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NEWS & VIEWS

Infection and Microbiome: Impact of Tuberculosis on Human Gut Microbiome of Indian Cohort

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Human Microbiome plays a key role in maintaining a healthy state by imparting normal metabolism and immunity to the host. In fact maintenance of good health has been contributed to the presence of healthy microbiome in human beings [1]. Any imbalance can lead to many diseases and make humans susceptible to attack by a variety of pathogens. While smooth functioning of the metabolic pathways ensures fitness and a state of well-being [2], a strong correlation has been established between human health and microbial diversity, which harbors on and within the body [3, 4]. Recent estimates have revealed that our body is inhabited by as many bacteria as our body cells [5]. Skin harbours a wide range of microbes, the dominant ones being those belonging to Bacteroidetes, Corynebacteria, Propionibacteria, Proteobacteria, and *Staphylococcus* [6]. These microbes help in protecting skin from getting infected by pathogens. Within the human gut, bacteria belonging to around 160 species have been identified [7] and 44–48% of the total population is represented by Firmicutes and Bacteroidetes [8, 9]. There are various factors, which modulate the human gut flora including diet [10], diseases like rheumatoid arthritis [11], type I diabetes [12], obesity [13] and inflammation of gut due to IBD and Crohn disease [14]. These studies have shown a significant shift in the community of gut microbes between healthy and diseased individuals mainly in lifestyle diseases [15]. But the role of gut microflora in infectious diseases like tuberculosis (TB) and the impact of antibiotic treatment has not been studied to great extent worldwide with only a few reports [16, 17] concerning the dysbiosis in the diversity of gut microflora during TB infection. Additionally, there is no study from the Indian subcontinent that took into account the shift in the bacterial community of gut and the functional implications of microbes on the gut-lung axis, especially during tuberculosis.

Tuberculosis (TB) has high burden both socially and economically in a developing country like India. The patients are prescribed with directly observed treatment, short course (DOTS) regimen and the treatment can extend up to 6–9 months. The treatment using the DOTS regimen has led to instances of Multi-Drug Resistant (MDR) in strains of *Mycobacterium tuberculosis.* MDR strains are very difficult to treat as *M. tuberculosis* has evolved in a way that it can develop resistance by way of developing mutation against multiple antibiotics if exposed for prolong duration below minimum inhibitory concentration (MIC) [18]. Therefore, studying the modulation of gut microbiome can provide insights into the pathophysiology of the infectious disease and thus can open new avenues for the research and development of new drugs and therapies for curing the disease. Restoration of gut microbiota has been shown as an effective treatment for patients suffering from *Clostridium difficile* infection (CDI) [19] and this can act as a primer for initiating therapies based on probiotics and faecal microbiome transplant.

A few attempts have been made to catalog the diversity of gut microbes in Indian ethnic cohort. But the majority of these studies reported only the taxonomic diversity of normal individuals like children [20], tribal people [21], or individuals suffering from type-I diabetes [22], IBD and colon cancer [23]. The major lacunae of these study were

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the absence of any functional characterization of the modified gut microflora and absenteeism of information about their role in maintaining a normal state and diseased conditions among the Indian cohort. To bridge this gap in knowledge, Indian researchers from the Department of Zoology, University of Delhi, Department of Plant Molecular Biology, University of Delhi and CSIR-Institute of Genomics and Integrative Biology, Delhi by a team led by Prof. Yogendra Singh and Prof. Rup Lal have planned and executed a study for deciphering dysbiosis in gut microflora of individuals suffering from tuberculosis in an Indian ethnic cohort [24]. The study recently published in Environmental Microbiology [24] has reported for the first time an in-depth functional characterization of gut microflora in Indian subjects. The investigators compared the taxonomic and functional diversity of gut microbiome from fecal samples of six treatment-naïve TB patients and follow up the same patients, receiving directly observed treatment, short course (DOTS) regimen, 1 week and 1 month after the beginning of treatment. Six healthy household contacts (HCs) were chosen as the controls to rule out biases of genetic background and influence of the environmental conditions.

They complimented the results from 16S amplicon sequencing with functional disparities obtained from shotgun sequencing [24]. Results revealed the abundance of *Prevotella* and *Bifidobacterium* in healthy household contacts (Control samples) whereas bacteria from different genera like *Faecalibacterium*, *Roseburia*, *Eubacterium,* and *Phascolarctobacterium* were plentiful in the patients that have not received any medication. These genera represent small chain fatty acid (SCFA) producers and had pathways for butyrate and propionate production. Enriched metabolism of butyrate and propionate led to reduced biosynthesis of vitamins and amino acids leading to hypercholesterolemia and impairment of immune system. The diseased individuals also had an abundance of *M. tuberculosis* which might have invaded the respiratory system. The decline in *Prevotella* abundance has been postulated to allow the increase in microbial diversity of these propionate and butyrate producers. In brief, there were significant taxonomic and functional alterations in the gut microbiome of control and diseased samples. The authors also attempted to unravel the effect of antibiotics on gut microbiome of the diseased individual, they found a drastic reduction of *M. tuberculosis* population but no other major taxonomic recovery was observed till 1 month of DOTS treatment. Despite small cohort size, statistically significant differences in microbial composition were obtained between the groups. The results obtained from this pilot study provide insights into the role played by the GM in a pulmonary infectious disease. Nonetheless, this study was successful in paving new directions for planning

