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Persistent bacterial infections and primary immune disorders

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Mycobacteria, *Salmonella* and *Helicobacter* species have all evolved mechanisms to evade host defenses and cause persistent infection in humans. Host control of mycobacteria and *Salmonella* is largely achieved by the IFN- γ /IL-12 pathway. Immune disorders affecting this pathway are characterized by disseminated infections with environmental or nontuberculous mycobacteria. *Helicobacter* is a predominantly extracellular bacterium that uses its remarkable genetic diversity (as well as other mechanisms) in order to evade host defenses. The importance of humoral immunity in containing *Helicobacter* infections to the mucosal surface is illustrated by the primary immune disorder, X-linked agammaglobulinemia in which patients are prone to chronic bacteremia and skin infections by *Helicobacter* and related species such as *Flexispira* and *Campylobacter*. Exploration of these particular infections in their specific immune defects sheds light on both host and bacterial mechanisms that have implications for pathogenesis and therapy.

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Introduction

In the majority of bacterial infections there is an interaction between the host immune system and the invading bacteria, and the bacteria are excluded or eradicated. Many of these infections are subclinical and no antimicrobials are warranted. Occasionally, the infection progresses to the point of clinical symptoms, and antibiotics might be given to assist in bacterial clearance. However, certain bacteria might persist in small numbers, often without overt symptoms. Here, we discuss some of the host and bacterial mechanisms behind persistent bacterial infections, as well as immune disorders that are associated with clinically apparent persistent infections. We focus on persistent bacterial infections with intracellular mycobacteria and *Salmonella* and the predominantly extracellular

Helicobacter and *Helicobacter*-like species. We also review some of the associated primary immune disorders.

Mycobacteria and *Salmonella* infections

The most famous of persistent bacterial infections is tuberculosis. *Mycobacterium tuberculosis* is estimated to infect one-third of the world's population. However, only a small portion of these individuals will develop clinically apparent illness. In the vast majority of humans, *M. tuberculosis* will remain latent for the life of the host, as it has evolved mechanisms to survive within macrophages, in part through altering the phagosomal maturation process and evading the bactericidal pathways of activated macrophages. The mycobacterial genes behind these mechanisms remain poorly understood. Using a method called transposon site hybridization (TraSH), mutagenesis and microarrays are combined to detect *M. tuberculosis* mutants that do not survive in murine macrophages [1^{*}]. Several pathways have been identified that appear to enable survival in macrophages, including those involved in phosphate transport (potentially to enable mycobacteria to survive in phosphate-limited phagosomes), lipid degradation, and mechanisms of facilitated bacterial transport across host membranes. The ability to metabolize fatty acids appears to be essential for persistent infection in murine tuberculosis models; deletion of the fatty acid catabolism genes *icl1* and *icl2* together (both encoding isocitrate lyases) results in the inability of *M. tuberculosis* to survive in macrophages and enables subsequent clearance from the lungs [2].

The exact mechanisms behind the switch from latent to active infection in tuberculosis remain poorly understood. The host immune response inhibits tuberculosis replication through lymphocyte secretion of tumor necrosis factor (TNF)- α and interferon (IFN)- γ to activate macrophages, and through secretion of TNF- α , interleukin (IL)-18 and IL-23 by the activated macrophage [3,4]. Activated macrophages also secrete IL-12, and in a mouse model, continuous IL-12 production was necessary to maintain CD4⁺ T-cell IFN- γ synthesis and prevent reactivation of disease [5]. There is a possible role for the immunosuppressive cytokine IL-10 in triggering reactivation of disease [6]. The mechanisms behind mycobacterial persistent infection and reactivation remain an area of active research with profound implications for etiology, pathogenesis and therapy.

