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HLA-A*0201-restricted CTL epitopes in Rv0350 and Rv0351 of latent *Mycobacterium tuberculosis*

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Background: *Mycobacterium tuberculosis* (Mtb) infects approximately one third of the world's population, 10% of which develop disease during lifetime. Beijing genotype strains are the most predominant strains in China. The aim of this study was to screen and validate the possible HLA*0201 restricted specific T cell epitopes of latent phase Mtb strains H37Rv and Beijing genotype.

Methods & Materials: MTB DNA microarray gene expression analysis was performed to screen the Mtb genes which expressed up-regulated under hypoxia. SYFPEITHI and NetCTLpan databases were used to predict the HLA-A*0201 restricted cytotoxic T lymphocyte (CTL) epitopes on Mtb, followed by peptide/HLA-A*0201 affinity and complex stability assays using the T2 cells. IFN-gamma-producing T cells were detected by enzyme-linked immunospot assay (ELISPOT) and a LDH release assay were performed to detect peptide-specific CTL activity using PBMC derived from HLA-A*0201-positive human donors latently infected with Mtb (LTBI).

Results: Using a whole genome microarray, we identified 130 genes of Mtb strain H37Rv and Beijing genotype whose expression was up-regulated under hypoxic conditions, 37 genes were responsible for encoding membrane protein, cell wall proteins or exported proteins. Of selected four proteins coded by up-regulated genes, Six potential epitopes on Rv0350, Rv0351 and Rv0440 were selected as candidate HLA-A*0201 restricted CTL epitopes by SYFPEITHI and NetCTLpan prediction. Four of these 6 study epitopes ($Rv0440_{p416-424}$, $Rv0440_{p362-370}$, $Rv0351_{p122-130}$ and $Rv0350_{p363-371}$) were showed high binding affinity and stabilization to HLA-A*0201 molecules by T2 binding studies. Synthesis of multi-epitope peptides Rv0351-A-T (containing $Rv0351_{p122-130}$, APDRE and Trojan peptide) and Rv0350-A-T (containing $Rv0350_{p363-371}$, APDRE and Trojan peptide) via ufrinsensitive linker VRKR. Cytotoxic activity showed that significant lysis of T2 cells pulsed with Rv0351-A-T or Rv0350-A-T was induced by peptide-specific T cells derived from HLA-A*0201-positive LTBI. IFN- gamma was released by PBMC *in vitro* from HLA-A*0201-positive LTBI when challenged with the peptides by an ELISPOT assay.

Conclusion: Our data suggest that $Rv0351_{p122-130}$ and $Rv0350_{p363-371}$ are HLA-A*0201-restricted CTL epitopes and could be useful in the design of an Mtb vaccine for LTBI.

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Early treatment outcomes of patients with extensively drug resistant tuberculosis in South Africa

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Background: Drug-resistant tuberculosis is a major public health threat. High mortality rates have been reported for patients with extensively drug-resistant tuberculosis (XDR TB), particularly in the case of co-infection with HIV. Early South-African reports tallied a near-100% mortality rate in the Tugela Ferry outbreak (Gandhi et al. Lancet 2006); pooled data from various institutions from South Africa including Sizwe Hospital reported an overall mortality rate for XDR-TB patients after initiation of therapy of 36% (Dheda et al. Lancet 2010).

Methods & Materials: This is a retrospective sub-analysis of case records of adult patients treated for XDR TB (culture confirmed), who were all admitted toSizweHospitalinJohannesburg,South Africa, between June 2004 and September 2008. Endpoints used were mortality and sputum culture conversion (defined as at least two consecutive negative cultures).

Results: Thirty-three patients for which comprehensive information was available from the case records were included in the analysis. The majority of patients was male (18/33, 54.5%) with a mean age of 39.6 years (95% CI 31.9-41.8). HIV infection was present in 22/33 (66.7%) individuals. Individuals were followed for a median time of 11.8 months (IQR 9.1 months). Five of these patients died (5/33, 15.2%), after a median time of 6.3 months (95% CI 2.0-10.5 months); 4 of them were HIV positive (4/5, 80%). Sputum culture conversion occurred in 10 individuals (10/33, 30.3%), after a median time of 12.2 months (95% CI 3.9-24.8 months).

Conclusion: In a specialized hospital setting, mortality rates for XDR TB patients can be considerably reduced well below a 20% mortality threshold.

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