AMERICAN SOCIETY FOR MICROBIOLOGY | mBio®

COMMENTARY

# Adding Another Piece to the Puzzle of Why NTM Infections Are Relatively Uncommon despite Their Ubiquitous Nature

Edward D. Chan,[a,b,c,d] Adela Cota-Gomez,[d] Brendan Podell[e]

[a]Rocky Mountain Regional Veterans Affairs Medical Center, Aurora, Colorado, USA
[b]Office of Academic Affairs, National Jewish Health, Denver, Colorado, USA
[c]Department of Medicine, National Jewish Health, Denver, Colorado, USA
[d]Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA
[e]Department of Microbiology, Immunology, and Pathology, Colorado State University, Fort Collins, Colorado, USA

**ABSTRACT** Since nontuberculous mycobacteria (NTM) are pervasive in the environment and NTM infections are relatively uncommon, underlying hereditary or acquired host susceptibility factors should be sought for in most NTM-infected patients. To facilitate identification of underlying risk factors, it is useful to classify NTM disease into skin-soft tissue infections, isolated NTM lung disease, and extrapulmonary visceral/disseminated disease because the latter two categories have unique sets of underlying host risk factors. Nakajima and coworkers (M. Nakajima, M. Matsuyama, M. Kawaguchi, T. Kiwamoto, et al., mBio 12:e01947-20, 2021, https://doi.org/10.1128/mBio.01947-20) in a recent issue of *mBio* found that Nrf2 (nuclear factor erythroid 2-related factor 2), a transcription factor that is induced by oxidative stress but induces antioxidant molecules, provides protection against an NTM infection in a murine model. While they showed that Nrf2 induction of Nramp-1 enhanced phagosome-lysosome fusion, we discuss other potential mechanisms by which oxidative stress predisposes to and Nrf2 protects against NTM infections.

**KEYWORDS** NF-kappa B, Nramp-1, Nrf2, mycobacteria, oxidative stress

Nontuberculous mycobacteria (NTM) are ubiquitous in the man-made and natural environments, and thus, exposure to them is likely pervasive. Yet, NTM infections are relatively uncommon in the general population. Thus, host behavior (that increases risk of repeated contacts to NTM) and host susceptibility factors (that increases vulnerability to NTM) are likely important factors in determining whether NTM disease manifests. Host behaviors that increases one's risk may be synopsized into activities that increase exposure to aerosolized water, soil, and biofilms, the principal niches for NTM. It is useful to classify NTM-related diseases into the following three groups because each group essentially has a unique set of underlying "events" or host risk factors: (i) skin, soft tissue, and orthopedic infections, (ii) isolated lung disease, and (iii) extrapulmonary visceral/disseminated infections.

Skin and soft tissue infections with or without extension into the joints or bones are most often due to (i) accidental trauma followed by contamination of the wound with environmental NTM or (ii) iatrogenic infections secondary to medical or surgical procedures using NTM-contaminated water, medications, or medical/surgical instruments. NTM foot infections acquired from contaminated foot baths in nail salons (1) and *Mycobacterium chimaera* infections from contaminated heater-cooler units ("heart-lung machine") used for open-chest heart surgery (2) may also be categorized in this rubric.

Isolated NTM lung disease (NTM-LD) occurs most often in those with preexisting structural pulmonary disorders such as emphysema and preexisting bronchiectasis (e.g.,

**Citation** Chan ED, Cota-Gomez A, Podell B. 2021. Adding another piece to the puzzle of why NTM infections are relatively uncommon despite their ubiquitous nature. mBio 12:e03577-20. https://doi.org/10.1128/mBio.03577-20.



Address correspondence to Edward D. Chan, ChanE@NJHealth.org.

For the article discussed, see https://doi.org/10.1128/mBio.01947-20.

