Published in final edited form as:
Curr Drug Targets. 2008 February ; 9(2): 150–157.

Molecular Mechanisms of Host-Pathogen Interactions and their Potential for the Discovery of New Drug Targets

Volker Briken*
Department of Cell Biology and Molecular Genetics and Maryland Pathogen Research Institute, University of Maryland, Microbiology Bldg. 231, Room 2201, College Park, MD, 20742, USA

Abstract

Vaccines and chemotherapy have undeniably been the discoveries in the field of biomedical research that have exerted the biggest impact on the improvement of public health. Nevertheless, the development of bacterial resistance to antibiotics has co-evolved over time with the discovery of new drugs. This entails the necessity for continuous research on new anti-infectious agents.The current review highlights recent discoveries in the molecular mechanisms of specific host pathogen interactions and their potential for drug discovery. The focus is on facultative and obligate intracellular pathogens (*Mycobacterium*, *Chlamydia* and *Legionella*) and their manipulation of host cells in regard to inhibition of phagosome maturation and cell death. Furthermore, the composition and role of the SecA2 and the ESX-1 secretion pathways in bacterial virulence and manipulation of infected host cells is discussed. The central hypothesis proposed in this review is that the characterization of bacterial proteins and lipids involved in host cell manipulation (modulins) will provide an abundance of new drug targets. One advantage of targeting such bacterial modulins for drug development is that these anti-modulin drugs will not disrupt the beneficial host microflora and therefore have fewer side effects.

Keywords

Apoptosis; phagosome; mycobacterium; secretion; cell wall; antibiotics; drug resistance; infection; modulin

INTRODUCTION

The era of chemotherapy began with the discovery of Salvarsan 606 by Dr. Sahachiro Hata in Paul Ehrlich's laboratory in 1909 for the treatment of syphilis following the unsuccessful screening of 605 chemical compounds. The rational for this effort was based on the “Magic Bullet Theory” formulated by Ehrlich which states that if a chemical can specifically stain bacteria and not host cells, then it should also be possible to identify compounds with specific toxicity to bacteria and not host cells [1]. The subsequent discovery of antibacterial compounds of synthetic, semisynthetic and natural origins led to a great reduction in mortality and morbidity due to bacterial infectious diseases [2]. However, cases of antibiotic resistance in bacterial infections have been increasing ever since the introduction of penicillin in the 1940s, and antibiotic resistance was instantaneous for the first treatment of a tuberculosis patient with the anti-tuberculosis antibiotic streptomycin [2-4]. Presently, there are several notable human pathogens with multi-drug resistance that pose a serious threat to public health (e.g., Staphyloccocus aureus, Pseudomonas aeruginosa, Mycobacterium tuberculosis). As a

Department of Cell Biology and Molecular Genetics and Maryland Pathogen Research Institute, University of Maryland, Microbiology Bldg. 231, Room 2201, College Park, MD, 20742, USA; Tel: 301 405 0289; Fax: 301 314 9489; E-mail: vbriken@umd.edu.

consequence there is a pressing need for the discovery of new and/or improved drugs and vaccines.

In general antibiotics inhibit essential enzymatic processes in the bacterium such as replication, transcription, translation or cell wall synthesis and either kill the bacteria (bactericidal) or inhibit bacterial replication (bacteriostatic). The current review proposes the hypothesis that a new class of anti-bacterial compounds (anti-modulins) that target the bacterial proteins/lipids that modulate the host immune response will be a significant asset for treatment of multidrug-resistant bacteria. By attacking specific virulence mechanisms of pathogens, these compounds have the benefit of not harming the normal human microflora which should result in reduced side effects for the patient. In addition, this approach may prove to be especially advantageous for the defense against facultative and obligate intracellular pathogens that rely on the manipulation of the host cell for their intracellular survival and long-term persistence in the host. Several host-pathogen interactions with the potential for new drug targets will be discussed. The focus is on the intracellular pathogen *Mycobacterium tuberculosis* but examples of other human pathogens that employ similar strategies to manipulate the host cell are given throughout the review.

BACTERIAL TARGETS THAT MODULATE SPECIFIC HOST CELL DEFENSE PATHWAYS

1) Inhibition of Phagosome-Lysosome Fusion ("Phagosome Maturation")

The first line of defense of the cellular innate immune response are the phagocytes that roam the body in search of invaders to ingest and kill. After initial phagocytosis the phagosome gradually changes its composition by fusing sequentially with early endosomes, late endosomes and finally lysosomes; a process defined as "phagosome maturation" [5-7]. The end result is a phagolysosome that has a low pH and a high concentration of activated proteases, lipases and DNAases ready to degrade the phagosome content [8,9]. This is an extremely efficient process that will kill most ingested bacteria. However, many facultative and obligate intracellular pathogens have developed strategies to avoid being in a phagolysosome.

To achieve this goal, one strategy is to inhibit the maturation of the phagosome. Thus it was demonstrated originally in the 1970's that *Mycobacterium tuberculosis* (Mtb) containing phagosomes do not acquire the characteristics of a phagolysosome [10]. During the following three decades, the characteristic composition of the Mtb-phagosome was studied intensively and a wealth of information was gathered (for review [11-13]). In essence, the Mtb-phagosome resembles an early phagosome which is reflected by its neutral pH due to exclusion of the host cell vacuolar proton pump, its accessibility to recycling cell surface molecules such as the transferrin receptor (important for supply of iron) and exclusion of lysosomal markers such as CD63. The Mtb-phagosome contains small Rab GTPases characteristic of early endosomes (Rab4, Rab5, Rab14 [14]) but not for late endosomes and lysosomes (Rab7, Rab9). In addition, the recruitment of host cell coronin-1 to the Mtb-phagosome is an important step since Mtb cannot inhibit phagosome-lysome fusion in coronin-1 deficient mice [15]. Furthermore, lipids also play an important role since the Mtb-phagosome has reduced levels of phosphatidylinositol 3-phosphate (PI3P), which consequently inhibits the recruitment of other FYVE-domain containing proteins that are important for the fusion with late endosomes [5,7,11-13,16].

How do Mtb bacteria achieve the inhibition of phagosome maturation? The secreted serine/threonine protein kinase G (PknG) of Mtb was characterized as an important mediator of phagosome maturation inhibition [17]. Interestingly, an inhibitor of PknG (AX20017) added to macrophages during infection resulted in the maturation of the Mtb-phagosome and intracellular killing of the bacteria [17]. The PknG kinase was identified as one of eleven

potential serine/threonine kinases in the genome of Mtb due to its homology with eukaryotic kinases [18]. Therefore, it was not unreasonable to assume that the PknG inhibitor, AX20017, might cross-react with kinases of the host cell. This hypothesis was tested by screening the effect of AX20017 on 28 eukaryotic kinases, which revealed no inhibitory activity of the compound on the tested eukaryotic kinases [19]. Furthermore, the resolution of the structure of the kinase-inhibitor complex revealed that the inhibitor is buried deep within the adenosine-binding site of the kinase and the AX20017-binding pocket is shaped by a unique set of amino acid side chains that are not found in any human kinase [19]. The authors conclude that these results not only explain the specific mode of action of AX20017 but also demonstrate that virulence factors which are highly homologous to host molecules can be successfully targeted to block replication of pathogens [19]. This important conclusion implies that bacterial targets for drug development should not be excluded *a priori* due to high homology to eukaryotic proteins.

