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Type 2 diabetes - tuberculosis co-morbidity is associated with diminished circulating levels of IL-20 subfamily of cytokines

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[2]National Institute for Research in Tuberculosis, Chennai, India Running title: IL-20 subfamily of cytokines in TB-DM

Abstract

IL-20 subfamily of cytokines play an important role in both host defense mechanisms and glucose metabolism. Since, the interaction between tuberculosis (TB) and diabetes (DM) involves both of the above processes, we examined the association of IL-20 subfamily of cytokines in TB-DM co-morbidity. We examined circulating plasma cytokine levels in individuals with active TB with (PTB-DM) or without (PTB) diabetes and also those with latent TB with (LTB-DM) or without (LTB) diabetes. PTB-DM is characterized by diminished circulating levels of IL-19, IL-20, IL-22 and IL-24 but increased levels of IL-10. Similarly, LTB-DM was also characterized by diminished circulating levels of IL-10, IL-19, IL-20 and IL-24 but increased levels of IL-22. Moreover, there was a significant negative correlation of IL-10, IL-19, IL-20, IL-22 and IL-24 levels with hemoglobin A1C (HbA1c) levels in both PTB and/or LTB individuals. Finally, PTB is characterized by diminished levels of IL-19, IL-20, IL-22 and IL-24 in comparison to LTB individuals. Our data reveal that coincident diabetes in either PTB or LTB is characterized by decreased production of the IL-20 subfamily of cytokines and suggest that these cytokines might play an important role in pathogenesis or protection.

Keywords

Bacterial; Cytokines; Tuberculosis; Diabetes; IL-10; IL-20 subfamily

INTRODUCTION

The IL-20 family of cytokines consists of five members: IL-19, IL-20, IL-22, IL-24 and IL-26 [1, 2]. These cytokines elicit different host defense mechanisms, especially from epithelial cells, during a variety of infections and are also pivotal in maintenance of tissue

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integrity and homeostasis [1, 3, 4]. They contribute to the tissue healing processes in injury or infection and promote innate immune responses to limit damage associated with viral and bacterial infections [1, 2, 5]. Thus, the IL-20 subfamily of cytokines exert profound effects on host innate immune responses, including promoting the production of antimicrobial peptides, strengthening barrier function at epithelial and mucosal surfaces and facilitating recruitment of leukocytes and their activation at the site of inflammation [6–8]. More recently, these cytokines have been shown to be involved in host metabolic processes [9, 10].

One of the prime examples of the interplay between infectious disease and metabolic disorders is the intimate association of pulmonary tuberculosis (PTB) with diabetes mellitus (DM) [11]. Typically, DM is thought to increase the risk of developing active TB by 3 fold [12] and to increase the severity of disease as well as treatment failure, relapse and death [11, 13]. Despite the clinical and public health significance posed by the dual burden of TB and DM, very little is known about the immunological and biochemical mechanisms underlying this susceptibility. Increased susceptibility to TB in TB-DM co-morbidity could be influenced by a variety of factors including those related directly to hyperglycemia and insulin resistance and to those indirect effects on immune cell function [11, 13, 14]. We and others have previously shown that circulating levels of cytokines, including both pro- and anti-inflammatory cytokines are profoundly altered in TB-DM [15–17]. While PTB-DM is associated with elevated levels of most pro-inflammatory cytokines, latent tuberculosis (LTB) in conjunction with DM is associated with diminished circulating levels of these cytokines [15, 18].

Amongst the cytokines altered in PTB-DM and LTB-DM are IL-10 and IL-22, two of the cytokines belonging to the above mentioned IL-20 subfamily [15, 19]. Moreover, IL-22 was the only cytokine that exhibited an opposite profile to other pro- or anti- inflammatory cytokines, in that it was increased in LTB-DM and decreased in PTB-DM [15, 19]. Interestingly, IL-22 has also recently been shown to exert profound effects on insulin sensitivity and glycemic control [9, 10]. Therefore, we examined the panel of IL-20 subfamily of cytokines in PTB-DM versus PTB individuals as well as in LTB-DM versus LTB individuals. Our data show that with the exception of IL-10 and IL-22, most of the other cytokines examined, including IL-19, IL-20 and IL-24 are diminished in both PTB and LTB with coincident DM.

MATERIALS AND METHODS

Ethics statement

All individuals were examined as part of a natural history study protocol approved by the Institutional Review Board of the National Institute of Research in Tuberculosis, and informed written consent was obtained from all participants.

