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Acquired and genetic host susceptibility factors and microbial pathogenic factors that predispose to nontuberculous mycobacterial infections

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Nontuberculous mycobacteria (NTM) are ubiquitous in the environment and human exposure is likely to be pervasive; yet, the occurrence of NTM-related diseases is relatively infrequent. This discrepancy suggests that host risk factors play an integral role in vulnerability to NTM infections. Isolated NTM lung disease (NTM-LD) is often due to underlying anatomical pulmonary or immune disorders, either of which may be acquired or genetic. However, many cases of NTM-LD have no known underlying risk factors and may be multigenic and/or multicausative. In contrast, extrapulmonary visceral or disseminated NTM diseases almost always have an underlying severe immunodeficiency, which may also be acquired or genetic. NTM cell wall components play a key role in pathogenesis and as inducers of the host immune response.

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Introduction

Nontuberculous mycobacteria (NTM) are environmental organisms commonly found in soil and water biofilms. Despite the ubiquitous presence of NTM in both natural and man-made niches and the plausible premise that human exposure to NTM is pervasive, the prevalence of NTM infections is fairly infrequent, suggesting that NTM possess low to moderate pathogenicity and that host risk factors play an integral role in vulnerability to NTM disease. Nevertheless, the incidence of NTM infection is increasing rapidly and now surpasses tuberculosis in resource-rich countries, making it imperative that we better understand why some individuals are susceptible to NTM infection. NTM lung disease (NTM-LD) typically occurs in the setting of pre-existing structural lung disease, most often emphysema or bronchiectasis, which may be acquired or the result of genetic disorders. In contrast, extrapulmonary visceral organ/disseminated infections almost always occur in individuals with frank immunocompromised states, which are also acquired or genetic. This review focuses on acquired and genetic host susceptibility factors to these two forms of NTM infections; in addition, we highlight NTM-derived components that contribute to disease pathogenesis or are exploited by the host to mount an effective immune response.

Acquired and classical genetic disorders that predispose to NTM-LD

Acquired and genetic disorders that predispose to NTM-LD can be broadly classified into those that result in anatomic lung abnormalities or immune dysfunction. Acquired disorders include tobacco-related emphysema, bronchiectasis as a sequela of prior unrelated infections, silicosis, chronic aspiration, and use of corticosteroids or other immunosuppressives such as TNFα antagonists [1–3]. A case–control study found that emphysema, prior hospitalization for pneumonia, thoracic skeletal abnormalities, low body mass index, and corticosteroid and/or immunomodulatory drug usage were each found to be significantly associated with *Mycobacterium avium* complex lung disease [1].

In terms of genetic disorders, cystic fibrosis (CF) is the best known genetic risk factor for NTM-LD [4•]. Susceptibility factors include the presence of pre-existing bronchiectasis, inspissated secretions, and corticosteroid use. While the intrinsic chloride channel defect may play a role in host susceptibility to NTM, a whole exome sequencing study of patients with NTM-LD and their family members indicated that variants of the *CF transmembrane conductance regulator* (*CFTR*) gene were more common in unaffected family members than patients with NTM-LD [5••]. Other classical genetic disorders

include primary ciliary dyskinesia, due to a defect in one of several cilia genes that encode microtubule and dynein arm proteins, resulting in ciliary dysfunction, decreased ability to clear airway infections and mucus, and a vicious cycle of airway inflammation, infection, and mucostasis, the denouement of which is bronchiectasis and recurrent infections including NTM [6•]. Alpha-1-antitrypsin (AAT) deficiency predisposes to emphysema, but bronchiectasis is also a known complication [7]. We previously reported that the presence of AAT anomalies — mostly heterozygous — were more common in patients with NTM-LD compared to the general U.S. population [8]. AAT deficiency may also compromise the ability of macrophages to control NTM infections [9]. Tracheobronchomegaly (Mounier–Kuhn syndrome) may be congenital, acquired, or may be secondary to other primary disorders [10,11]. Pathogenesis of the congenital form is due to atrophy or absence of elastic fibers and smooth muscle tissues of the large airways, resulting in gross enlargement of the trachea and main bronchi as well as airway wall diverticulae, which can serve as reservoirs for recurrent infections including NTM-LD. Pulmonary alveolar proteinosis (PAP) is characterized by diffuse accumulation of amorphous, lipoproteinaceous material in the distal air spaces. Congenital PAP is due to mutation of genes that encode α-subunit or β_c-subunit of GM-CSF receptor, or surfactant protein-B. The acquired form of PAP is primarily due to the presence of auto-antibodies to GM-CSF. Functional deficiency of the GM-CSF protein or signaling impairs surfactant disposal by lung macrophages and leads to the accumulation of surfactant in the alveolar spaces and intracellularly in phagocytes; the latter process further compromises both macrophage function and activation of adaptive immunity, and predisposes to opportunistic infections including NTM [12]. The underlying B and T cell defects observed with CVID can lead to recurrent airway infections and bronchiectasis, the latter a prime substrate for NTM infection [13].

NTM-LD due to more recently identified genetic factors

The occurrence of NTM-LD in individuals without any of the aforementioned risk factors is well recognized [14,15]. A significant fraction of such patients possess a life-long asthenic body habitus with thoracic cage abnormalities such as pectus excavatum and scoliosis, leading to the notion that an underlying connective tissue disorder predisposes to NTM-LD [15–18]. Reduced body fat in itself is a risk factor for NTM-LD [17–20]. A mechanism by which low body fat content predisposes to NTM-LD is relative deficiency of the fat-derived, satiety hormone leptin, which also drives the differentiation of uncommitted T_0 cells toward the T_H1, IFNγ-producing phenotype [21]. In corroboration, leptin-deficient mice are more susceptible to *Mycobacterium abscessus* lung infection [22]. Moreover, NTM-LD patients have reduced serum leptin levels [23], a loss in the normal direct relationship between serum leptin concentration and total body fat [17], and reduced IFNγ production by their immune cells [17,24•,25•,26].