In addition, at least four independent studies used genetic screens to isolate mutants of Mtb that are defective in inhibition of phagosome maturation, thus providing an array of new potential drug targets [20-23]. One of these genetic screens identified four mutations in genes of the ESX-1 secretion system [22]. This system is encoded by the RD1-locus which is not present in the genome of the tuberculosis vaccine strain *M. bovis* BCG and is the main cause of attenuation in BCG [24,25]. The results by MacGurn *et al.* thus confirmed a previous report that the ESX-1 system is important for the capacity of the bacteria to inhibit phagosome maturation [26]. Nevertheless, the secreted effector protein(s) seems to be encoded outside the ESX-1 complex [22]. The importance of the ESX-1 system for inhibition of phagosome maturation was further corroborated by the identification of a novel ESX-1-dependent secreted protein (espB) which is encoded by *Rv3881c* or *Mh3881c* in *M. tuberculosis* or *M. marinum*, respectively [27,28]. The deletion of espB results in acidification of the bacterial phagosome [28]. It is therefore likely that any drug that inhibits this secretion system will also inhibit the capacity of the bacteria to modulate the phagosome maturation process.

Mycobacteria are not the only pathogens that manipulate phagosome maturation and, as discussed for Mtb, the identification of bacterial effector proteins should provide good targets for drug development against these pathogens. The intracellular pathogen *Legionella pneumophila*, causative agent of Legionnaires' pneumonia, avoids phagosome maturation by recruiting early secretory vesicles from the host cell endoplasmic reticulum (ER) and thus transforms its phagosome into a ribosome-studded compartment that resembles the host cell rough ER [29-32]. The protein family of small GTPases are important regulators of intracellular vesicle trafficking and among them is the group of Rab proteins that has more than 60 members in mammalian cells [33,34]. The small GTPase Arf1, for example, is involved in the retrograde transport of vesicles from the Golgi to the ER [35]. *Legionella* targets and activates host cell Arf1 *via* secretion of a guanine nucleotide exchange factor RalF by the Dot/Icm secretion system [36,37]. The activation and recruitment of host cell Arf1 will presumably establish vesicular trafficking of the host cell Golgi to the *Legionella* phagosome with components that usually are transported to the host cell ER and thus support the creation of the ER-like characteristics of the phagosome. The second important intracellular target of *Legionella* is another small GTPase, Rab1, that is essential for anterograde ER to Golgi vesicle trafficking [33,34]. Two recent publications demonstrated that the Dot/Icm secreted protein, independently named either DrrA or SidM, is a Rab1 specific, guanine nucleotide-exchange factor that increases the activity of intracellular Rab1[38,39]. In addition, LidA of *Legionella* binds to Rab1 and synergizes with DrrA/SidM for the recruitment of activated Rab1 to the *Legionella* phagosome [39]. Although its function is less well defined, it seems as if SidJ is another protein important for maintaining the *Legionella* phagosome [40]. In summary, the manipulation of host cell small GTPases involved in ER to Golgi anterograde and retrograde

trafficking by secreted *Legionella* proteins is clearly important in establishing the unique characteristics of the *Legionella* phagosome.

Finally, members of the obligate intracellular bacteria of the genus *Chlamydia* are a leading cause of sexually transmitted disease cases in the USA and for infection-induced blindness world wide [41,42]. The bacteria replicate within a membrane-bound vacuole that avoids fusion with the endosomal/lysosomal pathway and instead fuses with vesicles derived from the Golgi-apparatus [43-45]. The *Chlamydia* vacuole recruits intracellular Rab6 proteins [46,47]. *Chlamydia* remains genetically intractable and therefore it is a challenge to identify bacterial proteins that manipulate the host cell. In an elegant study Cortes *et al*. used a combination of biochemical and genetic approaches to identify several proteins of *Chlamydia* that are contained in the vacuolar membrane and interact with host cell Rab1, Rab10 and Rab11 [46]. This study was an important step in laying the groundwork for a molecular analysis of the *Chlamydia*-mediated host cell manipulation, and in identifying a series of interesting drug targets.

2) Inhibition of Host Cell Death

Programmed cell death (PCD) or apoptosis plays an important role in the innate immune response (IR) against pathogens, a defense strategy that is evolutionarily conserved and extends even into the plant world [48-50]. It is therefore essential for persisting, intracellular pathogens to have strong anti-apoptosis mechanisms. Viral inhibition of host cell apoptosis has been extensively studied and there are numerous examples of viral proteins directly interfering with host cell apoptosis signaling [51-53]. Furthermore, an increasing number of protozoal pathogens have been shown to manipulate the PCD of the infected host cell [54,55]. This review examines the recent advances in the understanding of the Mtb-mediated host cell apoptosis inhibition but also introduces some important anti-apoptotic mechanisms of other bacterial pathogens that may serve as potential drug targets (also reviewed in [56-59].)

Virulent but not avirulent strains of mycobacteria inhibit apoptosis of primary human alveolar macrophages and therefore the capacity of Mtb to inhibit apoptosis was proposed to be a virulence factor [60]. The importance of apoptosis in the host's innate immune response was underlined by a report that apoptotic cell death reduced mycobacterial viability, whereas necrotic cell death had no effect on bacterial viability [61-63]. In line with these findings is a report demonstrating that the susceptibility of different mouse strains to mycobacterial infections could be linked to the capacity of infected macrophages to either undergo necrotic or apoptotic cell death upon infection, with the former imparting a susceptible phenotype and the latter a resistant phenotype [64]. The importance of apoptosis for the acquired immune response against Mtb was suggested by the demonstration that phagocytosis of apoptotic bodies containing mycobacteria by DCs could lead to the presentation of mycobacterial lipid and peptide antigens and subsequent activation of specific T-cells [65]. The phagocytosis of apoptotic bodies seems to be an important mechanism by which DCs gain access of extracellular antigens to MHC I molecules for priming of cytolytic T-cells, a process defined as “crosspriming” [66]. Remarkably, apoptotic bodies containing mycobacteria have the capacity to protect mice from challenge by virulent Mtb [67]. All of these results support the importance of the inhibition of apoptosis for the virulence of *M. tuberculosis*.

