Published in final edited form as:
Tuberculosis (Edinb). 2013 December ; 93(0): S10–S14. doi:10.1016/S1472-9792(13)70004-0.

Host-pathogen interactions in tuberculosis patients with type 2 diabetes mellitus

Blanca I. Restrepo[a,*] and **Larry S. Schlesinger**[b]

[a] UTHealth Houston, School of Public Health at Brownsville, 80 Fort Brown, Brownsville, Texas 78520, USA

[b] Center for Microbial Interface Biology and Department of Microbial Infection and Immunity, 460W 12th Ave, The Ohio State University, Columbus, Ohio 43210, USA

Abstract

Tuberculosis (TB) is known to be fueled by HIV as well as social and economic factors. With progression of the diabetes mellitus (DM) pandemic in countries where TB is also endemic, focus is increasing on the potential links between DM and TB. Despite the magnitude of the DM-TB association woldwide, it is striking how little we know about the underlying biology that promotes this association which is a major concern to public health. In this review we summarize current findings regarding the alterations in the innate and adaptive immune responses of DM patients to *Mycobacterium tuberculosis* (*Mtb*). Current findings suggest underperforming innate immunity followed by a hyper-reactive cellular response to *Mtb*, but the contribution of these altered responses to TB susceptibility or to the more adverse clinical outcomes of TB patients with DM remains unclear. Elucidating the basic mechanisms underlying the higher susceptibility of DM patients to TB should lead to a strategy for stratification of the millions of DM patients worldwide into those with the highest TB risk for targeted TB prevention.

Keywords

Tuberculosis; Diabetes; Innate immunity; Adaptive immunity; Review; Hyperglycemia

1. Epidemiological and clinical landscape of the association

Tuberculosis (TB) is the number one single bacterial killer worldwide.[1] Its association with diabetes mellitus (DM) was described centuries ago.[2] Prior to the 1950s a DM patient that was not dying from a diabetic comma was likely dying from TB.[3-5] This association disappeared from the literature with the advent of insulin to improve the management of DM and antibiotics to treat TB. Today the co-occurrence of both diseases has reappeared as a

* Corresponding author at: 80 Fort Brown, SPH Bldg, Brownsville, Texas 78520, USA. Tel.: 956 882 5172; Fax: 956 882 5152 blanca.i.restrepo@uth.tmc.edu or blancares2008@gmail.com (B.I. Restrepo)..

Author contributions
BIR and LSS wrote and approved the final version of the review

Competing interest
None declared.

consequence of the DM 'pandemic' which is predicted to reach 366 million patients by 2030 and is primarily attributed to type 2 DM.[6,7] Consequently, the World Health Organization has recently identified DM as a neglected, important and re-emerging risk factor for TB.[8-10] While studies prior to 1950s could not distinguish between coincidence or association between TB and DM, contemporary analyses with improved epidemiological tools are providing growing support for their association. Results suggest that DM patients have a 3-fold higher risk of developing TB, particularly those with poor DM control (high HbA_{1c}).[11,12] In countries where TB and DM are endemic such as India or Mexico, DM can account for up to 22% of the TB cases.[13,14] At the Texas-Mexico border our findings suggest that the attributable risk of TB due to DM is 28%, suggesting that DM is the underlying condition for nearly one-third of the TB cases in this region.[15] Thus, while the risk conferred by HIV is more than 50-fold at the individual level, the higher prevalence of DM in a community can have a relatively higher impact on TB control.[15-17] Therefore, the relative contribution of DM versus other risk factors for TB (e.g. HIV, malnutrition, excess alcohol, drug abuse, overcrowding) can vary substantially between communities and should be taken into consideration for tailored TB control.