A whole exome sequencing (WES) study of 15 NTM-LD patients with more than one family member with NTM-LD, 18 unaffected family members, and 54 patients with sporadic NTM-LD demonstrated that possessing variants of several genes in the immune, connective tissue, ciliary, and CFTR categories — 'multigenic' etiology as opposed to mutation of one dominant gene — additively increases vulnerability to NTM-LD [5••]. In another study, WES of 11 NTM-LD subjects with slender body habitus, pectus excavatum, and scoliosis identified four (two being sisters) subjects with heterozygous mutations of the *Macrophage-stimulating-1 Receptor* (*MST1R*) gene [24•]. MST1R is a tyrosine kinase receptor important for normal movement of cilia present on cells lining the luminal surface of fallopian tubes and airways [27]. These findings are consistent with previous work showing reduced ciliary beat frequency in the nasal epithelium as well as reduced nasal nitric oxide in NTM-LD patients compared to controls [28]. *Ex vivo* NTM infection of primary human bronchial epithelial cells decreased the expression of genes that encode for ciliary proteins as well as reduced the number of ciliated cells [29•]. In other words, pre-existing ciliary defects predispose to NTM and NTM infection itself may, in turn, adversely affect ciliary function [30].

The reason why NTM-LD appears to be more common in post-menopausal women is not known but is likely to be multifactorial, including the acquisition of other risk factors with aging (*e.g.* reduction in body fat, vitamin D level, and/or sex hormones, and cumulative exposure to environmental NTM) — resulting in a 'tipping point' where NTM-LD develops, analogous to the aphorism 'the straw that broke the camel's back' (Figure 1). This metaphor also serves as a reminder to clinicians to eliminate as many risk factors as possible to reduce the burden of NTM-LD.

Acquired and genetic disorders that predispose to extrapulmonary visceral organ and disseminated NTM infections

Acquired disorders that cause profound immunodeficiency and therefore increase susceptibility to extrapulmonary visceral/disseminated NTM disease include untreated AIDS, presence of anti-IFNγ autoantibodies, and the use of chemotherapeutics to treat cancer, potent immunosuppressives to prevent rejection after organ transplantation, and TNFα antagonists or other novel biologic agents to remedy inflammatory conditions [31•,32,33]. There is likely a genetic component to those with anti-IFNγ antibodies as this syndrome appears to be more common in Asians and in those with HLA DRB16:02 or DRB05:02 [31•]. In contrast, occurrence

Figure 1

Cartoon metaphor to illustrate that multiple factors contribute to the denouement of NTM-LD. Accumulation of multiple risk factors — for example, behaviors of humans and environmental factors that increase exposure to NTM, host genetic susceptibility factors, acquired risk factors, and other factors associated with aging — all unite to increase one's overall risk for developing NTM-LD. In this diagram, yellow 'bales of straw' are used to depict the multiple risk factors and that one additional risk factor — shown by the single, yellow falling straw — is enough to result in NTM-LD; that is, 'the straw that broke the camel's back.' This metaphor is a reminder that ways to minimize any risk factors — no matter how trifle it may seem — can be potentially beneficial.

of systemic NTM infections in very young individuals — often infants — suggests mutations in genes that are components of the IFNγ-IL-12 axes and other immune related genes that fall under the rubric of Mendelian Susceptibility to Mycobacterial Diseases (MSMD) [34–36]. MSDS disorders that have been linked to NTM disease, their mode of inheritance, the major clinical presentations, and diagnostic tests are listed in Table 1 and previously reviewed [37].

While only three cases of NTM infections in chronic granulomatous disease (CGD) patients have been reported in the literature, the unusual and extrapulmonary involvement in these patients suggest that CGD is a predisposing condition for NTM infections [38]. While this observation would suggest that reactive oxygen species (ROS) is an important host-defense factor against NTM infections, we have found that inhibiting ROS with a superoxide dismutase mimetic actually improved macrophage killing of *M. abscessus* by promoting phagosome-lysosome fusion [39].

Over-exuberant host immunity in NTM-LD

An overexuberant host immune response may also play a part in the pathogenesis of NTM-LD. In response to NTM lung infection, the release of elastase and metalloproteinases by recruited neutrophils can cause damage to the airway epithelium by eroding mucosal barriers, resulting in NTM-containing microabscesses. Elastase may also cause ciliary dysfunction, mucous gland hyperplasia, and mucus hypersecretion that enhance NTM biofilm formation [40,41]. Elastase and other proteases also cleave Fcγ receptors and complement receptor 1 from neutrophil surfaces as well as digest immunoglobulins and complement components from mycobacterial surfaces. These activities impair opsonization of mycobacteria and reduce their recognition by neutrophils, leading to decreased phagocytosis and bacterial clearance [40]. Elastase also inhibits efferocytosis, impairing clearance of apoptotic neutrophils [40]. The unphagocytosed, dead neutrophils incite further inflammation and release highly viscous DNA, contributing to the formation of inspissated mucus that further impairs NTM clearance.

NTM components that induces pathogenesis and/or host immune response

The most widely recognized immune modulatory component of *Mycobacteria* is its waxy cell envelope that facilitates survival in the environment and provides protection against antibiotics and host immune defenses. Lipids of various composition comprise up to 60% of the mycobacterial cell envelope compared to 20% in Gram-negative bacteria [42]. NTM-derived lipids subvert the host immune responses by suppressing host-protective IFNγ and TNFα production (Figure 2) [43]. Moreover, incubation of human peripheral blood mononuclear cells (PBMC) with total lipids from *M. avium* increased both the secretion of immunosuppressive molecules such as prostaglandin E_2 by macrophages and the replication of intracellular NTM [44].

