Date / Time:
Monday 31October 2011
11am – 12pm

Venue:
Department of Microbiology
Seminar Room,
Blk MD4,
5 Science Drive 2,
Level 3,
Singapore 117576

Convener:
Assoc Prof Thomas Dick

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Seminar Coordinators
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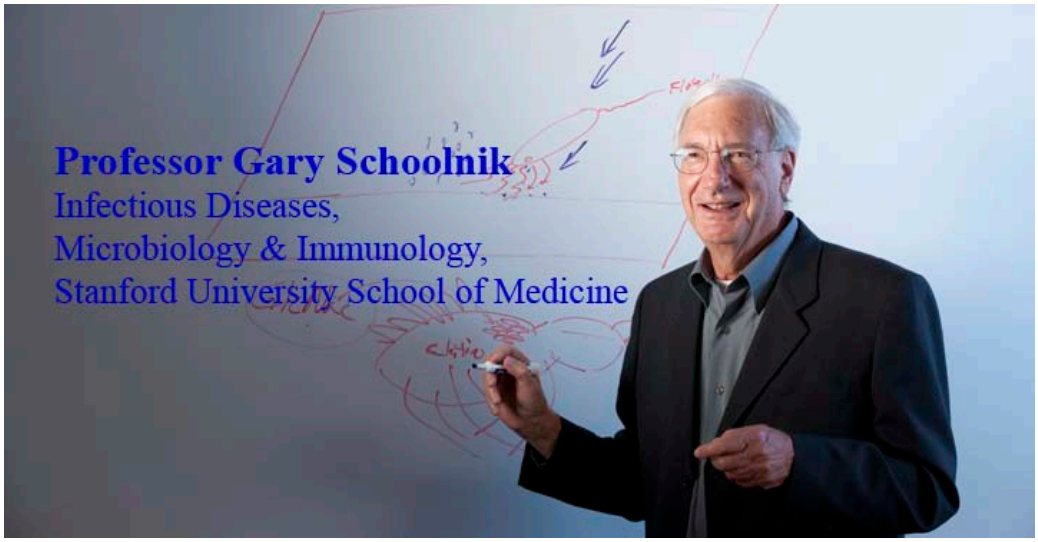
Tuberculosis: A Systems Biology Perspective of a Pathogen



Abstract

We have derived a genome scale model of the *Mycobacterium tuberculosis* (MTB) regulatory network, centered on regulators mediating the response of MTB to hypoxia and the regulation of lipid metabolism. We have further performed comprehensive profiling of gene expression, proteins, metabolites and lipids in MTB during a time-course of hypoxia and re-aeration and integrated these data with a model of the MTB metabolic network.

Using Chip-Seq, we identified binding sites for 47 of the predicted ~200 MTB transcription factors. We assessed the regulatory roles of binding using expression data from the upregulation of the same factors, constructed a regulatory network model based on these data, and assessed the power of the network for predicting expression changes. The network model reveals a direct and complex interconnection between the hypoxic response, lipid catabolism, lipid anabolism and the production of known immunomodulatory lipids, and protein degradation.

Consistent with this, we observe substantial alterations in lipid, amino acid, and protein content in response to oxygen availability. This includes restructuring of cell wall, the production of immunoreactive lipids and the accumulation and utilization of storage lipids, as well as large scale protein and amino acid degradation during hypoxia. These changes are also coupled with clear evidence for the buildup of propionate.

Propionate in MTB is generally considered a consequence of the digestion of external lipids. Our results indicate that hypoxia induces a regulatory and metabolic program that, independent of external lipid sources, leads to propionate through the catabolism of stored lipids and amino acids.

More broadly, our results provide a systems level view of the adaptation of a bacterial pathogen to stress conditions relevant to pathogenesis, and provide mechanistic insight into the complex regulation of this adaptation. The data are freely available to the scientific community through TBDB.org.

Selected Publications

Aderem A, Adkins JN, Ansong C, Galagan J, Kaiser S, Korth MJ, Law GL, McDermott JG, Proll SC, Rosenberger C, Schoolnik G, Katze MG. A systems biology approach to infectious disease research: innovating the pathogen-host research paradigm. *M. Bio*. 2: 325-10, 2011

Galagan JE, Sisk P, Stolte C, Weiner B, Koehrsen M, Wymore F, Reddy TB, Zucker JD, Engels R, Gellesch M, Hubble J, Jin H, Larson L, Mao M, Nitzberg M, White J, Zachariah ZK, Sherlock G, Ball CA, Schoolnik GK. TB database 2010: overview and update. *Tuberculosis*. 2010; 90:225-35.

Reddy,T.B.K., Mao, M., Hubble, J., Nitzberg, M., Zachariah, Z., Wymore, F., Riley, R., Weiner, B., Galagan, J., Sherlock,G., Ball,C., and G.K. Schoolnik. TB Database: An integrated platform for tuberculosis research. *Nucleic Acids Res*. 37: 499-508, 2009.