*The views expressed in this article do not necessarily reflect the views of the journal or of ASM.*

**Published** 20 April 2021

**TABLE 1** Some genes associated with NTM-LD[a]

| Gene (protein) | Findings |
|---|---|
| Fibrillin-2 | NTM-LD in patients with Marfanoid body habitus (taller stature, pectus excavatum, and scoliosis) are well described (34, 35). A patient with congenital contractural arachnodactyly, a genetic disorder due to *FIBRILLIN-2* gene mutation and which shares many clinical features with Marfan syndrome was reported with NTM-LD (36). |
| MICA | In 300 NTM-LD patients, the A6 allele for MICA was significantly more frequent than control subjects (37). MICA is a membrane-bound glycoprotein expressed on various cell types, including alveolar macrophages, epithelioid cells, multinucleated giant cells, intestinal epithelium, and bronchial epithelium, and engages the NKG2D receptor on NK cells, $\gamma$-$\delta$ T cells, and $CD8^+$ T cells. The A6 allele is a marker for high MICA expression on inflammatory cells and may be involved with increased tissue damage in NTM infections. |
| MST1R | Variants of the MST1R gene, which encodes a tyrosine kinase found in the cell surface of airway epithelial cells and fallopian tubes, and involved with ciliary function, were found to be more common in NTM-LD patients than controls (3, 38). |
| TLR2 | In 80 patients with NTM-LD and 84 healthy controls from Korea, using PCR and RFLP to analyze two polymorphisms of the TLR2 gene (Arg677Trp and Arg753Gln) found none of the patients or controls possessed either one (39). Shorter GT repeats in the intron II region of the TLR2 gene was more common in NTM-LD subjects compared to controls (40). |
| VDR | In 56 patients from United Kingdom with NTM-LD due to *Mycobacterium malmoense* in which three specific VDR polymorphisms were analyzed, there was decreased prevalence of the FokI polymorphism and increased frequency of ApaI and TaqI polymorphisms (41). However, two other studies from Far East Asia found no difference in either the FokI or TaqI polymorphisms between NTM-LD and healthy subjects (12, 42). |

[a]ApaI, *Acetobacter pasteuranis* subspecies I A; FokI, *Flavobacterium okeanokoites* I; MICA, major histocompatibility complex class I chain-related A; MST1R, gene that encodes macrophage-stimulating protein receptor; NK, natural killer; RFLP, restriction fragment length polymorphism; TaqI, *Thermus aquaticus* YTI; TLR2, Toll-like receptor 2; VDR, vitamin D receptor.

cystic fibrosis, alpha-1-antitrypsin deficiency, primary ciliary dyskinesia, prior tuberculosis, or idiopathic). However, NTM-LD may also occur in certain individuals with no known primary risk factors and NTM may be a *de novo* cause of bronchiectasis. Some of these individuals have minor variants of ciliary, connective tissue, cystic fibrosis transmembrane conductance regulator, and immune-related genes which, collectively via a multigenic paradigm, predispose them to NTM-LD (3). Some other associative genes that have been analyzed with NTM-LD are summarized in Table 1.

Extrapulmonary visceral/disseminated disease most often occurs in individuals with frank immunodeficiency. Such underlying disorders may be genetic/hereditary (e.g., defect in the interferon gamma [IFN-$\gamma$]—interleukin-12 [IL-12] axis, nuclear factor-kappa B [NF-κB] essential modulator [NEMO] mutation or GATA2 mutation) or acquired (e.g., untreated AIDS, anti-IFN-$\gamma$ antibody autoimmunity, or use of anti-tumor necrosis factor [TNF] agents).

Nakajima and coworkers (4) studied the role of Nrf2 (nuclear factor erythroid 2-related factor 2) in host defense against *Mycobacterium avium* complex (MAC) subsp. *hominissuis* infection in mice. Nrf2 is a transcription factor that is normally sequestered in the cytoplasm, but in an oxidative state, it translocates into the nucleus and induces phase II cytoprotective and antioxidant genes, providing negative feedback against oxidative and other cellular stress. They showed that mice with disruption of the *NFE2L2* gene, which encodes Nrf2, were more susceptible to an intranasal MAC infection with greater bacterial loads in the lungs, livers, and spleens, indicating the importance of Nrf2 in host defense. Fittingly, following MAC infection, the $Nrf2^{-/-}$ mice had decreased expression of natural resistance-associated macrophage protein 1 (Nramp-1) in the lungs as well as in their alveolar macrophages, decreased phagosome-lysosome (P-L) fusion, and increased NTM burden (Fig. 1). This reduction in P-L fusion in the $Nrf2^{-/-}$ mice is consistent with a previous report showing that mice with disruption of the *SLC11A1* gene that encodes Nramp-1 have reduced P-L fusion (5). Conversely, inducing Nrf2 in wild-type mice with sulforaphane increased expression of Nramp1 with increased resistance to MAC infection. There was no difference between the wild-type and $Nrf2^{-/-}$ mice in the influx of $T_H1$ cells or levels of $T_H1$ cytokines, indicating the importance of innate immunity against NTM infections. Interestingly, there was also no difference in oxidative stress levels between the wild-type and $Nrf2^{-/-}$ mice as measured by a DNA oxidative stress marker and a lipid peroxidation assay in the lung cells—even though one would have expected increased oxidative stress in the $Nrf2^{-/-}$

