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Examining the causal link between and air pollution, tuberculosis type 2 diabetes mellitus

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Abstract: Rapid urbanization, increasing population and increased industrialization to cater to demands of the growing population has imposed upon us a huge environmental cost. The significantly deteriorated air quality across the globe is associated with a direct and indirect impact on public health. While associated disorders such as chronic obstructive pulmonary diseases, heart failures are well documented, less is known about the biological basis of the process. We hypothesize that the worsening air quality may likely impact common systemic inflammatory processes, thus driving communicable and non-communicable diseases alike.Receptor mediated entry of particulate matter (PM2.5) results in activation of signaling cascades which culminate in production of inflammatory chemokine and cytokine responses, traversing through the blood mediating impacting not only on other organs but also dysbiosis of microflora. For the purpose of the review we choose tuberculosis (TB) as a model for communicable infectious disease and type 2 diabetes mellitus (T2DM) as a marker for non-communicable disorder. The increasing prevalence of these co-morbidities and the burdening of public health systems justifies this example. However the hypothesis may be applicable to other inflammation driven disorders also.

Key words: Tuberculosis, Type 2, diabetes mellitus PM2.5, air pollution, inflammation

Introduction

The focus of this article is the co-existence of two high morbidity and mortality associated diseases, one communicable and largely localized namely tuberculosis (TB) and other non-communicable but systemic- type 2 diabetes mellitus (T2DM). The co-morbidity has been recognised for over a century now[1]. However the concerns are due to the increasing evidence of association between TB and T2DM, often exceeding, levels of HIV-TB comorbidity[2]. Studies have reported a higher incidence of lower lung lobe involvement in T2DM-TB cases along with cavitary nodular lesions[3–5]. Type -2 diabetes mellitus may have a negative impact on the outcome of TB treatment: higher failure rates, higher rates of all-cause mortality, and death specifically related to TB. Impaired glucose tolerance has been reportedly associated with active TB. Anti-TB treatment (isoniazid, rifampicin and pyrazinamide) are also known to induce hyperglycaemic effects[6].

Eight percent new cases of active TB attributable to T2DM amount to more than 700 000 cases per year worldwide. In 8 of the 22 high TB burden countries, some of which are heavily

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populated, T2DM accounts for a greater proportion of TB cases as opposed to TB caused by HIV. A few examples include: Russia, where T2DM accounts for 14% of TB cases (*vs* 11% for HIV), India 23% (*vs* 5%), and Pakistan 9% (*vs* 1·5%)[7]. Notably, a common link between these regions has been the recording of high levels of both indoor and outdoor air pollution[8].

A number of common risk factors such as socio economical[9], genetic [10,11] and environmental [12,13]have been associated with the development of TB and T2DM. Independent associations between the risk factors and either of the co-morbidities have been established **but a mechanistic linkage between the TB-T2DM comorbidity through a common environment trigger is substantially less defined.**

We hypothesise that the existence of the co-morbidities is a not a chance event but may be interrelated; driven by an often overlooked but omnipresent factor of air pollutants. The biological basis to the intertwining of the TB- T2DM epidemics is the focus of this hypothesis. We systematically guide the reader through a brief review of the burden of air pollution in developing countries with a focus on India. We then move on to establish how air pollutants can drive a systemic or localized inflammatory response. We link how these inflammatory processes drive each other. And finally we relate inflammatory mechanisms to either expression (latent TB) or occurrence of the disease (T2DM) thus exacerbating co-morbidities.

The World Health Organization in its Air quality guidelines directs measure of particulate matter 2.5 (PM2.5) and 10 (PM10), Ozone (O3), Nitrogen-di-Oxide, and Sulphur-di-oxide (SO_2) as indicators of environmental air pollution which may be contributed by indoor (example, incomplete biomass combustion, smoking, molds and fungi) and outdoor activities (example, thermal power plants, vehicular pollution). The air is considered unsafe when measurements are above mean values as indicated in Table 1[14].