Study Population

We studied a group of 88 individuals with PTB, 44 of whom had DM (PTB-DM) and 44 of whom had no diabetes (PTB). We also studied another 88 individuals with LTB, 44 of whom had DM (LTB-DM) and 44 of whom had no diabetes (LTB). This group of

individuals had been previously assessed for Type 1, Type 2 and Type 17 cytokines [19]. The baseline characteristics including demographics and biochemical parameters of the study population are shown in Table 1. PTB diagnosis was based on culture positivity of sputum samples. Two sputum samples per subject were examined by fluorescence microscopy, processed by the modified Petroff's method and cultured on Lowenstein-Jensen medium. Presence of acid-fast bacilli (AFB) in sputum smears was also documented. LTB was diagnosed on the basis of being positive for the Mantoux skin test (induration > 12mm) using 2TU PPD (Serum Statens Institute) and also being Quantiferon-in-Tube Gold assay positive with no chest symptoms of TB and a normal chest radiograph [20]. Type 2 DM was diagnosed on the basis of glycated hemoglobin (HbA1c) levels and random blood glucose, according to the American Diabetes Association criteria (all Type 2 DM individuals had HbA1c levels > 6.5% and random blood glucose > 200 mg/dL) [21]. All the individuals were HIV negative. All individuals were anti-tuberculous treatment naïve. Biochemical parameters, including plasma glucose and HbA1c were obtained using standardized techniques.

Plasma ELISA

Plasma cytokines were measured using ELISA, according to the manufacturer's instructions. The parameters analyzed were IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26. All were from R&D Systems except IL-26, which was from eBiosciences. The threshold of detection was: IL-10 - 3.2 pg/ml; IL-19 - 3.2 pg/ml; IL-20 - 1.2 pg/ml; IL-22 - 5.6 pg/ml; IL-24 - 6.5 pg/ml and IL-26 - 2.2 pg/ml.

Statistical Analysis

Geometric means were used for measurements of central tendency. Statistically significant differences between two groups were analyzed using the nonparametric Mann-Whitney test. Multiple comparisons were corrected using the Holm's correction. Correlations were calculated using Spearman rank correlation. Multivariate linear models were built to test the association between the cytokine levels and the independent variables including age, sex and BMI. Analyses were performed using GraphPad PRISM Version 5.01 or R Version 2.15.2.

RESULTS

PTB-DM is characterized by diminished circulating levels of IL-20 subfamily of cytokines

We determined the influence of DM on IL-20 the subfamily of cytokines in PTB by measuring the circulating levels of IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26 in individuals with PTB-DM (n=44) or PTB alone (n=44). As shown in Figure 1, the systemic levels of most IL-20 subfamily of cytokines – IL-19 (geometric mean (GM) of 13.33 pg/ml in PTB-DM compared to 25.43 pg/ml in PTB), IL-20 (GM of 28.33 pg/ml in PTB-DM compared to 35.32 pg/ml in PTB), IL-22 (GM of 10.03 pg/ml in PTB-DM compared to 31.30 pg/ml in PTB) and IL-24 (GM of 54.66 pg/ml in PTB-DM compared to 74.44 pg/ml in PTB) were significantly lower in PTB-DM compared to PTB individuals. Surprisingly, only IL-10 (GM of 161.8 pg/ml in PTB-DM compared to 102.8 pg/ml in PTB) levels were significantly higher in PTB-DM compared to PTB individuals. In contrast, IL-26 levels were not significantly different between the two groups. Finally, multivariate logistic regression

analysis did not reveal any effect of age, sex or BMI on the cytokine levels in the two groups (data not shown). Thus, PTB with diabetes is associated with diminished levels of IL-20 subfamily of cytokines but enhanced IL-10 levels at homeostasis.

LTB-DM is also characterized by diminished circulating levels of IL-20 subfamily of cytokines

We determined the influence of DM on the IL-20 subfamily of cytokines in LTB by measuring the circulating levels of IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26 in individuals with LTB-DM (n=44) or LTB alone (n=44). As shown in Figure 2, the systemic levels of most IL-20 subfamily of cytokines – IL-19 (geometric mean (GM) of 35.68 pg/ml in PTB-DM compared to 48.42 pg/ml in PTB), IL-20 (GM of 36.92 pg/ml in PTB-DM compared to 53.37 pg/ml in PTB) and IL-24 (GM of 47.72 pg/ml in PTB-DM compared to 65.27 pg/ml in PTB) were significantly lower in PTB-DM compared to PTB individuals. In addition, IL-10 (GM of 56.89 pg/ml in PTB-DM compared to 96.87 pg/ml in PTB) circulating levels were also significantly lower in PTB-DM compared to PTB individuals. Surprisingly, only IL-22 (GM of 273 pg/ml in PTB-DM compared to 83.41 pg/ml in PTB) levels were significantly higher in PTB-DM compared to PTB individuals. In contrast, IL-26 levels were not significantly different between the two groups. Finally, multivariate logistic regression analysis did not reveal any effect of age, sex or BMI on the cytokine levels in the two groups (data not shown). Thus, LTB with diabetes is also associated with diminished levels of IL-20 subfamily of cytokines but enhanced IL-22 levels at homeostasis.

