The role of the microbiome in inflammation during tuberculosis

Anou M. Somboro, Dramane Diallo, Jane L. Holl, Mamoudou Maiga

A R T I C L E   I N F O

Article History:
Received 23 May 2021
Accepted 25 May 2021
Available online xxx

The human gut microbiota, comprised of a diverse microbial ecosystem, consists of hundreds of groups of species that are relatively stable in healthy individuals, but its composition can change rapidly as a result of illness, age, diet, antibiotic use, host genetics, and inflammation. Recent reports have shown that the microbiome may be implicated in tuberculosis (TB) infection [1,2]. TB is one of the most fatal infectious disease that is caused by the Mycobacterium tuberculosis complex and remains a major cause of global morbidity and mortality [3]. The microbiome and its associated metabolites are likely to play a role in susceptibility to TB infection and progression to and severity of disease. Changes in the structure of microbiome populations could impact immunity signaling. Gaining an in-depth understanding of the complex parameters of the relationship of the microbiome and TB infection could reveal key-elements that predict and modulate TB disease progression, severity, treatment outcomes and, possibly re-infection.

The role of the gut microbiome in host immunity and inflammation is mostly described by the capacity of certain microbial species to produce specific enzymes that ferment nutrients into absorbable forms, such as carbohydrates in the form of short-chain fatty acids (SCFAs) that possess anti-inflammatory and immunomodulatory properties [4]. Moreover, metabolites and other components of microbes like cell capsule carbohydrates, lipopolysaccharides, and endotoxins, produced to maintain the integrity of the gut wall, intervene in the production of vitamins, regulation of intestinal endocrine hormones, energy activation, stimulation or inhibition of certain specific key immune system signaling molecules [5]. Therefore, interaction between the gut microbiome and the immune signaling system may affect the inflammation response, as this interaction can lead to either an anti-inflammatory path by stimulation of regulatory cells or to pro-inflammation. On the other hand, gut microbiota can affect drug metabolism and provide protection against pathogenic organisms through colonization and competition for resources.

SCFAs, such as propionate, butyrate, acetate, and lactate are produced by the gut microbiome. They interact with G protein-coupled receptors to induce immune responses via signal transduction pathways. The mitogen-activated kinases (MAPK) pathway is involved in the pro-inflammatory response while the beta-arrestin-2 pathway is involved in the anti-inflammatory response. SCFAs bind to their receptors to stimulate IL-10 secretion from dendritic cells and macrophages in innate immunity. For an adaptive immune response, SCFAs can promote the expansion of regulatory T cells (Treg) and B cells in the gut-lung axis [4], all of which lead to the overall balance and modulation of the immune response.

Initial findings suggested that TB is associated with gut microbiome alterations [6–8]. They have found a significant decrease in microbial diversity in fecal samples of patients with TB compared to healthy controls. In this issue, Naidoo et al. described and compared different microbiome compartments, using oral wash, induced sputum, and stool samples in TB symptomatic cases, symptomatic no-TB controls, and no-TB household contacts of the previous two groups and performed a peripheral blood transcriptome comparative analysis. This represents the first TB microbiome study, to date, with the most comprehensive and thoughtful selection of control groups to reduce the maximum of bias. The study also linked the microbial changes to phenotype changes in inflammatory response during TB. The authors identified a distinct gut microbiome profile in TB infected cases as compared to their healthy close contacts, with Erysipelotrichaceae, Blautia, Anaerostipes in their stool, with precursor inferred pathways of short chain fatty acids that are known to modulate the immune response to TB [9]. The enriched gut anaerobes predict the upregulation of pro-inflammatory pathways related to TB disease and its severity, while different gut microbiome-transcriptome network interactions were involved in the household contacts. Also, in TB infected cases, anaerobes, such as Paludibacter, Lautropia were enriched in oral washes and induced sputum. Overall this study convincingly shows that this microbiome-inflammation pattern is unique to the TB infected group, which clearly demonstrates the interaction of the microbiome and TB disease via the SCFAs pathway [9]. The SCFAs microbial-related inflammation pathway has been described in other conditions, such as cancer, and certainly represents new avenues of research on TB biomarkers and on...
microbiome-targeted disease prevention or adjuvant treatments. In an earlier study, Namasivayam et al. found changes in the order Clostridiales of phylum Firmicutes and certain members of phylum Tenericutes with the mouse model [2], and similar observations were made by Hu et al. in pulmonary TB patients [10]. These commensals also produce metabolites that could modulate the immune signaling. This highlights some of the mechanistic differences between humans and mice, but outcome similarities, related to the TB and the microbiome.