Certain *Salmonella* species, typically *Salmonella enterica* serovar Typhi, might persist intracellularly for years with periods of reactivation in apparently immunocompetent individuals. After invasion of intestinal M cells in Peyer's

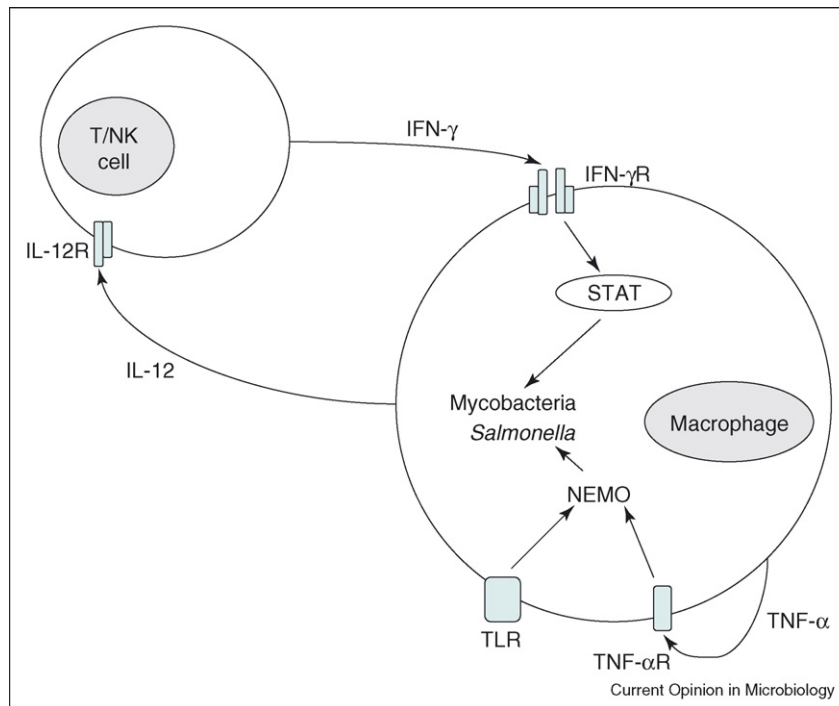
patches, *Salmonella* typically are phagocytosed by macrophages and taken to mesenteric lymph nodes, spleen, bone marrow, liver and gallbladder where they are able to persist [4]. Largely through study of mouse models of infection with *S. enterica* serovar Typhimurium, which closely resembles that of *S. typhi* in humans, bacterial virulence factors have been identified that enable *Salmonella* to persist in macrophages [4,7,8[•],9,10]. Through a genome-wide screen, it was found that many of the genes that appear to enable persistence of infection are within *Salmonella* pathogenicity islands (SPIs) 1 and 2 [8[•]]. SPI genes have been implicated in the ability of *Salmonella* to persist in macrophage vacuoles because of their inhibition of host defenses, such as the phagocyte NADPH oxidase [10]. Other important *Salmonella* genes identified in mouse infection are *mig-14* and *virK*, which code for proteins that give the bacteria resistance to mammalian host factors such as cathelicin-related antimicrobial protein (CRAMP) in activated macrophages [7]. Host control of persistent infection appears to be controlled largely by IFN- γ and TNF- α ; suppression of either of these host defenses leads to reactivation or worsening of infection [9,11].

Although both tuberculosis and *Salmonella* are able to cause persistent and even occasionally disseminated infection in apparently immunocompetent individuals,

the nontuberculous mycobacteria are far less virulent, and disseminated disease is typically associated with immune defects. Delineation of these immune defects has advanced understanding of the interactions between host and intracellular bacteria. These immune disorders are generally characterized by the inability to produce or respond to IFN- γ . We will briefly summarize the normal immune response to intracellular bacterial infection and then discuss several of the immune disorders characterized by disseminated mycobacterial and *Salmonella* disease.