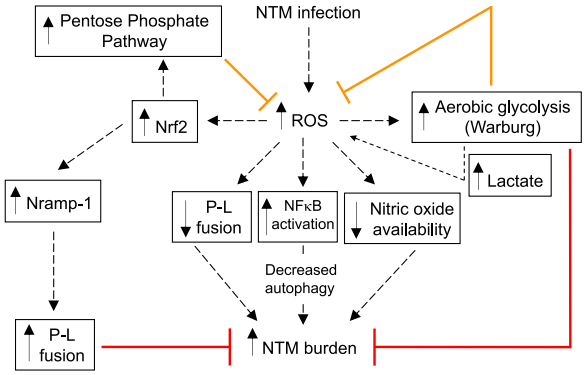


**FIG 1** Diagram showing the mechanisms by which oxidative stress—denoted by ROS—may increase susceptibility to NTM infections. ROS may decrease P-L fusion, autophagy, and NO availability. However, ROS may also activate counterregulatory signaling and metabolic pathways that reduce its own production (inhibitory lines [orange lines]), thus enhancing host immunity against NTM (inhibitory lines [red lines]). In addition to sequential activation of Nrf2, Nramp-1, and P-L fusion, ROS may also induce aerobic glycolysis that can ultimately inhibit oxidative stress as well as a primary effector cellular mechanism against NTM. Note that while lactate can induce a small burst of ROS (smaller angled arrow), this triggers Nrf2 activation to ultimately result in a net antioxidant effect. NF-κB, nuclear factor-kappa B; NO, nitric oxide; Nramp-1, natural resistance-associated macrophage protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; NTM, nontuberculous mycobacteria; P-L, phagosome-lysosome; ROS, reactive oxygen species.

mice. However, not all Nrf2-mediated protection is via antioxidants, as the "Nrf2-interactome" includes hundreds of other cytoprotective genes that might not manifest in an oxidative phenotype (6, 7). Furthermore, oxidative responses vary significantly depending on the insult, and DNA damage and lipid peroxidation are indirect measures that are far downstream from the processes that generate reactive oxygen species (ROS). More sensitive methods that measure ROS directly, such as electron paramagnetic resonance (EPR) or electron spin resonance (ESR), may provide a clearer picture of the redox status in these mice (8). While they showed that the Nrf2$^{-/-}$ mice were more susceptible to disseminated MAC disease—as opposed to isolated lung disease—this may be due to the type of murine model used and the large MAC inoculum administered. In contrast to the findings of Nakajima et al. (4), inhibition of either Nrf2 or its downstream target molecule heme oxygenase 1 (HO-1) in THP-1 cells resulted in the inhibition of *Mycobacterium abscessus*, reaching the opposite conclusion that Nrf2 and reduced oxidative stress in macrophages predispose to NTM infection (9).

While we are unaware of previous studies linking abnormalities of Nrf2 to human NTM-LD, specific polymorphisms in the gene for Nramp-1 have been associated with NTM-LD, highlighting the relevance of this study to human NTM infections (10–12). However, possessing such variants does not necessarily indicate that the Nramp1 protein is defective or even if dysfunctional, whether it is clinically relevant.