DM can also affect the clinical presentation and course of TB. TB patients with DM (TB-DM) have a higher risk of death when compared to TB without DM (TB-no DM).[18] The dysfunctional immune response in DM patients includes hyper-reactive T cells (see below) that may affect the clinical presentation of TB.[19-22] For example, DM patients are more likely to have pulmonary (versus extrapulmonary) TB and to have cavitary TB.[23-25] Given that lung cavities are associated with higher bacterial burden in sputa, TB-DM patients may be important contributors to the spread of TB. However, data indicating higher bacillary burden in sputa from TB-DM versus TB-no DM patients are conflicting.[26-28]

2. Mechanisms for dysfunctional immunity to *Mtb* in DM

DM is characterized by hyperglycemia due to defects in insulin secretion, insulin response, or both.[29] In this review DM will refer mostly to type 2 DM which is the most prevalent form due to its association with obesity. Poorly-controlled DM (chronic hyperglycemia with high HbA_{1c}) is associated with compromised immunity. Studies unrelated to TB show that transient or chronic hyperglycemia alters immune function.[30,31] The chronic up-regulation of glucose can lead to the abnormal accumulation of advanced glycation end products (AGE) that are highly reactive and can bind and modify immune response molecules (e.g. antibodies, complement).[32,33] Excess AGE may also promote constant stimulation of its scavenger receptor, RAGE, leading to aberrant stimulation of phagocytes with activation of NFNB and NADPH oxidase.[34,35] Excessive NADPH activity leads to the accumulation of reactive oxidative species and hence, to oxidative stress.

DM may alter TB immunity through one or several of the metabolic consequences of hyperglycemia. This is indirectly supported by the consistent relationship between blood glucose or HbA_{1c} levels and immune response outcomes in TB.[21,22,36,37] Furthermore, in a longitudinal cohort study, poorly-controlled DM (and not DM in itself) was associated with a higher risk of TB development.[12] However little is known about the underlying mechanisms. One study suggested that oxidative stress underlies altered responses in DM by

showing that PBMCs from DM patients secrete reduced IL-12 in response to *Mtb*, and this defect is corrected upon addition of antioxidants.[38] Otherwise, the mechanisms mediating the altered responses of DM patients to *Mtb* are essentially unexplored. Besides hyperglycemia, we cannot exclude the additional contribution of other host factors that are more frequent in DM patients versus non-DM, such as obesity and dyslipidemias, older age, vitamin D deficiency, anti-inflammatory effects of medications, and co-morbidities, among others.

3. Impact of DM on the natural history of TB

The risk of TB can be stratified into the risk of infection, which occurs in 30% of household contacts, followed by the risk of progression to TB, which occurs in 5-10% of those infected.[39,40] Innate and adaptive immune responses to *Mtb* play key roles in defining these outcomes, with details provided in recent reviews.[41,42] Inhaled *Mtb* is primarily phagocytosed by lung alveolar macrophages where a balance between the host response and the bacterial strategies to evade killing dictate the outcome. The localized inflammatory response includes cytokines (e.g. TNF-α, IL-1β, IL-12 and IL-10), chemokines (CCL2, 3, 4, 5 and CXCL9, CXCL10) and cells from the innate (macrophages, monocytes, NK cells, dendritic cells) and adaptive (CD4+, CD8+ and γδ-T cells and B lymphocytes) immune systems that contribute to the formation of a granuloma, the signature response to TB.[41,42] It is unclear whether DM increases susceptibility to *Mtb* infection or progression to active TB, but evidence for defects in innate and adaptive immunity of DM patients suggests this chronic disease can have an impact on both TB stages.

3.1 Innate immunity to Mtb in DM patients

In humans there are limited data on the events that shape the earliest encounter between *Mtb* and the innate immune system of the DM host. To address this we began in-vitro studies comparing the interaction of *Mtb* with human blood monocytes from *Mtb*-naïve individuals with and without DM. These studies were conducted in the presence of autologous serum because *Mtb* is an intracellular pathogen that can enter monocytes via serum-dependent or -independent pathways.[43] In addition, undefined factors in a DM patient's serum are likely to contribute to the overall immmune response and therefore, “foreign” serum adds additional complexity and potential artifacts to the models. Our findings indicate reduced binding and/or phagocytosis of *Mtb* by monocytes from DM patients versus non-DM controls.[36] This difference was only observed in media with high concentrations of autologous serum ($p=0.03$ with 20% serum). This suggests the defect in *Mtb* entry into DM monocytes lies, in part, in serum opsonins that deposit on the bacterial surface (C3b/iC3b and/or natural antibodies), and/or in their corresponding complement or Fcγ receptors.[43] Since heat-inactivation of sera abolished the difference between the monocytes of DM and control participants, we suspect the defect in DM is more likely to be in serum complement factors leading to C3b/iC3b opsonization and/ or its receptors. We are currently assessing these possibilities, and also evaluating the impact that altered entry of *Mtb* may have on its intracellular survival, replication and generated immune responses within the diabetic monocyte. To determine whether DM also affects monocytes from TB patients, we compared the expression of monocyte surface markers from TB-DM and TB-no DM

