

Hypoxia shapes immune cell organization and bacterial control in tuberculosis granulomas

Spatial profiling of tuberculosis granulomas from non-human primates reveals that the myeloid core is partitioned into two distinct metabolic zones, one of which is hypoxic. Hypoxia is associated with dysfunctional immune cell states and altered spatial organization, including lymphocyte exclusion, and may be a driver of impaired immunity in tuberculosis.

This is a summary of:

McCaffrey, E. F. et al. The immunometabolic topography of cellular organization and bacterial control in tuberculosis granulomas. *Nat. Immunol.* <https://doi.org/10.1038/s41590-026-02431-8> (2026).

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Published online: 3 March 2026

The question

Tuberculosis (TB) remains the world's leading cause of death from infectious disease, largely owing to the lack of an effective vaccine and the growing emergence of drug resistance. TB is characterized by the formation of organized immune structures, termed granulomas, at sites of infection¹. Paradoxically, despite dense immune cell infiltration, granulomas typically fail to clear the infection^{2,3}. After more than a century of research, the mechanisms that underlie this failure, and whether they can be disrupted therapeutically, remain poorly understood. Hypoxia is a long-recognized feature of TB granulomas, yet its effect on immune cell function and its relationship with bacterial control has not been resolved in situ. Drawing conceptual parallels from tumor immunology, we sought to determine how hypoxia shapes immune cell state and spatial organization within TB granulomas, and how these features affect infection control.

The observation

To address this question, we performed highly multiplexed spatial proteomic and transcriptomic analyses of 52 granulomas from 16 non-human primates infected with *Mycobacterium tuberculosis*. Importantly, the bacterial burden, size and inflammatory status were quantified for each granuloma, enabling direct linkage between spatial architecture, immune function and infection control^{3,4}. We found that the macrophage-rich myeloid core segregates into two distinct metabolic environments, one of which is clearly demarcated by hypoxia associated with central caseous necrosis. We used this metabolic partitioning as the basis for a revised framework of granuloma histopathology to examine how each microenvironment governs immune cell organization and function (Fig. 1a). Spatial proteomics identified a distinct subset of hypoxic macrophages that are spatially segregated from T cells and correlate with higher bacterial burden. Integration with spatial transcriptomics and single-cell RNA sequencing identified cytokine signaling and other functional pathways linked to this metabolically altered macrophage state.

By adapting a geospatial topography approach, we mapped the

coordination between metabolic zones, cellular composition, and functional protein expression across granulomas, revealing a radial immunometabolic trajectory. Immune effectors previously associated with control of TB, including interferon- γ , inducible nitric oxide synthase and activated T cells, were confined to peripheral regions and excluded from the hypoxic core (Fig. 1b). Notably, hypoxia-associated features correlated with poor bacterial control and were also observed in human pulmonary TB.

The implications

Our findings suggest that hypoxia is a global regulator of granuloma structure and function that drives bacterial persistence in TB. The immune cell states and spatial patterns we observed in hypoxic granulomas closely resemble those seen in hypoxic tumors, such as glioblastoma, in which hypoxia has been shown to induce a myeloid-rich niche that impedes immune-mediated tumor clearance⁵. We propose that a similar process occurs in TB granulomas, creating both physical and immunological barriers to infection resolution.

Because our study captures a single infection timepoint, future studies will be needed to determine how hypoxia influences host responses over the course of TB. Nonetheless, these findings provide a foundation for such investigations and have important implications for the development of metabolically targeted therapies that may be efficacious in both TB and cancer. Furthermore, we provide a publicly available resource comprising 1,979 images and over 1.2 million single cells across 52 specimens and 16 animals – the most comprehensive spatial profiling dataset of TB granulomas in non-human primates so far.

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This research was supported in part by the Intramural Research Program of the National Institutes of Health (NIH). The findings and conclusions presented in this paper are those of the authors and do not necessarily reflect the views of the NIH or the US Department of Health and Human Services.