In addition to the paradigm of ROS → Nrf2 → increased Nramp1 expression → increased P-L fusion, could ROS and Nrf2 affect other mechanisms that, respectively, predispose to or protect against NTM infections? Individuals with chronic granulomatous disease (CGD)—in which there is a defect in the NADPH oxidase enzyme in phagocytes with resultant defect in the formation of ROS—are predisposed to infections with *Staphylococcus aureus*, Gram-negative bacteria, and *Aspergillus* species. Even though CGD patients may be more predisposed to tuberculosis and BCG (13, 14), there is a paucity of data linking CGD to NTM infections (15, 16). In contrast, we previously showed that an antioxidant enhanced both P-L fusion and clearance of *M. abscessus* in macrophages (17, 18). ROS are known to either induce or inhibit various components of the NF-κB activation pathway (19). While NF-κB is important in the induction of host-protective molecules such as TNF, we have found that inhibition of NF-κB decreases A20 (a deubiquitination enzyme that inhibits autophagosome maturation by inhibiting

ubiquitination of Beclin-1), increases autophagosome-lysosome fusion, and helps in the clearance of MAC infection (20). However, it is important to emphasize that NF-κB activation is also important for host control of mycobacterial infections, as frank deficiency of NEMO (also known as IκB kinase-gamma, a component of the IκB kinase [IKK] complex required for NF-κB activation) predisposes to these infections (21). Since Nrf2 induces antioxidant molecules, one prediction is that $Nrf2^{-/-}$ mice would demonstrate increased NF-κB activation in macrophages with NTM infection, resulting in increased A20 expression, reduced autophagy, and decreased ability to clear NTM infections. Another plausible mechanism by which ROS may predispose to NTM infection is via reducing levels of antimycobacterial nitric oxide (NO) (22), as an $O_2$ radical readily combines with NO to form peroxynitrite ($ONOO^-$) (Fig. 1). One important caveat is that because mice produce significantly more NO than humans, endogenous NO may be significantly more protective against mycobacteria in mice than in humans. Nevertheless, Nakajima and coworkers (4) did not see evidence of increased oxidative stress based on indirect measurements in the $Nrf2^{-/-}$ mice compared to the wild-type mice even following MAC infection. However, other groups have measured elevated levels of ROS in $Nrf2^{-/-}$ mice by specific and highly sensitive methods (8); thus, it is possible that these mice do exhibit an overt oxidative phenotype that contributes to their susceptibility to NTM infection. Furthermore, since the $Nrf2^{-/-}$ mice are affected *in utero* and at birth (23), they may have adapted to oxidative stress by augmenting other antioxidative pathways by the time they reached maturity.

Nrf2 is a major transcriptional regulator of cellular metabolism and, in particular, induces a shift toward glucose metabolism (24, 25). Effective microbial defense by macrophages is linked to an infection-induced shift toward aerobic glycolysis, specifically in *M. tuberculosis* infection (26–28) (Fig. 1). This metabolic response resembles the "Warburg" effect known to dominate metabolism in cancer cells, where glycolysis is upregulated in the absence of an anaerobic environment. Although a direct relationship between Nrf2, microbial response, and glycolysis has not been established, activation of Nrf2 by sulforaphane, or knockout of the Nrf2 inhibitor Keap1, leads to increased glucose utilization by glycolysis, pentose phosphate shunt, and consequently, the generation of NADPH intermediates that are not only critical for maintaining redox homeostasis but also support anabolic pathways to promote cytoprotection (29). Thus, another potential explanation for impaired control and severe NTM-LD in the absence of Nrf2 could involve metabolic reprogramming. High levels of oxidative phosphorylation is reported in mycobacterial infection, with the potential to generate excess oxidative stress (30, 31). Counterregulatory (negative-feedback) mechanisms in response to the increased levels of ROS include the ability of ROS to (i) induce glycolysis which decreases ROS by less reliance on oxidative phosphorylation (32) and (ii) activate Nrf2 which induces antioxidant mechanisms, such as pentose phosphate pathway and NADPH production (Fig. 1). Interestingly, lactate generated from glycolysis has been shown to trigger a small ROS burst which then activates Nrf2 to induce a net increase in antioxidant defenses (Fig. 1) (33). Thus, while critical for the response to infection, an increase in glycolysis without effective redox balance could generate oxidative stress that is injurious to cell function, thereby impairing this basic defense mechanism.