Table 1: WHO guideline for permissive levels of Ozone, PM2.5, PM10, NO_2 and SO_2

Parameter	Permissible levels	
O3	100 µg/m^3 (8-hour mean)	
$PM_{2.5}$	10 µg/m^3 (annual mean)	25 µg/m^3(24-hour mean)
PM_{10}	20 µg/m^3 (annual mean)	50 µg/m^3(24-hour mean)
NO2	40 µg/m^3 (annual mean)	200 µg/m^3 (1-hour mean)
SO2	20 µg/m^3 (24-hour mean)	500 µg/m^3 (10-minute mean)

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India's urban average PM2.5 concentration in 2014 was recorded at 65.7 μg/m^3 and the averages across 25 monitoring stations in three metropolitan cities of the country range from 44-61 μg/m^3. Similarly, in other Asian regions such as China and Pakistan, recorded levels of PM2.5 were found to be 59.5 and 67.7 μg/m^3 respectively {WHO Global urban ambient air pollution database (update 2016), http://www.who.int/entity/phe/health_topics/outdoorair/databases/}. Since a variety of sources both organic and inorganic in origin can give rise to PM2.5 and PM10, the measurements of these suspended air particles have been chosen as sentinel markers of air pollution. Recent reports confirm that long term and short term exposure to PM2.5 and PM10 respectively, is linearly associated with mortality [8,15]. While no study has estimated the levels of air pollution and its impact on TB-T2DM co-morbidity, we found evidence pointing to high TB-T2DM burden in regions of high pollution namely, India and China. A recent review assessed the bi-directional burden of TB and T2DM. The review concludes that DM prevalence among TB patients as ranging from approximately 5% to more than 50%, whereas TB prevalence among diabetic patients were 1.8–9.5 times higher than in the general population [16].

Particulate matter 2.5 (PM2.5) and inflammation

The interaction of PM2.5 with alveolar macrophages (AMs) generates a localized inflammatory environment which subsequently leads to a systemic inflammatory environment characterized by the migration of inflammatory cells from bone marrow into the circulatory system, generation of acute phase proteins by the hepatocytes and an increase of circulatory inflammatory markers.

While the biological particles such as LPS, endotoxin and glucans interact via the Toll lke receptors (TLR 2 and TLR4), the unopsonized PM is phagocytosed through class A scavenger receptor (SR-A) and macrophage receptor with collagenous structure (MARCO). SRA and MARCO are known to be pro inflammatory by mediating their interaction with TLR 4 a known agonist for NF- KB activation and inflammatory cytokine production [17,18]. Interaction of PM with TLRs induces an inflammatory response which is augmented by involvement of non opsonic receptors such as SR-A and MARCO.

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Further evidence to establishment of a pro inflammatory response is through the polarization of AMs to an M1 phenotype. A seminal study by Zhao et al established that exposure of macrophages to PM2.5 enhanced M1 polarization through activation of reactive oxygen species (ROS) leading to an increased expression of pro-inflammatory cytokines granulocyte-macrophage colonystimulating factor (GM-CSF), interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor alpha (TNFα). Simultaneously, it inhibited M2 polarization (a predominant Th2 driven anti-inflammatory phenotype characterized by the presence of IL-10, a sentinel marker) through an mTOR dependent pathway [19].

This locally generated inflammation may give rise to systemic inflammation by either a direct or indirect 'spill over'. Studies have shown movement of proteins from lung surface to systemic circulation. Animal studies have shown the detectionof aerosolized proteins from the lungs in the lymph and plasma [20]. In addition, the proteins are functional as has been demonstrated independently in the systemic therapeutic effect of aerosolized insulin[21]. Further, an inverse correlation between the transit times of neutrophils from the bone marrow with higher fraction of AMs phagocytosing PM has been demonstrated by Eeden et al [22]. It is also likely that the IL-1β and IL-6 generated in the lung upon exposure to PM enhance the expression of C- reactive protein and other acute phase proteins in the hepatocytes (by a systemic spill over) causing their release in the system and thereby enhancing the systemic inflammatory response. Such independent evidence in different settings indicate the likely migration of a localized inflammatory response to the systemic level [23].

