in 10). Defects in either IFN- γ R1, which serves as a binding site for IFN- γ , or IFN- γ R2, which stabilizes the active receptor, can disrupt surface expression or responsiveness of IFN- γ R, resulting in an impaired microbicidal macrophage response against phagocytized mycobacteria.

Depending on the mutation in *IFNGR1* or *IFNGR2*, disease severity can vary significantly. Three distinct phenotypes resulting from loss-of-function mutations in *IFNGR1* have been defined based on mode of inheritance and the effect of the mutation on surface expression and responsiveness of IFN- γ R. The more severe form of IFN- γ R1 deficiency, referred to as recessive complete IFN- γ R1 deficiency (RC-IFN- γ R1), arises from autosomal recessive loss-of-function mutations

that cause a complete loss of IFN- γ binding (11, 12) or cellular responsiveness to IFN- γ signaling (4, 6, 13). A mutation resulting in a recessive partial phenotype (RP-IFN- γ R1) with residual IFN- γ responsiveness has also been described (14). The mild form of IFN- γ R1 deficiency, referred to as dominant partial IFN- γ R1 deficiency (DP-IFN- γ R1), usually results from autosomal dominant loss-of-function mutations in *IFNGR1* that disrupt a peptide sequence required for removal of the receptor from the cell surface, causing defective IFN- γ R1 subunits to accumulate. The defective subunits bind to and impair the function of IFN- γ R1 subunits encoded by the wild-type allele, resulting in diminished cellular response to IFN- γ signaling (5, 15, 16). Similarly, mutations in *IFNGR2* that allow residual IFN- γ signaling lead to a milder disease phenotype (partial IFN- γ R2 deficiency), while mutations that prevent surface expression of IFN- γ R2 result in complete loss of IFN- γ signaling and give rise to more severe disease (complete IFN- γ R2 deficiency) (2).

Clinical Presentation

Patients with IFN- γ R deficiency exhibit unusual susceptibility to infection by moderately virulent mycobacterial species. The most frequently observed pathogens are bacillus Calmette-Guérin (BCG), usually following BCG vaccination, and environmental nontuberculous mycobacteria (1). With the exception of salmonellosis, which is observed in almost 50% of cases, patients with IFN- γ R deficiency are generally not at risk for infection by other opportunistic pathogens (2). However, infection by cytomegalovirus, herpes simplex virus, varicella, *Listeria monocytogenes*, and *Histoplasma capsulatum* have each been observed in at least one patient (1, 2). Patients with complete IFN- γ R deficiency suffer from more severe disease, characterized by earlier onset, increased severity and number of infections, and decreased rate of survival (1). Patients with partial IFN- γ R deficiency experience milder disease, frequently associated with non-tuberculous mycobacterial osteomyelitis (3). A correlation between clinical outcome and the type of granulomatous BCG lesions has also been noted. Patients with lepromatous-like granulomas are at

greater risk of death from overwhelming infections, while patients with tuberculoid granulomas have less severe disease (17).

Diagnosis

IFN- γ R deficiency is usually diagnosed in children, although onset of infections can occur in adults (2). IFN- γ R deficiency is suspected in patients suffering from atypical mycobacterial infection, after other causes of immunodeficiency have been ruled out. Diagnosis currently relies on determination of serum IFN- γ levels by ELISA, where elevated IFN- γ levels indicate complete IFN- γ R deficiency, while low or undetectable levels suggest partial IFN- γ deficiency. However, this technique cannot distinguish between the possible molecular causes of the disease (reviewed in 2). Flow cytometric evaluation of IFN- γ R1 expression levels can be used to establish a diagnosis of IFN- γ R1 deficiency, where an absence of IFN- γ R1 expression on monocytes is indicative of the more severe RC-IFN- γ R1 phenotype, while a 5-10-fold over-accumulation of IFN- γ R1 on the cell surface suggests the milder DP-IFN- γ R1 phenotype (reviewed in 3). Due to the lack of a robust assay for specific detection of IFN- γ R2, definitive diagnosis of interferon- γ R2 deficiency can be difficult, and sequence analysis is recommended (3). Since published studies have established a relationship between mutations in *IFNGR1* and *IFNGR2* and IFN- γ R deficiency, a firm diagnosis of *IFNGR1*- or *IFNGR2*-related IFN- γ R deficiency may be achieved through genetic testing. Through identification of the pathogenic mutation, genetic testing can help to establish a more precise disease prognosis and thereby facilitate selection of the most appropriate therapy, since the majority of mutations that give rise to the milder DP phenotype result from a four-base-pair deletion at or near base 818 (818del4) (5, 15, 16). By revealing the mode of inheritance, genetic testing can also improve genetic counseling, carrier detection, and early diagnosis of affected descendants.

Treatment

The recommended treatment for IFN- γ R deficiency is dependent on whether the patient is suffering from partial or complete IFN- γ R deficiency. Since patients with partial deficiency have residual IFN- γ activity, their infections can be successfully treated with IFN- γ

therapy and prophylactic antibiotics. In contrast, patients with complete IFN- γ R deficiency often develop serious, life-threatening infections, requiring aggressive, long-term antimicrobial therapy. Stem-cell transplantation should be considered for these patients (reviewed in 2, 3).

References

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