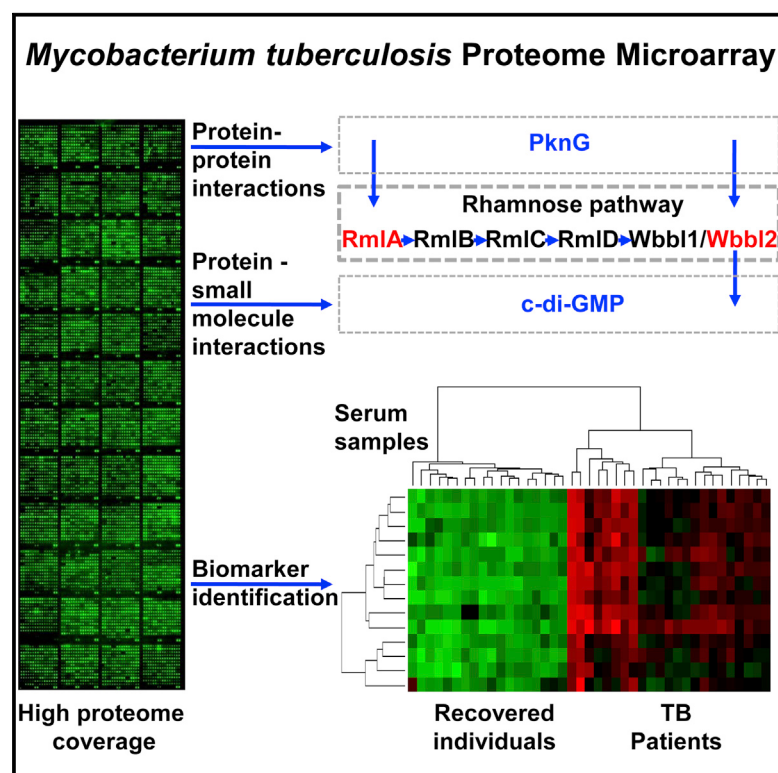


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Mycobacterium Tuberculosis Proteome Microarray for Global Studies of Protein Function and Immunogenicity

Graphical Abstract



Authors

Jiaoyu Deng, Lijun Bi, ..., Sheng-ce Tao, Xian-En Zhang

Correspondence

taosc@sjtu.edu.cn (S.-c.T.),
zhangxe@sun5.ibp.ac.cn (X.-E.Z.)

In Brief

Deng et al. present a functional *Mycobacterium tuberculosis* proteome microarray covering most of the proteome and an ORFome library ready for protein expression and demonstrate its broad applicability for rapidly generating insightful proteome-wide information on this slow-growing pathogen by investigating global PknG and c-di-GMP interactions and identifying serum biomarkers.

Highlights

- An MTB functional proteome microarray covering most of the proteome is presented
- Applications include global protein-biomolecule interactions and biomarker discovery
- The MTB ORFome library is ready for protein expression
- The MTB rhamnose pathway is likely regulated by both PknG and c-di-GMP



Mycobacterium Tuberculosis Proteome Microarray for Global Studies of Protein Function and Immunogenicity

Jiaoyu Deng,^{3,8} Lijun Bi,^{1,7,8} Lin Zhou,^{4,8} Shu-juan Guo,² Joy Fleming,¹ He-wei Jiang,² Ying Zhou,¹ Jia Gu,³ Qiu Zhong,⁴ Zong-xiu Wang,² Zhonghui Liu,¹ Rui-ping Deng,² Jing Gao,³ Tao Chen,⁴ Wenjuan Li,¹ Jing-fang Wang,² Xude Wang,³ Haicheng Li,⁴ Feng Ge,⁵ Guofeng Zhu,⁶ Hai-nan Zhang,² Jing Gu,³ Fan-lin Wu,² Zhiping Zhang,³ Dianbing Wang,¹ Haiying Hang,^{1,7} Yang Li,² Li Cheng,² Xiang He,² Sheng-ce Tao,^{2,*} and Xian-En Zhang^{1,*}