In general, apoptosis can be induced *via* two pathways: the extrinsic pathway, which involves death receptors like CD95 that activate Caspase-8/10 upon ligation, and the intrinsic pathway, which is triggered upon intracellular stress sensed by the mitochondria and initiated by activation of Caspase-9. Both pathways converge at the level of the Caspase-3/6/7 activation which then triggers the subsequent events associated with apoptosis, e.g. fragmentation of genomic DNA (for a detailed review see [68,69]). Some evidence suggests that Mtb inhibits the intrinsic pathway of apoptosis induction since Mtb induces upregulation of anti-apoptosis

genes *mcl-1* and *A1* which both encode for Bcl-2-like proteins localized in the mitochondria. In addition, these results were corroborated by functional data using either anti-sense oligonucleotides to knock-down mcl-1 expression [70] or A1 knock-out mice to demonstrate the importance of these genes for Mtb mediated host cell apoptosis inhibition [71,72]. On the other hand, virulent Mtb strains inhibit FasL-induced apoptosis in Fas (CD95) expressing cells [73], which suggests an Mtb-mediated inhibition of the extrinsic apoptosis pathway. The same group reported recently that Mtb lipoglycan stimulates the activation of NF-κB *via* TLR-2 and that the subsequent upregulation of cellular anti-apoptotic protein FLIP leads to inhibition of FasL-mediated apoptosis [74]. Furthermore, it was suggested that Mtb stimulates the secretion of soluble TNF-R2, which leads to the reduction of bioactive TNF-α in the medium and therefore less stimulation of the TNF-R1 [75]. Altogether, virulent Mtb appear able to inhibit induction of host cell apoptosis *via* multiple pathways; clearly the extrinsic apoptosis pathway *via* death receptors (FasL, TNF-R) is affected but also the intrinsic pathway, through the increase in anti-apoptotic mitochondrial proteins like mcl-1, is modulated by Mtb.

The molecular mechanisms of the Mtb-mediated apoptosis inhibition are poorly understood largely due to a lack of defined apoptosis mutants. In order to identify genes of Mtb that are important for the inhibition of apoptosis, we recently performed a “gain-of-function” genetic screen. The apoptosis-inducing, nonpathogenic *M. smegmatis* (Msmeg) was complemented with genomic DNA fragments of virulent *M.tuberculosis* and 312 individual Msmeg-clones were screened for a reduction in infection-induced apoptosis. This led to the identification of three independent regions in the genome of Mtb that could mediate inhibition of apoptosis in a human macrophage-like cell line ([76] and V.Briken unpublished data). Surprisingly, the anti-apoptotic gene of one of these regions (*nuoG*) encodes for a subunit of the NADH-dehydrogenase, NDH-1. The deletion of *nuoG* in Mtb lead to an increase of apoptosis in macrophages after infection and an attenuation of the mutant in infected mice [76]. How the NDH-1 mediates apoptosis inhibition is not clear, but what is certain is that the enzymatic activity of NDH-1 is lost by the deletion of *nuoG* (C. Vilcheze, W.R. Jacobs Jr. [HHMI] and V.Briken, unpublished results). Therefore it seems likely that the enzymatic activity of NDH-1 plays an essential role in host cell apoptosis inhibition. If that conclusion is valid, then any drug that specifically inhibits this enzyme, but not its eukaryotic homolog located in the respiratory chain of mitochondria, will be of interest for therapeutic use. The anti-apoptotic genes in the other genomic regions remain to be identified but should also provide new drug targets for interference with the capacity of Mtb to inhibit host cell apoptosis.

Superoxide dismutase A (SodA) of Mtb has been demonstrated to be involved in apoptosis inhibition of host cells [77,78]. The study by Hinchey *et al.* also very convincingly shows the importance of host cell apoptosis for the induction of a cytolytic T-cell response by comparing antigen specific $CD8^+$ T-cells in mice infected with wild-type and SodA deficient Mtb. The mice infected with the SodA mutant produced an increased cytolytic T-cell response when compared to mice infected with wt-Mtb which underlines the importance of host cell apoptosis for an efficient induction of the acquired host immune response [78]. Superoxide dismutases of pathogens have been implicated in the bacterial defense against phagosomal reactive oxygen species (ROS)[8]. However, their role in inhibition of host cell apoptosis has not been appreciated, although interestingly it is well documented that eukaryotic superoxide dismutase is very important in protecting cells against apoptosis induction *via* protection from mitochondrial ROS [79,80]. SodA is a major secreted protein of Mtb and is thus an appealing drug target. The major challenge will be to identify a drug that does not interfere with the host cell's superoxide dismutases.

Finally, a third anti-apoptotic protein of Mtb has recently been identified that is part of the family of serine-threonine protein kinases. As described above PknG is important for the inhibition of Mtb phagosome maturation. The promoter of *PknE* has been shown to be induced

by nitric oxide (NO) stress conditions [81]. The deletion of *PknE* resulted in a mutant that was more susceptible to NO exposure and also capable of inducing a higher level of apoptosis in human macrophages compared to wt [82].

An increasing number of pathogenic bacteria are being identified that mediate host cell apoptosis inhibition, and among them the best studied to date is *Chlamydia* spp. (for detailed review see [59]). The first description of the anti-apoptotic capacity of *Chlamydia* demonstrated that infected cells are resistant to apoptosis induction *via* a wide array of external pro-apoptotic ligands [83]. Subsequent reports demonstrated that infection with *Chlamydia* mediated the specific degradation of pro-apoptotic proteins which lead to the inhibition of mitochondrial and CD95 induced apoptosis [84-87]. Unfortunately, *Chlamydia* bacteria are still genetically intractable and thus genetic screens or other genetic approaches to identify bacterial mediators of apoptosis inhibition are not possible. This drawback is compounded by the biology of *Chlamydia* which, as an obligate intracellular pathogen, does not grow *in vitro* and therefore the biochemical approaches to identifying important mediators are difficult. Combining genomics and bioinformatics *in silico* has allowed the prediction of target proteins. One such candidate, the CPAF (*Chlamydia* protease-like activity factor) was recently shown to be important for the degradation of pro-apoptotic host cell proteins [88-91]. In addition, this protease is involved in the degradation of host cell transcription factors important for initiation of MHC class I and class II gene transcription, thus reducing the levels of these two major classes of antigen presenting molecules in the infected cells [92]. Consequently, CPAF is a prominent drug target for inhibiting the capacity of *Chlamydia* to modulate the infected host cell. Further bioinformatic analysis revealed a list of 100 hypothetical proteins in the *Chlamydia* genome that are predicted to be in the membrane of the inclusion body and could thus modulate the host cell response. This information can now be used to generate antibodies against the proteins, confirm their localization and subsequently help to further our understanding of this complex host-pathogen interaction [88,93-96].

In a twist on the current theme of clear-cut bacteria mediated host cell apoptosis inhibition, Abu-Zant *et al.* report that *Legionella pneumophila,* despite Caspase-3 activation early during infection in human macrophages, inhibits the subsequent stages in the apoptosis pathway by upregulation of at least 12 anti-apoptosis genes of the host cells [97,98,99]. A separate study implicated Dot/Icm-dependent upregulation of anti-apoptotic genes in the prevention of host cell death after low-dose *Legionella* infection, presumably for injection of the yet to be determined bacterial effector proteins into the host cell cytosol [100]. This hypothesis was recently confirmed by identifying the Dot/Icm substrate, SdhA, as important for Legionella mediated apoptosis inhibition [101]. The *Legionella* SdhA mutant is deficient in intra-cellular growth and induces caspase activation, mitochondrial membrane damage and apoptosis [101]. *Legionella* SidF is able to directly bind and inactivate two pro-apoptotic members of the Bcl2 family of mitochondrial proteins which is important for its capacity to inhibit host cell apoptosis [102]. These two recent reports thus provide potential targets for drug development. Interestingly, during the later stages of infection in mice, *Legionella* will induce apoptosis, a step that is potentially important for the virulence of the bacteria since in the nonpermissive BALB/c mouse strain no caspase-3 activation and no host cell apoptosis induction is observed [103]. In summary, *Legionella* may have evolved to inhibit host cell death pathways during its early infection phase, which is required for intracellular replication; once a critical mass of bacteria is in the host cell, the induction of cell death is advantageous for the spread of the bacteria to uninfected cells.

