Using evolution to decipher how mycobacteria regulate responses

August 6 2014

UCD researchers have published the first study in mycobacteria to identify genome-wide regulatory elements using comparative transcriptomics (RNA profiles).

In order to understand how evolution shapes regulatory architecture, the study compared two members of the Mycobacterium tuberculosis complex (MTBC); M. tuberculosis and M. bovis, the causative agents of tuberculosis in humans and animals, with a closely related environmental mycobacteria, M. marinum.

The analysis identified several novel regulatory elements controlling the expression of important virulence associated genes. One such element was associated with whiB7, a master regulator that controls intrinsic (innate) antibiotic resistance across the mycobacterial clade.

Certain bacteria including members of the MTBC are particularly hard to treat as they display an intrinsic resistance or insensitivity to many commonly used antibiotics which severely limits therapeutic options available.

"Our discovery of a control element governing expression of this master regulator provides not only mechanistic insight into antibiotic resistance in mycobacteria but should facilitate the identification of inhibitors that could render pathogens such as M. tuberculosis more sensitive to antibiotics," said Conway Fellow, Professor Brendan Loftus of UCD School of Medicine & Medical Science who led the study.

The study also uncovered evidence that members of the MTBC have accumulated a large amount of non-protein coding RNA transcripts resulting in a comparatively high level of background transcriptional "noise" compared to environmental mycobacteria.

The increased potential for stochastic variation or "noise" between cells of a population at the RNA level has been linked to the ability of differing cells to react differently to fluctuating environmental conditions.

The study concluded that such noise is a consequence of the evolutionary history of the MTBC, which forfeited much of its capacity to spring-clean its genome of accumulated mutations during the transition to becoming an obligate pathogen.

The study's findings indicate that, in general, bacterial transcriptomes are a blend of those elements that nature has selected for interspersed with a healthy quotient of genetic hitchhikers just along for the ride.

The findings of the study are published in the current issue of mBio, an open access journal of the American Society of Microbiology.

More information: "Relaxed Selection Drives a Noisy Noncoding Transcriptome in Members of the Mycobacterium tuberculosis Complex." Adam M. Dinan, Pin Tong, Amanda J. Lohan, Kevin M. Conlon, Aleksandra A. Miranda-CasoLuengo, Kerri M. Malone, Stephen V. Gordon, and Brendan J. Loftus. *mBio* 5:4 e01169-14; Published 5 August 2014, DOI: 10.1128/mBio.01169-14

Provided by University College Dublin