Relationship between systemic cytokines and HbA1c levels in PTB

HbA1c is a very accurate indicator of the level of diabetic control, and increased values reflect poor control [21]. Since HbA1c levels have been previously shown to correlate with Type 1 and Type 17 cytokine levels in active TB individuals [15, 17], we wanted to examine if this relationship exists for IL-20 subfamily of cytokines as well. Thus, we assessed the association IL-10, IL-19, IL-20, IL-22, IL-22 and IL-24 with HbA1c levels (in %) in all the PTB individuals with DM or no-DM in the study. As shown in Figure 3, the systemic levels of IL-19, IL-20, IL-22 and IL-24 all exhibit a significantly negative correlation with HbA1c levels. In marked contrast, IL-10, the only cytokine present at significantly higher levels in PTB-DM was also the only cytokine that exhibited a significantly positive relationship with HbA1c levels. This suggests that perturbations in the homeostatic levels of different IL-20 subfamily of cytokines in PTB is influenced by the glycemic status.

Relationship between systemic cytokines and HbA1c levels in LTB

Since HbA1c levels have been previously shown to correlate with Type 1 and Type 17 cytokine levels in latent TB individuals [19], we also wanted to examine if this relationship exists for IL-20 subfamily of cytokines as well. Thus, we assessed the association IL-10, IL-19, IL-20, IL-22, IL-22 and IL-24 with HbA1c levels (in %) in all the LTB individuals with DM or no-DM in the study. As shown in Figure 4, the systemic levels of IL-10, IL-19, IL-20 and IL-24 all exhibit a significantly negative correlation with HbA1c levels. In marked contrast, IL-22, the only cytokine present at significantly higher levels in LTB-DM was also the only cytokine that exhibited a significantly positive relationship with HbA1c

levels. This suggests that perturbations in the homeostatic levels of different IL-20 subfamily of cytokines in LTB is also influenced by the glycemic status.

PTB is characterized by elevated IL-10 and IL-26 but diminished circulating levels of other IL-20 subfamily of cytokines

We wanted to assess the differences in the IL-20 subfamily of cytokines between active and latent TB infection, independent of diabetes. To this end, we measured the circulating levels of IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26 in individuals with PTB (n=44) or LTB (n=44) alone. As shown in Table 2, the systemic levels of most IL-20 subfamily of cytokines – IL-19, IL-20, IL-22 and IL-24 were significantly lower in PTB compared to LTB individuals. In contrast, IL-10 and IL-26 levels were significantly increased in PTB compared to LTB individuals. Thus, PTB is also associated with altered circulating levels of IL-20 subfamily of cytokines, independent of DM.

DISCUSSION

The role of the IL-20 subfamily of cytokines is still not completely clear. While IL-22, the most well studied cytokine amongst the family, is indispensable for host defense during infection with extracellular pathogens (*Citrobacter rodentium* [22], *Klebsiella pneumoniae* [23] or yeast [24]), IL-19, IL-20 and IL-24 are known to exert host detrimental effects during infection with *Staphyloccus aureus* [25]. So, depending on the infectious context and the exact cytokine examined, they can play a protective or pathogenic role. Type 2 DM is associated with dysregulation in immune function with changes in the components of both the innate and adaptive immune system including altered levels of specific cytokines and chemokines, changes in the number and activation state of various immune cell subsets and increased apoptosis and tissue fibrosis [26]. How these alterations impact the immune response to infections or bystander antigens remains unclear. We have previously shown that host protective Type 1 and Type 17 cytokines are present at exacerbated levels in PTB-DM, while being present at diminished levels in LTB-DM [15, 19]. Thus, DM might play a major role in promoting susceptibility to TB disease by altering the cytokine milieu. Therefore, we examined the association of IL-20 subfamily of cytokines with PTB-DM or LTB-DM.