Mycobacterial glycopeptidolipids (GPL) are absent from *Mycobacterium tuberculosis* and *Mycobacterium leprae* but are produced solely by NTM (Figure 2) [45]. GPL are essential for both sliding motility and biofilm formation [46,47]. The two main classes of GPL are: first, apolar, non-specific GPL (nsGPL) produced by many NTM, particularly *M. abscessus* and second, polar, serovar-specific GPLs (ssGPL) produced by *M. avium* [48].

The composition and concentration of GPL vary among species and can impact colony morphology. The nsGPL found in the outer layer of the smooth morphotype of *M. abscessus* cloaks its phosphatidyl-myo-inositol mannoside residues located in the cell wall, thereby hindering recognition of this *M. abscessus* strain by TLR2-bearing immune cells [49]. As a result, *M. abscessus* smooth variants — which are typically found in the environment — infect susceptible hosts. For reasons not well understood, the rough

Table 1

Clues to the presence of an underlying genetic cause for extrapulmonary visceral/disseminated NTM disease.

Host gene abnormality (protein) Mode of inheritance	Relative age at presentation	Clues to presence of host risk factor	Diagnostic test(s)
***IFNGR1* mutations** (IFNγR1[a]) AR, PE–, complete[b] AR, PE+, complete AR, PE+, partial[b] AD, PE++, partial	Infants, young children	Disseminated NTM, BCG, and non-typhoidal Salmonella infections	Surface expression by flow cytometry; functional analysis of IFNγR[c]; gene sequencing
***IFNGR2* mutations** (IFNγR2) AR, PE–, complete AR, PE+, complete AR, PE+, partial AD, PE+, partial	Infants, young children	Disseminated NTM, BCG, and non-typhoidal Salmonella infections	As above
***IL12B* mutations** (IL-12p40 subunit[d]) AR, PE–, complete	Infants, young children	Disseminated NTM, BCG, and non-typhoidal Salmonella infections; mucocutaneous candidal infections[e]	Stimulate PBMC with mitogen ± IFNγ, measure IL-12; gene sequencing
***IL12RB1* mutations** (IL-12Rβ1 subunit[d]) AR, PE–, complete AR, PE+, complete AR, PE-, partial-severe	Infants, young children	Disseminated NTM, BCG, and non-typhoidal Salmonella infections; mucocutaneous candidal infections[e]	Surface expression by flow cytometry; functional testing of IL-12R[f]; gene sequencing
***STAT1* mutation** (Stat1α) AR, PE–, P–, B–, complete AR, PE+, P+, B+, partial AD, PE+, P–, B+, partial AD, PE+, P+, B–, partial	Infants, young children	Disseminated NTM, BCG, and non-typhoidal Salmonella infections	Functional analysis of Stat1α[g]; gene sequencing
***IKBKG* mutation** (NEMO, IKKγ) X-linked	Male children	Ectoderm developmental abnormalities, venous/lymphatic vasculature abnormalities, autoimmune/inflammatory conditions, and infections with bacteria, extrapulmonary NTM, viruses, and fungi	Functional analysis of NFκB[h]; gene sequencing
***GATA2* mutation** (GATA2) AD	Young child to older adults	Disseminated infection with NTM, fungus, or HPV. May be complicated by lymphedema, PAP, myelodysplasia, acute and chronic myeloid leukemia	Gene sequencing, cytopenias (monocytes, DC, B cells, NK cells); bone marrow shows hypocellularity, fibrosis, multilineage dysplasia, etc.
Anti-IFNγ autoantibody[i] Associated with DRB16:02 and DRB 05:02	More common in Asian adults	Extrapulmonary visceral/ disseminated infection with NTM, Salmonella, fungi, and cytomegalovirus, and varicella-zoster virus reactivation	Anti-IFNγ antibody testing by particle-based technology or ELISA

AD = autosomal dominant; AR = autosomal recessive; HPV = human papilloma virus; IFNγR1 = IFNγ receptor subunit 1; IFNγR2 = IFNγ receptor subunit 2; IL-12Rβ1 = IL-12 receptor subunit β1; NEMO = NFκB essential modulator (=IκBα kinase γ subunit, IKKγ), P = phosphorylation, PE = protein expression, B = DNA binding, PAP = pulmonary alveolar proteinosis. Adapted from [34].

[a] Autosomal dominant IFNγR1 deficiency lacks Jak1-binding and STAT1α binding domains and thus can bind IFNγ but cannot signal downstream. In such cases, there is expression of proteins on the cell membrane but the defective IFNγR1 accumulates and competes with functioning normally functioning IFNγR1. Most patients with complete autosomal recessive forms do not express IFNγR1 on the cell surface because of stop mutations in the extracellular domain.

[b] Complete and partial refers to signaling defect.

[c] Stimulation of PBMC with IFNγ and assaying for Stat1α phosphorylation.

[d] IL-12 is comprised of two subunits, IL-12p40 (*IL12B* gene) and IL-12p35 (*IL12A* gene). IL-12 receptor is comprised of two subunits, IL-12Rβ1 (*IL12RB1* gene) and IL-12Rβ2 (*IL12RB2* gene).

[e] While mutation is in the IL-12Rβ1 subunit, the susceptibility to mucosal fungal infections is due to defective IL-23 signaling, which is required to stimulate proliferation of T_H17 cells that are required for mucosal antifungal immunity, as IL-12 and IL-23 share the IL-12p40 subunit and IL-12R and IL-23R share the IL-12Rβ1 subunit.

