Mycobacterium tuberculosis and the host macrophage: maintaining homeostasis or battling for survival?

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***Mycobacterium tuberculosis* is endowed with the ability to persist within its intracellular niche for years, often tilting the balance of the host–pathogen interaction in its favour. The host resists infection by releasing damaging free radicals, pushing the pathogen towards lysosomal degradation, releasing an arsenal of cytokines for triggering adaptive immunity and facilitating apoptosis for effective T cell antigen presentation. The bacterium counters these mechanisms and also metabolically reprograms the macrophage to its own benefit. Recent advances in these areas are reviewed here.**

Keywords: Autophagy, cell death, innate immunity, *Mycobacterium tuberculosis*, macrophage.

Introduction

MYCOBACTERIUM tuberculosis (*Mtb*) is one of the most successful intracellular pathogens responsible for chronic infection. It infects approximately one third of the human population[1]. For the purpose of this review, our focus will be on pulmonary tuberculosis. Following inhalation, bacilli are internalized within the macrophages followed by an early proinflammatory response accompanied by recruitment of fresh phagocytes and initiation of formation of a granuloma. Macrophages are found as foamy macrophages laden with lipid and multinucleated giant cells. Infected neutrophils are also present within the granulomas[2]. The lymphocytes sequester around the periphery of the granulomatous structure. As active infection progresses, the centre of the granuloma becomes necrotic and caseating eventually spilling out live bacteria into the airways[3]. The oversimplified view of the granuloma as a structure containing infection, has been contradicted in the zebrafish model of infection. Macrophages are constantly recruited within the granulomas and phagocytose dying cells facilitating bacterial proliferation[4,5]. This process requires the region of difference 1 (RD1), a 9.5-kb genomic region that is absent from all strains of BCG but present in all strains of virulent *Mtb*[6,7]. Whether the disease progresses into its active stage, is dictated by the balance between the antimicrobial mechanisms elicited by the host cells and the ability of the bacterium to counter the antimicrobial arsenal of the host.

Effective vaccination against tuberculosis remains a challenge and there are few new drugs that are likely to be widely introduced in the near future. An alternate viewpoint for therapy rests on the idea of manipulating the immune response of the host, as opposed to targeting the bacterium. With this background, the aim of this review will be to introduce the reader to some of our current knowledge on the interplay between *Mtb* and its host, the macrophage.

Oxidative and nitrosative bursts

The first checkpoint that *Mtb* has to overcome is the oxidative and nitrosative burst of the host. Phagocytosis of a bacterium is followed by phagosome maturation, during which the phagosome forms transient interactions with intracellular organelles. Recruitment of the NADPH complex at the phagocytic cup and the generation of reactive oxygen species (ROS)[8] facilitate an antimicrobial response at the cell surface dependent on the superoxide-generating NADPH oxidase (NOX) family proteins, including the catalytic subunit NOX2/gp91phox[9]. *Mtb* actively avoids the detrimental effects of the transient superoxide burst using its superoxide dismutase[10,11] and cell surface glycolipids that possibly scavenge oxygen radicals[12]. Studies with the zebrafish model of infection by *M. marinum*, suggest that the oxidative burst of the neutrophil could play a protective role in containing infection[13]. Signals from dying infected macrophages within the granuloma facilitate recruitment of neutrophils, which then kill the internalized mycobacteria through NADPH oxidase-dependent mechanisms.

Household contacts of TB patients produce high amounts of bactericidal NO[14], suggesting a likely protective role of NO. However, while NO is strongly induced in murine macrophages during infection, isolated human macrophages fail to do so. It is important to emphasize that for want of a better method of analysing the initial events of *Mtb* infection, cultured macrophages have been the tools of choice. Nonetheless, the macrophage in culture is not the equivalent of the tissue macrophage in its

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milieu. Further, the differences in behaviour between human and mouse macrophages may indeed reflect differences in macrophage immune mechanisms between the two species.