patients.[44] By multivariate analysis the monocytes from TB-DM had higher expression of CCR2, which coincides with the reported up-regulation of its ligand CCL2 (MCP-1) in sera from DM patients.[45] Future studies will determine whether this higher CCR2 expression may restrain the migration of diabetic monocytes from the blood to the site of *Mtb* infection in the lung, or within the lung and its regional lymph nodes as suggested in the mouse model of TB and DM.[46]

Once *Mtb* is inside the mononuclear phagocyte, the DM host may have a limited ability to contain its growth due to deficiencies in anti-mycobactericidal pathways. In a longitudinal follow-up of individuals transitioning from pre-DM to DM, researchers noted a reduction in the expression of genes encoding for products that contribute to anti-mycobacterial activities of phagocytes: i) the vacuolar ATPase (ATP6V1H) acidifies the phagosome-lysosome compartment and facilitates *Mtb* killing;[47] ii) the hexokinase 2 (HK2) is an enzyme involved in aerobic glycolysis which is the main energy source for macrophages, and iii) CD28 is required for effective co-stimulation of T lymphocytes by antigen-presenting cells.[48] Functional studies are needed to confirm the relationship between these alterations in gene expression in DM and *Mtb* susceptibility. Another study suggested that DM patients with latent or active TB have reduced expression of antimicrobial peptides (e.g. cathelicidin-LL37, human neutrophil peptide-1 and human beta-defensins-2 and -3), when compared to non-DM controls.[49] These findings are interesting given the growing recognition of the anti-mycobacterial activity of cathelicidin-LL37 by human monocytes and macrophages.[50-52] Expression of this antimicrobial peptide requires vitamin D, and coincidently, DM patients are more likely to have lower serum levels of this vitamin.[53,54] The relationship between cathelicidin-LL37 expression, DM and TB susceptibility deserves further evaluation.

In summary, DM patients appear to have alterations in innate immunity with reduction in *Mtb* phagocytosis, expression of genes that contribute to *Mtb* containment or antigen presentation and secretion of anti-mycobacterial peptides. Peripheral blood monocytes may also have defects in cell trafficking. While DM may first induce immune defects and then predispose to TB, TB and DM patients may also share similar genetic or acquired deficiencies that simultaneously (additive or synergistic) predispose them to both diseases.

3.2 Adaptive immunity to Mtb in DM patients

Studies comparing TB-DM versus TB-no DM have provided insights into the role of DM in adaptive immunity to *Mtb*. At baseline, the plasma from TB-DM patients appears to have higher levels of Th1 (IFN-γ, IL-2) and Th17 (IL-17A, but not IL-22) cytokines, and a lower frequency of natural T-regulatory (CD4+,CD25+,CD127-) cells. However, this is accompanied by higher IL-10 as well, suggesting that both anti- and pro-inflammatory cytokines are up-regulated in TB-DM versus TB-no DM patients.[20] In the broncho alveolar lavage of TB-DM patients, Sun *et al* also found higher baseline IL-10, but lower IFN-γ suggesting the lung compartment may have a biased Th2 response in DM.[55]

Several studies have compared the cytokine responses of TB-DM versus TB-no DM following in-vitro stimulation of white blood cells with complex or purified mycobacterial antigens. The secretion of IFN-γ has been evaluated in all of the reports, but results are conflicting with studies showing either no difference,[56] lower,[37,57] higher[20-22] or variable[19]