¹National Key Laboratory of Biomacromolecules, Key Laboratory of Non-Coding RNA and Key Laboratory of Protein and Peptide Pharmaceuticals, Institute of Biophysics, Chinese Academy of Sciences, Beijing 100101, China

²Shanghai Center for Systems Biomedicine, Key Laboratory of Systems Biomedicine (Ministry of Education); State Key Laboratory of Oncogenes and Related Genes; and School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai 200240, China

³State Key Laboratory of Virology, Wuhan Institute of Virology, Chinese Academy of Sciences, Wuhan 430071, China

⁴Center for Tuberculosis Control of Guangdong Province, Guangzhou 510630, China

⁵Key Laboratory of Algal Biology, Institute of Hydrobiology, Chinese Academy of Sciences, Wuhan 430071, China

⁶Shanghai Municipal Center for Disease Control and Prevention, Shanghai 200336, China

⁷TB Healthcare Biotechnology Co., Ltd., Foshan, Guangdong 528000, China

⁸Co-first author

*Correspondence: taosc@sjtu.edu.cn (S.-c.T.), zhangxe@sun5.ibp.ac.cn (X.-E.Z.)

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SUMMARY

Poor understanding of the basic biology of *Mycobacterium tuberculosis* (MTB), the etiological agent of tuberculosis, hampers development of much-needed drugs, vaccines, and diagnostic tests. Better experimental tools are needed to expedite investigations of this pathogen at the systems level. Here, we present a functional MTB proteome microarray covering most of the proteome and an ORFome library. We demonstrate the broad applicability of the microarray by investigating global protein-protein interactions, small-molecule-protein binding, and serum biomarker discovery, identifying 59 PknG-interacting proteins, 30 bis-(3'-5')-cyclic dimeric guanosine monophosphate (c-di-GMP) binding proteins, and 14 MTB proteins that together differentiate between tuberculosis (TB) patients with active disease and recovered individuals. Results suggest that the MTB rhamnose pathway is likely regulated by both the serine/threonine kinase PknG and c-di-GMP. This resource has the potential to generate a greater understanding of key biological processes in the pathogenesis of tuberculosis, possibly leading to more effective therapies for the treatment of this ancient disease.

INTRODUCTION

Mycobacterium tuberculosis (MTB), the etiological agent of tuberculosis and one of the most successful human pathogens,

caused 8.6 million incident cases of tuberculosis (TB) and claimed 1.3 million lives in 2012 (WHO, 2013) in spite of century-long efforts to combat it. More effective drugs, vaccines, and diagnostic tests for TB are clearly needed, but their development is hampered by poor understanding of the basic biology of this pathogen (Galagan et al., 2013). Global studies on MTB at the systems level rather than traditional one-gene or one-protein approaches should lead to breakthroughs (Boshoff and Lun, 2010), but better tools with which to investigate the basic biology of MTB and its interactions with the host at the systems level are urgently needed (McFadden et al., 2013).

High-throughput “omics” techniques have been applied to the study of MTB biology in recent years to address questions at the systems level; genomic studies are increasing our understanding of MTB evolution (Comas et al., 2013) and the development of drug resistance (Farhat et al., 2013; Zhang et al., 2013), while proteomic studies, which have identified ~80% of all annotated MTB proteins (Schubert et al., 2013), the protein constituents of different cellular locations (Gu et al., 2003), and the in vivo MTB proteome (Albrethsen et al., 2013), and metabolomic studies are opening up our understanding of the real-time physiological status of bacilli in the host (Shin et al., 2011).

Proteome microarrays, usually composed of thousands of proteins from one species that are affinity purified and functionally active, are powerful highly parallel, high-throughput platforms for globally profiling thousands of molecular interactions in a single experiment (Chen et al., 2008; Zhu et al., 2001). Their use in the discovery of serum biomarkers for various diseases (Gnjatic et al., 2010) and global investigations of protein interactions with other proteins (PPI) (Chen et al., 2013), with DNA (Lin et al., 2009), with RNA (Zhu et al., 2007), with lipids (Lu et al., 2012), and with a range of small molecules (Huang et al., 2004) demonstrate the power of this approach. Furthermore, they

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