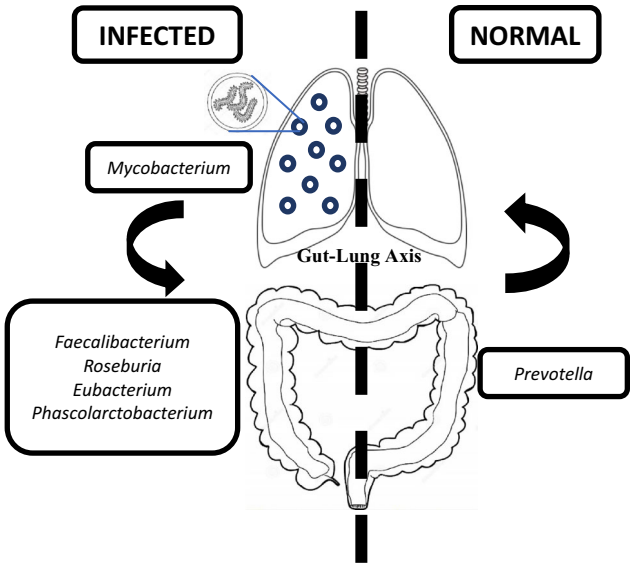

Fig. 1 Microbial dysbiosis along a gut-lung axis in TB infected Indian population. *Prevotella* is abundant genera in gut microflora of healthy Indian individuals. Infection by *M. tuberculosis* causes a dysbiosis with increase abundance of small chain fatty acid (SCFA) producers like *Faecalibacterium*, *Roseburia*, *Eubacterium,* and *Phascolarctobacterium* that had pathways for butyrate and propionate production

future large-scale epidemiological studies for Indian populations focusing on microbiome analysis of the patients and deduces the holistic map to develop strategies in treating infectious disease using pro-biotics and nutritional supplements rather than antibiotics and formulate preventive strategies through dietary changes. To study the role of antibiotics, the timeline of sampling must have been more, but still, this study can act as a pilot for an in-depth analysis that can be done in the future increasing our understanding on the impact of antibiotics and restoration of gut microbiome at the end of the treatment (Fig. 1).

References

1. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett C, Knight R, Gordon JI (2007) The human microbiome project: exploring the microbial part of ourselves in a changing world. Nature 449:804
2. Gerritsen J, Smidt H, Rijkers GT, de Vos WM (2011) Intestinal microbiota in human health and disease: the impact of probiotics. Genes Nutr 6:209–240. https://doi.org/10.1007/s12263-011-0229-7
3. Kalia VC (2015) Microbes: the most friendly beings? In: Kalia VC (ed) Quorum sensing vs quorum quenching: a battle with no end in sight, pp 1–5. Springer India. https://doi.org/10.1007/978-81-322-1982-8_1
4. Purohit HJ (2017) Gut-bioreactor and human health in future. Indian J Microbiol 58:1–5. https://doi.org/10.1007/s12088-017-0697-6