IFN-γ secretion by TB-DM versus TB-no DM. The researchers reporting lower ex-vivo IFN-γ secretion by TB-DM patients found that after 6 months of anti-TB therapy the production of IFN-γ returned to normal in patients with well-controlled DM but remained low in those with poor glycemic control.[37] The various studies reporting higher expression of type 1 cytokines in TB-DM versus TB-no DM controls have used various methods and different mycobacterial antigens. We used in-house and commercial (QuantiFERON-Gold) whole blood cell assays to screen for differences in cytokine secretion in response to purified protein derivative (PPD) or recombinant *Mtb*-specific antigens (ESAT-6 and CFP-10) from *Mtb*, respectively. Multivariate analysis indicated that type 1 cytokines (IFN-γ, IL-2, GM-CSF) were significantly higher among TB-DM, and cytokine levels correlated with poor glucose control (high HbA_{1c}).[21,22] Kumar *et al* confirmed and extended these findings by showing that TB-DM patients (versus TB-no DM) secreted higher Th17 cytokines (IL-17 along with IFN-γ or IL-10, but not IL-22) in response to complex (PPD) or purified mycobacterial antigens (CFP-10 or ESAT-6). TB-DM cases also had elevated frequency of single- and double-cytokine producing CD4+ Th1 cells in response to *Mtb* antigens: either IFN-γ, TNF-α or IL-2 alone, or their combination. These higher cytokine responses were not observed upon polyclonal stimulation with anti-CD3, suggesting that the altered response was limited to *Mtb*-specific T cells.[20] Another study also reported higher secretion of IFN-γ by PBMCs from TB-DM versus TB-no DM, but only in response to peptides encoded in the region-of-difference 1 (RD1) of *Mtb* (where ESAT-6 and CFP-10 are encoded). The opposite result (lower IFN-γ by TB-DM) was observed with pools of peptides for RD4, RD6 or RD10.[19]

The conflicting results among the studies regarding type 1 cytokine expression are a reflection of the limited knowledge and difficulties related to studies in DM patients. Such differences may be attributed to variations in the study populations, particularly among the DM patients who can vary extensively in their level of glucose control, sociodemographics, comorbidities or medications as described above. Other factors contributing to variations may be technical, such as the preparation of white blood cells (e.g. whole or diluted blood, purified PBMCs), mycobacterial antigens, or concentration and source of sera (autologous versus commercial AB serum).

Overall, most adaptive immune response studies suggest that TB-DM patients have a hyper-reactive cell-mediated response to *Mtb* antigens. This distinction from non-DM TB patients provides indirect support for dysfunctional immunity in DM patients which leads to TB susceptibility, but this hyper-response is intriguing and requires further evaluation to determine: i) its relationship to the higher susceptibility of DM patients to TB; ii) its role in immune pathology and the more adverse clinical outcomes of TB-DM patients; and iii) its ineffectiveness in *Mtb* elimination. Regarding the latter, two studies suggest that IL-10 is also up-regulated in TB-DM versus TB-no DM patients,[19,20] and one of these further found the ratio of IFN-γ to IL-10 was significantly lower in the TB-DM patients.[19] Thus, the ratio of Th1 and Th17 versus IL10 or other anti-inflammatory cytokines deserves further study in DM patients.