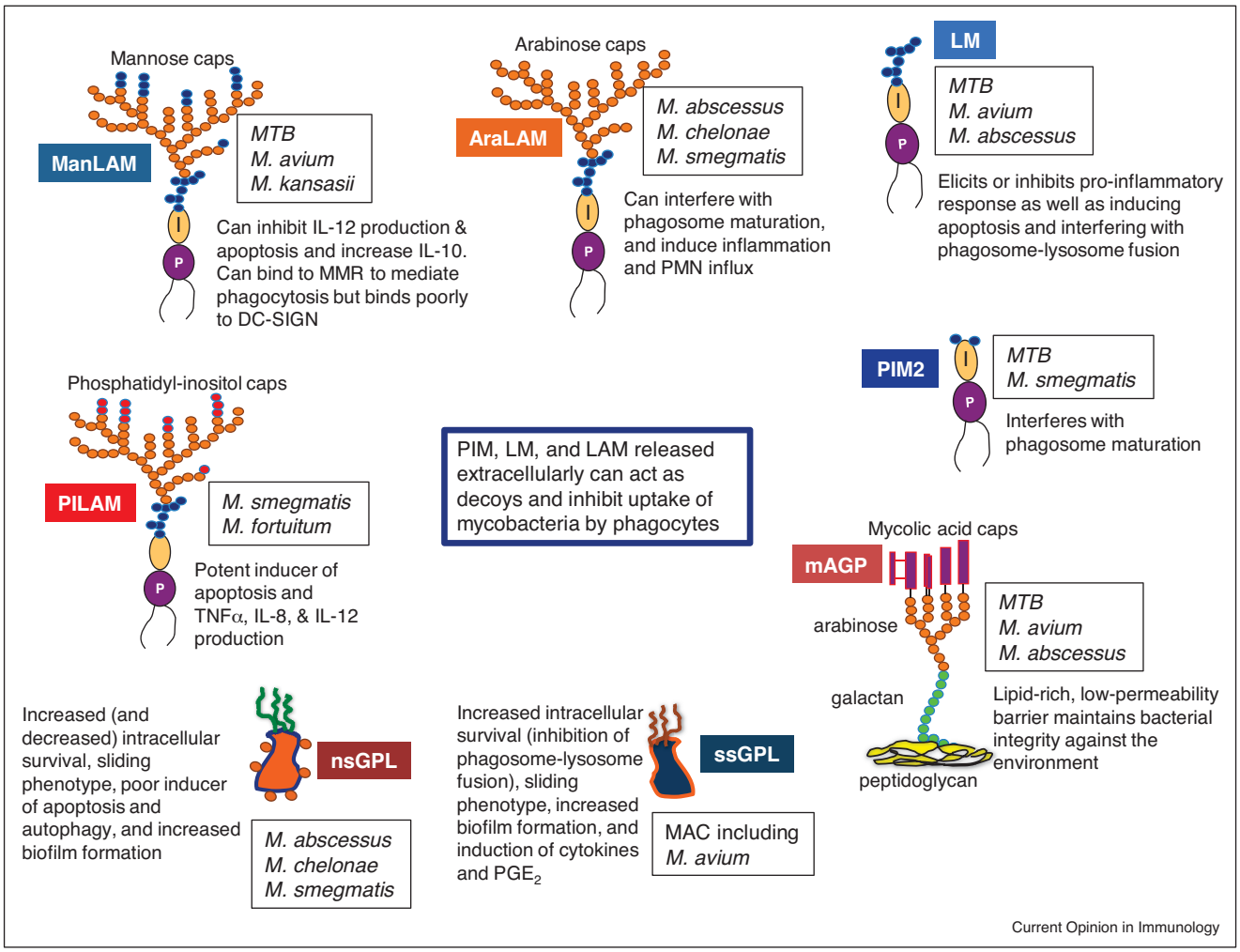
[f] Stimulation of PBMC with IL-12 and assaying for Stat4 phosphorylation.

[g] Stimulation of PBMC with IFNγ and assay for Stat1α phosphorylation and binding to the *cis*-GAS DNA sequence.

[h] Stimulation of PBMC with lipopolysaccharide or relevant cytokine and assay for NFκB binding to its cis-regulatory element.

[i] While anti-IFNγ antibody syndrome is considered acquired, it is associated with certain HLA genes.

Figure 2



Cartoon depicting some of the major glycolipids of *M. tuberculosis* and NTM. Included are the non-specific glycopeptidolipids (nsGPL) and serovar-specific GPL (ssGPL) that are present only on NTM. Some of the host immune effects of these different components are listed; as can be seen, a panoply and occasional opposing effects have been reported. While many of the components are found in both *M. tuberculosis* and NTM, most of the effects listed were studied with *M. tuberculosis* components; that is, except for the GPL, much fewer studies have been performed with glycolipids from NTM. AraLAM = arabinose-capped lipoarabinomannan, ManLAM = mannose-capped LAM, PILAM = phosphatidylinositol-capped LAM, LM = lipomannan, PIM2 = phosphatidylinositol dimannoside, mAGP = mycolic acid-arabinogalactan-peptidoglycan complex.

morphotype — which lacks nsGPL and is considered more virulent — emerges later, sometimes several years after the initial infection [50,51]. Human monocytes eradicated smooth *M. abscessus* whereas rough variants persisted and propagated in the intracellular phagosome [50]. Epidemiologic and clinical data also associate rough variants with more severe and persistent lung disease [52].

In contrast to the finding that the absence of nsGPL from *M. abscessus* facilitates intracellular survival, *M. avium* ssGPL is required for intracellular survival and impacts cytokine responses, suggesting that serovar oligosaccharides contribute to species-specific pathogenesis [53]. The immunomodulatory activities of *M. avium* ssGPL are varied and depend on the serovar from which it was extracted; for example, ssGPLs from *M. avium* serovar 1, 2, and 8 — which are different from the ssGPLs of serovars 4 or 20 — induce the production of TNFα and/or prostaglandin E_2 by human PBMC (Figure 2) [53,54]. ssGPL also promotes phagocytosis and inhibits phagosome–lysosome fusion [55]. However, neither *M. abscessus* nsGPL nor *M. avium* ssGPL contribute to resistance to the LL-37 antimicrobial peptide [55].

