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Identification of Promiscuous Epitopes for Cellular Immune Responses in the Major Antigenic Protein Rv3873 Encoded by Region of Difference 1 of Mycobacterium tuberculosis

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Abstract : Rv3873 is a relatively large size protein (371 amino acids in length) and its gene is located in the immunodominant genomic region of difference (RD)1 that is present in the genome of Mycobacterium tuberculosis but deleted from the genomes of all the vaccine strains of Bacillus Calmette Guerin (BCG) and most other mycobacteria. However, when tested for cellular immune responses using peripheral blood mononuclear cells from tuberculosis patients and BCG-vaccinated healthy subjects, this protein was found to be a major stimulator of cell mediated immune responses in both groups of subjects. In order to further identify the sequence of immunodominant epitopes and explore their Human Leukocyte Antigen (HLA)-restriction for epitope recognition, 24 peptides (25-mers overlapping with the neighboring peptides by 10 residues) covering the sequence of Rv3873 were synthesized chemically using fluorenylmethyloxycarbonyl chemistry and tested in cell mediated immune responses. The results of these experiments helped in the identification of an immunodominant peptide P9 that was recognized by people expressing varying HLA-DR types. Furthermore, it was also predicted to be a promiscuous binder with multiple epitopes for binding to HLA-DR, HLA-DP and HLA-DQ alleles of HLA-class II molecules that present antigens to T helper cells, and to HLA-class I molecules that present antigens to T cytotoxic cells. In addition, the evaluation of peptide P9 using an immunogenicity predictor server yielded a high score (0.94), which indicated a greater probability of this peptide to elicit a protective cellular immune response. In conclusion, P9, a peptide with multiple epitopes and ability to bind several HLA class I and class II molecules for presentation to cells of the cellular immune response, may be useful as a peptide-based vaccine against tuberculosis.

Keywords : mycobacterium tuberculosis, PPE68, peptides, vaccine
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