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Microbes helping Microbes

Evidence for gut microbiota establishing conditions permissive to pulmonary infection with *M. Tuberculosis*

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MicroRNAs, small non-coding RNAs that regulate gene expression post-transcriptionally, have emerged as key players in immune regulation and disease pathogenesis.1 Among these, miR-21 is one of the most highly expressed miRNAs in various tissues and has been implicated in modulating numerous inflammatory responses and immune functions. While the impact of miRNAs on bacterial pathogen-host interactions has been extensively studied, our understanding of their role in gastrointestinal (GI) tract immunity, particularly in the context of Tuberculosis (TB), remains limited.

In the article "MiR-21 is Remotely Governed by the Commensal Bacteria and Impairs Anti-TB Immunity by Down-Regulating IFN-γ," Yang et al. examine the interaction between gut microbiota, miR-21, and immunity in TB pathogenesis. MicroRNAs are known to regulate gene expression, and previous work specifically indicates roles in regulating immune function.[1] A growing body of research has explored the connection between the gut microbiome and lung diseases, a concept termed the "gut-lung axis."[2] This area of study suggests that gut-derived factors, including surviving bacteria, metabolites produced by gut bacteria, or other molecules, may travel into the circulatory system by way of the lymphatic system, potentially triggering immune responses in the lungs.[3] Through a "loss of function" model involving antibiotic-induced dysbiosis of the gut microbiota, the authors investigate the impact of this dysbiosis on immune responses to pulmonary *M. tuberculosis* infection, identifying miR-21 as a potential mediator of host-microbiota interactions in TB.[4]

Understanding the mechanisms by which commensal bacteria regulate interferon gamma (IFN-γ) production via miR-21 offers valuable insight into TB pathogenesis and potential treatment targets and vaccines.[5,6] Traditionally, TB infection occurs through aerosol absorption of *M. tuberculosis* by lung tissues. However, intraperitoneal (i.p.) infection in mouse models has been shown to mimic the chronic TB infection seen in low-dose aerosol exposure, providing several advantages for research. The model used in this study established a steady state level of bacterial burden in organs, resembling clinical latency characterized by low bacillary loads in humans. Furthermore, i.p. infections enable reliable, dose-dependent challenges, with higher doses triggering systemic immune responses relevant to TB pathogenesis.[4]

A key finding of this research is the modulation of miR-21-3p expression by gut dysbiosis induced by antibiotics. MiRNAs, which play critical roles in both innate and adaptive immunity, have been linked to commensal bacteria and disease development. Specifically, upregulated miR-21 expression has been associated with immune evasion by *Mycobacterium leprae*. In the context of TB, dysbiosis-driven changes in miR-21-3p expression affect immune responses, notably by inhibiting IFN-γ production, which is crucial for anti-TB immunity. Mechanistically, the presence of gut microbiota is required for miR-21-3p expression, which directly targets IFN-γ expression by T Cells resident in the lungs, highlighting its role in modulating immune protection against TB (See **Figure 1**). Additionally, fecal microbiota transplantation (FMT) from healthy mice restored gut microbiota and increased miR-21-3p expression in the lungs, providing further evidence linking gut microbiota, miRNAs, and immune responses in TB pathogenesis.

This research underscores the importance of understanding host-microbiota interactions in TB pathogenesis. By elucidating the regulatory pathways involving gut dysbiosis, miR-21-3p, and IFN-γ, the study provides a foundation for developing targeted therapies to enhance immune protection against TB. Given the global prevalence of TB, Tuberculosis, a disease claiming nearly 2 million lives each year, further investigations into the gut-lung axis and miRNA-mediated immune regulation hold promise for advancing TB control strategies and improving global health outcomes.[6]

References

1. Zhang, T., Yang, Z., Kusumanchi, P., Han, S. & Liangpunsakul, S. Critical Role of microRNA-21 in the Pathogenesis of Liver Diseases. Front. Med. 7, 7 (2020).
2. Dumas, A., Bernard, L., Poquet, Y., Lugo-Villarino, G. & Neyrolles, O. The role of the lung microbiota and the gut-lung axis in respiratory infectious diseases. Cell. Microbiol. 20, e12966 (2018).
3. Bradley, C. P. et al. Segmented Filamentous Bacteria Provoke Lung Autoimmunity by Inducing Gut-Lung Axis Th17 Cells Expressing Dual TCRs. Cell Host Microbe 22, 697-704. e4 (2017).
4. Yang, F. et al. MiR-21 Is Remotely Governed by the Commensal Bacteria and Impairs Anti-TB Immunity by Down-Regulating IFN-γ. Front. Microbiol. 11, 512581 (2021).
5. Dheda, K. et al. Global control of tuberculosis: from extensively drug-resistant to untreatable tuberculosis. Lancet Respir. Med. 2, 321–338 (2014).
6. Maartens, G. & Wilkinson, R. J. Tuberculosis. Lancet Lond. Engl. 370, 2030–2043 (2007).

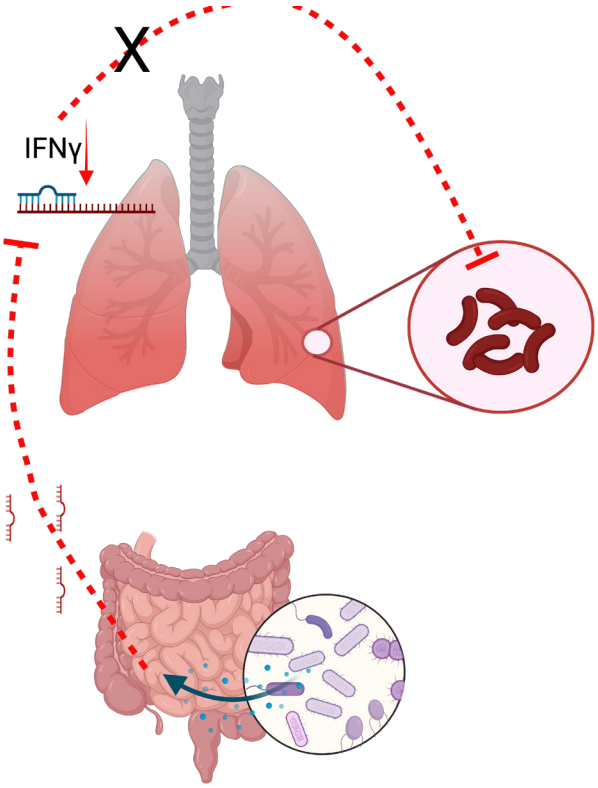

Figure 1: MiR-21 produced in the gut in response to microbiota modulates the expression of IFN-γ by lung-resident T Cells, resulting in an inability to clear pulmonary *M. tuberculosis infection.*