Our study on the homeostatic (or steady state) levels of IL-20 subfamily of cytokines reveals several major features. First, IL-10, which is known to play a important role in the host immune response to TB [27], displays a dichotomous profile, with PTB-DM individuals having higher levels and LTB-DM individuals having lower levels of IL-10 compared to their respective counterparts without DM. In conjunction with the fact that IL-10 is present at significantly higher levels in PTB compared to LTB in the absence of DM, it appears that the predominant effect on the homeostatic levels of IL-10 in TB-DM co-morbidity is exerted by the stage of TB infection or disease. Second, IL-22 also displays a differential profile in PTB-DM and LTB-DM but in the opposite direction of IL-10. The role of IL-22 in resistance or susceptibility to TB infection/disease is still not completely clear [28], although mouse models of infection do not indicate a major role [29]. In contrast, IL-22 has marked effects on metabolic processes, especially those related to insulin and glucose metabolism. Thus, IL-22 is known to dramatically reduce blood glucose levels, alleviate hyperglycemia

and hepatic steatosis, restore insulin sensitivity, modulate lipid metabolism and protect against the development of metabolic syndrome [9, 10]. Hence, the profile of IL-22 production in diabetes coincident with active or latent tuberculosis, suggests that IL-22 potentially can exert major effects on this co-morbidity, including effects on TB and DM pathogenesis, which requires further study.

Third, all the major IL-20 subfamily of cytokines that signal through the IL-20 receptor (IL-19, IL-20 and IL-24) - display exactly similar profiles in PTB -DM and LTB-DM. The diminished production of these cytokines in both TB infection states suggests that they might exert protective effects against TB infection and disease, although at this point the data is merely associative. Also, of interest, IL-24 has been shown to worsen glucose tolerance by inducing beta cell oxidative and ER stress [9], but whether IL-19 and IL-20 also do the same is not known. Finally, IL-26, which clearly acts as a pro-inflammatory cytokine in a variety of infectious and inflammatory settings [30, 31], appears not to be modulated in TB-DM co-morbidity. This does not rule out a role for IL-26 in host immunity against TB since IL-26 produced by alveolar macrophages has been shown to exert antibacterial host defense in experimental human infection locally [32]. Our data also suggest that it is poor glycemic control (or underlying mechanisms of insulin resistance) that may be associated with the modulation of systemic levels of the IL-20 subfamily of cytokines. This is clearly evident from the positive or negative relationship exhibited by the IL-20 subfamily of cytokines with HbA1c levels.. Finally, the influence of DM on the homeostatic levels of systemic levels of these cytokines appears to be independent of age, sex or BMI.

Typically, Type 2 DM is known to be associated with a chronic inflammatory milieu with activation of the innate immune system and increased production of pro-inflammatory cytokines[33]. Moreover, we and others have previously shown that DM in the context of active pulmonary TB is associated with heightened inflammatory response and elevated levels of Type 1, Type 2 and other pro-inflammatory cytokines [15–17]. In contrast, DM in the context of latent TB is associated with a down modulated inflammatory response and diminished levels of Type 1, Type 2 and Type 17 cytokines. This study adds to our understanding of systemic cytokine regulation in PTB and LTB with coincident DM and reveals interesting facets of the IL-20 subfamily of cytokines in this co-morbid state. Our study also examines the important association of poor glucose control and/or nascent or full-blown insulin resistance with PTB and LTB and offers important insights into the potential mechanism by which Type 2 DM could influence the acquisition of infection or progression from latent to active tuberculosis. Our study did not address the role of the IL-20 family of cytokines in TB-uninfected individuals with or without DM. However, our main goal in this study was to examine the potential impact of DM on either progression of LTB to PTB (which was studied by contrasting responses LTB-DM versus LTB) or on PTB disease per se (which was studied by contrasting responses in PTB-DM versus PTB). It would be important in future studies to also examine the potential impact of DM on acquisition of infection by contrasting LTB individuals with TB-uninfected individuals. Our study also did not address the effect of TB treatment on the cytokine responses in PTB individuals (with or without DM) and we plan to address this in future experiments. Our data support the growing body of evidence that suggests immune dysfunction is an integral part of DM and that this dysregulation could affect immunity to pathogens. While our study by design was

cross-sectional and cannot delineate causal parameters, it does provide an impetus to perform longitudinal studies examining the role of immune compromise in the progression from latent to active TB and the role played by poor glucose control. In a broader context, the present study suggests that the IL-20 subfamily of cytokine is associated with the regulation of both host immunity and metabolic processes in the context of co-morbidity.

