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Mycobacterial phenotypic variation: Insights and opportunities

Abstract

Tuberculosis remains a major global health threat, while infections caused by nontuberculous mycobacteria are increasingly recognized as a growing clinical burden. In both settings, bacterial heterogeneity can contribute to variable infection outcomes and complicate patient management. Even within genetically clonal mycobacterial populations, individual cells can display substantial phenotypic variation, generating functionally distinct subpopulations with different capacities to adapt to stressful microenvironments, survive antibiotic treatment, interact with the host, and persist.

Our research focuses on understanding the mechanisms underlying mycobacterial phenotypic variation, how the environment influences bacterial diversification, and its functional consequences for pathogen survival. We develop single-cell and microfluidic approaches to follow these processes dynamically in both fast- and slow-growing pathogenic mycobacteria and to identify phenotypes that remain hidden in population-level measurements.

Using examples of mycobacterial phenotypic variation, I will present published and unpublished work showing how functionally important differences among individual bacteria can be revealed and followed over time using fluorescence-based reporters, live-cell imaging, and microfluidic systems. I will also discuss how this knowledge can be exploited therapeutically, including approaches aimed at decreasing cell-to-cell variation to enhance drug susceptibility and strategies that use single-cell information to selectively target stress-responsive bacilli. A major goal of our current work is to leverage functionally relevant bacterial phenotypes to identify new therapeutic targets and diagnostic markers.

Finally, I will discuss how these insights might be translated beyond the laboratory. Label-free imaging offers the possibility of extending single-cell phenotyping to clinical isolates and patient-derived samples, helping bridge the gap between mechanistic studies of microbial individuality and clinical applications. By probing phenotypic variation in real-world samples, we aim to develop new ways of understanding and ultimately improving the management of tuberculosis and nontuberculous mycobacterial infections.

References

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