Pseudomonas aeruginosa is an important human pathogen that inhibits TNF-α induced macrophage cell death [104] and infection-induced cell death in corneal epithelial cells [105]. In the related plant pathogen *P. syringae* secreted protein AvrPtoB has been demonstrated to have E3 ubiquitin ligase activity and that this activity is necessary to inhibit host cell apoptosis

[106,107]. It remains to be seen if an AvrPtoB homolog in *P. aeruginosa* has the same activity and could thus serve as new drug target. This is especially important for future treatment of *P. aeruginosa* because of the high incidences of isolates with multiple antibiotic resistances [108]. Only one more bacterial effector protein has been identified to date which is involved in apoptosis inhibition; the BepA protein of *Bartonella henselae* and *B. quintana* was shown to be translocated into the cytosol of infected endothelial cells *via* a type IV secretion system and to localize to the host cell plasma membrane. The intracellular levels of cyclic adenosine monophosphate (cAMP) and subsequently cAMP-responsive gene expression were increased after infection. These events protected infected cells from apoptosis induction by cytotoxic T lymphocytes [109,110].

Finally, several other pathogens are able to inhibit host cell apoptosis but their interaction with the host cell is poorly understood. The obligate intracellular pathogen *Rickettsia rickettsii*, the etiologic agent of Rocky Mountain spotted fever, has been shown to inhibit apoptosis of infected endothelial cells in an NFκB dependent manner [111,112]. *Porphyromonas gingivalis*, is a major cause of periodontal diseases and, as an opportunistic pathogen, is present even in the absence of obvious pathology. It is estimated that about 50% of adults in developed countries have some form of chronic periodontitis [113]. In gingival epithelial cells, *Porphyromonas* induces major changes in the host cell proteome[114]. One way the bacteria mediate host cell apoptosis inhibition is through manipulation of the JAK/STAT pathway that controls mitochondria mediated cell death pathways [114]. However, a conflicting report demonstrates an induction of apoptosis in a caspase-3 independent pathway by the same pathogen [115]. These differences may be due to variations in host cells and/or bacterial isolates used for the studies. Finally, *Coxiella burnetii* , the causative agent of Q fever, inhibits apoptosis in human and monkey alveolar macrophages [116]. This inhibition seems to involve the prevention of cytochrome C release from mitochondria [117] but can be overcome by stimulating of the macrophages with IFN-γ [118].

BACTERIAL TARGETS THAT REGULATE VIRULENCE FACTOR EXPRESSION AND/OR SECRETION

1) Cell Wall Synthesis

Inhibition of cell wall synthesis is a primary antibiotic target for Gram-positive and Gram-negative bacteria and will continue to provide new targets for drug development [119]. Mycobacteria are Gram-positive and have a very complex cell wall, that not only protects the bacteria from toxic compounds within the macrophages (e.g. reactive oxygen species), but also contains components with important immunomodulatory function [11,120-123]. Understanding the biosynthetic pathways of these immunomodulins will generate new targets for drug development. There have been several recent reviews on this topic ([124-128]), and here the discussion will be limited to one component of the complex cell wall and its implication in pathogenicity of Mtb.

Lipoarabinomannan (LAM) is an important lipoglycan that has been implicated in the inhibition of phagosome maturation, host cell apoptosis, IFN-γ signalling and host cell IL-12 cytokine secretion [11,122,123,129]. For example, the coupling of Mtb-LAM to latex beads inhibited their fusion with lysosomes [130,131]. Interestingly, LAM isolated from mycobacterial species that are able to inhibit phagosome maturation is modified with terminal mannosyl residues (ManLAM) whereas LAM of species that cannot inhibit phagosome maturation is either not modified (AraLAM) or contains a phospho-*myo*-inositol residue (PILAM) [122]. The mannose-caps mediate the binding of LAM with host cell mannose receptors (MR) and this interaction is important for the capacity of purified LAM to inhibit phagosome maturation of LAM-coated latex beads [132]. Another important aspect of these

interactions with the MR and/or the dendritic cell specific receptor (DC-SIGN) is that they contribute to the inhibitory activity of ManLAM on the secretion of IL-12 by the host cell [122,123]. Thus the recent identification of the mannosyltransferase encoded by *Rv1635c* of Mtb that mediates the addition of mannose caps to LAM is of great significance [133]. The defined set of mutant and wild-type bacteria will now allow scientists to carefully analyze the importance of mannose caps in the context of the interaction of whole bacteria with host cells.

Another group of potential drug targets are the enzymes that add the arabinose residues to its biosynthetic cell wall precursor lipomannan (LM), since purified LM can induce host cell apoptosis and secretion of IL-8, IL-12 and TNF-α [134-136]. It is therefore likely that an inhibitor of LAM biosynthesis at this level will induce an increase of LM in the cell wall of mycobacteria. This should render the bacterium less virulent since it would now induce host cell apoptosis and cytokine secretion instead of inhibiting these responses, which would stimulate the innate and subsequent acquired immune responses [122]. The *embC* gene of the nonpathogenic *M. smegmatis* has been shown to be critical in modifying the mannan core since its deletion resulted in the absence of full-length PILAM but instead only LM with a couple of arabinose residues could be isolated [137-139]. Nevertheless, to date it has not been possible to create an *embC* mutant in the background of a virulent strain of mycobacteria, pointing to the possibility that *embC* has another essential function in these strains. Eukaryotic cells do not express LAM and therefore enzymes involved in its biosyn-thesis should be sufficiently different from enzymes in eukaryotic cells to serve as drug targets.

2) Secretion Systems

The importance of secretion systems not only for bacterial viability but also for pathogenicity is well established. Highlighted here are two secretion systems that, albeit being first described and best studied in mycobacteria, are not unique to this genus and have a great potential as a target for development of new drugs against Gram-positive bacteria.