Other glycolipids including phosphatidylinositol (PI), lipomannan (LM), lipoarabinomannans (LAM), and the mycolic acid-arabinogalactan-peptidoglycan (mAGP) complex are ubiquitous mycobacterial lipids that provide

a barrier against toxic agents and also modulate host immune responses. Mycobacterial-derived PI plays important structural and physiological roles [56]. LM elicits a strong proinflammatory cytokine response, including IL-12 production, and apoptosis of macrophage cell lines [57]. LM from *M. chelonae*, *M. kansasii*, and *M. bovis* perform dual functions by both stimulating and inhibiting pro-inflammatory cytokine production in bone marrow-derived macrophages from MyD88-deficient and TLR-deficient mice [58]. Various forms of LAM have been described. ManLAM of pathogenic *M. tuberculosis*, *M. leprae*, and *M. avium* binds poorly to the pattern-recognition receptor DC-SIGN [59]. PILAM (LAM with phosphatidylinositol caps) of *M. fortuitum* and *M. smegmatis* induces the production of pro-inflammatory cytokines IL-12, TNFα, and IL-8 from differentiated THP-1 human macrophages [60]. AraLAM (LAM without caps) is found in *M. chelonae* and several other rapidly growing mycobacteria [61]. Purified AraLAM from *M. smegmatis* administered into the lungs of various genetically modified mice triggered — through TLR2 — an acute inflammatory response and neutrophil influx essential for *M. smegmatis* clearance [62].

New sequencing technologies are revolutionizing our ability to understand NTM pathogenesis. Whole genome sequencing and bioinformatic methodologies have been used to obtain information about NTM taxonomy, biology, and pathogenesis. For example, an *in silico* study identified mycobacterial genes from a novel clinical NTM organism including pathogenicity genes associated with cell wall integrity, resistance to host toxic compounds, and immune evasion. Similarly, hierarchical *in silico* approaches identified plasmids, virulence factors and resistance genes with potential as drug/vaccine targets [63]. Bioinformatic studies have also revealed deletions of *M. tuberculosis* virulence gene complexes including phospholipase C, phenolglycolipids, and the ESX secretion system in *Mycobacterium colombiense* [64••]. More provocative studies indicate *M. abscessus* has also incorporated phospholipase and transporter genes from distantly related environmental bacteria including other actinobacteria that may have important roles in organism virulence [65].

Conclusion

Patients with NTM-LD or extrapulmonary visceral/disseminated NTM disease each have a unique set of acquired and/or genetic risk factors. Other host factors such as low body fat as well as exposure to environmental sources of NTM coupled to host behaviors that increase exposure and acquisition of NTM infection play important roles in the pathogenesis of NTM disease. In addition, NTM virulence and immune evasive mechanisms — largely attributed to glycolipid cell wall components — play a crucial part in determining the development of *bona fide* NTM disease.

Conflict of interest statement

Nothing declared.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as

- • of special interest
- •• of outstanding interest

1. Dirac MA, Horan KL, Doody DR, Meschke JS, Park DR, Jackson LA, Weiss NS, Winthrop KL, Cangelosi GA: **Environment or host? A case–control study of risk factors for *Mycobacterium avium* complex lung disease**. *Am J Respir Crit Care Med* 2012, **186**:684-691.

2. Kim YM, Kim M, Kim SK, Park K, Jin S-H, Lee US, Kim Y, Chae GT, S-B Lee: **Mycobacterial infections in coal workers' pneumoconiosis patients in South Korea**. *Scand J Infect Dis* 2009, **41**:656-662.

3. Sonnenberg P, Murray J, Glynn JR, Thomas RG, Godfrey-Faussett P, Shearer S: **Risk factors for pulmonary disease due to culture-positive *M. tuberculosis* or non-tuberculous mycobacteria in South African gold miners**. *Eur Respir J* 2000, **15**:291-296.

4. • Martiniano SL, Nick JA, Daley CL: **Nontuberculous mycobacterial infections in cystic fibrosis**. *Clin Chest Med* 2016, **37**:83-96.
Comprehensive and authoritative review of NTM lung disease in the cystic fibrosis population.

5. •• Szymanski EP, Leung JM, Fowler CJ, Haney C, Hsu AP, Chen F, Duggal P, Oler AJ, McCormack R, Podack E *et al.*: **Pulmonary nontuberculous mycobacterial infection. A multisystem, multigenic disease**. *Am J Respir Crit Care Med* 2015, **192**:618-628.
A key study implicating that a combination of minor gene defects may collaborate to increase susceptibility to NTM lung disease in individuals without known risk factors.

6. • Damseh N, Quercia N, Rumman N, Dell SD, Kim RH: **Primary ciliary dyskinesia: mechanisms and management**. *Appl Clin Genet* 2017, **10**:67-74.
A current and concise review of the clinical, diagnostic, and genetic aspects of primary ciliary dyskinesia.

7. Parr DG, Guest PG, Reynolds JH, Dowson LJ, Stockley RA: **Prevalence and impact of bronchiectasis in A1-antitrypsin deficiency**. *Am J Respir Crit Care Med* 2007, **176**:1215-1221.

8. Chan ED, Kaminska AM, Gill W, Chmura K, Feldman NE, Bai X, Floyd CM, Fulton KE, Huitt GA, Strand MJ *et al.*: **Alpha-1-antitrypsin (AAT) anomalies are associated with lung disease due to rapidly growing mycobacteria and AAT inhibits *Mycobacterium abscessus* infection of macrophages**. *Scand J Infect Dis* 2007, **39**:690-696.

9. Chan ED, Bai A, Eichstaedt C, Hamzeh NY, Harbeck R, Honda JR, Frazer-Abel A, Kosmider B, Sandhaus RA, Bai X: **Alpha-1-antitrypsin increases autophagosome number and production of host-protective cytokines in *Mycobacterium* intracellular-infected macrophages**. *Am J Respir Crit Care Med* 2017, **195**: A2906.