Particulate matter 2.5 (PM2.5) , gut and inflammation

Particles deposited in the nasal cavities also find their way in the gut[24] Human studies have also shown muco-ciliary transport of the PM cleared from lungs and deposited in the intestine. PM may induce gut inflammation either directly or indirectly. It has been shown that ingestion of PM increased small intestine permeability accompanied by an inflammatory response. The gut permeability is increased through rearrangement of epithelial tight junctions. Increased permeability causes release of reactive oxygen species (ROS). These further induce cytokine secretion inducing breakdown of barrier and systemic inflammation. ROS is known to impact vital organs of the body with more damaging effects on pancreatic β cells and adipocytes. An indirect onset of inflammation may be mediated by the impact of PM2.5 on reduced microbial

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diversity and altered composition. The altered composition may contribute to decrease production of useful metabolites such as butyrate and short chain fatty acids. Production of toxic metabolites through altered gut microbial composition additionally may result in low grade inflammation [25].

PM 2.5 driven inflammatory pathways in tuberculosis and type 2 diabetes mellitus

Protective Th1 responses have often been implicated in clearance of the pathogen and limiting of disease. However strong Th1 responses characterized by inflammatory markers have been identified in patients presenting with severe forms of TB and a non-contained state of infection[26]. As explained, exposure to PM2.5 is associated with an onset of systemic inflammation. A recent study also indicates that exposure to PM2.5 results in significantly higher levels of neutrophils[27]. The increased neutrophils are not only found in circulation but are also reported in bronchoalveolar lavage [28]. Neutrophils are the primary polymorph leukocytes to be recruited in infection of lower lung lobes and are believed to contain infection[29]. However, during TB infection, recruitment of neutrophils and uptake of mycobacteria in early post infection results in tissue pathology [30,31]. We propose that PM2.5 exposure, induces neutrophilleucocytosis and enhances the recruitment of these cells to the lung (post TB infection). This results in a cell phenotype that survives longer, contains more mycobacteria, displays low antimycobacterial phenotype and is resistant to IFN γ[31]. Additionally, cytokines/ chemokines secreted by neutrophils have an autocrine effect resulting in an increased number of neutrophils. Neutrophil associated chemokines induce migration of other cell types, resulting in formation of granuloma, which is a known protective structure allowing proliferation of mycobacteria.Additionally,a recent study establishes that a rich granulocytic inflammation generates a nutrient-replete niche that supports *M. tuberculosis* growth [32]. The dysbiosis of the gut may also contribute to progression of mycobacterial infection to disease. The microbiota imbalance negatively influences antigen processing and presentation. This may consequently repress development of Tcell immunity and development of CCR4+Tcells which are antigen specific Tcells capable of homing to the lung [33,34]. The absence of the development of this Tcell phenotype depresses bacterial clearance in the lungs. Overall the process exemplifies how PM2.5 exposure may result in progression of TB disease.

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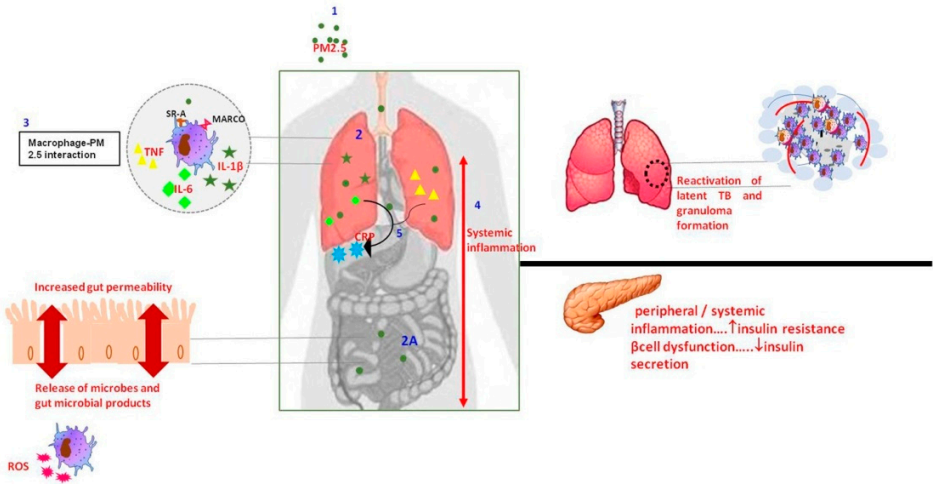
Insulin resistance (IR) is a sentinel mechanism of pathogenesis and etiology of type 2 diabetes mellitus. During low-grade systemic inflammation, macrophages infiltrate the adipose, hepatic and muscular tissue. Macrophages are major producers of TNF, which interferes with the ability of these tissues to respond to insulin.

