Solution Structure of the Mycobacterium tuberculosis Complex Protein MPB70

FROM TUBERCULOSIS PATHOGENESIS TO INHERITED HUMAN CORNEAL DISEASE*

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The Journal of Biological Chemistry Vol. 278, No. 44, Issue of October 31, pp. 43736–43743, 2003

Received for publication, July 7, 2003

The closely related mycobacteria responsible for tuberculosis produce an unusually high number of secreted proteins, many of which are clearly implicated in pathogenesis and protective immunity. Falling within this category are the closely related proteins MPB70 and MPB83. The structure of MPB70 reveals a complex and novel bacterial fold, which has clear structural homology to the two C-terminal FAS1 domains of the cell adhesion protein fasciclin I, whose structures were reported very recently. Assessment of the surface features of MPB70, the sequence divergence between MPB70 and MPB83, the conservation of residues across a group of FAS1 domains, and the locations of disease-inducing mutations in βig-h3 strongly suggests that MPB70 and MPB83 contain two functional surfaces on opposite faces, which are probably involved in binding to host cell proteins. This analysis also suggests that these functional surfaces are retained in the FAS1 proteins associated withmediating interactions between cells and the extracellular matrix (fasciclin I, periostin, and βig-h3) and furthermore that some of the human corneal disease-inducing substitutions identified in βig-h3 will perturb interactions at these sites.

Tuberculosis remains one of the most significant infectious diseases of humans, with about one-third of the world’s population currently infected resulting in about 3 million deaths annually (1, 2). The bacteria responsible for tuberculosis belong to the Mycobacterium tuberculosis complex, which is a group of highly related mycobacteria. The complex includes M. tuberculosis, which causes the majority of human tuberculosis, and Mycobacterium bovis, which leads to tuberculosis in a range of domesticated and wild animals. Analysis of the complete M. tuberculosis H37Rv genome has identified the genes for 4006 proteins (3, 4), however, it has so far proved possible to assign specific functions to only about half of the predicted proteins. In addition, we still have relatively little information about which M. tuberculosis complex proteins are essential for pathogenesis, or associated with the stimulation of protective immunity, and even less knowledge of their structures, functions, and mechanisms of action. The finding that only live mycobacterial vaccines provide significant protection against tuberculosis infection (5) clearly indicates a key role for secreted M. tuberculosis complex proteins in stimulating protective immunity and highlights the importance of investigating major secreted antigenic proteins such as MPB70, MPB83, ESAT-6, and CFP-10 (6–10).

The mature M. bovis protein MPB70 and its identical M. tuberculosis homologue MPT70 (Rv2875) are stable, 163-residue polypeptides, that are efficiently secreted from mycobacterial cells following cleavage of a 30-residue signal peptide (3, 6). The proteins contain a single disulfide bond linking Cys-8 and Cys-142 but show no other form of post-translational modification. MPB70 is a major serodominant antigen of M. bovis, which also stimulates cellular immune responses during infection and is able to elicit a strong, delayed type hypersensitivity response in M. bovis infected cattle (11–14). Virulent M. bovis strains secrete high levels of MPB70 when grown in culture, but the protein is produced at much lower levels by M. tuberculosis and by a number of M. bovis BCG strains including Pasteur, Copenhagen, and Glaxo (7, 15, 16). Despite significant differences in expression levels in culture both M. bovis and M. tuberculosis stimulate a strong immune response to MPB70 upon infection, suggesting that expression of the protein is up-regulated by M. tuberculosis in vivo (17, 18). In addition, the treatment of M. tuberculosis-infected mice with a DNA vaccine encoding MPB70 has a pronounced therapeutic effect, indicating an essential role for MPB70 during infection of the host (19). Although MPB70 is clearly linked to the stimulation of protective immunity and implicated in tuberculosis pathogenesis, the function of the protein remains unknown. Interestingly, residues 26–162 from MPB70 show significant sequence homology (up to 30% identity) to the FAS1 domains of several extracellular matrix proteins (fasciclin I, βig-h3, and periostin), which are known to be involved in mediating interactions between cells and the extracellular matrix (20, 21).