10. Krustins E: **Mounier–Kuhn syndrome: a systematic analysis of 128 cases published within last 25 years**. *Clin Respir J* 2016, **10**:3-10.

11. Payandeh J, McGillivray B, McCauley G, Wilcox P, Swiston JR, Lehman A: **A clinical classification scheme for tracheobronchomegaly (Mounier–Kuhn syndrome)**. *Lung* 2015, **193**:815-822.

12. Abdul-Rahman JA, Moodley YP, Phillips MJ: **Pulmonary alveolar proteinosis associated with psoriasis and complicated by mycobacterial infection: successful treatment with granulocyte–macrophage colony stimulating factor after a partial response to whole lung lavage**. *Respirology* 2004, **9**:419-422.

13. Arora R, Hagan L, Conger NG: ***Mycobacterium simiae* infection in a patient with common variable immunodeficiency**. *J Allergy Clin Immunol* 2004, **113**:S123.

14. Griffith DE, Girard WM, Wallace RJ: **Clinical features of pulmonary disease caused by rapidly growing mycobacteria: an analysis of 154 patients**. *Am Rev Respir Dis* 1993, **147**:1271-1278.

15. Okumura M, Iwai K, Ogata H, Ueyama M, Kubota M, Aoki M, Kokuto H, Tadokoro E, Uchiyama T, Saotome M *et al.*: **Clinical factors on cavitary and nodular bronchiectatic types in pulmonary *Mycobacterium avium* complex disease**. *Intern Med* 2008, **47**:1465-1472.

16. Iseman MD, Buschman DL, Ackerson LM: ***Pectus excavatum* and scoliosis. Thoracic anomalies associated with pulmonary disease caused by *Mycobacterium avium* complex**. *Am Rev Respir Dis* 1991, **144**:914-916.

17. Kartalija M, Ovrutsky AR, Bryan CL, Pott GB, Fantuzzi G, Thomas J, Strand MS, Bai X, Ramamoorthy R, Rothman MS *et al.*: **Patients with non-tuberculous mycobacterial lung disease exhibit unique body and immune phenotypes**. *Am J Respir Crit Care Med* 2012, **187**:197-205.

18. Kim RD, Greenberg DE, Ehrmantraut ME, Guide SV, Ding L, Shea Y, Brown MR, Chernick M, Steagall WK, Glasgow CG *et al.*: **Pulmonary nontuberculous mycobacterial disease: prospective study of a distinct preexisting syndrome**. *Am J Respir Crit Care Med* 2008, **178**:1066-1074.

19. Chan ED, Iseman MD: **Slender, older women appear to be more susceptible to nontuberculous mycobacterial lung disease**. *Gend Med* 2010, **7**:5-18.

20. Wakamatsu K, Nagata N, Maki S, Omori H, Kumazoe H, Ueno K, Matsunaga Y, Hara M, Takakura K, Fukumoto N *et al.*: **Patients with MAC lung disease have a low visceral fat area and low nutrient intake**. *Pulm Med* 2015, **2015**:218253.

21. Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, Lechler RI: **Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression**. *Nature* 1998, **394**:897-901.

22. Ordway D, Henao-Tamayo M, Smith E, Shanley C, Harton M, Troudt JL, Bai X, Basaraba RJ, Orme IM, Chan ED: **Animal model of *Mycobacterium abscessus* lung infection**. *J Leukoc Biol* 2008, **83**:1502-1511.

23. Tasaka S, Hasegawa N, Nishimura T, Yamasawa W, Kamata H, Shinoda H, Kimizuka Y, Fujiwara H, Hirose H, Ishizaka A: **Elevated serum adiponectin level in patients with *Mycobacterium avium*-intracellular complex pulmonary disease**. *Respiration* 2010, **79**:383-387.

24. • Becker K, Arts P, Jaeger M, Plantinga T, Gilissen C, van Laarhoven A, van Ingen J, Veltman J, Joosten L, Hoischen A *et al.*: **MST1R mutation as a genetic cause of Lady Windermere syndrome**. *Eur Respir J* 2017, **49**:1601478.

Whole exome sequencing of 11 individuals with a body phenotype characterized by aesthenic body habitus, scoliosis, pectus excavatum revealed four with variants of the MST1R mutation — a gene that normally encodes a tyrosine kinase receptor that augments ciliary beat frequency in airway epithelial cells.

25. • Cowman SA, Jacob J, Hansell DM, Kelleher P, Wilson R, Cookson WOC, Moffatt MF, Loebinger MR: **Whole blood gene expression in pulmonary non-tuberculous mycobacterial infection**. *Am J Respir Cell Mol Biol* 2018, **58**:510-518.

Gene expression profile of the blood of patients with NTM lung disease and control subjects revealed downregulated genes in the NTM infected individuals were enriched for T cell signaling and interferon-gamma expression. This study supports others showing that while patients with isolated NTM lung disease do not have profound defect of IFNγ-interleukin 12 signaling/production, they may have partial reduction in IFNγ, predisposing them to NTM lung disease if additional risk factors are present.

26. Vankayalapati R, Wizel B, Samten B, Griffith DE, Shams H, Galland MR, Von Reyn CF, Girard WM, Wallace RJ, Barnes PF: **Cytokine profiles in immunocompetent persons infected with *Mycobacterium avium* complex**. *J Infect Dis* 2001, **183**:478-484.

27. Sakamoto O, Iwama A, Amitani R, Takehara T, Yamaguchi N, Yamamoto T, Masuyama K, Yamanaka T, Ando M, Suda T: **Role of macrophage-stimulating protein and its receptor, RON tyrosine kinase, in ciliary motility**. *J Clin Invest* 1997, **99**:701-709.

