Paradox of autoantibodies and immune deficiency: Interferon gamma antibodies and susceptibility to intracellular pathogens

*S Sehgal, D Suri

Role of Interferon Gamma in Host Defense

Familial Bacillus Calmette–Guérin (BCG) disease has been reported by several investigators before the precise genes involved in protection against mycobacteria were recognized[1] D'Souza et al. first documented defective antigen processing in such cases.[2] Subsequently, Vesterhus et al. also described familial cases of infection with atypical mycobacteria.[3] Interferon gamma (IFNG) receptor deficiency was first described in an infant with fatal BCG disease in 1997. The same year Newport et al. described mutations in IFNG receptor and susceptibility to mycobacterial disease.[4,5] Several investigators since then have revealed the correlation of partial or complete deficiency of interleukin-12 (IL-12), IFNG, IFNG receptor and tumour necrosis factor (TNF) alpha pathways causing susceptibility of the host to salmonella, listeria etc.[6-12]

Fieschi et al. reported high levels of IFNG in plasma of patients with complete receptor deficiency.[13] IFNG, a major TH1 cytokine, is produced predominantly by T-cells, NK cells and monocytes in response to a variety of inflammatory or immune stimuli and up-regulates the development and function of immune effector cells. IFNG receptors are expressed on almost all nucleated cells and show species specificity in their ability to bind IFNG. The extracellular portion of IFNG RI contains the IFNG ligand-binding domain; the intracellular portion contains domains necessary for signal transduction and receptor recycling. The extracellular domain of IFNG R2 interacts with the IFNG R1/IFNG complex but does not itself play a major role in ligand-binding.[14]

Functional integrity of mononuclear phagocytes and their interaction with T-cells and IFNG production are crucial factors in the elimination of both tuberculosis (TB) and the non-tuberculous group of mycobacteria (NTM) (e.g., Mycobacterium fortuitum, M. chelonea, M. abscessus, M. avium complex, M. kansasi, M. simiae and M. marinum).

Genetic defect of IFNG receptor results in reduced production of TNF alpha and other pro-inflammatory cytokines in response to IFNG and endotoxin, defective MHC Class II expression in response to specific stimulation and poor presentation of antigen to T-cells.[6] These findings were later corroborated in IFNG R1 knockout mice which showed a marked susceptibility to challenge with mycobacteria with failure to develop mature granulomas and protective immunity. The significance of IFNG pathways has been elegantly demonstrated in mice with targeted disruptions of other related genes also.[9] In fact IFNG and IL-12 pathway defects lead to the Mendelian susceptibility to mycobacterial diseases (MSMD); there are more than 12 genes[15] upstream and downstream along STAT 1/TYK2/JAK1, 2 pathways [Figure 1] which if mutated, result in MSMD (OMIM 209950). India has a large reservoir of mycobacterial TB (MTB) patients and it is highly likely that some of these patients might carry Mendelian susceptibility to mycobacterial infections.

Mycobacterial Infections in the Un-immunocompromised Host: Antibodies to Interferon Gamma

Apart from genetic defects in IFNG pathways, some patients do suffer from infections akin to those occurring in immune deficiency states due to autoantibodies to IFNG but surprisingly they do not exhibit either lowering of CD 4 cells or mutations in the IFNG/IL-12/23 pathways.

It is clear that If IFNG is so crucial for eliminating mycobacteria and other intracellular pathogens, it is logical to infer that antibodies to IFNG may seriously interfere
with elimination of mycobacteria and other intracellular pathogens, and this is indeed true.

Madariaga et al. in 1998[16] first reported anti-IFN antibodies in a Spanish patient with pulmonary tuberculosis. Hori et al. described rapidly growing mycobacteria in 20 patients from Thailand.[17] Later, naturally occurring anti-IFNG auto antibodies associated with severe infections with M. cheloneae and Burkholderia cocovenenans were reported by Höflich et al.[18] Today, a vast body of literature emphasizes the association of opportunistic infections, normal CD4 cells, a clinical picture of profound T-cell dysfunction and presence of autoantibodies to IFNG particularly in patients from Thailand and Taiwan.[19-22]

Disseminated Mycobacterium avium intracellulare (MAI) complex infection, a hallmark of AIDS, was first reported in a patient with autoantibody to IFNG from Kyoto by Tanaka et al.[23] M. avium complex was isolated from several body fluids. Phytohemagglutinin stimulated mononuclear cells (PBMC) of the patient failed to produce IFNG in the presence of autologous plasma while the defect was rectified by the addition of normal donor plasma. This observation was authenticated by other authors.[24] Auto antibodies IFNG and immune deficiency associated with opportunistic infections have also been reported in patients with acquired immune deficiency with disseminated penicilliosis, bacteremic non-typhoidal salmonellosis and burkholderiosis and in travellers returning from the region.[25,26]

