Published: March 2013

Understanding TB latency using computational and dynamic modelling procedures

Gesham Magombedze - Postdoctoral Research Associate, University of Tennessee, USA

The Mycobacterium tuberculosis (TB) bacilli's potency to cause persistent latent infection that is unresponsive to the current cocktail of TB drugs is strongly associated with its ability to adapt to changing intracellular environments, and tolerating, evading and subverting host defence mechanisms. We applied a combination of bioinformatics and mathematical modelling methods to enhance the understanding of TB latency dynamics. Analysis of time course microarray gene expression data was carried out and gene profiles for bacilli adaptation and survival in latency, simulated by hypoxia were determined. Reverse network engineering techniques were used to predict gene dependencies and regulatory interactions. Significant regulatory genes involved in latency were determined by a combination of systems biology procedures and mathematical modelling techniques.

This study predicted the role of dosR-regulon genes as central in the regulation of latency. These genes were predicted to cluster with adaptation, detoxification and virulence genes and several other genes of unknown or putative functions (Rv3131, Rv0569, Rv2032, Rv2530c, and Rv2694c), some of which were predicted both in the regulation of the stationary and non-replicating phase of the bacteria.

This study furthermore predicted that other genes (Rv1133c, Rv2890c, Rv1177, Rv2710, Rv2532c and Rv0982) also regulate latency. These gene were shown in other studies to be essential for H37Rv growth and *in vivo* bacterial survival. Through sensitivity analysis of the predicted gene regulatory networks and computational gene deletion experiments, the genes Rv2031, Rv3133c, Rv2032, Rv3131, Rv2530c, Rv2527, Rv1909c, and Rv0569 were identified most potent in disrupting the bacteria latency and dormancy program. Hypothetically, these genes are possible drug targets. Interestingly, Rv3131, a putative NAD(P)H nitroreductase, which is quite central in regulation of the stationary phase was shown in other studies to be essential for bacterial growth, making it an attractive drug target. The predicted genes have functions that are linked to human immune response mechanisms, such as induction of interferon-c (IFN-c) and interleukin-2 (IL-2) (Rv2032, Rv3133c, Rv3131, and Rv2031c), oxidative stress (Rv1909c) and nitrosative stress (Rv3131, Rv3133c, Rv2031c). The latter are associated with nitrogen and oxygen reactive intermediate effector mechanisms of the immune response and were shown in other studies to have the potential to prime the human immune response.

Although these genes are predicted in this and other studies to be involved in the regulation of TB latency, it must be highlighted that: (i) they are not fully annotated and characterised, (ii) they have not been assigned to any functional class, (iii) no assay information is available on them and (iv) they have not been mapped to any specific metabolic KEGG pathways. Nevertheless, it remains imperative that they should be tested through biological experiments for verification and validation to determine if they can be used for possible latency TB drug design.

This study predicted the latency regulatory mechanism to be dynamic with respect to the stress and time spent under the stress. This suggests that experiments simulating latency have a good chance of closely predicting and explaining what takes place in latency if they are carried out over a long time period.

Gesham Magombedze, Postdoctoral Research Associate, University of Tennessee, USA. Areas of interest: Mathematical modelling of Mycobacterial infections. *gmagombedze@gmail.com*

Reference:
Magombedze G, Mulder N. Understanding TB latency using computational and dynamic modelling procedures.Infect Genet Evol. 2013;13:267-83.