## REFERENCES


1. Winthrop KL, Abrams M, Yakrus M, Schwartz I, Ely J, Gillies D, Vugia DJ. 2002. An outbreak of mycobacterial furunculosis associated with footbaths at a nail salon. N Engl J Med 346:1366–1371. https://doi.org/10.1056/NEJMoa012643.
2. Hasse B, Hannan MM, Keller PM, Maurer FP, Sommerstein R, Mertz D, Wagner D, Fernández-Hidalgo N, Nomura J, Manfrin V, Bettex D, Hernandez Conte A, Durante-Mangoni E, Tang TH-C, Stuart RL, Lundgren J, Gordon S, Jarashow MC, Schreiber PW, Niemann S, Kohl TA, Daley CL, Stewardson AJ, Whitener CJ, Perkins K, Plachouras D, Lamagni T, Chand M, Freiberger T, Zweifel S, Sander P, Schulthess B, Scriven JE, Sax H, van Ingen J, Mestres CA, Diekema D, Brown-Elliott BA, Wallace RJ, Baddour LM, Miro JM, Hoen B, *M. chimaera* ISCVID Investigators, ISCVID Executive Committee, Athan E, Bayer A, Barsic B, Corey GR, Chu VH, Durack DT, Fortes CQ, et al. 2020. International Society of Cardiovascular Infectious Diseases guidelines for the diagnosis, treatment and prevention of disseminated *Mycobacterium chimaera* infection following cardiac surgery with cardiopulmonary bypass. J Hosp Infect 104:214–235. https://doi.org/10.1016/j.jhin.2019.10.009.
3. Szymanski EP, Leung JM, Fowler CJ, Haney C, Hsu AP, Chen F, Duggal P, Oler AJ, McCormack R, Podack E, Drummond RA, Lionakis MS, Browne SK, Prevots DR, Knowles M, Cutting G, Liu X, Devine SE, Fraser CM, Tettelin H, Olivier KN, Holland SM. 2015. Pulmonary nontuberculous mycobacterial infection. A multisystem, multigenic disease. Am J Respir Crit Care Med 192:618–628. https://doi.org/10.1164/rccm.201502-0387OC.