28. Fowler CJ, Olivier KN, Leung JM, Smith CC, Huth AG, Root H, Kuhns DB, Logun C, Zelazny A, Frein CA *et al.*: **Abnormal nasal nitric oxide production, ciliary beat frequency, and Toll-like receptor response in pulmonary nontuberculous mycobacterial disease epithelium**. *Am J Respir Crit Care Med* 2013, **187**:1374-1381.

29. • Matsuyama M, Martins AJ, Shallom S, Kamenyeva O, Kashyap A, Sampaio EP, Kabat J, Olivier KN, Zelazny AM, Tsang JS *et al.*: **Transcriptional response of respiratory epithelium to nontuberculous mycobacteria**. *Am J Respir Cell Mol Biol* 2018, **58**:241-252.

Ex vivo study of primary human bronchial epithelial cells showing that NTM infection decreased expression of ciliary genes. The implication is that NTM infection itself may cause ciliary dysfunction in addition to the well-known fact that ciliary defect may predispose to NTM lung disease.

30. Honda JR, Bai X, Chan ED: **Elucidating the pathogenesis for NTM lung disease: lesson from the six blind men and the elephant (editorial)**. *Am J Respir Mol Cell Biol* 2018, **58**:142-143.

31. • Chi CY, Chu CC, Liu JP, Lin CH, Ho MW, Lo WJ, Lin PC, Chen HJ, Chou CH, Feng JY *et al.*: **Anti-IFN-γ autoantibodies in adults with disseminated nontuberculous mycobacterial infections are associated with HLA-DRB1•16:02 and HLA-DQB1•05:02 and the reactivation of latent varicella-zoster virus infection**. *Blood* 2013, **121**:1357-1366.

32. Doucette K, Fishman JA: **Nontuberculous mycobacterial infection in hematopoietic stem cell and solid organ transplant recipients**. *Clin Infect Dis* 2004, **38**:1428-1439.

33. Winthrop KL, Baxter R, Liu L, Varley CD, Curtis JR, Baddley JW, McFarland B, Austin D, Radcliffe L, Suhler E *et al.*: **Mycobacterial diseases and antitumour necrosis factor therapy in USA**. *Ann Rheum Dis* 2013, **72**:37-42.

34. Haverkamp MH, van de Vosse E, van Dissel JT: **Nontuberculous mycobacterial infections in children with inborn errors of the immune system**. *J Infect* 2014, **68**:S134-S150.

35. Honda JR, Knight V, Chan ED: **Pathogenesis and risk factors for nontuberculous mycobacterial lung disease**. *Clin Chest Med* 2015, **36**:1-11.

36. Hsu AP, Johnson KD, Falcone EL, Sanalkumar R, Sanchez L, Hickstein DD, Cuellar-Rodriguez J, Lemieux JE, Zerbe CS, Bresnick EH *et al.*: **GATA2 haploinsufficiency caused by mutations in a conserved intronic element leads to MonoMAC syndrome**. *Blood* 2013, **121**:3830-3837.

37. Chan ED: **Vulnerability to non-tuberculous mycobacterial lung disease or systemic infection due to genetic/heritable disorders**. In *Nontuberculous Mycobacterial Disease: A Comprehensive Approach to Diagnosis and Management.* Edited by Griffith DE. Springer; 2018.

38. Ohga S, Ikeuchi K, Kadoya R, Okada K, Miyazaki C, Suita S, Ueda K: **Intrapulmonary *Mycobacterium avium* infection as the first manifestation of chronic granulomatous disease**. *J Infect* 1997, **34**:147-150.

39. Oberley-Deegan RE, Rebits BW, Weaver MR, Tollefson AK, Bai X, McGibney M, Ovrutsky AR, Chan ED, Crapo JD: **An oxidative environment promotes growth of *Mycobacterium abscessus***. *Free Radic Biol Med* 2010, **49**:1666-1673.

40. Chan ED, Iseman MD: **Bronchiectasis**. In *Textbook of Respiratory Medicine,* 6th edn. Edited by Broaddus CEJ, King TE, Lazarus SC, Mason R, Murray J, Nadel J, Slutsky AS.Elsevier Press; 2017.

41. Malcolm KC, Nichols EM, Caceres SM, Kret JE, Martiniano SL, Sagel SD, Chan ED, Caverly L, Solomon GM, Reynolds P *et al.*: ***Mycobacterium abscessus*** **induces a limited pattern of neutrophil activation that promotes pathogen survival**. *PLoS ONE* 2013, **8**:e57402.

42. Puzo G: **The carbohydrate- and lipid-containing cell wall of mycobacteria, phenolic glycolipids: structure and immunological properties**. *Crit Rev Microbiol* 1990, **17**:305-327.

43. Pourshafie MR, Sonnenfeld G, Barrow WW: **Immunological and ultrastructural disruptions of T lymphocytes following exposure to the glycopeptidolipid isolated from the *Mycobacterium avium* complex**. *Scand J Immunol* 1999, **49**:405-410.

44. Barrow WW, de Sousa JP, Davis TL, Wright EL, Bachelet M, Rastogi N: **Immunomodulation of human peripheral blood mononuclear cell functions by defined lipid fractions of *Mycobacterium avium***. *Infect Immun* 1993, **61**:5286-5293.

45. Enomoto K, Oka S, Fujiwara N, Okamoto T, Okuda Y, Maekura R, Kuroki T, Yano I: **Rapid serodiagnosis of *Mycobacterium avium-intracellular* complex infection by ELISA with cord factor (trehalose 6,6'-dimycolate), and serotyping using the glycopeptidolipid antigen**. *Microbiol Immunol* 1998, **42**:689-696.

46. Freeman R, Geier H, Weigel KM, Do J, Ford TE, Cangelosi GA: **Roles for cell wall glycopeptidolipid in surface adherence and planktonic dispersal of *Mycobacterium avium***. *Appl Environ Microbiol* 2006, **72**:7554-7558.

