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## **Intricate Genetic Programs Controlling Dormancy in *Mycobacterium tuberculosis***

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### **Abstract:**

*Mycobacterium tuberculosis* (MTB) displays the remarkable ability to transition in and out of dormancy, a hallmark of the pathogen's capacity to evade the immune system and exploit susceptible individuals. Uncovering the gene regulatory programs that underlie the phenotypic shifts in MTB during disease latency and reactivation has posed a challenge. We develop an experimental system to precisely control dissolved oxygen levels in MTB cultures in order to capture the transcriptional events that unfold as MT transitions into and out of hypoxia-induced dormancy. Using a comprehensive genome-wide transcription factor binding map and insight from network topology analysis, we identify regulatory circuits that deterministically drive sequential transitions across six transcriptionally and functionally distinct states encompassing more than three-fifths of the MTB genome. The architecture of the genetic programs explains the transcriptional dynamics underlying synchronous entry of cells into a dormant state that is primed to infect the host upon encountering favorable conditions.

Keywords: hypoxia-induce dormancy, network topology analysis, genome-wide transcription factor binding map, regulatory circuits, transcriptional dynamics, immune system