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References

1. Ouyang W, Rutz S, Crellin NK, Valdez PA, Hymowitz SG. Regulation and functions of the IL-10 family of cytokines in inflammation and disease. Annu Rev Immunol. 2011; 29:71–109. [PubMed: 21166540]
2. Rutz S, Wang X, Ouyang W. The IL-20 subfamily of cytokines--from host defence to tissue homeostasis. Nat Rev Immunol. 2014; 14:783–95. [PubMed: 25421700]
3. Leng RX, Pan HF, Tao JH, Ye DQ. IL-19, IL-20 and IL-24: potential therapeutic targets for autoimmune diseases. Expert Opin Ther Targets. 2011; 15:119–26. [PubMed: 21073280]
4. Sabat R, Ouyang W, Wolk K. Therapeutic opportunities of the IL-22-IL-22R1 system. Nat Rev Drug Discov. 2013; 13:21–38. [PubMed: 24378801]
5. Sabat R. IL-10 family of cytokines. Cytokine Growth Factor Rev. 2010; 21:315–24. [PubMed: 21112807]
6. Boniface K, Bernard FX, Garcia M, Gurney AL, Lecron JC, Morel F. IL-22 inhibits epidermal differentiation and induces proinflammatory gene expression and migration of human keratinocytes. J Immunol. 2005; 174:3695–702. [PubMed: 15749908]
7. Eidenschenk C, Rutz S, Liesenfeld O, Ouyang W. Role of IL-22 in microbial host defense. Curr Top Microbiol Immunol. 2014; 380:213–36. [PubMed: 25004820]
8. Wolk K, Kunz S, Witte E, Friedrich M, Asadullah K, Sabat R. IL-22 increases the innate immunity of tissues. Immunity. 2004; 21:241–54. [PubMed: 15308104]
9. Hasnain SZ, Borg DJ, Harcourt BE, Tong H, Sheng YH, Ng CP, Das I, Wang R, Chen AC, Loudovaris T, Kay TW, Thomas HE, Whitehead JP, Forbes JM, Prins JB, McGuckin MA. Glycemic control in diabetes is restored by therapeutic manipulation of cytokines that regulate beta cell stress. Nat Med. 2014; 20:1417–26. [PubMed: 25362253]
10. Wang X, Ota N, Manzanillo P, Kates L, Zavala-Solorio J, Eidenschenk C, Zhang J, Lesch J, Lee WP, Ross J, Diehl L, van Bruggen N, Kolumam G, Ouyang W. Interleukin-22 alleviates metabolic disorders and restores mucosal immunity in diabetes. Nature. 2014; 514:237–41. [PubMed: 25119041]
11. Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infect Dis. 2009; 9:737–46. [PubMed: 19926034]
12. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med. 2008; 5:e152. [PubMed: 18630984]
13. Martinez N, Kornfeld H. Diabetes and immunity to tuberculosis. Eur J Immunol. 2014; 44:617–26. [PubMed: 24448841]
14. Restrepo BI, Schlesinger LS. Host-pathogen interactions in tuberculosis patients with type 2 diabetes mellitus. Tuberculosis (Edinb). 2013; 93(Suppl):S10–4. [PubMed: 24388642]
15. Kumar NP, Sridhar R, Banurekha VV, Jawahar MS, Fay MP, Nutman TB, Babu S. Type 2 diabetes mellitus coincident with pulmonary tuberculosis is associated with heightened systemic type 1, type 17, and other proinflammatory cytokines. Ann Am Thorac Soc. 2013; 10:441–9. [PubMed: 23987505]