Under normal conditions insulin adheres to a receptor located on the surface of the adipocyes, hepatocytes and miocytes, initiating an intracellular signalling cascade mediated by the insulinreceptor substrate (IRS), which activates AKT and finally induces the mobilisation of glucose transporter proteins (GLUT-2 and 4) for the incorporation of glucose to the inside of the cell. The presence of TNF in an ERK dependent pathway interferes with the IRS-AKT-GLUT signaling, thereby inhibiting phosphorylation of IRS-2, AKT, GLUT-2 and -4 leading to a state of hyperglycaemia and later hyperinsulinameia.

Another pro inflammatory cytokine, IL-6 induces activation of suppressor of cytokine signaling (SOCS) protein. The SOCS inhibits IRS through threeknown mechanisms (1) competitive inhibition of docking site (2) Proteasomal degradation of IRS (3) inhibition of IR kinase causing tyrosine phosphorylation of the docking site. [35,36]. The seminal work of Cani and colleagues [37,38] has already demonstrated that gut dysbiosis can lead to insulin resistance. In a series of studies, the investigators have shown that gut microbiota produce LPS. The leaky gut, which may also be contributed by exposure to air pollutants (PM2.5), may lead to translocation of these molecules to the blood stream. The presence of LPS in the blood stream leads to a state of metabolic endotoxemia, also known to be associated with obesity; a preceding factor to development of T2DM. Our observations are summarized in Figure 1.



While this hypothesis is based on observations from current literature, its existence bears testing through use of modern, high throughput genetic tools. For example, the use of cytokine biomarkers or markers of activated inflammasomes in individuals exposed to pollutants and in a pollution free environment and their clinical testing for the presence of infectious diseases such as TB and non-infectious diseases such as T2DM and/or cardiovascular diseases[8]. Additionally, testing for a proof of concept using animal models for anti-inflammatory agents in groups exposed to pollutants and its impact on development of co-morbidities with presence of risk may be a helpful assessment.

The nature and dimension of these emerging problems in low and middle-income countries need attention. Interventions have to be directed towards assessment of risk factors to the effects of air pollution. Vulnerable informal settlements in urban areas of developing nations often form a part of high risk communities which need targeted attention through convergences in water supply and sanitation, solid waste management, regulation on industrial effluents, vehicular emissions and archetypal modifications to name a few. Diet and physical activity have been routinely stressed upon as adjunct therapies for long term host benefits but recent studies indicate to the contrary. A compilation of several studies has shown the acute deleterious effect of even short term exposure to air pollution[39–41] . While exercise imparted benefits are not doubted it is likely that its impact may be reduced in high pollution areas. The realization that air borne pollution is responsible for onset of both communicable and non-communicable diseases, should spur national governments of affected countries to put in place environmental safeguards more stringently and effectively.

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References

1. Sullivan, T.; Ben Amor, Y. The Co-Management of Tuberculosis and Diabetes: Challenges and Opportunities in the Developing World. *PLoS Med.***2012**, *9*, e1001269, doi:10.1371/journal.pmed.1001269.

2. Restrepo, B. I.; Camerlin, A. J.; Rahbar, M. H.; Wang, W.; Restrepo, M. A.; Zarate, I.;

Mora-Guzmán, F.; Crespo-Solis, J. G.; Briggs, J.; McCormick, J. B.; Fisher-Hoch, S. P. Cross-sectional assessment reveals high diabetes prevalence among newly-diagnosed tuberculosis cases. *Bull. World Health Organ.***2011**, *89*, 352–359, doi:10.2471/BLT.10.085738.

3. Umut, S.; Tosun, G. A.; Yildirim, N. Radiographic Location of Pulmonary Tuberculosis in Diabetic Patients. *Chest***1994**, *106*, 326, doi:10.1378/CHEST.106.1.326A.