Mycobacteria of the M. tuberculosis complex produce another major secreted protein termed MPB83 in M. bovis and MPT83

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sequence-specific backbone resonance assignments for MPB70 to the side chain or slowly exchanging backbone amide protons (750 peaks). Among these, 350 peaks were assigned to unique pairs of protons using CANDID but also included 350 side chain or slowly exchanging backbone amide protons (750 peaks), and all NOEs between aliphatic protons (3434 peaks). In addition, the CANDID stage included constraints corresponding to the single disulfide bond present in MPB70 (Cys-8 to Cys-142) and to 35 C2 angles (2.30°) derived from analysis of TOCSY-HSQC and NHNHB spectra. The NOE peak lists were prepared using XEASY, and the volumes of the cross-peaks were calculated using the Lorentzian line fitting and integration routines available in SPSCAN (www.molebio.uni-jena.de/~reg/scan). The CANDID calculations were carried out using the default parameter settings in CYANA 1.05 apart from increasing the average target value for NOEs involving backbone protons from 3.8 to 4.0 Α° in the structure-independent NOE calibration routine used in cycle 1, raising the upper limit for observable NOEs to 6.0 Α° and setting the chemical shift uncertainties to 0.02 ppm for 1H, 0.3 ppm for 15N, and 0.2 ppm for 13C.

The final converged MPB70 structures were produced from 100 random starting coordinates using a torsion angle-based simulated annealing protocol combined with four cycles of redundant dihedral angle search and structure-dependent NOE assignments. The hydrogen bond constraints were included for residues with backbone amide signals still detectable after the final round of the calculations to 45 hydrogen bonds involving backbone amide groups. The hydrogen bond constraints were only included for residues with backbone amide signals still detectable after 8 weeks in D2O and where the distance between the hydrogen bond acceptor and donor atoms was less than 2.5 Α° and the NH to O bond angle was greater than 135° in converged structures obtained from the penultimate calculation cycle (residues 40, 41, 43–49, 51, 55, 61, 66–70, 72, 77, 96, 103, 105, 114, 116, 118, 121, 124, 126, 127, 134, 135, 140, 141, 145, 147, 151, 153–155, and 159). The standard simulated annealing protocol used consisted of a high temperature conformational search phase of 2000 steps followed by slow cooling over 8000 steps and conjugate gradient minimization at the end.

The family of MPB70 structures obtained were analyzed using the program CYANA (39) and using the program YAS (38). A significance search of the MPB70 coordinates against all structures deposited in the Protein Data Bank was carried out using DALI (Ref. 45; available at www.ebi.ac.uk/dali), and optimal alignments between the structures for MPB70 and the fasciclin domains of fascin I were calculated using CE (Ref. 46; available at clsdce.edu).
the only signals that remained unidentified were from the TOCSY spectra. Apart from exchangeable side-chain groups, served in DQF-COSY, TOCSY, TOCSY-HSQC, and HCCH-spectrum and 96.3% (4030/4184) of those identified in the ribbon representation of MPB70 shown in Fig. 2.

ments reported for MPB70 previously (9) were readily extended to the $^{13}$C and $^1$H side-chain signals using correlations observed in DQF-COSY, TOCSY, TOCSY-HSQC, and HCCH-TOCSY spectra. Apart from exchangeable side-chain groups, the only $^1$H signals that remained unidentified were from the backbone amides of G1 and D2 and from the H y of the side chain of Leu-119. The extent of the assignments obtained for $^{13}$C resonances was equally comprehensive with just 11 residues lacking complete assignments for the aliphatic signals (Gly-1, Leu-3, Thr-41, Thr-42, Val-55, Leu-94, Thr-107, Leu-119, Ile-155, and Pro-161), with resonances from typically only a single group remaining unidentified. In the case of MPB70, no attempts were made to assign the $^{13}$C signals of the aromatic rings, because this information was not required for the analysis of the $^{13}$C-edited NOESY spectrum, which was acquired from a sample of MPB70 in which the side chains of the aromatic residues were not $^{13}$C-labeled.