The early secretory antigenic target 6 (ESAT-6) system 1 (ESX-1) secretion apparatus is present and functional in virulent and nonpathogenic species of mycobacteria and shows some functional homology with type IV secretion systems of Gram-negative bacteria such as the Dot/Icm system of *L. pneumophilia* [140]. ESX-1 is absolutely required for pathogenicity of virulent mycobacteria and therefore it is likely that although the secretory machinery is conserved among species, virulent mycobacteria have a unique subset of secreted effector proteins [140]. Genetic screens identified *Rv3868*, *Rv3870*, *Rv3871* and *Rv3877-79* as being essential for the secretion of ESAT-6 and CFP-10 [141-143]. Other substrates for ESX-1 mediated secretion are encoded by *Rv3116c/EspA* [144], *Rv3483c* and *Rv3881c/EspB*, although the ESX-1-dependent secretion of the latter two has only been demonstrated in the fish pathogen *M. marinum* so far [27,28]. The importance of the ESX-1 system for necrosis of epithelial cells [24], and the inhibition of phagosome maturation [26,28] was demonstrated. In addition, a recent report demonstrated a direct interaction of secreted ESAT-6 with Toll-like Receptor (TLR)2 to inhibit TLR signaling on macrophages [145]. It is likely that the ESX-1 system is also involved in other host-pathogen interactions but evidence for this hypothesis remains to be discovered. The development of drugs against the core proteins of this secretion system are therefore likely to disrupt the interaction of virulent *M. tuberculosis* with host cells at several levels and thus increase the efficacy of these drugs. ESX-1 secretion systems do not seem to be unique to mycobacteria, since the human pathogen *Staphylococcus aureus* secretes ESAT-6-like proteins which are important for virulence of the bacteria [146].

Another secretion system important for pathogenicity of bacteria is the alternate SecA system, SecA2. Whereas SecA is found in many bacteria and is an essential secretion system, the alternate SecA2 system is found in at least nine species of pathogenic Gram-positive bacteria and is not essential for the *in vitro* growth of the bacteria [147]. Among the bacteria that encode

alternate SecA systems are *M.tuberculosis* [148], *Listeria monocytogenes* [147] and *Streptococcus agalactiae* [149] and *Streptococcus gordonii* [150,151]. The deletion of *secA2* in *M.tuberculosis* attenuated the bacteria for growth in mice [152]. Subsequent proteomic analysis of secreted proteins in wild-type and SecA2 deficient bacteria demonstrated that an important subset of secreted proteins depends on the SecA2 system [152]. Nevertheless, a significant subset of SecA2-dependent secreted proteins most likely remains to be discovered since their transcription/translation may only be induced after ingestion of the bacteria by the macrophage.

One SecA2-dependent secreted protein is the superoxide dismutase A (SodA) of Mtb. This protein is important to inhibit infection-induced apoptosis in human and murine macrophages [78]. A yet to be identified SecA2-dependent effector is important to mediate the inhibition of IFN-γ signaling in Mtb-infected macrophages [153]. It is likely that SecA2 is implicated in other host-pathogen interactions and it is this broad involvement that explains the attenuation of the SecA2-Mtb mutant and makes the SecA2 system a prominent target for drug development.

CONCLUSION

The increase in antibiotic resistance in a multitude of important human pathogens highlights the need for continued drug development. A class of drug targets that has not been previously exploited is bacterial proteins and lipids that are important for bacterial virulence because they manipulate the infected cells. The targeting of these pathogenicity factors, instead of general housekeeping proteins and lipids, might have the advantage of identifying drugs that specifically target pathogenic bacteria without disrupting the normal microflora. Nevertheless, it remains to be seen if inhibition of the virulence mechanisms of the bacteria alone is sufficient for effective treatment. Alternatively, these anti-modulin drugs could be used in conjunction with traditional antibiotics to increase their efficiency and reduce development of drug resistance. Only a detailed understanding of human pathogens will allow for generation of new drug classes for treatment of resistant bacteria. This basic research will always be in demand since the acquisition of drug-resistance by pathogens will never end.

ACKNOWLEDGEMENT

Research of V.Briken is supported by NIH/NIAID grant R56AI072584. I would like to thank J. Miller, B.Hurley and Dr. S. Bohlson for editing the manuscript.

REFERENCES

1. Winau F, Westphal O, Winau R. Microbes. Infect 2004;6:786. [PubMed: 15207826]
2. Rolinson GN. J. Antimicrob. Chemother 1998;41:589. [PubMed: 9687097]
3. Thomson JM, Bonomo RA. Curr. Opin. Microbiol 2005;8:518. [PubMed: 16126451]
4. Dorman SE, Chaisson RE. Nat. Med 2007;13:295. [PubMed: 17342143]
5. Russell DG. Nat. Rev. Mol. Cell Biol 2001;2:569. [PubMed: 11483990]
6. Haas A. Traffic 2007;8:311. [PubMed: 17274798]
7. Deretic V, Singh S, Master S, Kyei G, Davis A, Naylor J, de Haro S, Harris J, Delgado M, Roberts E, Vergne I. Biochem. Soc. Symp 2007;141
8. Fang FC. Nat. Rev. Microbiol 2004;2:820. [PubMed: 15378046]
9. Segal AW. Annu. Rev. Immunol 2005;23:197. [PubMed: 15771570]
10. Armstrong JA, Hart PD. J. Exp. Med 1971;134:713. [PubMed: 15776571]
11. Russell DG. Nat. Rev. Microbiol 2007;5:39. [PubMed: 17160001]
12. Deretic V, Singh S, Master S, Harris J, Roberts E, Kyei G, Davis A, de Haro S, Naylor J, Lee HH, Vergne I. Cell Microbiol 2006;8:719. [PubMed: 16611222]