4. Morris, J. T.; Seaworth, B. J.; McAllister, C. K. Pulmonary tuberculosis in diabetics. *Chest***1992**, *102*, 539–41, doi:10.1378/CHEST.102.2.539.

5. Weaver, R. A. Unusual radiographic presentation of pulmonary tuberculosis in diabetic patients. *Am. Rev. Respir. Dis.***1974**, *109*, 162–3, doi:10.1164/arrd.1974.109.1.162.

6. van Crevel, R.; Dockrell, H. M. TANDEM: understanding diabetes and tuberculosis. *Lancet Diabetes Endocrinol.***2014**, *2*, 270–272, doi:10.1016/S2213-8587(14)70011-7.

7. *Collaborative Framework for Care and Control of Tuberculosis and Diabetes*; World Health Organization, 2011; ISBN 9789241502252.

8. Cohen, A. J.; Brauer, M.; Burnett, R.; Anderson, H. R.; Frostad, J.; Estep, K.; Balakrishnan, K.; Brunekreef, B.; Dandona, L.; Dandona, R.; Feigin, V.; Freedman, G.; Hubbell, B.; Jobling, A.; Kan, H.; Knibbs, L.; Liu, Y.; Martin, R.; Morawska, L.; Pope, C. A.; Shin, H.; Straif, K.; Shaddick, G.; Thomas, M.; van Dingenen, R.; van Donkelaar, A.; Vos, T.; Murray, C. J. L.; Forouzanfar, M. H. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet (London, England)***2017**, *389*, 1907–1918, doi:10.1016/S0140-6736(17)30505-6.

9. Gupta, S.; Shenoy, V. P.; Bairy, I.; Srinivasa, H.; Mukhopadhyay, C. Diabetes mellitus and HIV as co-morbidities in tuberculosis patients of rural south India. *J. Infect. Public Health***2011**, *4*, 140–144, doi:10.1016/j.jiph.2011.03.005.

10. Abou-Hussein, S.; Savona-Ventura, C.; Grima, S.; Felice, A. Genetic factors in risk assessment for the development of type 2 diabetes mellitus in a small case series. *Int. J. Risk Saf. Med.***2011**, *23*, 119–23, doi:10.3233/JRS-2011-0522.

11. Abel, L.; El-Baghdadi, J.; Bousfiha, A. A.; Casanova, J.-L.; Schurr, E. Human genetics of tuberculosis: a long and winding road. *Philos. Trans. R. Soc. B Biol. Sci.***2014**, *369*, 20130428–20130428, doi:10.1098/rstb.2013.0428.

12. Rajagopalan, S.; Brook, R. D. Air Pollution and Type 2 Diabetes: Mechanistic Insights. *Diabetes***2012**, *61*, 3037–3045, doi:10.2337/db12-0190.

13. Cohen, A.; Mehta, S. Pollution and Tuberculosis: Outdoor Sources. *PLoS Med.***2007**, *4*, e142, doi:10.1371/journal.pmed.0040142.

14. *WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide*; Geneva, 2005;

15. Mishra, S. Is smog innocuous? Air pollution and cardiovascular disease. *Indian Heart J.***2017**, *69*, 425–429, doi:10.1016/j.ihj.2017.07.016.

16. Zheng, C.; Hu, M.; Gao, F. Diabetes and pulmonary tuberculosis: a global overview with special focus on the situation in Asian countries with high TB-DM burden. *Glob. Health Action***2017**, *10*, 1–11, doi:10.1080/16549716.2016.1264702.

17. Mukhopadhyay, S.; Varin, A.; Chen, Y.; Liu, B.; Tryggvason, K.; Gordon, S. SR-A/MARCO–mediated ligand delivery enhances intracellular TLR and NLR function, but ligand scavenging from cell surface limits TLR4 response to pathogens., doi:10.1182/blood-2010-03.

18. Ozment, T. R.; Ha, T.; Breuel, K. F.; Ford, T. R.; Ferguson, D. A.; Kalbfleisch, J.; Schweitzer, J. B.; Kelley, J. L.; Li, C.; Williams, D. L. Scavenger Receptor Class A Plays a Central Role in Mediating Mortality and the Development of the Pro-Inflammatory Phenotype in Polymicrobial Sepsis. *PLoS Pathog.***2012**, *8*, e1002967, doi:10.1371/journal.ppat.1002967.