Structural Calculations—The recently developed CANDID protocol proved very effective at determining unique assignments for the NOEs identified in three-dimensional $^{15}$N- and $^{13}$C-edited NOESY spectra (40). At the end of the procedure (cycle 7) unique assignments were obtained for 94.3% (1498/1589) of the NOE peaks picked in the $^{13}$N/$^1$H NOESY-HSQC spectrum and 96.3% (4030/4184) of those identified in the $^{13}$C/$^1$H HMQCN-NOESY spectrum. This level of success compares very favorably with our experience of manual iterative assignment of NOE peaks in protein spectra (42, 43, 47), and the automatic approach took only a few days as compared with several months for manual assignment. The uniquely assigned NOE peaks produced 2845 non-redundant $^1$H to $^1$H upper distance limits, which were used as the principle constraints in the final rounds of structural calculations. In contrast to the success in assigning NOEs, CANDID was relatively poor at producing MPB70 structures with no significant violations of NMR constraints or van der Waals interactions, with typically only one or two fully converged structures obtained from 100 random starting coordinates. This convergence problem may well reflect the complex topology of the MPB70 backbone and was solved by the inclusion of redundant dihedral angle constraints in the final rounds of simulated annealing calculations (41).

The final family of MPB70 structures was determined using a total of 3066 NMR-derived structural constraints (an average of 18.8 per residue), including 2845 NOE-based upper distance limits (542 intra residue, 733 sequential (i, i+1), 562 medium range (i, i ≤ 4), and 1008 long range (i, i ≥ 5)) and 35 $^2$ torsion angle constraints. The calculations also included 180 distance constraints required to impose 45 backbone hydrogen bonds and 6 distance constraints corresponding to the Cys-8 to Cys-142 disulfide bond. After the final round of CYANA calculations, 39 satisfactorily converged MPB70 structures were obtained from 100 random starting conformations. The converged structures contain no distance constraint or van der Waals violations greater than 0.5 Å and no dihedral angle violations greater than 5°, with an average value for the CYANA target function of 9.5 ± 1.3. The sums of the violations for upper distance limits, lower distance limits, van der Waals contacts, and torsion angle constraints were 39.8 ± 3.3 Å, 2.1 ± 0.3 Å, 18.3 ± 2.1 Å, and 11.7 ± 3.8°, respectively. Similarly, maximum violations for the converged structures were 0.39 ± 0.05 Å, 0.22 ± 0.03 Å, 0.30 ± 0.03 Å, and 3.35 ± 0.90°, respectively. The family of converged MPB70 structures, together with the NMR constraints, has been deposited in the Protein Data Bank (accession code 1NYO).

The solution structure of MPB70 is determined to high precision, which is clearly evident from the superposition of the protein backbone shown for the family of converged structures in Fig. 1 (best fit for residues 3–128 and 132–162) and is reflected in low root mean squared deviation (r.m.s.d.) values to the mean structure for both the backbone and all heavy atoms.
The MPB70 structures show good non-
being somewhat less well defined, probably as a consequence of
of Gln-129, which results in the conformations of these regions
no long range NOEs and medium range NOEs only in the case
from fasciclin I. FAS1 domains 3 (residues 330–463) and 4 (residues 467–616) from fasciclin I are depicted
Amino acid residues represented by shaded circles are buried within the hydrophobic core of the protein and have solvent-accessible surfaces of
lengths. The residues with side chains that contribute to the core of the barrel are underlined, and backbone hydrogen bonds are depicted by dashed lines. An asterisk to the side of a residue indicates that the backbone amide proton exchanges very slowly with water and was still
detectable in NMR spectra after over 2 months in a D$_2$O solution. The S value represents the β-barrel shear number and is equal to the residue
offset resulting from one traverse around the barrel.

of 0.43 ± 0.05 Å and 0.71 ± 0.05 Å, respectively. A few N- and C-terminal residues (Gly-1, Asp-2, and Ala-163), together with a short surface loop formed from Gln-129 to Asn-131, showed no long range NOEs and medium range NOEs only in the case of Gln-129, which results in the conformations of these regions being somewhat less well defined, probably as a consequence of rapid local mobility. The MPB70 structures show good non-
boned contacts, with 62% of the non-glycine and non-proline residues found to have backbone torsion angles in the most
favored regions, 33% in additional allowed regions, 3% in generously allowed regions, and only 1% in disallowed regions. In addition, no residues consistently adopt unfavorable backbone conformations.

