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Functional Characterization of Rv1019, a Putative TetR Family Transcriptional Regulator of Mycobacterium Tuberculosis H37Rv

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Abstract : Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), is one of the leading causes of death by an infectious disease. In spite of the availability of effective drugs and a vaccine, TB is a major health concern and was declared a global emergency by the World Health Organization (WHO). The success of intracellular pathogens like Mtb depends on its ability to overcome the challenging environment in the host. Gene regulation controlled by transcriptional regulators (TRs) plays a crucial role for the bacteria to adapt to the host environment. In vitro studies on gene regulatory mechanisms during dormancy and reactivation have provided insights into the adaptations employed by Mtb to survive in the host. Here we present our efforts to functionally characterize Rv1019, a putative TR of Mtb H37Rv which was found to be present at significantly varying levels during dormancy and reactivation in vitro. The expression of this protein in the dormancy-reactivation model was validated by qRT-PCR and western blot. By DNA- protein interaction studies and reporter assays we found that under normal laboratory conditions of growth this protein behaves as an auto-repressor and tetracycline was found to abrogate this repression by interfering with its ability to bind DNA. Further, by cDNA analysis, we found that this TR is co-transcribed with its downstream genes Rv1020 (mfd) and Rv1021 (mazG) which are involved in DNA damage response in Mtb. Constitutive expression of this regulator in the surrogate host M. smegmatis showed downregulation of the orthologues of downstream genes suggested that Rv1019 could negatively regulate these genes. Our finds also show that M. smegmatis expressing Rv1019 is sensitive to DNA damage suggests the role of this protein in regulating DNA damage response induced by oxidative stress. Because of its role in regulating DNA damage response which may help in the persistence of Mtb, Rv1019 could be used as a prospective target for therapeutic intervention to fight TB.

Keywords : auto-repressor, DNA repair, mycobacterium smegmatis, mycobacterium tuberculosis, tuberculosis
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