Poster J-11

Computational predicted protein associations of Mycobacteriun tuberculosis under hypoxic conditions associated with latency.

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Short Abstract: A set of Mycobacteriun tuberculosis functional annotated proteins up-expressed under hypoxic conditions associated with latency, were analysed using computational methods for the inference of protein–protein associations. This approach reveals certain signatures, including associations of proteins involved in fatty acid b-oxidation, nitrite/nitrate metabolism, and protection against stress.

Long Abstract:

Mycobacterium tuberculosis is the bacterium responsible for human tuberculosis, and epidemiological data suggest that possibly up to one-third of the human population is latently infected, comprising a critical reservoir for disease reactivation (Sudre et.al, 1992). Despite the importance of latency in maintaining M. tuberculosis in the human population, little is known about the mycobacterial factors that regulate persistence and reactivation. Several lines of evidence link latent tuberculosis and inhibition of M. tuberculosis, growth and metabolism with hypoxic conditions within the host. Tuberculosis infections are preferentially associated with the most oxygen-rich sites in the body, suggesting that reduced levels of O2 may limit M. tuberculosis growth in vivo.

A set of M. tuberculosis functional annotated proteins up expressed in hypoxic conditions according to results of microarray experiments, done by Sherman et. al (2001), were analysed using Rosetta Stone, Conserved Genomic Neighborhood, co-expression analysis and Phylogenetic Profile computational methods for the inference of protein–protein associations. For this purpose, we used STRING databases of known and predicted protein-protein interactions (von Mering et.al, 2005), available at http://string.embl.de/. Protein networks were constructed using functional linkages between proteins whose predicted association had an assigned STRING confidence score, greater than or equal to 0.800.

This combined approach let us identify signatures which may play critical roles in the survival of M. tuberculosis in hypoxic conditions. One of the signatures or networks included a group of enzymes of fatty acid degradation by a b-oxidation that could function under anaerobic growth conditions in the presence of a terminal electron acceptor. This could let bacterium grow on fatty acids under anaerobic conditions. Genes whose proteins are included in this signature were pks16, Rv2182c, fadE5, echA19, fadA2, and scoA. Another protein network contained products of genes involved in nitrate/nitrite metabolism like nirB, narX, narG, narH, and narK2. Nitrate is a potential electron acceptor, that could be necessary to support anaerobic growth, and it has shown being the most efficient anaerobic electron acceptor in other bacterials (Campbell et.al, 2003, Zumft, 2005)

Another prominent signature is the association of genes related to stress response like chaperonins (dnaJ, clpB, groES, groEL1, dnaK, and grpE) and ferredoxin oxidoreductases (fprB, Rv2455c and Rv2454c). These genes could play a role in the adaptation of mycobacteria to oxygen deprivation and furthermore, that they may feature in the development of latent tuberculosis.

Besides, proteins coded by these up-expressed genes were compared with proteins from the host H. sapiens, by performing a BLASTp. Proteins, which did not have hits below the e-value inclusion threshold of 10-6 and scores greater than 80, were picked out as potential drug targets. As a case study, we have built a homology model of one of the potential drug targets predicted nirB nitrite reductase using using the Swiss-Model server (http://swissmodel.expasy.org//SWISS-MODEL.html).

REFERENCES

Campbell JW, Morgan-Kiss RM, Cronan JE Jr. 2003. A new Escherichia coli metabolic competency: growth on fatty acids by a novel anaerobic beta-oxidation pathway.
Mol Microbiol; 47(3):793-805.

Sherman DR, Voskuil M, Schnappinger D, Liao R, Harrell MI, Schoolnik GK. 2001. Regulation of the Mycobacterium tuberculosis hypoxic response gene encoding alpha -crystallin. Proc Natl Acad Sci U S A; 98(13):7534-9.

Sudre P, ten Dam G, Kochi A. 1992. Tuberculosis: a global overview of the situation today. Bull World Health Organ.; 70(2):149-59

von Mering C, Jensen LJ, Snel B, Hooper SD, Krupp M, Foglierini M, Jouffre N, Huynen MA, Bork P. 2005. STRING: known and predicted protein-protein associations, integrated and transferred across organisms. Nucleic Acids Res. 33(Database issue):D433-7.