47. Howard ST, Rhoades E, Recht J, Pang X, Alsup A, Kolter R, Lyons CR, Byrd TF: **Spontaneous reversion of *Mycobacterium abscessus* from a smooth to a rough morphotype is associated with reduced expression of glycopeptidolipid and reacquisition of an invasive phenotype**. *Microbiology* 2006, **152**:1581-1590.

48. Chatterjee D, Khoo KH: **The surface glycopeptidolipids of mycobacteria: structures and biological properties**. *Cell Mol Life Sci* 2001, **58**:2018-2042.

49. Rhoades ER, Archambault AS, Greendyke R, Hsu FF, Streeter C, Byrd TF: ***Mycobacterium abscessus*** **glycopeptidolipids mask underlying cell wall phosphatidyl-myo-inositol mannosides blocking induction of human macrophage TNF-alpha by preventing interaction with TLR2**. *J Immunol* 2009, **183**:1997-2007.

50. Byrd TF, Lyons CR: **Preliminary characterization of a *Mycobacterium abscessus* mutant in human and murine models of infection**. *Infect Immun* 1999, **67**:4700-4707.

51. Catherinot E, Roux AL, Macheras E, Hubert D, Matmar M, Dannhoffer L, Chinet T, Morand P, Poyart C, Heym B *et al.*: **Acute respiratory failure involving an R variant of *Mycobacterium abscessus***. *J Clin Microbiol* 2009, **47**:271-274.

52. Sanguinetti M, Ardito F, Fiscarelli E, la Sorda M, D'Argenio P, Ricciotti G, Fadda G: **Fatal pulmonary infection due to multidrug-resistant *Mycobacterium abscessus* in a patient with cystic fibrosis**. *J Clin Microbiol* 2001, **39**:816-819.

53. Sweet L, Schorey JS: **Glycopeptidolipids from *Mycobacterium avium* promote macrophage activation in a TLR2- and MyD88-dependent manner**. *J Leukoc Biol* 2006, **80**:415-423.

54. Barrow WW, Davis TL, Wright EL, Labrousse V, Bachelet M, Rastogi N: **Immunomodulatory spectrum of lipids associated with *Mycobacterium avium* serovar 8**. *Infect Immun* 1995, **63**:126-133.

55. Takegaki Y: **Effect of serotype specific glycopeptidolipid (GPL) isolated from *Mycobacterium avium* complex (MAC) on phagocytosis and phagosome-lysosome fusion of human peripheral blood monocytes**. *Kekkaku* 2000, **75**:9-18.

56. Jackson M, Crick DC, Brennan PJ: **Phosphatidylinositol is an essential phospholipid of mycobacteria**. *J Biol Chem* 2000, **275**:30092-30099.

57. Dao DN, Kremer L, Guerardel Y, Molano A, Jacobs WR Jr, Porcelli SA, Briken V: ***Mycobacterium tuberculosis*** **lipomannan induces apoptosis and interleukin-12 production in macrophages**. *Infect Immun* 2004, **72**:2067-2074.

58. Quesniaux VJ, Nicolle DM, Torres D, Kremer L, Guérardel Y, Nigou J, Puzo G, Erard F, Ryffel B: **Toll-like receptor 2 (TLR2)-dependent-positive and TLR2-independent-negative regulation of proinflammatory cytokines by mycobacterial lipomannans**. *J Immunol* 2004, **172**:4425-4434.

59. Maeda N, Nigou J, Herrmann JL, Jackson M, Amara A, Lagrange PH, Puzo G, Gicquel B, Neyrolles O: **The cell surface receptor DC-SIGN discriminates between *Mycobacterium* species through selective recognition of the mannose caps on lipoarabinomannan**. *J Biol Chem* 2003, **278**:5513-5516.

60. Vignal C, Guerardel Y, Kremer L, Masson M, Legrand D, Mazurier J, Elass E: **Lipomannans, but not lipoarabinomannans, purified from *Mycobacterium chelonae* and *Mycobacterium kansasii* induce TNF-alpha and IL-8 secretion by a CD14-toll-like receptor 2-dependent mechanism**. *J Immunol* 2003, **171**:2014-2023.

61. Chatterjee D, Khoo KH: ***Mycobacterial lipoarabinomannan*****: an extraordinary lipoheteroglycan with profound physiological effects**. *Glycobiology* 1998, **8**:113-120.

62. Wieland CW, Knapp S, Florquin S, de Vos AF, Takeda K, Akira S, Golenbock DT, Verbon A, van der Poll T: **Non-mannose-capped lipoarabinomannan induces lung inflammation via toll-like receptor 2**. *Am J Respir Crit Care Med* 2004, **170**:1367-1374.

63. Shanmugham B, Pan A: **Identification and characterization of potential therapeutic candidates in emerging human pathogen *Mycobacterium abscessus*: a novel hierarchical in silico approach**. *PLoS ONE* 2013, **8**:e59126.

64. •• Gonzalez-Perez MN, Murcia MI, Parra-Lopez C, Blom J, Tauch A: **Deciphering the virulence factors of the opportunistic pathogen *Mycobacterium colombiense***. *New Microbes New Infect* 2016:98-105.

Using bioinfomatic tools to interrogate the genome of*M. colombiense*, these investigators showed that this NTM — a member of the *Mycobacterium avium* complex — lacks several virulence genes present in *M. tuberculosis*. Such analysis is not only useful in characterizing different species and strains of NTM but also future studies to determine if such differences correlate with clinical outcome as well as development of species-specific and strain-specific diagnostic tests.

65. Ripoll F, Pasek S, Schenowitz C, Dossat C, Barbe V, Rottman M, Macheras E, Heym B, Herrmann JL, Daffé M *et al.*: **Non mycobacterial virulence genes in the genome of the emerging pathogen *Mycobacterium abscessus***. *PLoS ONE* 2009, **4**:e5660.