3.3 Contribution of mouse models of type 2 DM to understanding TB immunity in DM patients

Findings in a mouse model of TB and type 2 DM developed by Martens and collaborators complement and expand the observations in humans.[58] In this mouse model C57BL/6 mice are treated with streptozotocin to kill pancreatic beta islet cells which leads to acute (≤ 1 month) or chronic (≥ 3 months) DM, and then they are exposed to a low dose of aerosolized *Mtb*. Researchers found that chronic DM (but not acute) was associated with delayed innate immunity to *Mtb* resulting in late delivery of mycobacterial antigens by dendritic cells from the lung to the draining lymph nodes. This delayed the priming and recruitment of T lymphocytes necessary for the initial restriction of *Mtb* growth.[46] Consistent with this prediction, at 2 months post-infection the DM (versus control mice) had a higher pulmonary *Mtb* burden and more extensive inflammation with higher expression of pro-inflammatory cytokines like IFN-γ.[58] In another mouse model using streptozotocin, Yamashiro *et al* showed that mice with DM were also more susceptible to TB, but had lower expression of IFN-γ and IL-12.[59] The difference in Th1 cytokines between models may be due to technical variations, given that Yamashiro and colleagues infected mice after 3-5 weeks of streptozotocin treatment (acute DM) and with a high, intravenous dose of *Mtb*. These differences between mouse studies are analogous to the variations observed in the patient studies described above, and reinforce the impact of DM chronicity and bacterial burden on the dysregulated immune response seen in the DM host.

4. Future perspectives

The limited data on TB and DM suggest that the DM host has an underperforming innate immune system to *Mtb* that is followed by a hyper-reactive adaptive immune system. The latter exaggerated response contrasts with the immune “compromise” underlying other risk factors for TB such as HIV, TNF-α blockers or genetic defects in the IL-12/IFN-γ axis.[60] Therefore, the enlarging contribution of DM to TB provides a novel perspective and opportunity for scientists to gain further insights into the pathogenesis of TB. We envision that the combination of basic science and epidemiological research teams working together will ultimately lead to the identification of a strategy to stratify the millions of DM patients into those with the highest risk of *Mtb* infection or TB disease. This would provide the basis for recommending LTBI treatment to those with the highest benefit-to-risk ratio, or tailoring TB treatment to those with the worst prognosis (e.g. delayed time to bacterial clearance during treatment or higher risk of death).[18,27] Huge and exciting work is ahead of us!

Acknowledgments

We thank the physicians, researchers, health authorities, field and laboratory workers from the Texas-Mexico border who have contributed throughout the years to the development of basic and epidemiological studies of TB and diabetes.

Funding

NIH 1 R21 AI064297-01-A1 and UL1 TR000371 (to BIR). NIH had no role in the decision to publish.