The largest multicentre study was, however, conducted by Browne et al.[27] The group described 203 patients suspected of having adult-onset immunodeficiency from Thailand and Taiwan reported earlier and reiterated that the adult-onset immunodeficiency in patients from Thailand and Taiwan was strongly associated with high-titre neutralizing antibodies to IFNG. The authors could not identify the cause of impaired cell-mediated immunity, none of them was HIV infected, had not received any immunosuppressive agents, and had no underlying diseases to explain compromise of their immune system. The patients were divided into 5 groups viz those with NTM, (group 1), opportunistic infections, (group 2), disseminated TB (group 3), pulmonary TB (group 4) and controls (group 5). Antibodies to IFNG were present in 81% of patients in group 1 and in 96% of patients in group 2. In group 3, 11% of patients revealed anti-IFN antibodies while in group 4 and 5, anti-IFN antibodies were insignificant. Healthy controls and the patients had agricultural occupation mostly.

The spectrum of infections was quite typical. If the groups 1 and 2 were combined (97 cases) then 75 had rapidly growing mycobacteria, 23 had slow growing mycobacteria, 14 had MTB, 25 patients had salmonella species, 4 had burkholderia, 24 had fungal infections and 18 had local or disseminated varicella-zoster. The absolute CD4+ cell count was comparable between patients and healthy controls. Confirmation of antibody to IFNG was performed using inhibition assay performed in all cases; binding activity of autoantibody to IFN-c was inhibited if sera were pre-incubated with soluble IFNG in a dose-dependent manner which confirmed the presence of autoantibody to IFNG in all the positive sera. Plasma samples positive for anti-IFN antibodies inhibited IFN induced STAT1 phosphorylation. When mononuclear cells of these patients were washed free of the antibody, their capacity to induce IFNG and TNF was restored.
A detailed study of cell-mediated immune deficiency in these HIV-negative, adult-onset immune deficient patients was reported separately in 20 patients from the Northern Thailand at Chiang Mai University Hospital between 2011 and 2012 who had similar clinical presentation as described earlier by Brown et al. and had at least 2 episodes of histologically or microbiologically proven opportunistic infections. In this recent study Wongkulab et al. documented that autoantibodies to INFγ were detected in 100% of patients with adult-onset immunodeficiency while the titres were higher in patients with active infections.

Kampmann et al. from the UK conducted intensive investigations in another set of three patients with severe progressive NTM disease in whom the phenotype was similar to that of mutations in the IFNG pathway. Using high-density c DNA microarrays, they concluded that these antibodies act at three different levels. First by blocking the TNF alpha production in response to endotoxins, second by blocking the IFNG inducible genes and third by inhibiting upregulation of HLA class two molecules on PBMC's. There have been patients at our institute in the past who presented with unexplained cryptococcal infection in the joint or a young patient with Zoster infection or MAI infection without any predisposing cause. In retrospect such patients could fit into this category but were missed as no attempt was made to test for anti-INFγ antibodies at that time.

Antibodies to IFNG have been reported in patients with HIV/AIDS, but their significance has not been studied in detail. It is extremely relevant to recognize this entity and treat promptly to reduce the burden of these microbes in the population. The role of anti-IFNG autoantibodies in Indian patients with NTM and other opportunistic infections needs to be elucidated since many patients with anti-IFNG autoantibodies remain actively infected despite antimicrobial therapy. In cases with autoantibodies to IFNG, targeting of auto antibodies may have a role in the management of mycobacterial infections unresponsive to the standard treatment protocols.

Similarly, anti-granulocyte-macrophage colony stimulating factor (GMCSF) auto antibodies have been associated with Cryptococcal meningitis. These cases have been successfully treated with Rituximab along with antifungal agents. It is suggested by some investigators that infection with Cryptococcal gattii is more common in these individuals. Further, adult form of pulmonary alveolar proteinosis has also been linked to autoantibodies to GMCSF. As the techniques are refined further, we may find antibodies to other cytokines as well. It is now possible to rapidly study the presence of multiple auto antibodies to various cytokines using automation employing chemiluminescence assays. Further, this area will open up the flood gates of knowledge regarding protective mechanisms involved in these pathogens. Brown et al. elegantly elucidated the role of anti-cytokine antibodies in health and disease and how they can “provide an insight into biology of immunity, infection and inflammation”. As new information is unfolding in this area, India should also conduct multicentre studies in patients with atypical pathogens enumerated above as observations are likely to have sinister therapeutic and epidemiological implications.

References

13. Fieschi C, Dupuis S, Picard C, Smith CI, Holland SM,


How to cite this article: Sehgal S, Suri D. Paradox of autoantibodies and immune deficiency: Interferon gamma antibodies and susceptibility to intracellular pathogens. Indian J Med Microbiol 2015;33:473-6.