**DISCUSSION**

**Structural Features of MPB70**—The backbone topology of MPB70 is illustrated by the ribbon diagram shown in Fig. 2, with the protein consisting of a seven-stranded β-barrel (β1 66–71, β2 102–104, β3 114–117, β4 123–128, β5 133–135, β6 138–147, and β7 150–155) and eight α-helices (α1 7–14, α2 22–27, α3 31–36, α4 41–48, α5 58–61, α6 73–78, a7 81–87, and α8 93–100) that pack together on one side of the barrel. The β-barrel is closed by one hydrogen bond between β2 and β3, and so, it alternatively can be thought of as a β-sandwich with strand 6 coiling to form part of two sheets (β6–β7–β1–β2 and β3–β4–β5–β6). All the strands are anti-parallel to each other except β1 and β7, and the residue offset for one transverse around the barrel is 10 (the shear number). As shown in Fig. 2, the circumference of the barrel is wider at the bottom than at the top, with its base plugged by the side chain of Val-112 (in the loop between β2 and β3) and the top by Leu-159 (from the C terminus of the protein). Strands β3, β4, β5, β6, and β7 form a β-meander, and are all joined by small surface loops or tight turns, whereas strands β1 and β2 are joined by a long loop (29 residues) containing helices α6, a7, and α8. The stability of the β-barrel structure is reflected in the large number of residues that exhibit slowly exchanging backbone amide protons, particularly in the two parallel strands β1 and β7. These data, together with a schematic view of the barrel, is shown in Fig. 3.

**Sheet 1** (β6–β7–β1–β2) forms the hydrophobic core of MPB70 with its side chains being either part of the β-barrel interior or involved in the packing of helices a1, a2, a3, and α5 against the strands. In contrast, the opposite face of the barrel (sheet 2: β3–β4–β5–β6) is entirely solvent-exposed. Helices a2, a3, and a4 essentially run in a zigzag manner, with a2 and a3 packing against the face of strands β1, β6, and β7, and a4 packing against α6, a7, and α8, which are positioned in a U-shaped...
arrangement at the top of the β-barrel (the tapered end). The N-terminal helix (α1) is perpendicular to α2 (both being parallel to the bottom rim of the barrel) and anchored to the β-barrel via a disulfide bond to strand β6 (Cys-8 to Cys-142). Strand β6 forms the bottom rim of the barrel in this region and contains two β-bulges in its hydrogen bonding network with β7 at Val-141 to Cys-142 and Gly-144 to Val-145.

Structural Homology between MPB70 and Fasciclin I—Comparison of the backbone topology of MPB70 with other known folds in the Protein Data Bank using Dali (45) identified no significant similarities; however, the structures of the third and fourth FAS1 domains from fasciclin I and MPB70, with α-helical regions shown in red and β-strands in green. The symbols shown below the alignment indicate the positions of residues either absolutely conserved across the group of sequences (*) or conserved within close structural groups (:). The residues in domain 4 of βig-h3 affected by the mutations responsible for the inherited human corneal dystrophies are highlighted in magenta.

Fig. 5. A multiple sequence alignment illustrating the sequence similarity between MPB70, MPB83, FAS1 domains 3 and 4 from fasciclin I (residues 330–463 and 466–616, respectively) and FAS1 domain 4 from βig-h3 (residues 501–635). The locations of elements of regular secondary structure are indicated above the sequence alignment for MPB70 and also by color coding of the sequences for both fasciclin I (domains 3 and 4) and MPB70, with α-helical regions shown in red and β-strands in green.