It is now evident that the gut microbiota community composition and associated inflammation metabolic pathways change considerably in TB infected cases compared to the healthy household controls [9,10]. The differential abundance of gut microbiota may serve as microbiota biosignatures that discriminate active TB disease from healthy individuals and, could potentially be used as a therapeutic target of an immunomodulator adjuvant to TB treatment regimens or as a target for nutritional prevention of TB or severe disease [6]. Prebiotics, probiotics, and gut microbiome transfer strategies are potential options for such interventions.

Contributors

All authors contributed to Conceptualization (AMS, DD, JLH and MM), data curation (AMS, DD and MM), formal analysis (AMS, DD and MM), investigation (AMS, DD, JLH and MM), methodology (AMS, DD, JLH and MM), Resources (MM), supervision (MM), validation (AMS, DD, JLH and MM), visualization (AMS, DD, JLH and MM), writing original draft (AMS, DD and MM), writing review and editing (AMS, DD, JLH and MM).

Declaration of Competing Interest

There are no conflicts of interest.

Acknowledgements

This work was supported by the National Institutes of Health (R21AI148033 and D43TW010543).

References

[1] Mori G, Morrison M, Blumenthal A. Microbiome-immune interactions in tuberculosis. PLOS Pathog 2021;17:e1009377. doi: 10.1371/journal.ppat.1009377.
[2] Namasivayam S, Maiga M, Yuan W, Thovarai V, Costa DL, Mittereder LR, et al. Longitudinal profiling reveals a persistent intestinal dysbiosis triggered by conventional anti-tuberculosis therapy. Microbiome 2017;5:71. doi: 10.1186/s40168-017-0286-2.
[3] Kone B, Somboro AM, Holl JL, Baya B, Togo AA, Sarro YDS, et al. Exploring the usefulness of molecular epidemiology of tuberculosis in Africa: a systematic review. Int J Mol Epidemiol Genet 2020;11:1–15.
[4] Eribo OA, du Plessis N, Ozturk M, Guler R, Walzl G, Chegou NN. The gut microbiome in tuberculosis susceptibility and treatment response: guilty or not guilty? Cell Mol Life Sci 2020;77:1497–509.
[5] Venegas DP, De La Fuente MK, Landskron G, Gonzalez MJ, Quera R, Dijkstra G, et al. Short chain fatty acids (SCFAs) mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. Front Immunol 2019;10:277. doi: 10.3389/fimmu.2019.00277.
[6] Hu Y, Feng Y, Wu J, Liu F, Zhang Z, Hao Y, et al. The gut microbiome signatures discriminate healthy from pulmonary tuberculosis patients. Front Cell Infect Microbiol 2019;9: doi: 10.3389/fmicb.2019.00920.
[7] Li W, Zhu Y, Liao Q, Wang Z, Wan C. Characterization of gut microbiota in children with pulmonary tuberculosis. BMC Pediatr 2019. doi: 10.1186/s12822-019-1782-2.
[8] Namasivayam S, Diarra B, Diabate S, Sarro YDS, Kone A, Kone B, et al. Patients infected with Mycobacterium africanum versus Mycobacterium tuberculosis possess distinct intestinal microbiota. PLoS Negl Trop Dis 2020;14:e0008230.
[9] Naidoo CC, Nyawo GR, Sulaiman I, Wu BG, Turner CT, Bu K, et al. Anaerobe-enriched gut microbiota predicts pro-inflammatory responses in pulmonary tuberculosis. EBioMedicine 2021;67:103374. doi: 10.1016/j.ebiom.2021.103374.
[10] Hu Y, Yang Q, Liu B, Dong J, Sun L, Zhu Y, et al. Gut microbiota associated with pulmonary tuberculosis and dysbiosis caused by anti-tuberculosis drugs. J Infect 2019;78:317–22.