13. Nguyen L, Pieters J. Trends Cell Biol 2005;15:269. [PubMed: 15866031]
14. Kyei GB, Vergne I, Chua J, Roberts E, Harris J, Junutula JR, Deretic V. Embo J 2006;25:5250. [PubMed: 17082769]
15. Jayachandran R, Sundaramurthy V, Combaluzier B, Mueller P, Korf H, Huygen K, Miyazaki T, Albrecht I, Massner J, Pieters J. Cell 2007;130:37. [PubMed: 17632055]
16. Trimble WS, Grinstein S. Cell 2007;130:12. [PubMed: 17632049]
17. Walburger A, Koul A, Ferrari G, Nguyen L, Prescianotto-Baschong C, Huygen K, Klebl B, Thompson C, Bacher G, Pieters J. Science 2004;304:1800. [PubMed: 15155913]
18. Cole ST, Brosch R, Parkhill J, Garnier T, Churcher C, Harris D, Gordon SV, Eiglmeier K, Gas S, Barry CE 3rd, Tekaia F, Badcock K, Basham D, Brown D, Chillingworth T, Connor R, Davies R, Devlin K, Feltwell T, Gentles S, Hamlin N, Holroyd S, Hornsby T, Jagels K, Krogh A, McLean J, Moule S, Murphy L, Oliver K, Osborne J, Quail MA, Rajandream MA, Rogers J, Rutter S, Seeger K, Skelton J, Squares R, Squares S, Sulston JE, Taylor K, White-head S, Barrell BG. Nature 1998;393:537. [PubMed: 9634230]
19. Scherr N, Honnappa S, Kunz G, Mueller P, Jayachandran R, Winkler F, Pieters J, Steinmetz MO. Proc. Natl. Acad Sci. U. S. A 2007;104:12151. [PubMed: 17616581]
20. Pethe K, Swenson DL, Alonso S, Anderson J, Wang C, Russell DG. Proc. Natl. Acad. Sci. U. S. A 2004;101:13642. [PubMed: 15340136]
21. Stewart GR, Patel J, Robertson BD, Rae A, Young DB. PLoS. Pathog 2005;1:269. [PubMed: 16322769]
22. MacGurn JA, Cox JS. Infect. Immun 2007;75:2668. [PubMed: 17353284]
23. Robinson N, Wolke M, Ernestus K, Plum G. Infect Immun 2007;75:581. [PubMed: 17088345]
24. Hsu T, Hingley-Wilson SM, Chen B, Chen M, Dai AZ, Morin PM, Marks CB, Padiyar J, Goulding C, Gingery M, Eisenberg D, Russell RG, Derrick SC, Collins FM, Morris SL, King CH, Jacobs WR Jr. Proc. Natl. Acad. Sci. U. S. A 2003;100:12420. [PubMed: 14557547]
25. Pym AS, Brodin P, Brosch R, Huerre M, Cole ST. Mol. Microbiol 2002;46:709. [PubMed: 12410828]
26. Tan T, Lee WL, Alexander DC, Grinstein S, Liu J. Cell Microbiol 2006;8:1417. [PubMed: 16922861]
27. McLaughlin B, Chon JS, MacGurn JA, Carlsson F, Cheng TL, Cox JS, Brown EJ. PLoS. Pathog 2007;3:e105. [PubMed: 17676952]
28. Xu J, Laine O, Masciocchi M, Manoranjan J, Smith J, Du SJ, Edwards N, Zhu X, Fenselau C, Gao LY. Mol. Microbiol. 2007
29. Horwitz MA. J. Exp. Med 1983;158:1319. [PubMed: 6619736]
30. Horwitz MA. J. Exp. Med 1983;158:2108. [PubMed: 6644240]
31. Swanson MS, Isberg RR. Infect. Immun 1995;63:3609. [PubMed: 7642298]
32. Tilney LG, Harb OS, Connelly PS, Robinson CG, Roy CR. J. Cell Sci 2001;114:4637. [PubMed: 11792828]
33. Chavrier P, Goud B. Curr. Opin. Cell Biol 1999;11:466. [PubMed: 10449335]
34. Grosshans BL, Ortiz D, Novick P. Proc. Natl. Acad. Sci. U. S. A 2006;103:11821. [PubMed: 16882731]
35. D'Souza-Schorey C, Chavrier P. Nat. Rev. Mol. Cell Biol 2006;7:347. [PubMed: 16633337]
36. Amor JC, Swails J, Zhu X, Roy CR, Nagai H, Ingmundson A, Cheng X, Kahn RA. J. Biol. Chem 2005;280:1392. [PubMed: 15520000]
37. Nagai H, Kagan JC, Zhu X, Kahn RA, Roy CR. Science 2002;295:679. [PubMed: 11809974]
38. Murata T, Delprato A, Ingmundson A, Toomre DK, Lambright DG, Roy CR. Nat. Cell Biol 2006;8:971. [PubMed: 16906144]
39. Machner MP, Isberg RR. Dev. Cell 2006;11:47. [PubMed: 16824952]
40. Liu Y, Luo ZQ. Infect. Immun 2007;75:592. [PubMed: 17101649]
41. Thylefors B, Negrel AD, Pararajasegaram R, Dadzie KY. Bull World Health Organ 1995;73:115. [PubMed: 7704921]
42. Miller WC, Ford CA, Morris M, Handcock MS, Schmitz JL, Hobbs MM, Cohen MS, Harris KM, Udry JR. Jama 2004;291:2229. [PubMed: 15138245]

43. Hackstadt T, Fischer ER, Scidmore MA, Rockey DD, Heinzen RA. Trends Microbiol 1997;5:288. [PubMed: 9234512]
44. Scidmore MA, Fischer ER, Hackstadt T. Infect Immun 2003;71:973. [PubMed: 12540580]
45. Scidmore MA, Rockey DD, Fischer ER, Heinzen RA, Hackstadt T. Infect Immun 1996;64:5366. [PubMed: 8945589]
46. Cortes C, Rzomp KA, Tvinnereim A, Scidmore MA, Wizel B. Infect Immun. 2007
47. Moorhead AR, Rzomp KA, Scidmore MA. Infect Immun 2007;75:781. [PubMed: 17101644]
48. Abramovitch RB, Martin GB. Curr. Opin. Plant Biol 2004;7:356. [PubMed: 15231256]
49. Greenberg JT, Yao N. Cell Microbiol 2004;6:201. [PubMed: 14764104]
50. Stuart LM, Ezekowitz RA. Immunity 2005;22:539. [PubMed: 15894272]
51. Boya P, Pauleau AL, Poncet D, Gonzalez-Polo RA, Zamzami N, Kroemer G. Biochim. Biophys. Acta 2004;1659:178. [PubMed: 15576050]
52. Hilleman MR. Proc. Natl. Acad. Sci. U. S. A 2004;101(Suppl 2):14560. [PubMed: 15297608]
53. Keckler MS. Front Biosci 2007;12:725. [PubMed: 17127333]
54. Gavrilescu LC, Denkers EY. Infect Immun 2003;71:6109. [PubMed: 14573625]
55. Carmen JC, Sinai AP. Mol. Microbiol 2007;64:904. [PubMed: 17501916]
56. DeLeo FR. Apoptosis 2004;9:399. [PubMed: 15192322]
57. Hacker G, Kirschnek S, Fischer SF. Med. Microbiol. Immunol. (Berl). 2005
58. Barry DP, Beaman BL. Apoptosis 2006;11:1695. [PubMed: 16850163]
59. Miyairi I, Byrne GI. Curr. Opin. Microbiol 2006;9:102. [PubMed: 16406838]
60. Keane J, Remold HG, Kornfeld H. J. Immunol 2000;164:2016. [PubMed: 10657653]
61. Molloy A, Laochumroonvorapong P, Kaplan G. J. Exp. Med 1994;180:1499. [PubMed: 7931080]
62. Fratazzi C, Arbeit RD, Carini C, Remold HG. J. Immunol 1997;158:4320. [PubMed: 9126994]
63. Keane J, Shurtleff B, Kornfeld H. Tuberculosis (Edinb) 2002;82:55. [PubMed: 12356455]
64. Pan H, Yan BS, Rojas M, Shebzukhov YV, Zhou H, Kobzik L, Higgins DE, Daly MJ, Bloom BR, Kramnik I. Nature 2005;434:767. [PubMed: 15815631]
65. Schaible UE, Winau F, Sieling PA, Fischer K, Collins HL, Hagens K, Modlin RL, Brinkmann V, Kaufmann SH. Nat. Med 2003;9:1039. [PubMed: 12872166]
66. Guermonprez P, Amigorena S. Springer Semin Immunopathol 2005;26:257. [PubMed: 15592842]
67. Winau F, Weber S, Sad S, de Diego J, Hoops SL, Breiden B, Sandhoff K, Brinkmann V, Kaufmann SH, Schaible UE. Immunity 2006;24:105. [PubMed: 16413927]
68. Maiuri MC, Zalckvar E, Kimchi A, Kroemer G. Nat. Rev. Mol. Cell Biol 2007;8:741. [PubMed: 17717517]
69. Siegel RM. Nat. Rev. Immunol 2006;6:308. [PubMed: 16557262]
70. Sly LM, Hingley-Wilson SM, Reiner NE, McMaster WR. J. Immunol 2003;170:430. [PubMed: 12496428]
71. Kausalya S, Somogyi R, Orlofsky A, Prystowsky MB. J. Immunol 2001;166:4721. [PubMed: 11254733]
72. Kremer L, Estaquier J, Brandt E, Ameisen JC, Locht C. Eur. J. Immunol 1997;27:2450. [PubMed: 9341792]
73. Oddo M, Renno T, Attinger A, Bakker T, MacDonald HR, Meylan PR. J. Immunol 1998;160:5448. [PubMed: 9605147]
74. Loeuillet C, Martinon F, Perez C, Munoz M, Thome M, Meylan PR. J. Immunol 2006;177:6245. [PubMed: 17056554]
75. Balcewicz-Sablinska MK, Keane J, Kornfeld H, Remold HG. J. Immunol 1998;161:2636. [PubMed: 9725266]
76. Velmurugan K, Chen B, Miller JL, Azogue S, Gurses S, Hsu T, Glickman M, Jacobs Jr WR Jr. Porcelli SA, Briken V. PLOS Pathogens 2007;3:e110. [PubMed: 17658950]
77. Edwards KM, Cynamon MH, Voladri RK, Hager CC, DeStefano MS, Tham KT, Lakey DL, Bochan MR, Kernodle DS. Am. J. Respir. Crit. Care Med 2001;164:2213. [PubMed: 11751190]