16. 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]
17. Restrepo BI, Fisher-Hoch SP, Pino PA, Salinas A, Rahbar MH, Mora F, Cortes-Penfield N, McCormick JB. Tuberculosis in poorly controlled type 2 diabetes: altered cytokine expression in peripheral white blood cells. Clin Infect Dis. 2008; 47:634–41. [PubMed: 18652554]
18. Kumar NP, George PJ, Kumaran P, Dolla CK, Nutman TB, Babu S. Diminished systemic and antigen-specific type 1, type 17, and other proinflammatory cytokines in diabetic and prediabetic individuals with latent Mycobacterium tuberculosis infection. J Infect Dis. 2014; 210:1670–8. [PubMed: 24907382]
19. Kumar NP, George PJ, Kumaran P, Dolla CK, Nutman TB, Babu S. Diminished Systemic and Antigen-Specific Type 1, Type 17, and Other Proinflammatory Cytokines in Diabetic and Prediabetic Individuals With Latent Mycobacterium tuberculosis Infection. J Infect Dis. 2014
20. Andrade BB, Pavan Kumar N, Mayer-Barber KD, Barber DL, Sridhar R, Rekha VV, Jawahar MS, Nutman TB, Sher A, Babu S. Plasma heme oxygenase-1 levels distinguish latent or successfully treated human tuberculosis from active disease. PLoS One. 2013; 8:e62618. [PubMed: 23671613]
21. Association AD. Standards of medical care in diabetes--2013. Diabetes Care. 2013; 36(Suppl 1):S11–66. [PubMed: 23264422]
22. Zheng Y, Valdez PA, Danilenko DM, Hu Y, Sa SM, Gong Q, Abbas AR, Modrusan Z, Ghilardi N, de Sauvage FJ, Ouyang W. Interleukin-22 mediates early host defense against attaching and effacing bacterial pathogens. Nat Med. 2008; 14:282–9. [PubMed: 18264109]
23. Aujla SJ, Chan YR, Zheng M, Fei M, Askew DJ, Pociask DA, Reinhart TA, McAllister F, Edeal J, Gaus K, Husain S, Kreindler JL, Dubin PJ, Pilewski JM, Myerburg MM, Mason CA, Iwakura Y, Kolls JK. IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. Nat Med. 2008; 14:275–81. [PubMed: 18264110]
24. De Luca A, Zelante T, D'Angelo C, Zagarella S, Fallarino F, Spreca A, Iannitti RG, Bonifazi P, Renauld JC, Bistoni F, Puccetti P, Romani L. IL-22 defines a novel immune pathway of antifungal resistance. Mucosal Immunol. 2010; 3:361–73. [PubMed: 20445503]
25. Myles IA, Fontecilla NM, Valdez PA, Vithayathil PJ, Naik S, Belkaid Y, Ouyang W, Datta SK. Signaling via the IL-20 receptor inhibits cutaneous production of IL-1beta and IL-17A to promote infection with methicillin-resistant Staphylococcus aureus. Nat Immunol. 2013; 14:804–11. [PubMed: 23793061]
26. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nat Rev Immunol. 2011; 11:98–107. [PubMed: 21233852]
27. Redford PS, Murray PJ, O'Garra A. The role of IL-10 in immune regulation during M. tuberculosis infection. Mucosal Immunol. 2011; 4:261–70. [PubMed: 21451501]
28. Scriba TJ, Kalsdorf B, Abrahams DA, Isaacs F, Hofmeister J, Black G, Hassan HY, Wilkinson RJ, Walzl G, Gelderbloem SJ, Mahomed H, Hussey GD, Hanekom WA. Distinct, specific IL-17- and IL-22-producing CD4+ T cell subsets contribute to the human anti-mycobacterial immune response. J Immunol. 2008; 180:1962–70. [PubMed: 18209095]
29. Wilson MS, Feng CG, Barber DL, Yarovinsky F, Cheever AW, Sher A, Grigg M, Collins M, Fouser L, Wynn TA. Redundant and pathogenic roles for IL-22 in mycobacterial, protozoan, and helminth infections. J Immunol. 2010; 184:4378–90. [PubMed: 20220096]
30. Anuradha R, George PJ, Hanna LE, Kumaran P, Chandrasekaran V, Nutman TB, Babu S. Expansion of parasite-specific CD4+ and CD8+ T cells expressing IL-10 superfamily cytokine members and their regulation in human lymphatic filariasis. PLoS Negl Trop Dis. 2014; 8:e2762. [PubMed: 24699268]
31. Corvaisier M, Delneste Y, Jeanvoine H, Preisser L, Blanchard S, Garo E, Hoppe E, Barre B, Audran M, Bouvard B, Saint-Andre JP, Jeannin P. IL-26 is overexpressed in rheumatoid arthritis and induces proinflammatory cytokine production and Th17 cell generation. PLoS Biol. 2012; 10:e1001395. [PubMed: 23055831]
32. Che KF, Tengvall S, Levanen B, Silverpil E, Smith ME, Awad M, Vikstrom M, Palmberg L, Qvarfordt I, Skold M, Linden A. Interleukin-26 in antibacterial host defense of human lungs.

Effects on neutrophil mobilization. Am J Respir Crit Care Med. 2014; 190:1022–31. [PubMed: 25291379]

33. Nikolajczyk BS, Jagannathan-Bogdan M, Shin H, Gyurko R. State of the union between metabolism and the immune system in type 2 diabetes. Genes Immun. 2011; 12:239–50. [PubMed: 21390053]