4. Nakajima M, Matsuyama M, Kawaguchi M, Kiwamoto T, Matsuno Y, Morishima Y, Yoshida K, Sherpa M, Yazaki K, Osawa H, Muratani M, Ishii Y, Hizawa N. 2021. Nrf2 regulates granuloma formation and macrophage activation during *Mycobacterium avium* infection via mediating Nramp1 and HO-1 expressions. mBio 12:e01947-20. https://doi.org/10.1128/mBio.01947-20.
5. Frehel C, Canonne-Hergaux F, Gros P, De Chastellier C. 2002. Effect of Nramp1 on bacterial replication and on maturation of *Mycobacterium avium*-containing phagosomes in bone marrow-derived mouse macrophages. Cell Microbiol 4:541–556. https://doi.org/10.1046/j.1462-5822.2002.00213.x.
6. Papp D, Lenti K, Modos D, Fazekas D, Dul Z, Turei D, Foldvari-Nagy L, Nussinov R, Csermely P, Korcsmaros T. 2012. The NRF2-related interactome and regulome contain multifunctional proteins and fine-tuned autoregulatory loops. FEBS Lett 586:1795–1802. https://doi.org/10.1016/j.febslet.2012.05.016.
7. Turei D, Papp D, Fazekas D, Foldvari-Nagy L, Modos D, Lenti K, Csermely P, Korcsmaros T. 2013. NRF2-ome: an integrated web resource to discover protein interaction and regulatory networks of NRF2. Oxid Med Cell Longev 2013:737591. https://doi.org/10.1155/2013/737591.
8. Hirayama A, Yoh K, Nagase S, Ueda A, Itoh K, Morito N, Hirayama K, Takahashi S, Yamamoto M, Koyama A. 2003. EPR imaging of reducing activity in Nrf2 transcriptional factor-deficient mice. Free Radic Biol Med 34:1236–1242. https://doi.org/10.1016/s0891-5849(03)00073-x.
9. Abdalla MY, Ahmad IM, Switzer B, Britigan BE. 2015. Induction of heme oxygenase-1 contributes to survival of *Mycobacterium abscessus* in human macrophages-like THP-1 cells. Redox Biol 4:328–339. https://doi.org/10.1016/j.redox.2015.01.012.
10. Koh W-J, Kwon OJ, Kim EJ, Lee KS, Ki C-S, Kim JW. 2005. NRAMP1 gene polymorphism and susceptibility to nontuberculous mycobacterial lung diseases. Chest 128:94–101. https://doi.org/10.1378/chest.128.1.94.
11. Sapkota BR, Hijikata M, Matsushita I, Tanaka G, Ieki R, Kobayashi N, Toyota E, Nagai H, Kurashima A, Tokunaga K, Keicho N. 2012. Association of SLC11A1 (NRAMP1) polymorphisms with pulmonary *Mycobacterium avium* complex infection. Hum Immunol 73:529−536. https://doi.org/10.1016/j.humimm.2012.02.008.
12. Tanaka G, Shojima J, Matsushita I, Nagai H, Kurashima A, Nakata K, Toyota E, Kobayashi N, Kudo K, Keicho N. 2007. Pulmonary *Mycobacterium avium* complex infection: association with NRAMP1 polymorphisms. Eur Respir J 30:90–96. https://doi.org/10.1183/09031936.00042506.
13. Zhou Q, Hui X, Ying W, Hou J, Wang W, Liu D, Wang Y, Yu Y, Wang J, Sun J, Zhang Q, Wang X. 2018. A cohort of 169 chronic granulomatous disease patients exposed to BCG vaccination: a retrospective study from a single center in Shanghai, China (2004–2017). J Clin Immunol 38:260–272. https://doi.org/10.1007/s10875-018-0486-y.
14. Pereira NM, Shah I. 2016. Familial chronic granulomatous disease affecting three siblings and causing recurrent tuberculosis. J Clin Immunol 36:743–746. https://doi.org/10.1007/s10875-016-0338-6.
15. Ohga S, Ikeuchi K, Kadoya R, Okada K, Miyazaki C, Suita S, Ueda K. 1997. Intrapulmonary *Mycobacterium avium* infection as the first manifestation of chronic granulomatous disease. J Infect 34:147–150. https://doi.org/10.1016/s0163-4453(97)92509-3.
16. Allen DM, Chng HH. 1993. Disseminated *Mycobacterium flavescens* in a probable case of chronic granulomatous disease. J Infect 26:83–86. https://doi.org/10.1016/0163-4453(93)97000-N.
17. Oberley RE, Lee Y-M, Morey GE, Cook DM, Chan ED, Crapo JD. 2009. The antioxidant mimetic, MnTE-2-PyP, reduces intracellular growth of *Mycobacterium abscessus*. Am J Respir Cell Mol Biol 41:170–178. https://doi.org/10.1165/rcmb.2008-0138OC.
18. Oberley-Deegan RE, Rebits BW, Weaver MR, Tollefson AK, Bai X, McGibney M, Ovrutsky AR, Chan ED, Crapo JD. 2010. An oxidative environment promotes the growth of *Mycobacerium abscessus*. Free Radic Biol Med 49:1666–1673. https://doi.org/10.1016/j.freeradbiomed.2010.08.026.
19. Morgan MJ, Liu Z-G. 2011. Crosstalk of reactive oxygen species and NF-kB signaling. Cell Res 21:103–115. https://doi.org/10.1038/cr.2010.178.
20. Bai X, Bai A, Honda JR, Eichstaedt C, Musheyev A, Feng Z, Huitt G, Harbeck R, Kosmider B, Sandhaus RA, Chan ED. 2019. Alpha-1-antitrypsin enhances primary human macrophage immunity against non-tuberculous mycobacteria. Front Immunol 10:1417. https://doi.org/10.3389/fimmu.2019.01417.
21. Filipe-Santos O, Bustamante J, Haverkamp MH, Vinolo E, Ku CL, Puel A, Frucht DM, Christel K, von Bernuth H, Jouanguy E, Feinberg J, Durandy A, Senechal B, Chapgier A, Vogt G, de Beaucoudrey L, Fieschi C, Picard C, Garfa M, Chemli J, Bejaoui M, Tsolia MN, Kutukculer N, Plebani A, Notarangelo L, Bodemer C, Geissmann F, Israël A, Véron M, Knackstedt M, Barbouche R, Abel L, Magdorf K, Gendrel D, Agou F, Holland SM, Casanova JL. 2006. X-linked susceptibility to mycobacteria is caused by mutations in NEMO impairing CD40-dependent IL-12 production. J Exp Med 203:1745–1759. https://doi.org/10.1084/jem.20060085.