19. Zhao, Q.; Chen, H.; Yang, T.; Rui, W.; Liu, F.; Zhang, F.; Zhao, Y.; Ding, W. Direct effects of airborne PM2.5 exposure on macrophage polarizations. *Biochim. Biophys. Acta - Gen. Subj.***2016**, *1860*, 2835–2843, doi:10.1016/j.bbagen.2016.03.033.

20. Smith, R. M.; Traber, L. D.; Traber, D. L.; Spragg, R. G. Pulmonary deposition and clearance of aerosolized alpha-1-proteinase inhibitor administered to dogs and to sheep. *J.*

*Clin. Invest.***1989**, *84*, 1145–1154, doi:10.1172/JCI114278.

21. Steiner, S.; Pfützner, A.; Wilson, B.; Harzer, O.; Heinemann, L.; Rave, K. Technosphere ™ /Insulin - proof of concept study with a new insulin formulation for pulmonary delivery. *Exp. Clin. Endocrinol. Diabetes***2002**, *110*, 17–21, doi:10.1055/s-2002-19989.

22. Eeden, S. F. van; Hogg, J. C. Systemic inflammatory response induced by particulate matter air pollution: the importance of bone-marrow stimulation. *J. Toxicol. Environ. Heal. Part A***2002**, *65*, 1597–1613, doi:10.1080/00984100290071685.

23. Black, S.; Kushner, I.; Samols, D. C-reactive Protein. *J. Biol. Chem.***2004**, *279*, 48487–90, doi:10.1074/jbc.R400025200.

24. Southam, D. S.; Dolovich, M.; O'Byrne, P. M.; Inman, M. D. Distribution of intranasal instillations in mice: effects of volume, time, body position, and anesthesia. *Am. J. Physiol. Lung Cell. Mol. Physiol.***2002**, *282*, L833-9, doi:10.1152/ajplung.00173.2001.

25. Salim, S. Y.; Kaplan, G. G.; Madsen, K. L. Air pollution effects on the gut microbiota: a link between exposure and inflammatory disease. *Gut Microbes***2014**, *5*, 215–9, doi:10.4161/gmic.27251.

26. Zumla, A.; Rao, M.; Parida, S. K.; Keshavjee, S.; Cassell, G.; Wallis, R.; Axelsson-Robertsson, R.; Doherty, M.; Andersson, J.; Maeurer, M. Inflammation and tuberculosis: host-directed therapies. *J. Intern. Med.***2015**, *277*, 373–387, doi:10.1111/joim.12256.

27. He, M.; Ichinose, T.; Yoshida, Y.; Arashidani, K.; Yoshida, S.; Takano, H.; Sun, G.; Shibamoto, T. Urban PM2.5 exacerbates allergic inflammation in the murine lung via a TLR2/TLR4/MyD88-signaling pathway. *Sci. Rep.***2017**, *7*, 11027, doi:10.1038/s41598-017-11471-y.

28. Xing, Y.-F.; Xu, Y.-H.; Shi, M.-H.; Lian, Y.-X. The impact of PM2.5 on the human respiratory system. *J. Thorac. Dis.***2016**, *8*, E69-74, doi:10.3978/j.issn.2072-1439.2016.01.19.

29. Craig, A.; Mai, J.; Cai, S.; Jeyaseelan, S. Neutrophil recruitment to the lungs during bacterial pneumonia. *Infect. Immun.***2009**, *77*, 568–75, doi:10.1128/IAI.00832-08.

30. Yeremeev, V.; Linge, I.; Kondratieva, T.; Apt, A. Neutrophils exacerbate tuberculosis infection in genetically susceptible mice. *Tuberculosis***2015**, *95*, 447–451, doi:10.1016/J.TUBE.2015.03.007.