EXPERT OPINION

"This is a very well-executed and highly important study that provides a new framework for understanding the spatial immunometabolic organization of TB granulomas. The data are rigorously collected, expertly analyzed and clearly presented. In addition to being a fantastic

resource for the community, the paper is thought provoking; for example, the finding of high bacterial burden in the hypoxic zone in TB granulomas is unexpected and striking." **Olivier Neyrolles, Geanncarlo Lugo and Tejan Lodhiya, Université de Toulouse, Toulouse, France.**

FIGURE

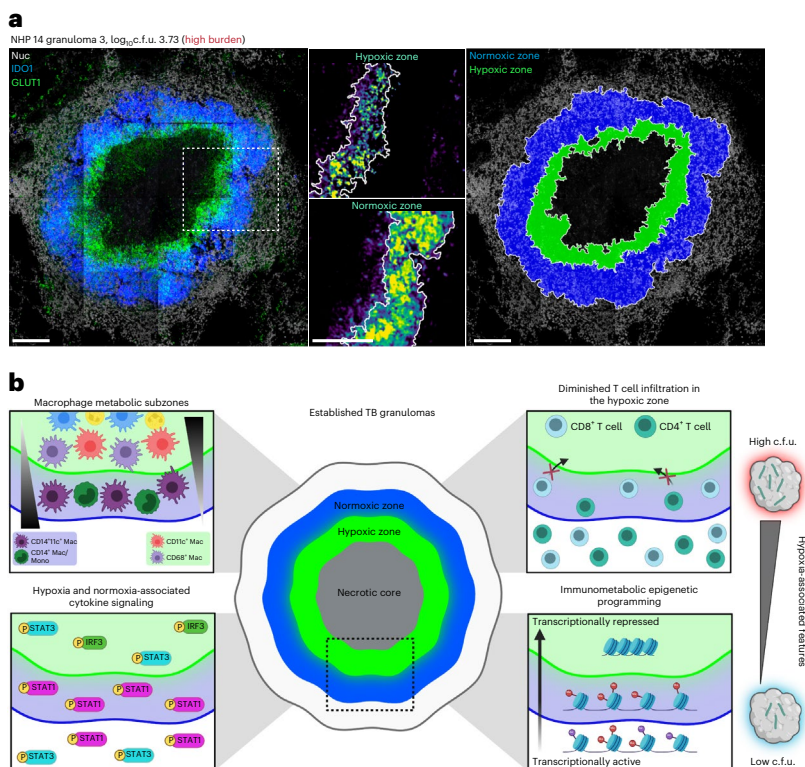


Fig. 1 | A model of hypoxia-mediated subversion of host immunity in TB granulomas. a, Representative images of metabolic partitioning in the myeloid core of TB granulomas as revealed by multiplexed imaging, showing IDO1 (blue) and GLUT1 (green) expression (white shows nuclei (Nuc), left). White-dashed box indicating insets. Scale bars, 200 μ m. b, A graphical overview showing how hypoxia organizes the established TB granuloma and influences bacterial control. Mtb, *M. tuberculosis*. Image in b created in BioRender; McCaffrey, E. <https://biorender.com/9gz66zw> (2025). © 2026, McCaffrey, E. F. et al.

BEHIND THE PAPER

The conceptual basis for our investigation into hypoxia arose from preliminary images showing a profound demarcation of metabolic environments in TB granulomas. Almost like layers of an onion, we could clearly see multiple rings of concentric niches radiating from the center of the granuloma. In addition to making beautiful images, we suspected that this patterning held crucial insight on how immune cell function is imprinted in granulomas. When discussing these images, we quipped that

the hypoxic zone resembled a mountain range standing between lymphocytes and the hub of infection. What started as a simple analogy evolved into a collaboration with geospatial scientists to adapt computational tools designed for topography to our imaging data. The analyses that followed taught us that, much like in tumors, immune cell function and metabolism are inextricably linked in TB granulomas. **E.F.M. & A.C.D.**

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FROM THE EDITOR

"We liked this paper for its methodologies that produce some stunning images and spatial immunometabolic analysis of TB granulomas in non-human primates, which are inherently difficult tissues and animals to study." **Nick Bernard, Senior Editor, Nature Immunology.**