22. Akaki T, Sato K, Shimizu T, Sano C, Kajitani H, Dekio S, Tomioka H. 1997. Effector molecules in expression of the antimicrobial activity of macrophages against *Mycobacterium avium* complex: roles of reactive nitrogen intermediates, reactive oxygen intermediates, and free fatty acids. J Leukoc Biol 62:795–804. https://doi.org/10.1002/jlb.62.6.795.
23. Sussan TE, Sudini K, Talbot CC, Jr, Wang X, Wills-Karp M, Burd I, Biswal S. 2017. Nrf2 regulates gene-environment interactions in an animal model of intrauterine inflammation: implications for preterm birth and prematurity. Sci Rep 7:40194. https://doi.org/10.1038/srep40194.
24. Mitsuishi Y, Taguchi K, Kawatani Y, Shibata T, Nukiwa T, Aburatani H, Yamamoto M, Motohashi H. 2012. Nrf2 redirects glucose and glutamine into anabolic pathways in metabolic reprogramming. Cancer Cell 22:66–79. https://doi.org/10.1016/j.ccr.2012.05.016.
25. Ohl K, Fragoulis A, Klemm P, Baumeister J, Klock W, Verjans E, Böll S, Möllmann J, Lehrke M, Costa I, Denecke B, Schippers A, Roth J, Wagner N, Wruck C, Tenbrock K. 2018. Nrf2 is a central regulator of metabolic reprogramming of myeloid-derived suppressor cells in steady state and sepsis. Front Immunol 9:1552. https://doi.org/10.3389/fimmu.2018.01552.
26. Shi L, Salamon H, Eugenin EA, Pine R, Cooper A, Gennaro ML. 2015. Infection with *Mycobacterium tuberculosis* induces the Warburg effect in mouse lungs. Sci Rep 5:18176. https://doi.org/10.1038/srep18176.
27. Gleeson LE, Sheedy FJ, Palsson-McDermott EM, Triglia D, O'Leary SM, O'Sullivan MP, O'Neill LAJ, Keane J. 2016. Cutting edge: *Mycobacterium tuberculosis* induces aerobic glycolysis in human alveolar macrophages that is required for control of intracellular bacillary replication. J Immunol 196:2444–2449. https://doi.org/10.4049/jimmunol.1501612.
28. Osada-Oka M, Goda N, Saiga H, Yamamoto M, Takeda K, Ozeki Y, Yamaguchi T, Soga T, Tateishi Y, Miura K, Okuzaki D, Kobayashi K, Matsumoto S. 2019. Metabolic adaptation to glycolysis is a basic defense mechanism of macrophages for *Mycobacterium tuberculosis* infection. Int Immunol 31:781–793. https://doi.org/10.1093/intimm/dxz048.
29. Heiss EH, Schachner D, Zimmermann K, Dirsch VM. 2013. Glucose availability is a decisive factor for Nrf2-mediated gene expression. Redox Biol 1:359–365. https://doi.org/10.1016/j.redox.2013.06.001.
30. Haugen Frenkel JD, Ackart DF, Todd AK, DiLisio JE, Hoffman S, Tanner S, Kiran D, Murray M, Chicco A, Obregón-Henao A, Podell BK, Basaraba RJ. 2020. Metformin enhances protection in guinea pigs chronically infected with *Mycobacterium tuberculosis*. Sci Rep 10:16257. https://doi.org/10.1038/s41598-020-73212-y.
31. Singhal A, Jie L, Kumar P, Hong GS, Leow MKS, Paleja B, Tsenova L, Kurepina N, Chen J, Zolezzi F, Kreiswirth B, Poidinger M, Chee C, Kaplan G, Wang YT, De Libero G. 2014. Metformin as adjunct antituberculosis therapy. Sci Transl Med 6:263ra159. https://doi.org/10.1126/scitranslmed.3009885.
32. Movahed ZG, Rastegari-Pouyani M, Mohammadi MH, Mansouri K. 2019. Cancer cells change their glucose metabolism to overcome increased ROS: one step from cancer cell to cancer stem cell? Biomed Pharmacother 112:108690. https://doi.org/10.1016/j.biopha.2019.108690.
33. Tauffenberger A, Fiumelli H, Almustafa S, Magistretti PJ. 2019. Lactate and pyruvate promote oxidative stress resistance through hormetic ROS signaling. Cell Death Dis 10:653. https://doi.org/10.1038/s41419-019-1877-6.
34. Kartalija M, Ovrutsky AR, Bryan CL, Pott GB, Fantuzzi G, Thomas J, Strand MJ, Bai X, Ramamoorthy P, Rothman MS, Nagabhushanam V, McDermott M, Levin AR, Frazer-Abel A, Giclas PC, Korner J, Iseman MD, Shapiro L, Chan ED. 2013. Patients with nontuberculous mycobacterial lung disease exhibit unique body and immune phenotypes. Am J Respir Crit Care Med 187:197–205. https://doi.org/10.1164/rccm.201206-1035OC.
35. Kim RD, Greenberg DE, Ehrmantraut ME, Guide SV, Ding L, Shea Y, Brown MR, Chernick M, Steagall WK, Glasgow CG, Lin J, Jolley C, Sorbara L, Raffeld M, Hill S, Avila N, Sachdev V, Barnhart LA, Anderson VL, Claypool R, Hilligoss DM, Garofalo M, Fitzgerald A, Anaya-O'Brien S, Darnell D, DeCastro R, Menning HM, Ricklefs SM, Porcella SF, Olivier KN, Moss J, Holland SM. 2008. Pulmonary nontuberculous mycobacterial disease: prospective study of a distinct preexisting syndrome. Am J Respir Crit Care Med 178:1066–1074. https://doi.org/10.1164/rccm.200805-686OC.
36. Paulson ML, Olivier KN, Holland SM. 2012. Pulmonary non-tuberculous mycobacterial infection in congenital contractural arachnodactyly. Int J Tuber Lung Dis 16:561–563. https://doi.org/10.5588/ijtld.11.0301.
37. Shojima J, Tanaka G, Keicho N, Tamiya G, Ando S, Oka A, Inoue Y, Suzuki K, Sakatani M, Okada M, Kobayashi N, Toyota E, Kudo K, Kajiki A, Nagai H, Kurashima A, Oketani N, Hayakawa H, Takemura T, Nakata K, Ito H, Morita