References

1. World Health Organization. Global tuberculosis report 2012. 2012. Available at: http://apps.who.int/iris/bitstream/10665/75938/1/9789241564502_eng.pdf
2. Morton, R. Phthisiologia, Or a Treatise of Consumptions. London, England: 1694. p. 360
3. Banyai AL. Diabetes and pulmonary tuberculosis. Am Rev Tuberc. 1931; 24:650–67.
4. Oscarsson PN, Silwer H. Incidence of pulmonary tuberculosis among diabetics. Acta Med Scand. 1958; 335:23–48.
5. Root HF. The association of diabetes and tuberculosis. N Engl J Med. 1934; 210:1–13.
6. Prentice AM. The emerging epidemic of obesity in developing countries. Int J Epidemiol. 2006; 35:93–9. [PubMed: 16326822]
7. International Diabetes Federation. Diabetes Atlas. 2009. Available at: http://www.diabetesatlas.org/
8. Dye C. Global epidemiology of tuberculosis. Lancet. 2006; 367:938–40. [PubMed: 16546542]
9. Jeon CY, Harries AD, Baker MA, Hart JE, Kapur A, Lonnroth K, et al. Bi-directional screening for tuberculosis and diabetes: a systematic review. Trop Med Int Health. 2010; 15:1300–14. [PubMed: 20958887]
10. Ottmani SE, Murray MB, Jeon CY, Baker MA, Kapur A, Lonnroth K, et al. Consultation meeting on tuberculosis and diabetes mellitus: meeting summary and recommendations. Int J Tuberc Lung Dis. 2010; 14:1513–17. [PubMed: 21180207]
11. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med. 2008; 5:1091–101.
12. Leung CC, Lam TH, Chan WM, Yew WW, Ho KS, Leung GM, et al. Diabetic control and risk of tuberculosis: a cohort study. Am J Epidemiol. 2008; 167:1486–94. [PubMed: 18400769]
13. Stevenson CR, Forouhi NG, Roglic G, Williams BG, Lauer JA, Dye C, et al. Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence. BMC Public Health. 2007; 7:234. [PubMed: 17822539]
14. Ponce-De-Leon A, Garcia-Garcia MdL, Garcia-Sancho MC, Gomez-Perez FJ, Valdespino-Gomez JL, Olaiz-Fernandez G, et al. Tuberculosis and diabetes in southern Mexico. Diabetes Care. 2004; 27:1584–90. [PubMed: 15220232]
15. Restrepo B, Camerlin A, Rahbar M, Restrepo M, Zarate I, Wing R, et al. Cross-sectional assessment reveals high diabetes prevalence among newly-diagnosed tuberculosis patients. Bull World Health Organ. 2011; 89:352–9. [PubMed: 21556303]
16. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med. 2003; 163:1009–21. [PubMed: 12742798]
17. Pablos-Mendez A, Blustein J, Knirsch CA. The role of diabetes mellitus in the higher prevalence of tuberculosis among Hispanics. Am J Public Health. 1997; 87:574–9. [PubMed: 9146434]
18. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lonnroth K, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. BMC Med. 2011; 9:81. [PubMed: 21722362]
19. Al-Attiyah RJ, Mustafa AS. Mycobacterial antigen-induced T helper type 1 (Th1) and Th2 reactivity of peripheral blood mononuclear cells from diabetic and non-diabetic tuberculosis patients and Mycobacterium bovis bacilli Calmette-Guerin (BCG)-vaccinated healthy subjects. Clin Exp Immunol. 2009; 158:64–73. [PubMed: 19737232]
20. Kumar NP, Sridhar R, Banurekha VV, Jawahar MS, Nutman TB, Babu S. Expansion of pathogen-specific T-helper 1 and T-helper 17 cells in pulmonary tuberculosis with coincident type 2 diabetes mellitus. J Infect Dis. 2013; 208:739–48. [PubMed: 23715661]
21. Restrepo B, Fisher-Hoch S, Pino P, Salinas A, Rahbar MH, Mora F, et al. Tuberculosis in poorly controlled type 2 diabetes: altered cytokine expression in peripheral white blood cells. Clin Infect Dis. 2008; 47:634–41. [PubMed: 18652554]
22. Walsh M, Camerlin A, Miles R, Pino P, Martinez P, Mora-Guzman F, et al. Sensitivity of Interferon-gamma release assays is not compromised in tuberculosis patients with diabetes. Int J Tuberc Lung Dis. 2010; 15:179–84. [PubMed: 21219678]

