Can peptidoglycan remodeling reveal novel drug targets and probe for phenotypic complexity in sputum-derived mycobacteria?

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Abstract

Tuberculosis (TB) continues to cause a massive loss of human life despite global effort to vaccinate, treat, prevent infection and interrupt transmission. The lack of novel shorter TB treatment regimens, together with insufficient understanding of bacterial physiology during transmission and pathogenesis, constitute critical barriers to the eradication of TB. To address this, we studied remodeling of the mycobacterial peptidoglycan layer to identify new drug targets and assess the complexity of bacterial physiological states in TB-diseased individuals. Two classes of peptidoglycan hydrolases, amidases and resuscitation promoting factors (Rpfs) were selected for analysis. Notable division defects occurred upon depletion or disruption of amidases, which were due to collapse of the cell division machinery and ectopic localization of cell elongation enzymes. These observations highlight specialist roles for amidases in mycobacterial proliferation and validate them as novel drug targets. Next, we turned our attention to the role of Rpfs in modulating bacterial growth in sputum. Previous work demonstrated that sputum from TB patients harbours drug tolerant, differentially culturable tubercle bacteria (DCTB) that are unable to grow on solid media but can be recovered in liquid media supplemented with Rpfs. This phenomenon was interrogated further to reveal five operationally distinct bacterial subpopulations in the sputum of treatment naïve individuals. DCTB populations identified in this cohort displayed variable dependency on Rpfs, with the additional presence of a novel subclass of Rpf-independent DCTB. Moreover, the distribution of DCTB was dependent on the host immune response. These data draw attention to a previously undescribed complexity of phenotypic states in sputum-resident bacteria and provide a novel diagnostic biomarker that could be used to monitor treatment response and risk of recurrent TB disease.

Biography: Bavesh Kana

Professor Bavesh Kana is head of the University of the Witwatersrand (Wits) node of the DST/NRF Centre of Excellence for Biomedical TB Research, Johannesburg, South Africa, where he studies tuberculosis with a focus on identifying new drug targets and biomarkers to monitor treatment response and risk of disease recurrence. He obtained his PhD at Wits and has worked in several US institutions including the University of Pennsylvania, Texas A&M University, the Public Health Research Institute and Harvard Medical School. He has held grants from the NRF, the NHLS, the Fogarty International Centre, the US National Institutes of Health and the Bill and Melinda Gates Foundation. He is the recipient of the Friedel Sellschop Research Award, the South African MRC Career Development Award, and was part of the team that received the National Health Laboratory Service Innovation Award. Prof. Kana was also appointed as an Early Career Scientist of the Howard Hughes Medical Institute (2012-2016); he is one of 26 scientists worldwide to receive this accolade. In 2012, he was selected as one of the 200 top young South Africans by the Mail and Guardian newspaper. More recently, Prof. Kana was awarded the first-time inventor's award and first-time innovator's award by Wits Enterprise for the creation of novel diagnostic reagents that are currently being marketed in over 30 countries. He has been admitted to the Academy of Science of South Africa and was also selected for the CEO Titan Award, which recognized his outstanding contribution to medical science in South Africa, the SADC region and the African continent.