78. Hinchey J, Lee S, Jeon BY, Basaraba RJ, Venkataswamy MM, Chen B, Chan J, Braunstein M, Orme IM, Derrick SC, Morris SL, Jacobs WR, Porcelli SA. J. Clin. Invest, 2007;117:2279. [PubMed: 17671656]
79. Kahl R, Kampkotter A, Watjen W, Chovolou Y. Drug Metab. Rev 2004;36:747. [PubMed: 15554245]
80. Pham CG, Papa S, Bubici C, Zazzeroni F, Franzoso G. Dev. Cell 2005;8:452. [PubMed: 15809025]
81. Singh A, Singh Y, Pine R, Shi L, Chandra R, Drlica K. Tuberculosis (Edinb) 2006;86:28. [PubMed: 16256441]
82. Jayakumar D, Jacobs WR Jr. Narayanan S. Cell Microbiol. 2007
83. Fan T, Lu H, Hu H, Shi L, McClarty GA, Nance DM, Greenberg AH, Zhong G. J. Exp. Med 1998;187:487. [PubMed: 9463399]
84. Fischer SF, Harlander T, Vier J, Hacker G. Infect. Immun 2004;72:1107. [PubMed: 14742558]
85. Fischer SF, Vier J, Kirschnek S, Klos A, Hess S, Ying S, Hacker G. J. Exp. Med 2004;200:905. [PubMed: 15452181]
86. Dong F, Pirbhai M, Xiao Y, Zhong Y, Wu Y, Zhong G. Infect Immun 2005;73:1861. [PubMed: 15731089]
87. Ying S, Seiffert BM, Hacker G, Fischer SF. Infect Immun 2005;73:1399. [PubMed: 15731037]
88. Dong F, Flores R, Chen D, Luo J, Zhong Y, Wu Z, Zhong G. Infect Immun 2006;74:6479. [PubMed: 17057097]
89. Dong F, Zhong Y, Arulanandam B, Zhong G. Infect Immun 2005;73:1868. [PubMed: 15731091]
90. Pirbhai M, Dong F, Zhong Y, Pan KZ, Zhong G. J. Biol. Chem 2006;281:31495. [PubMed: 16940052]
91. Sharma J, Dong F, Pirbhai M, Zhong G. Infect. Immun 2005;73:4414. [PubMed: 15972540]
92. Zhong G, Fan P, Ji H, Dong F, Huang Y. J. Exp. Med 2001;193:935. [PubMed: 11304554]
93. Chen C, Chen D, Sharma J, Cheng W, Zhong Y, Liu K, Jensen J, Shain R, Arulanandam B, Zhong G. Infect Immun 2006;74:4826. [PubMed: 16861671]
94. Luo J, Jia T, Flores R, Chen D, Zhong G. Infect Immun 2007;75:497. [PubMed: 17101661]
95. Luo J, Jia T, Zhong Y, Chen D, Flores R, Zhong G. Microb. Pathog 2007;42:111. [PubMed: 17236746]
96. Luo J, Liu G, Zhong Y, Jia T, Liu K, Chen D, Zhong G. BMC Microbiol 2007;7:38. [PubMed: 17504539]
97. Abu-Zant A, Jones S, Asare R, Suttles J, Price C, Graham J, Kwaik YA. Cell Microbiol 2007;9:246. [PubMed: 16911566]
98. Abu-Zant A, Santic M, Molmeret M, Jones S, Helbig J, Abu Kwaik Y. Infect. Immun 2005;73:5339. [PubMed: 16113249]
99. Gao LY, Abu Kwaik Y. Infect Immun 1999;67:4886. [PubMed: 10456945]
100. Losick VP, Isberg RR. J. Exp. Med 2006;203:2177. [PubMed: 16940169]
101. Laguna RK, Creasey EA, Li Z, Valtz N, Isberg RR. Proc. Natl. Acad. Sci. U. S. A 2006;103:18745. [PubMed: 17124169]
102. Banga S, Gao P, Shen X, Fiscus V, Zong WX, Chen L, Luo ZQ. Proc. Natl. Acad. Sci. U. S. A 2007;104:5121. [PubMed: 17360363]
103. Santic M, Asare R, Doric M, Abu Kwaik Y. Infect Immun 2007;75:2903. [PubMed: 17420236]
104. Ashare A, Monick MM, Nymon AB, Morrison JM, Noble M, Powers LS, Yarovinsky TO, Yahr TL, Hunninghake GW. J. Immunol 2007;179:505. [PubMed: 17579071]
105. Zhang J, Li H, Wang J, Dong Z, Mian S, Yu FS. Invest Ophthalmol. Vis. Sci 2004;45:2569. [PubMed: 15277479]
106. Abramovitch RB, Janjusevic R, Stebbins CE, Martin GB. Proc. Natl. Acad. Sci. U. S. A 2006;103:2851. [PubMed: 16477026]
107. Janjusevic R, Abramovitch RB, Martin GB, Stebbins CE. Science 2006;311:222. [PubMed: 16373536]
108. Falagas ME, Bliziotis IA. Int. J. Antimicrob. Agents 2007;29:630. [PubMed: 17306965]
109. Schmid MC, Scheidegger F, Dehio M, Balmelle-Devaux N, Schulein R, Guye P, Chennakesava CS, Biedermann B, Dehio C. PLoS Pathog 2006;2:e115. [PubMed: 17121462]
110. Schmid MC, Schulein R, Dehio M, Denecker G, Carena I, Dehio C. Mol. Microbiol 2004;52:81. [PubMed: 15049812]

