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First comprehensive regulatory map is a blueprint for how to defeat tuberculosis

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Despite decades of research on the bacterium that causes tuberculosis (TB), scientists have not had a comprehensive understanding of how the bacterium is wired to adapt to changing conditions in the host. Now, researchers at Stanford University, Seattle BioMed, Boston University and the Broad Institute, Max Planck Institute of Biology in Berlin, Germany, Caprion Proteomics Inc. in Montreal, Canada, Brigham and Woman's Hospital (Harvard University), and Colorado State University have taken the first steps toward a complete representation of the regulatory network for *Mycobacterium tuberculosis*. This map of the network of genes that control the TB bacterium will yield unique insights into how the bacteria survive in the host, and how they can be tackled with new drug interventions.

The landmark results are published this week in the journal *Nature*.

The burden of tuberculosis

One third of the world's population is latently infected with TB, harboring the bacteria in a dormant form in the lungs. In 2011 alone, 8.7 million people fell ill with the active form of TB, and 1.4 million died.

For hundreds of years, people have associated reduced oxygen tension with the control of TB. Artificially collapsing an infected lung using a pneumothorax device, or inserting golf ball-sized items into the pleural cavity, were common ways to treat the disease before the rise of

antibiotics. Despite the prevalence of these treatment methods, the bacteria appeared to survive in the host, even in hypoxic environments.

"We needed a window into how tuberculosis adapts to change, whether that is a lack of oxygen or a new drug," explains David Sherman, Ph.D., a lead researcher from Seattle BioMed. "In order to do that, we needed to understand how TB is wired—how its genes and the molecules that regulate them are related—so we can see how it changes its behavior depending on the environment."

Mapping tuberculosis

In order to create a map of how TB genes are regulated, researchers led by Gary K. Schoolnik, Ph.D., at the Stanford Medical School, David Sherman, Ph.D., of Seattle BioMed and James E. Galagan, Ph.D., of Boston University and the Broad Institute, turned to technologies that identified the key players in the system. Using ChIP-Seq, a method to analyze how proteins interact with DNA, they identified where 50 of TB's regulatory transcription factors bound to DNA, thereby providing the wiring diagram of genetic connections.

Though this kind of linking of transcription factors to genes had been done piecemeal in the past, Sherman explains, this is the first time that such a comprehensive study has been done all at once. "Nobody has ever done ChIP-Seq for every transcription factor in an organism," he says. "This is a far more global view of one organism's wiring than anyone has ever achieved before."

Creating a road map for future interventions

Because the regulatory map yields a systems view of how different genes in the TB bacterium interact, it will be useful to virtually everyone who

studies TB, says Sherman. The network provides key insights into the relative regulatory importance of some genes, and yields unexpected relationships between others.

"Everyone who studies TB can now look at this wiring diagram and gain a better understanding of how their favorite genes relate in a larger context," he says. "Suddenly, we can see how different areas connect, in intimate and important detail."

Though this map is the most comprehensive to date, Sherman and his colleagues plan to fill it out even further by incorporating the sequences of the remaining transcription factors and their relationship to the TB genome. The map will eventually provide a window into how targeted drugs or immunological interventions could interfere with TB's ability to survive in the host, adding a critical weapon to the fight against TB's worldwide devastation.

More information: Pape: dx.doi.org/10.1038/nature12337

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