23. Reis-Santos B, Locatelli R, Horta BL, Faerstein E, Sanchez MN, Riley LW, et al. Socio-Demographic and Clinical Differences in Subjects with Tuberculosis with and without Diabetes Mellitus in Brazil - A Multivariate Analysis. PLoS ONE. 2013; 8:e62604. [PubMed: 23638123]
24. Restrepo BI, Fisher-Hoch SP, Crespo JG, Whitney E, Perez A, Smith B, et al. Type 2 diabetes and tuberculosis in a dynamic bi-national border population. Epidemiol Infect. 2007; 135:483–91. [PubMed: 16863600]
25. Lin JN, Lai CH, Chen YH, Lee SS, Tsai SS, Huang CK, et al. Risk factors for extra-pulmonary tuberculosis compared to pulmonary tuberculosis. Int J Tuberc Lung Dis. 2009; 13:620–5. [PubMed: 19383196]
26. Bacakoglu F, Basoglu OO, Cok G, Sayiner A, Ates M. Pulmonary tuberculosis in patients with diabetes mellitus. Respiration. 2001; 68:595–600. [PubMed: 11786714]
27. Restrepo B, Fisher-Hoch S, Smith B, Jeon S, Rahbar MH, McCormick J. Mycobacterial clearance from sputum is delayed during the first phase of treatment in patients with diabetes. Am J Trop Med Hyg. 2008; 79:541–4. [PubMed: 18840741]
28. Guler M, Unsal E, Dursun B, Aydln O, Capan N. Factors influencing sputum smear and culture conversion time among patients with new case pulmonary tuberculosis. Int J Clin Pract. 2007; 61:231–5. [PubMed: 17166185]
29. American Diabetes Association. Standards of Medical Care in Diabetes-2010. Diabetes Care. 2010; 33:S11–S61. [PubMed: 20042772]
30. Nandy D, Janardhanan R, Mukhopadhyay D, Basu A. Effect of hyperglycemia on human monocyte activation. J Investig Med. 2011; 59:661–7.
31. Hair PS, Echague CG, Rohn RD, Krishna NK, Nyalwidhe JO, Cunnion KM. Hyperglycemic conditions inhibit C3-mediated immunologic control of Staphylococcus aureus. J Transl Med. 2012; 10:35. [PubMed: 22390383]
32. Dolhofer R, Siess EA, Wieland OH. Nonenzymatic glycation of immunoglobulins leads to an impairment of immunoreactivity. Biol Chem Hoppe Seyler. 1985; 366:361–6. [PubMed: 4026990]
33. Niemann MA, Bhown AS, Miller EJ. The principal site of glycation of human complement factor B. Biochem J. 1991; 274(Pt 2):473–80. [PubMed: 2006911]
34. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001; 414:813–20. [PubMed: 11742414]
35. Lapolla A, Fedele D, Seraglia R, Catinella S, Traldi P. Matrix-assisted laser desorption/ionization capabilities in the study of non-enzymatic protein glycation. Rapid Commun Mass Spectrom. 1994; 8:645–52. [PubMed: 7949331]
36. Gomez DI, Twahirwa M, Schlesinger LS, Restrepo BI. Reduced Mycobacterium tuberculosis association with monocytes from diabetes patients that have poor glucose control. Tuberculosis (Edinb). 2013; 93:192–7. [PubMed: 23131496]
37. Tsukaguchi K, Okamura H, Matsuzawa K, Tamura M, Miyazaki R, Tamaki S, et al. [Longitudinal assessment of IFN-gamma production in patients with pulmonary tuberculosis complicated with diabetes mellitus]. Kekkaku. 2002; 77:409–13. [PubMed: 12073618]
38. Tan KS, Lee KO, Low KC, Gamage AM, Liu Y, Tan GY, et al. Glutathione deficiency in type 2 diabetes impairs cytokine responses and control of intracellular bacteria. J Clin Invest. 2012; 122:2289–300. [PubMed: 22546856]
39. Grzybowski S, Barnett GD, Styblo K. Contacts of cases of active pulmonary tuberculosis. Bull Int Union Tuberc. 1975; 50:90–106. [PubMed: 1218291]
40. Richeldi L, Ewer K, Losi M, Bergamini BM, Roversi P, Deeks J, et al. T cell-based tracking of multidrug resistant tuberculosis infection after brief exposure. Am J Respir Crit Care Med. 2004; 170:288–95. [PubMed: 15130907]
41. Guirado E, Schlesinger LS. Modeling the Mycobacterium tuberculosis Granuloma - the Critical Battlefield in Host Immunity and Disease. Front Immunol. 2013; 4:98. [PubMed: 23626591]
42. Ernst JD. The immunological life cycle of tuberculosis. Nat Rev Immunol. 2012; 12:581–91. [PubMed: 22790178]
43. Schlesinger LS. Entry of Mycobacterium tuberculosis into mononuclear phagocytes. Curr Top Microbiol Immunol. 1996; 215:71–96. [PubMed: 8791710]