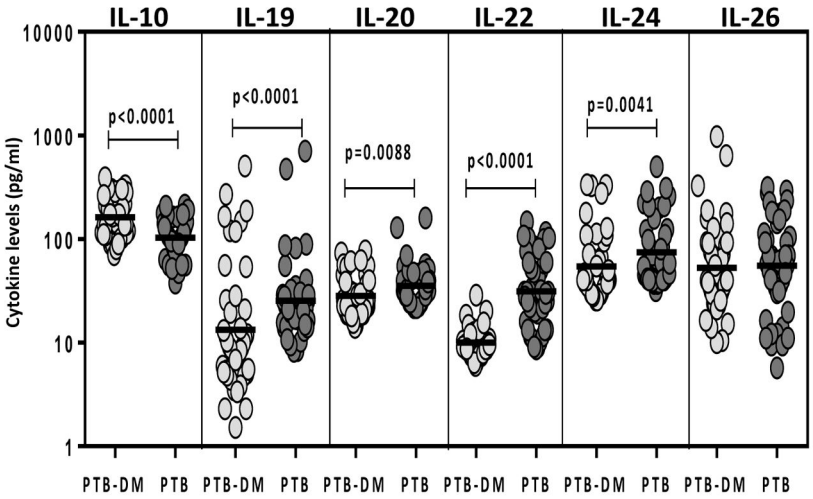

Figure 1.

Diminished systemic levels of IL-20 subfamily of cytokines and increased IL-10 levels in PTB-DM individuals. The plasma levels of IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26 were measured by ELISA in PTB-DM (n=44) and PTB (n=44) individuals. The data are represented as scatter plots with each circle representing a single individual and the bar representing the geometric mean. P values were calculated using the Mann-Whitney test.

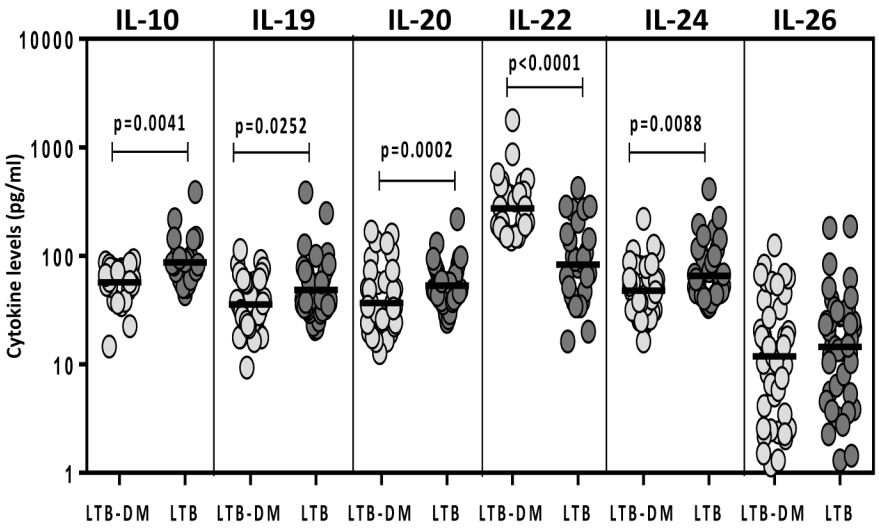

Figure 2.

Diminished systemic levels of IL-20 subfamily of cytokines and increased IL-22 levels in LTB-DM individuals. The plasma levels of IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26 were measured by ELISA in LTB-DM (n=44) and LTB (n=44) individuals. The data are represented as scatter plots with each circle representing a single individual and the bar representing the geometric mean. P values were calculated using the Mann-Whitney test.

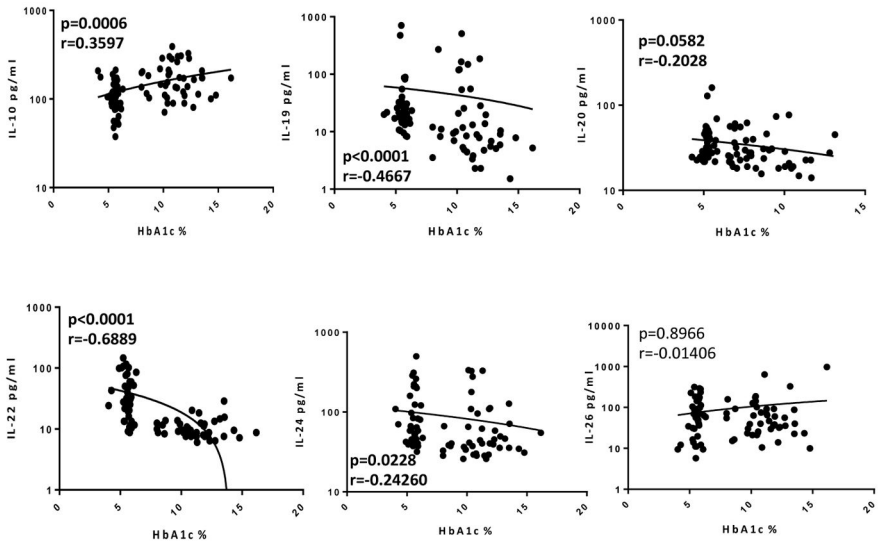

Figure 3.