Multiple defects along the IFN- γ /IL-12 pathway have been described and result in persistent, disseminated and often fatal infection with mycobacteria and occasionally *Salmonella* (Figure 1, Table 1) [12[•]]. Normally, antigen-presenting cells such as macrophages secrete IL-12 after stimulation especially during intracellular infection with agents such as mycobacteria and *Salmonella*. IL-12 binds to its receptor on natural killer (NK) cells and activated T cells, which induces the production of IFN- γ . IFN- γ binds to its heterodimeric receptor (IFN- γ R1 and IFN- γ R2) on macrophages. Macrophage activation and subsequent killing of intracellular bacteria depends in part on the JAK-STAT (Janus kinases and signal transducers and activators of transcription) signaling pathway.

Figure 1



IFN- γ /IL-12 pathway. Intracellular infection with organisms such as mycobacteria and *Salmonella* result in IL-12 secretion by macrophages. IL-12 binds to its receptor on activated T-cells and NK cells, resulting in IFN- γ secretion. IFN- γ binds to its heterodimeric receptor on macrophages, which utilizes a JAK-STAT pathway for intracellular killing. Signal transduction through Toll-like receptors (TLR) and TNF- α receptors leads to activation of NF- κ B through NEMO, resulting in macrophage activation.

Table 1

Immune disorders associated with persistent bacterial infections.			
Immunodeficiency	Inheritance	Typical infection susceptibility	Associated features
IFN- γ R1 or R2 deficiency	Autosomal recessive or dominant	Disseminated mycobacteria, <i>Salmonella</i>	
NF- κ B essential modulator deficiency (NEMO)	X-linked	Disseminated mycobacteria, <i>Salmonella</i> , viruses, pneumocystis	Ectodermal dysplasia
Anti-IFN- γ autoantibodies	Unknown; adult onset	Disseminated mycobacteria	Other autoantibodies? Higher incidence in women?
X-linked agammaglobulinemia	X-linked	Bacterial including <i>Helicobacter</i> , <i>Flexispira</i> , <i>Campylobacter</i> , Enterovirus	Chronic skin ulcers/cellulitis with <i>Helicobacter</i> , <i>Flexispira</i> and <i>Campylobacter</i>

IFN- γ receptor deficiency

Both recessive and dominant forms of IFN- γ R1 deficiency have been described, with high allelic heterogeneity: only three mutations in R2 have been reported [13–16]. Clinical features of 22 patients with recessive complete IFN- γ R1 deficiency compared to 38 patients with dominant partial IFN- γ R1 deficiency showed tight correlation between genotype and clinical phenotype (Table 2) [14]. Mycobacterial disease was seen in 95% of the patients, with *Mycobacterium avium* complex infection occurring most frequently. Other mycobacteria that were detected included Bacillus of Calmette and Guérin (BCG), *Mycobacterium kansasii*, rapid growing mycobacteria and *M. tuberculosis* complex (in 3% overall). Compared to those with dominant disease, those with recessive disease had a younger mean age of onset of mycobacterial disease (3.1 years for recessive versus 13.4 years for dominant), more persistent disease despite antibiotics with frequent relapses observed, more organs infected with mycobacteria, and a higher incidence of death in childhood (55% before age 10 years). Isolated mycobacterial osteomyelitis was seen exclusively in those with dominant disease, although osteomyelitis in the setting of widespread disease was also seen in those with

recessive disease. Interestingly, BCG vaccination delayed the onset of environmental nontuberculous mycobacterial disease in all patients; however, all recessive and most dominant patients who developed BCG infection received antibiotic therapy that might have postponed the onset of environmental nontuberculous mycobacterial disease. Other serious infections described infrequently in IFN- γ R deficiency include: salmonellosis, disseminated histoplasmosis, listeriosis and disseminated herpesvirus infections, such as by cytomegalovirus [14,15,17,18].