31. Eruslanov, E. B.; Lyadova, I. V; Kondratieva, T. K.; Majorov, K. B.; Scheglov, I. V; Orlova, M. O.; Apt, A. S. Neutrophil responses to Mycobacterium tuberculosis infection in genetically susceptible and resistant mice. *Infect. Immun.***2005**, *73*, 1744–53, doi:10.1128/IAI.73.3.1744-1753.2005.

32. Mishra, B. B.; Lovewell, R. R.; Olive, A. J.; Zhang, G.; Wang, W.; Eugenin, E.; Smith, C. M.; Phuah, J. Y.; Long, J. E.; Dubuke, M. L.; Palace, S. G.; Goguen, J. D.; Baker, R. E.; Nambi, S.; Mishra, R.; Booty, M. G.; Baer, C. E.; Shaffer, S. A.; Dartois, V.; McCormick, B. A.; Chen, X.; Sassetti, C. M. Nitric oxide prevents a pathogen-permissive granulocytic inflammation during tuberculosis. *Nat. Microbiol.***2017**, *2*, 17072, doi:10.1038/nmicrobiol.2017.72.

33. Mikhak, Z.; Strassner, J. P.; Luster, A. D. Lung dendritic cells imprint T cell lung homing and promote lung immunity through the chemokine receptor CCR4. *J. Exp. Med.***2013**, *210*, 1855–1869, doi:10.1084/jem.20130091.

34. Bordon, Y. Mucosal immunology: Air miles for T cells. *Nat. Rev. Immunol.***2013**, *13*, 705–705, doi:10.1038/nri3537.

35. Chen, L.; Chen, R.; Wang, H.; Liang, F. Mechanisms Linking Inflammation to Insulin Resistance. *Int. J. Endocrinol.***2015**, *2015*, 508409, doi:10.1155/2015/508409.

36. Rehman, K.; Akash, M. S. H. Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked? *J. Biomed. Sci.***2016**, *23*, 87, doi:10.1186/s12929-016-0303-y.

37. Cani, P. D.; Knauf, C.; Iglesias, M. A.; Drucker, D. J.; Delzenne, N. M.; Burcelin, R.; Burcelin, R. Improvement of glucose tolerance and hepatic insulin sensitivity by oligofructose requires a functional glucagon-like peptide 1 receptor. *Diabetes***2006**, *55*, 1484–90, doi:10.2337/diabetes.

38. Cani, P. D.; Osto, M.; Geurts, L.; Everard, A. Involvement of gut microbiota in the

development of low-grade inflammation and type 2 diabetes associated with obesity. *Gut Microbes***2012**, *3*, 279–288, doi:10.4161/gmic.19625.

39. Yu, I. T. S.; Wong, T. W.; Liu, H. J. Impact of air pollution on cardiopulmonary fitness in schoolchildren. *J. Occup. Environ. Med.***2004**, *46*, 946–52.

40. Kubesch, N. J.; de Nazelle, A.; Westerdahl, D.; Martinez, D.; Carrasco-Turigas, G.; Bouso, L.; Guerra, S.; Nieuwenhuijsen, M. J. Respiratory and inflammatory responses to short-term exposure to traffic-related air pollution with and without moderate physical activity. *Occup. Environ. Med.***2015**, *72*, 284–293, doi:10.1136/oemed-2014-102106.

41. Kubesch, N.; De Nazelle, A.; Guerra, S.; Westerdahl, D.; Martinez, D.; Bouso, L.; Carrasco-Turigas, G.; Hoffmann, B.; Nieuwenhuijsen, M. Arterial blood pressure responses to short-term exposure to low and high traffic-related air pollution with and without moderate physical activity. *Eur. J. Prev. Cardiol.***2015**, *22*, 548–557, doi:10.1177/2047487314555602.

Figure legend

Figure 1: induction of inflammation and its consequences on activation of latent TB infection and induction of Type 2 diabetes mellitus (T2DM).(1) PM2.5 are inhaled or ingested by alveolar macrophages through surface receptor A and macrophage receptor with collagenous structure (MARCO) (2) inhaled particles get deposited in the lungs and are processed by (3)macrophages, activating them, inducing an inflammatory response. (2A) Ingested particles induce inflammation through increasing gut permeability. (4) The localized inflammation may give rise to systemic inflammation, which may consequently develop into active TB disease and T2DM.