Relationship between systemic levels of cytokines and HbA1c levels in PTB-DM and PTB individuals. The relationship between the plasma levels of IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26 and HbA1c levels was examined in all PTB (n=88) individuals. The data are represented as scatter plots with each circle representing a single individual. P values were calculated using the Spearman rank correlation.

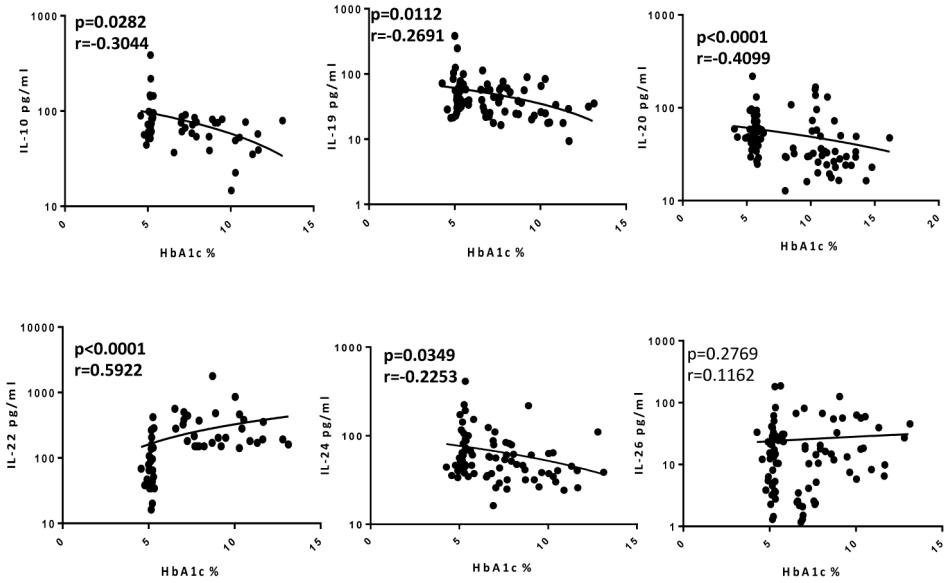

Figure 4.

Relationship between systemic levels of cytokines and HbA1c levels in LTB-DM and LTB individuals. The relationship between the plasma levels of IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26 and HbA1c levels was examined in all LTB (n=88) individuals. \ The data are represented as scatter plots with each circle representing a single individual. P values were calculated using the Spearman rank correlation.

Table 1

Demographics of the study population

Study Demographics	PTB-DM	PTB-NDM	P Value	LTB-DM	LTB-NDM	P Value
No. subjects recruited	44	44		44	44	
Age (yrs)	49 (40 – 58)	45 (40 – 55)	p=NS	45 (28 – 65)	34 (19 – 60)	p=NS
Sex M/F	31/13	38/6	p=NS	30/14	25/19	p=NS
BMI (Kg/m^2)	23.90(19.53 – 33.38)	22.16 (18.01 – 31.22)	p=NS	27.65 (19.21–38.23)	26.32 (17.55 – 39.13)	p=NS
HbA1c(%)	11.2 (7.54 – 14.78)	5.33 (4.46 – 6.12)	p<0.0001	8.92 (6.53 – 13.13)	5.1(4.57 – 5.36)	p<0.0001
Random glucose (mg/dl)	280.4 (200 – 587)	95.5 (76 – 177)	p<0.0001	200 (71 – 537)	94 (64 – 139)	p<0.0001
Mantoux Skin test Positive >12mm	NA	NA		>12 mm	>12 mm	
Interferon gamma release assay	NA	NA		Positive	Positive	

The values represent geometric means and range (except for age where median and range are shown) and NS stands for Not significant.

Table 2

Circulating levels of IL-20 subfamily of cytokine in PTB and LTB individuals

	PTB (44)	LTB (44)	P Value
IL-10	102.8 (37.6 – 212.9)	86.8 (44.1 – 386.8)	p=0.0255
IL-19	25.4 (8.2 – 706.5)	48.4 (21.1 – 383)	p<0.0001
IL-20	35.3 (21.7 – 160.5)	53.3 (24.6 – 218.2)	p<0.0001
IL-22	31.3 (8.7 – 146.9)	83.4 (16.2 – 421.6)	p<0.0001
IL-24	74.4 (31.8 – 498.8)	65.2 (33.6 – 411.8)	NS
IL-26	55.1 (9.4 – 314.1)	14.5 (2.2 – 187)	p<0.0001

The values represent geometric means and range.