T, Matsushita I, Hijikata M, Sakurada S, Sasazuki T, Inoko H. 2009. Identification of MICA as a susceptibility gene for pulmonary Mycobacterium avium complex infection. J Infect Dis 199:1707–1715. https://doi.org/10.1086/598982.
38. Becker K, Arts P, Jaeger M, Plantinga T, Gilissen C, van Laarhoven A, van Ingen J, Veltman J, Joosten L, Hoischen A, Netea M, Iseman M, Chan ED, van de Veerdonk F. 2017. MST1R mutation as a genetic cause of Lady Windermere syndrome. Eur Respir J 49:1601478. https://doi.org/10.1183/13993003.01478-2016.
39. Ryu YJ, Kim EJ, Koh WJ, Kim H, Kwon OJ, Chang JH. 2006. Toll-like receptor 2 polymorphisms and nontuberculous mycobacterial lung diseases. Clin Vaccine Immunol 13:818–819. https://doi.org/10.1128/CVI.00025-06.
40. Yim J-J, Kim HJ, Kwon OJ, Koh W-J. 2008. Association between microsatellite polymorphisms in intron II of the human Toll-like receptor 2 gene and nontuberculous mycobacterial lung disease in a Korean population. Hum Immunol 69:572–576. https://doi.org/10.1016/j.humimm.2008.06.003.
41. Gelder CM, Hart KW, Williams OM, Lyons E, Welsh KI, Campbell IA, Marshall SE. 2000. Vitamin D receptor gene polymorphisms and susceptibility to *Mycobacterium malmoense* pulmonary disease. J Infect Dis 181:2099–2102. https://doi.org/10.1086/315489.
42. Park S, Kim EJ, Lee S-H, Suh GY, Chung MP, Kim H, Kwon OJ, Koh W-J. 2008. Vitamin D-receptor polymorphisms and non-tuberculous mycobacterial lung disease in Korean patients. Int J Tuber Lung Dis 12:698–700.