Deciphering a Sleeping Pathogen: Uncovering Novel Transcriptional Regulators of Hypoxia-Induced Dormancy in Mycobacterium Tuberculosis

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Along the pathogenesis of Mycobacterium Tuberculosis (MTB), hypoxia-induced dormancy is a process involving the oxygen-depleted environment encountered inside the lung granuloma, where bacilli enter a viable, non-replicating state termed as latency. Affecting nearly two billion people, latent TB can linger in the host for indefinite periods of time before resuscitating, which significantly strains the accuracy of treatment options and patient prognosis. Transcriptional factors thought to mediate this process have only conferred mild growth defects, signaling that our current understanding of the MTB genetic architecture is highly insufficient. In light of these inconsistencies, the objective of this study was to characterize regulatory mechanisms underlying the transition of MTB into dormancy. The project methodology involved a three-part approach: constructing an aggregate hypoxia dataset, inferring a gene regulatory network based on those observations, and leveraging several downstream network analyses to make sense of it all. Results indicated dormancy to be functionally associated with cell redox homeostasis, metal ion cycling, and cell wall metabolism – all of which modulate essential host-pathogen interactions. Additionally, the crosstalk between individual regulons (Rv0821c and Rv0144; Rv1152 and Rv2359) was shown to be critical in facilitating bacterial persistence and allowing MTB to gain control over key micronutrients within the cell. Defense antioxidants and nutritional immunity were also identified as future avenues to explore further. In providing some of the first insights into the methods utilized by MTB to endure in a hypoxic state, this research suggests multiple strategies that might significantly aid in improved clinical outcomes of TB treatment.

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