between the three FAS1 domains. Backbone fold comparisons were carried out using combinatorial extension (CE, 46), and r.m.s.d. values of 2.0 and 1.9 Å were obtained for the backbone of MPB70 matched to Fas3 (residues 37–159 from MPB70 and 330–463 for fasciclin I) and Fas4 (residues 27–159 of MPB70 and 467–616 from fasciclin I), respectively. Although the overall structural similarity was higher for Fas4, the β-barrel topology is more similar between Fas3 and MPB70. A superposition of the backbone atoms for analogous residues in the β-strands of Fas3 and Fas4 generated an r.m.s.d. value of 0.99 Å, whereas with Fas4 a similar comparison resulted in an r.m.s.d. value of 1.66 Å. Careful analysis of the hydrogen bond networks in the β-barrels of Fas3 and Fas4 revealed an important difference. The β-barrel of Fas4 is slightly expanded with a shear number of 12, whereas Fas3 and MPB70 have very similar barrels with a shear number of 10. The Fas3 and Fas4 structures were found to be less similar to each other by CE analysis (backbone atom r.m.s.d. of 2.4 Å for residues 330–463 in Fas3 fitted to residues 477–616 in Fas4) than either was to MPB70, which is illustrated by the superposition of the protein backbones for MPB70 and the two FAS1 domains from fasciclin I shown in Fig. 4.
Comparisons of MPB70 and MPB83—The multiple sequence alignment shown in Fig. 5 highlights the sequence similarity between MPB70, MPB83, FAS1 domains 3 and 4 from fasciclin I, and FAS1 domain 4 from βig-h3, mutations which are responsible for inherited corneal dystrophies. The homology between MPB70 and the C-terminal region of MPB83 (residues 33–195) clearly extends over the entire MPB70 sequence with MPB83 containing substitutions at 43 of the 163 residues, which are highlighted on the space-filled views of MPB70 shown in panels A and B of Fig. 6. Nearly half of the residue changes introduced in MPB83 (21 of 43) are within strongly conserved structural groups, such as T95S and V140L, and only seven of these result in a change in amino acid charge (E10Q, Q50K, Q54D, Q65E, E86Q, N90D, and N131D) with those residues all limited to the surface of MPB70 with an average solvent accessibility of 39.3 ± 15.0%, as illustrated in Fig. 6. A number of the structural and charge neutral substitutions in MPB83 occur for residues within the core of MPB70, for example, V103I, V112I, and V124L, but these changes are very conservative and are not expected to introduce any significant structural perturbations. A further 13 of the 43 amino acid changes in MPB83 fall within weakly conserved structural groups (G1A, A20G, S26A, V32T, S63G, G136N, S146H, S77D, S92K, N111R, S123D, S132D, and D139G), but with the exception of A20G affect residues on the surface of MPB70 and should therefore be accommodated without significant changes in the structure of the protein. The A20G substitution in MPB83 occurs in a loop between helices 1 and 2 in MPB70, and the residue involved is close to the surface of the protein, which suggests that the change will only lead to local structural rearrangements of the affected loop. The nine non-conservative amino acid changes in MPB83 all occur in residues exposed on the surface of MPB70 with an average solvent accessibility of 30.7 ± 12.5% and are expected to have no significant affect on the structure of the protein backbone or conformations of buried amino acid side chains. Clearly, the C-terminal region of MPB83 will adopt a very similar structure to that described here for MPB70, with any significant differences limited to surface features and properties.

Visual inspection of the surface views of MPB70 shown in panels A and B of Fig. 6, together with the ribbon representation of the protein displayed in Fig. 2, clearly shows that many of the residues substituted in MPB83 are clustered together on the exposed sides and base of the β barrel (16 of the 43 amino acids). The residue changes here tend to be non-conservative in terms of charge and/or structure, which perhaps suggests that this region of MPB70 and MPB83 is not involved in functional interactions with target molecules. The remaining amino acid substitutions present in MPB83 tend to be located toward the edges of the protein as depicted in Fig. 6, with the central surfaces on opposite faces of MPB70 remaining largely unchanged in MPB83, which may hint at some functional significance. Many of the substitutions in MPB83 leading to changes in amino acid charge appear to be compensated for by changes in neighboring residues, for example, E86Q and N90D at the top of the protein (Fig. 6); however, the region encompassing the E10Q, A14Q, and E39M substitutions will be significantly less charged and polar in MPB83.