111. Clifton DR, Goss RA, Sahni SK, van Antwerp D, Baggs RB, Marder VJ, Silverman DJ, Sporn LA. Proc. Natl. Acad. Sci. U. S. A 1998;95:4646. [PubMed: 9539792]
112. Clifton DR, Rydkina E, Freeman RS, Sahni SK. Infect. Immun 2005;73:155. [PubMed: 15618150]
113. Albandar JM. Dent. Clin. North. Am 2005;49:517. [PubMed: 15978239]
114. Mao S, Park Y, Hasegawa Y, Tribble GD, James CE, Handfield M, Stavropoulos MF, Yilmaz O, Lamont RJ. Cell. Microbiol 2007;9:1997. [PubMed: 17419719]
115. Desta T, Graves DT. Cell Microbiol. 2007
116. Voth DE, Howe D, Heinzen RA. Infect. Immun 2007;75:4263. [PubMed: 17606599]
117. Luhrmann A, Roy CR. Infect Immun. 2007
118. Dellacasagrande J, Capo C, Raoult D, Mege JL. J. Immunol 1999;162:2259. [PubMed: 9973502]
119. Wright GD. Science 2007;315:1373. [PubMed: 17347430]
120. Reed MB, Domenech P, Manca C, Su H, Barczak AK, Kreiswirth BN, Kaplan G, Barry CE 3rd. Nature 2004;431:84. [PubMed: 15343336]
121. Ehrt S, Schnappinger D. Nat. Med 2007;13:284. [PubMed: 17342139]
122. Briken V, Porcelli SA, Besra GS, Kremer L. Mol. Microbiol 2004;53:391. [PubMed: 15228522]
123. Karakousis PC, Bishai WR, Dorman SE. Cell Micro-biol 2004;6:105.
124. Bhatt A, Molle V, Besra GS, Jacobs WR Jr. Kremer L. Mol. Microbiol 2007;64:1442. [PubMed: 17555433]
125. Dover LG, Alderwick LJ, Brown AK, Futterer K, Besra GS. Curr. Mol. Med 2007;7:247. [PubMed: 17504111]
126. Brennan PJ, Crick DC. Curr. Top Med. Chem 2007;7:475. [PubMed: 17346193]
127. Tonge PJ, Kisker C, Slayden RA. Curr. Top Med. Chem 2007;7:489. [PubMed: 17346194]
128. Gokhale RS, Saxena P, Chopra T, Mohanty D. Nat. Prod. Rep 2007;24:267. [PubMed: 17389997]
129. Nigou J, Gilleron M, Rojas M, Garcia LF, Thurnher M, Puzo G. Microbes. Infect 2002;4:945. [PubMed: 12106787]
130. Vergne I, Chua J, Deretic V. Traffic 2003;4:600. [PubMed: 12911814]
131. Vergne I, Chua J, Deretic V. J. Exp. Med 2003;198:653. [PubMed: 12925680]
132. Kang PB, Azad AK, Torrelles JB, Kaufman TM, Beharka A, Tibesar E, DesJardin LE, Schlesinger LS. J. Exp. Med 2005;202:987. [PubMed: 16203868]
133. Dinadayala P, Kaur D, Berg S, Amin AG, Vissa VD, Chatterjee D, Brennan PJ, Crick DC. J. Biol. Chem 2006;281:20027. [PubMed: 16704981]
134. Vignal C, Guerardel Y, Kremer L, Masson M, Legrand D, Mazurier J, Elass E. J. Immunol 2003;171:2014. [PubMed: 12902506]
135. Dao DN, Kremer L, Guerardel Y, Molano A, Jacobs WR Jr. Porcelli SA, Briken V. Infect. Immun 2004;72:2067. [PubMed: 15039328]
136. Quesniaux VJ, Nicolle DM, Torres D, Kremer L, Guerardel Y, Nigou J, Puzo G, Erard F, Ryffel B. J. Immunol 2004;172:4425. [PubMed: 15034058]
137. Zhang N, Torrelles JB, McNeil MR, Escuyer VE, Khoo KH, Brennan PJ, Chatterjee D. Mol. Microbiol 2003;50:69. [PubMed: 14507364]
138. Shi L, Berg S, Lee A, Spencer JS, Zhang J, Vissa V, McNeil MR, Khoo KH, Chatterjee D. J. Biol. Chem 2006;281:19512. [PubMed: 16687411]
139. Berg S, Kaur D, Jackson M, Brennan PJ. Glycobiology 2007;17:35. [PubMed: 17261566]
140. DiGiuseppe Champion PA, Cox JS. Cell Microbiol 2007;9:1376. [PubMed: 17466013]
141. Stanley SA, Raghavan S, Hwang WW, Cox JS. Proc. Natl. Acad. Sci. U. S. A 2003;100:13001. [PubMed: 14557536]
142. Guinn KM, Hickey MJ, Mathur SK, Zakel KL, Grotzke JE, Lewinsohn DM, Smith S, Sherman DR. Mol. Microbiol 2004;51:359. [PubMed: 14756778]
143. Gao LY, Guo S, McLaughlin B, Morisaki H, Engel JN, Brown EJ. Mol. Microbiol 2004;53:1677. [PubMed: 15341647]
144. Fortune SM, Jaeger A, Sarracino DA, Chase MR, Sassetti CM, Sherman DR, Bloom BR, Rubin EJ. Proc. Natl. Acad. Sci. U. S. A 2005;102:10676. [PubMed: 16030141]

145. Pathak SK, Basu S, Basu KK, Banerjee A, Pathak S, Bhattacharyya A, Kaisho T, Kundu M, Basu J. Nat. Immunol 2007;8:610. [PubMed: 17486091]

146. Burts ML, Williams WA, DeBord K, Missiakas DM. Proc. Natl. Acad. Sci. U. S. A 2005;102:1169. [PubMed: 15657139]

147. Lenz LL, Mohammadi S, Geissler A, Portnoy DA. Proc. Natl. Acad. Sci. U. S. A 2003;100:12432. [PubMed: 14527997]

148. Braunstein M, Brown AM, Kurtz S, Jacobs WR Jr. J. Bacteriol 2001;183:6979. [PubMed: 11717254]

149. Seifert KN, Adderson EE, Whiting AA, Bohnsack JF, Crowley PJ, Brady LJ. Microbiology 2006;152:1029. [PubMed: 16549667]

150. Bensing BA, Sullam PM. Mol. Microbiol 2002;44:1081. [PubMed: 12010500]

151. Bensing BA, Takamatsu D, Sullam PM. Mol. Microbiol 2005;58:1468. [PubMed: 16313630]

152. Braunstein M, Espinosa BJ, Chan J, Belisle JT, Jacobs WR Jr. Mol. Microbiol 2003;48:453. [PubMed: 12675804]

153. Kurtz S, McKinnon KP, Runge MS, Ting JP, Braunstein M. Infect Immun 2006;74:6855. [PubMed: 17030572]