NEMO

Patients with hypomorphic mutations in the nuclear factor- κ B essential modulator (NEMO), a molecule required for NF- κ B activation and translocation, exhibit X-linked susceptibility to mycobacteria and other infections. At least 36 patients have been described with 28 different mutations, but many more are unreported [19^{*}]. Most of the initial patients reported with NEMO mutations have had some degree of ectodermal dysplasia associated with their immunodeficiency, leading to the name ectodermal dysplasia associated with immune deficiency (EDA-ID). Because activation of the NF- κ B

Table 2

Recessive vs dominant IFN- γ R1 deficiency ^a .			
Disease characteristics	Recessive complete IFN- γ R1 deficiency	Dominant partial IFN- γ R1 deficiency	P
Mean age of onset (SD) of environmental mycobacterial disease	3.1 (\pm 2.5) years	13.4 (\pm 14.3) years	0.001
Adult onset of first environmental mycobacterial infection	No	Yes	
Environmental mycobacterial disease	17 of 22 (77%)	30 of 38 (79%)	0.88
Incidence of environmental mycobacterial disease (episodes per 100 persons-years observation)	19	8	0.001
Rapid grower mycobacterial infection	7 of 22 (32%)	1 of 38 (3%)	0.002
BCG disease among vaccinated patients	9 of 9 (100%)	11 of 15 (73%)	0.26
Death from mycobacterial disease during first recognized mycobacterial infection	7 of 22 (33%)	1 of 38 (3%)	0.002
<i>Salmonella</i> infection	3 of 22 (14%)	2 of 38 (5%)	0.26
HHV-8 infection Kaposi's sarcoma) or Cytomegalovirus infection	4 of 22 (18%)	0	<0.05

^a The data for this table was compiled from a study of 22 patients with recessive and 38 with dominant mutations [14].

signaling pathway is essential for antibody class switch recombination, NEMO can cause one of the hyper-IgM syndromes [20]. However, mutations in NEMO show large variations in the degree of immunoglobulin abnormalities and ectodermal dysplasia [19[•]]. Two types of mutations and their immunologic phenotypes were recently described [19[•],21]. Mutations in the leucine zipper of NEMO lead to delayed nuclear accumulation of NF- κ B and c-Rel in response to CD40 signaling, resulting in impaired IL-12 production and thus, decreased IFN- γ production by T-cells [19[•]]. Mutations in the NEMO zinc finger region lead to NEMO not being properly ubiquitinated, resulting in no c-Rel activity and thus no c-Rel-dependent IL-12 production, again causing diminished IFN- γ production [21].

Patients with NEMO mutations have increased susceptibility to mycobacterial infections and a wide range of other pathogens including Gram-positive and Gram-negative bacteria, fungi (including *Pneumocystis*) and viruses [19[•],22]. Features of ectodermal dysplasia that are often present but in varying degrees include conical teeth, sparse hair, aberrant hair whorls and decreased or absent sweat production. Mortality is high in some series. Mycobacterial infection might be especially tenacious.

Acquired IFN- γ deficiency

Disseminated mycobacterial disease has been associated with high-titer anti-IFN- γ autoantibodies. These patients have been predominantly of East Asian descent, and the majority have been women [23–25,26[•]]. The reported individuals all presented with mycobacterial disease in their adult years, and most were previously healthy. Despite combination antimicrobial therapy and in some instances IFN- γ therapy, some of these infections have been persistent. Associations with other autoantibodies and cutaneous manifestations, such as Sweet's syndrome, have been variable.

Therapy

The mainstay of therapy of patients with persistent mycobacterial infection is aggressive, long-term antibiotic therapy. IFN- γ therapy has been effectively used to augment antibiotic therapy in patients with partial IFN- γ R activity, and NEMO [14,27]. Patients with IFN- γ R recessive disease typically do not respond to IFN- γ therapy, are very difficult to treat, and bone marrow transplantation has been used with variable success [15].

Helicobacter and *Helicobacter*-like organisms

Similar to tuberculosis, *Helicobacter pylori* infection persists in many immunocompetent individuals for many years; however, both the bacterial mechanisms of persistence, as well as the immune responses, are very different for this predominantly extracellular pathogen than those for intracellular organisms such as the mycobacteria and *Salmonella*. In immunocompetent individuals, *H. pylori*

remains a superficial chronic gastritis, with a small percentage of individuals progressing to duodenal or peptic ulcers and rarely to gastrointestinal malignancies. In the primary immune disorder Bruton's X-linked agammaglobulinemia (XLA; resulting from a mutation in Bruton's tyrosine kinase), *Helicobacter* and the closely related species *Flexispira* and *Campylobacter* can cause persistent bacteremia, as well as skin and bone infections [28–30].