Functional Sites on βig-h3, MPB70, and MPB83—The representative alignment of FAS1 domain sequences shown in Fig. 5 is based on a structural alignment of the domains from change in charge. Similarly, residues replaced in MPB83 with a weak structural homologue are shown in either yellow or orange (change in charge), and non-conservative substitutions are depicted in either red or magenta (change in charge).
MPB70 and fasciclin I, with optimal alignments of MPB83 and domain 4 of βig-h3 subsequently obtained on the basis of sequence conservation. The alignment of the MPB70 and MPB83 sequences is clearly very straightforward, but the optimal match between domain 4 from βig-h3 and MPB70/MPB83 is also very clear and indicates that the structure determined for MPB70 serves as a good model for βig-h3 domain 4. A group of inherited human corneal dystrophies have recently been ascribed to a spectrum of mutations in domain 4 of βig-h3, which include single residue substitutions at 12 positions, deletion of 1 amino acid and a replacement of 2 contiguous residues with 3, all of which lead to severe impairment of vision through progressive degeneration of the cornea (27). The disease-inducing mutations are listed in Table I, together with their equivalent residues in MPB70 and an indication of solvent accessibility. Clearly, 8 of the 12 sites of substitution and the site of deletion correspond to core residues in MPB70, many of which are also highly conserved across FAS1 domains (Fig. 5), and, given the non-conservative nature of most of the mutations at these positions, are expected to significantly perturb at least the local structure of the domain, which presumably leads to some partial or complete loss of βig-h3 function. The remaining four disease-inducing substitutions in βig-h3 occur at residues that are significantly solvent-exposed in MPB70 (Ser-26, Asn-73, Ile-84, and Asn-149) and where the changes are unlikely to cause more than relatively minor local structural alterations. Similarly, the 3 for 2 residue insertion involves amino acids in a solvent-exposed loop in MPB70 (Asp-156 and Ser-157) and should be accommodated with only local structural perturbations. This suggests that the disease-causing mutations predicted to map to the surface of domain 4 of βig-h3 probably affect interaction sites for functional partners such as fibronectin (21).

Across the representative group of FAS1 domains shown in Fig. 5, 10 residues are absolutely conserved and a further 20 are conserved within a close structural group. The majority of these residues map to the core of the MPB70 structure and are clearly conserved to satisfy a structural role. However, 2 invariant and 5 tightly conserved residues, corresponding to Asn-62, Asn-149, Asp-59, Asn-73, Leu-119, Asn-137, and Ala-148 in MPB70, are largely solvent-exposed in MPB70, which suggests some essential functional role. The positions of these conserved surface residues, together with surface sites mutated in domain 4 of βig-h3, are indicated on the space-filled views of MPB70 shown in Fig. 7 and clearly show that these two groups of residues form loose clusters on opposite faces of MPB70, which generally fall outside of the regions that differ between

| Mutation | Average solvent accessibility of equivalent residue in MPB70 % |
|----------|---------------------------------------------------------------|
| P501T    | 16.4                                                          |
| L518R/P  | 0.3                                                           |
| L527R    | 5.1                                                           |
| T538R    | 0                                                             |
| N544S    | 19.3                                                          |
| A546T    | 0                                                             |
| R555W/Q  | 9.9                                                           |
| N622H/K  | 16.5                                                          |
| G623D    | 0                                                             |
| HE626R/P | 0.3                                                           |
| V627S    | 0.2                                                           |
| V631D    | 0.9                                                           |
| ΔF540    | 0                                                             |
| T629/N630 to N629/V630/P631 | 17.1/7.6          |

Fig. 7. Space-filled views of the surface of MPB70 with residues colored on the basis of conservation across the representative group of FAS1 domains shown in Fig. 5 and on whether mutations in the equivalent residues in βig-h3 result in inherited human corneal dystrophies. The orientation of MPB70 in A is identical to that of the ribbon representation shown in Fig. 2, with B rotated by 180° to reveal the opposite face of the protein. Residues shown in green are identical in MPB70, MPB83, FAS1 domains 3 and 4 of fasciclin I, and FAS1 domain 4 of βig-h3, whereas those depicted in cyan are conserved within a close structural group. The amino acids highlighted in red correspond to sites of substitution in corneal dystrophy associated variants of βig-h3.
MPB70 and MPB83 (compare Figs. 6 and 7). It is tempting to
speculate that these clusters may reflect two quite extensive
functional surfaces on opposite faces of some FAS1 domains,
such as domain 4 of $\beta$h3, which are probably the sites of
interaction with functional partner proteins. This proposal fits
well with the proposed roles of several FAS1-containing extra-
cellular matrix proteins (fasciclin I, $\beta$h3, and periostin),
which appear to bridge interactions between cell surface and
extracellular matrix proteins (20, 21).

In the case of MPB70 and MPB83, it seems reasonable to
suggest that they may also bind to one or more cell surface host
proteins via the sites identified and induce changes in host cell
behavior of advantage to the pathogen, perhaps through the
modulation of signaling pathways. This type of function has
importance of MPB70 and MPB83 in tuberculosis pathogenesis
ating interactions with specific host cell proteins would also
suggest that they may also bind to one or more cell surface host
proteins via the sites identified and induce changes in host cell
behavior of advantage to the pathogen, perhaps through the
modulation of signaling pathways. This type of function has