44. Stew SS, Martinez PJ, Mora-Guzman F, Schlesinger LS, Restrepo BI. Differential expression of monocyte surface markers among TB patients with diabetes co-morbidity. Tuberculosis (Edinb). 2013; 93(Suppl 1):S78–82. [PubMed: 24388654]
45. Panee J. Monocyte Chemoattractant Protein 1 (MCP-1) in obesity and diabetes. Cytokine. 2012; 60:1–12. [PubMed: 22766373]
46. Vallerskog T, Martens GW, Kornfeld H. Diabetic mice display a delayed adaptive immune response to Mycobacterium tuberculosis. J Immunol. 2010; 184:6275–82. [PubMed: 20421645]
47. Molina MF, Qu HQ, Rentfro AR, Nair S, Lu Y, Hanis CL, et al. Decreased expression of ATP6V1H in type 2 diabetes: a pilot report on the diabetes risk study in Mexican Americans. Biochem Biophys Res Commun. 2011; 412:728–31. [PubMed: 21871445]
48. Qu HQ, Rentfro AR, Lu Y, Nair S, Hanis CL, McCormick JB, et al. Host susceptibility to tuberculosis: insights from a longitudinal study of gene expression in diabetes. Int J Tuberc Lung Dis. 2012; 16:370–2. [PubMed: 22230325]
49. Gonzalez-Curiel I, Castaneda-Delgado J, Lopez-Lopez N, Araujo Z, Hernandez-Pando R, Gandara-Jasso B, et al. Differential expression of antimicrobial peptides in active and latent tuberculosis and its relationship with diabetes mellitus. Hum Immunol. 2011; 72:656–62. [PubMed: 21539878]
50. Fabri M, Stenger S, Shin DM, Yuk JM, Liu PT, Realegeno S, et al. Vitamin D is required for IFN-gamma-mediated antimicrobial activity of human macrophages. Sci Transl Med. 2011; 3:104ra102.
51. Liu PT, Modlin RL. Human macrophage host defense against Mycobacterium tuberculosis. Curr Opin Immunol. 2008; 20:371–6. [PubMed: 18602003]
52. Martineau AR, Nhamoyebonde S, Oni T, Rangaka MX, Marais S, Bangani N, et al. Reciprocal seasonal variation in vitamin D status and tuberculosis notifications in Cape Town, South Africa. Proc Natl Acad Sci U S A. 2011; 108:19013–17. [PubMed: 22025704]
53. Mathieu C, Gysemans C, Giulietti A, Bouillon R. Vitamin D and diabetes. Diabetologia. 2005; 48:1247–57. [PubMed: 15971062]
54. Palomer X, Gonzalez-Clemente JM, Blanco-Vaca F, Mauricio D. Role of vitamin D in the pathogenesis of type 2 diabetes mellitus. Diabetes Obes Metab. 2008; 10:185–97. [PubMed: 18269634]
55. Sun Q, Zhang Q, Xiao H, Cui H, Su B. Significance of the frequency of CD4+CD25+C. Respirology. 2012; 17:876–82. [PubMed: 22524702]
56. Stalenhoef JE, Alisjahbana B, Nelwan EJ, van d V, Ottenhoff TH, van der Meer JW, et al. The role of interferon-gamma in the increased tuberculosis risk in type 2 diabetes mellitus. Eur J Clin Microbiol Infect Dis. 2008; 27:97–103. [PubMed: 17962984]
57. Tsukaguchi K, Okamura H, Ikuno M, Kobayashi A, Fukuoka A, Takenaka H, et al. [The relation between diabetes mellitus and IFN-gamma, IL-12 and IL-10 productions by CD4+ alpha beta T cells and monocytes in patients with pulmonary tuberculosis]. Kekkaku. 1997; 72:617–22. [PubMed: 9423299]
58. Martens GW, Arikan MC, Lee J, Ren F, Greiner D, Kornfeld H. Tuberculosis Susceptibility of Diabetic Mice. Am J Respir Cell Mol Biol. 2007; 37:518–24. [PubMed: 17585110]
59. Yamashiro S, Kawakami K, Uezu K, Kinjo T, Miyagi K, Nakamura K, et al. Lower expression of Th1-related cytokines and inducible nitric oxide synthase in mice with streptozotocin-induced diabetes mellitus infected with Mycobacterium tuberculosis. Clin Exp Immunol. 2005; 139:57–64. [PubMed: 15606614]
60. Flynn JL, Chan J. Immunology of tuberculosis. Annu Rev Immunol. 2001; 19:93–129. [PubMed: 11244032]