5. Sender R, Fuchs S, Milo R (2016) Revised estimates for the number of human and bacteria cells in the body. PLoS Biol 14:e1002533. https://doi.org/10.1371/journal.pbio.1002533
6. Kalia VC (2014) Microbes, antimicrobials and resistance: the battle goes on. Indian J Microbiol 54:1–2. https://doi.org/10.1007/s12088-013-0443-7
7. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T, Mende DR, Li J, Xu J, Li S, Li D, Cao J, Wang B, Liang H, Zheng H, Xie Y, Tap J, Lepage P, Bertalan M, Batto JM, Hansen T, Le Paslier D, Linneberg A, Nielsen HB, Pelletier E, Renault P, Sicheritz-Ponten T, Turner K, Zhu H, Yu C, Li S, Jian M, ZhouY Li Y, Zhang X, Li S, Qin N, Yang H, Wang J, Brunak S, Doré J, Guarner F, Kristiansen K, Pedersen O, Parkhill J, Weissenbach J, MetaHIT Consortium, Bork P, Ehrlich SD, Wang J (2010) A human gut microbial gene catalogue established by metagenomic sequencing. Nature 464:59–65. https://doi.org/10.1038/nature08821
8. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI (2006) An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 444:1027–1131. https://doi.org/10.1038/nature05414
9. Wexler HM (2007) Bacteroides: the good, the bad, and the nitty-gritty. Clin Microbiol Rev 20:593–621. https://doi.org/10.1128/CMR.00008-07
10. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, Egholm M, Henrissat B, Heath AC, Knight R, Gordon JI (2009) A core gut microbiome in obese and lean twins. Nature 457:480–484. https://doi.org/10.1038/nature07540
11. Wu HJ, Ivanov II, Darce J, Hattori K, Shima T, Shima T, Umesaki Y, Littman DR, Benoist C, Mathis D (2010) Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells. Immunity 32:815–827. https://doi.org/10.1016/j.immuni.2010.06.001
12. Wen L, Ley RE, Volchkov PY, Stranges PB, Avanesyan L, Stonebraker AC, Hu C, Wong FS, Szot GL, Bluestone JA, Gordon JI, Chervonsky AV (2008) Innate immunity and intestinal microbiota in the development of Type 1 diabetes. Nature 455:1109–1113. https://doi.org/10.1038/nature07336
13. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, Biddinger SB, Dutton RJ, Turnbaugh PJ (2014) Diet rapidly and reproducibly alters the human gut microbiome. Nature 505:559–563. https://doi.org/10.1038/nature12820
14. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR (2007) Molecular phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci USA 104:13780–13785. https://doi.org/10.1073/pnas.0706625104
15. Honda K, Littman DR (2012) The microbiome in infectious disease and inflammation. Annu Rev Immunol 30:759–795. https://doi.org/10.1146/annurev-immunol-020711-074937
16. Wipperman MF, Fitzgerald DW, Juste MAJ, Taur Y, Namasivayam S, Sher A, Bean JM, Bucci V, Glickman MS (2017) Antibiotic treatment for Tuberculosis induces a profound dysbiosis of the microbiome that persists long after therapy is completed. Sci Rep 7:e10767. https://doi.org/10.1038/s41598-017-10346-6
17. Wood MR, Yu EA, Mehta S (2017) The human microbiome in the fight against tuberculosis. Am J Trop Med Hyg 96:1274–1284. https://doi.org/10.4269/ajtmh.16-0581
18. Singh P, Kumari R, Lal R (2017) Bedaquiline: fallible hope against drug resistant tuberculosis. Indian J Microbiol 57:371–377. https://doi.org/10.1007/s12088-017-0674-0
19. Bakken JS, Borody T, Brandt LJ, Brill JV, Demarco DC, Franzos MA, Kelly C, Khoruts A, Louie T, Martinelli LP, Moore TA (2011) Treating *Clostridium difficile* infection with fecal microbiota transplantation. Clin Gastroenterol Hepatol 9:1044–1049. https://doi.org/10.1016/j.cgh.2011.08.014
20. Kumbhare SV, Kumar H, Chowdhury SP, Dhotre DP, Endo A, Mättö J, Ouwehand AC, Rautava S, Joshi R, Patil NP, Patil RH (2017) A cross-sectional comparative study of gut bacterial community of Indian and Finnish children. Sci Rep 7:e10555. https://doi.org/10.1038/s41598-017-11215-y
21. Dehingia M, Talukdar NC, Talukdar R, Reddy N, Mande SS, Deka M, Khan MR (2015) Gut bacterial diversity of the tribes of India and comparison with the worldwide data. Sci Rep 5:e18563. https://doi.org/10.1038/srep18563
22. Bhute SS, Suryavanshi MV, Joshi SM, Yajnik CS, Shouche YS, Ghaskadbi SS (2017) Gut microbial diversity assessment of Indian type-2-diabetics reveals alterations in Eubacteria, Archaea, and Eukaryotes. Front Microbiol 8:214. https://doi.org/10.3389/fmicb.2017.00214
23. Bamola VD, Ghosh A, Kapardar RK, Lal B, Cheema S, Sarma P, Chaudhry R (2017) Gut microbial diversity in health and disease: experience of healthy Indian subjects, and colon carcinoma and inflammatory bowel disease patients. Microb Ecol Health Dis 28:1322447. https://doi.org/10.1080/16512235.2017.1322447
24. Maji A, Misra R, Dhakanb DB, Gupta V, Mahato NK, Saxena R, Mittal P, Thukral N, Sharma E, Singh A, Virmani R, Gaur M, Singh H, Hasija Y, Arora G, Agrawal A, Chaudhry A, Khurana JP, Sharma VK, Lal R, Singh Y (2017) Gut microbiome contributes to impairment of immunity in pulmonary tuberculosis patients by alteration of butyrate and propionate producers. Environ Microbiol. https://doi.org/10.1111/1462-2920.14015