H. pylori survives through numerous mechanisms aimed at adapting to the host immune response as well as to the gastric environment. *H. pylori* has remarkable genetic diversity and is thought to be the most genetically diverse bacterial species [31[•]]. There are many theories of how this vast genetic variation might contribute to the ability of *H. pylori* to evade host immunity. Through variation of epitopes, *H. pylori* is able to evade humoral immune responses: through the alteration of outer membrane proteins, adhesion to various cellular receptors can be varied. *Helicobacter* is also able to modulate the expression of virulence factors [31[•],32].

Despite the fact that *H. pylori* infection typically elicits vigorous chronic inflammation, characterized by neutrophils, plasma cells, lymphocytes and macrophages, it has evolved mechanisms to persist in this milieu. *H. pylori* expresses flagellin proteins that are not recognized by TLR-5, the Toll-like receptor that typically responds to bacterial flagellin [33]. *H. pylori* evades extracellular superoxide and hydrogen peroxide produced by phagocytes through expression of catalase and superoxide dismutase. It diminishes nitric oxide production derived from the substrate L-arginine by producing its own arginase [4,31[•],34]. *H. pylori* weakens host lymphocyte proliferation and cytokine production by inducing an increased number of CD4⁺ CD25^{high} FOXP3⁺ regulatory T-cells in *H. pylori*-infected gastric mucosa. *H. pylori* also secretes vacuolating toxin (VacA), which inhibits T-cell proliferation [35,36]. In addition, *H. pylori* appears to use some aspects of the host response to its benefit. For instance, anti-*H. pylori* IgA antibodies in a mouse model appear to promote, rather than prevent infection and *H. pylori* seems to take advantage of nutrients released through inflammation-mediated damage to the gastric mucosa [31[•],37].

Patients with XLA are susceptible to infections with *Helicobacter*, *Campylobacter* and *Flexispira* (Table 1) [28–30]. These infections typically present in a subacute or chronic manner with recurrent episodes of cellulitis or ulcers of the lower extremities often associated with fever; arthritis and osteomyelitis have been described as well. Patients are typically bacteremic with these organisms, although the bacteria might be very difficult to grow in culture. Treatment is difficult and many patients remain persistently bacteremic if only treated with short courses of antibiotics; sterilization of the blood

and resolution of symptoms typically requires prolonged combination intravenous antibiotics. Because, in XLA, T-cell function is reportedly normal and B-cells are absent, the predisposition to bacteremia with organisms that are typically confined to gastrointestinal mucosal surfaces indicates a crucial role for humoral immunity. This is further emphasized by the fact that patients with XLA are particularly susceptible to enteric infections. Interestingly, these same organisms are also occasional problems in HIV infected patients.

Conclusion

Persistent bacterial infections in immunocompetent hosts are characterized by a balance between mechanisms the bacterium has evolved to survive, and host defenses evolved to keep the infection localized. *M. tuberculosis* and *Salmonella* are both able to persist intracellularly and asymptotically but might re-activate and cause disseminated infection. Through understanding the pathogenesis of primary immune disorders that are characterized by disseminated mycobacteria and *Salmonella* infections, we have learned the importance of the IFN- γ and IL-12, and the NEMO pathways in controlling these infections. *Helicobacter* and related species are predominantly extracellular bacteria that cause primarily asymptomatic mucosal infections but, in the primary immune deficiency XLA, can lead to bacteremia and extensive skin, bone and joint involvement, demonstrating the necessity of the humoral response. Through understanding the mechanisms that the host and the bacteria use in order to repress and maintain persistent infections we will discover new ways to treat and resist these common infections.

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