Among the mechanisms used by *Mycobacterium* spp. to persist in the host is to exploit the production of arginase 1 by macrophages. Mice deficient in Arg1 control TB more efficiently than wild type mice[15,16]. MyD88-dependent production of the cytokines IL-6, IL-10 induces STAT3-dependent autocrine–paracrine synthesis of arginase 1[17]. Recent studies demonstrate that NO suppresses IL-1β production by inhibiting the NLRP3 inflammosome[18]. NO-dependent S-nitrosylation of NLRP3 is independent of the antimicrobicidal function of NO.

Arrest of phagosomal maturation

The bacterium must arrest phagosomal maturation in order to escape lysosomal degradation. Mycobacterial lipoarabinomannan (LAM) plays a prominent role in this process. Mannose-capped LAM (ManLAM) modulates protein trafficking pathways associated with phagosome maturation arrest[19]. It incorporates into lipid rafts[20] and inhibits phagosomal maturation in macrophages[21]. Phosphatidylinositol 3-phosphate (PI3P) recruits the endosomal tethering molecule EEA1 to the endocytic organelles[22,23], whereas ManLAM inhibits the recruitment of EEA1 to phagosomal membranes through a block in $[Ca^{2+}]_c$ rise[24].

Pathogenic mycobacteria counter phagosomal acidification[25] by excluding the proton pump from mycobacterial phagosomes[26]. The notion that *Mtb* remains within intracellular phagosomes has been challenged. In dendritic cells (DCs), *Mtb* resides in a compartment that is positive for the lysosome-associated membrane proteins LAMP-1, LAMP-2 and CD63, and the lysosomal aspartic proteinase cathepsin D[27]. The ESX-1 secretion system is required for phagosomal escape[28,29]. Recent studies show that inhibition of the Abl tyrosine kinase by imatinib upregulates the expression of the vacuolar-type H^+ adenosine triphosphatase, reduces lysosomal pH and limits the multiplication of *Mtb* in macrophages[30,31].

Metabolic reprogramming as a result of interplay between *Mtb* and the macrophage

The 'foamy' phenotype of macrophages infected with *Mtb* is characterized by accumulation of intracellular lipid bodies[32], which serve as a reservoir of nutrients in the form of fatty acids[33]. Exemplary of metabolic reprogramming of the *Mtb*-infected macrophage is the accumulation of triacylglycerol (TAG). *Mtb* utilizes host TAG-derived fatty acids to synthesize mycobacterial lipids[34]. Reduction in intra-phagosomal lipolysis correlates with increase in the retention of host lipids in the infected macrophage[35]. Utilization of host TAG therefore helps in establishment of a persister population of *Mtb*. ESAT-6 triggers a metabolic pathway activating a G protein coupled receptor (GPR109A) leading to reduction in cellular cAMP levels and culminating in reduced turnover of TAG and enhanced lipid body formation. Mycobacteria released into these lipid bodies are protected from the host microbicidal pathways[36]. *Mtb* reprograms its own metabolic pathways to relieve the pressures arising out of the generation of propionyl CoA during utilization of cholesterol and fatty acids by the bacterium. The bacterium exploits pathways which allow incorporation of propionyl CoA into methyl-branched lipids in the cell wall[37].

Pattern recognition receptors and their mycobacterial ligands

Central to the innate immune system are the germline-encoded pattern recognition receptors (PRRs) which are expressed on innate immune cells and sense pathogen-associated molecular patterns (PAMPs)[38–40]. The membrane-bound receptors include the mannose receptor (MR or CD206), dendritic cell-specific ICAM-3-grabbing non-integrin (DC-SIGN) (CD209) [expressed predominantly on dendritic cells], Dectin-1, Toll-like receptors (TLRs) and complement receptor 3 (CR3, CD11b/CD18). The MR binds to ManLAM of *Mtb* and creates an immunosuppressive environment partly through upregulation of PPARγ signalling[41]. Dectin-1, a β-glucan collaborates with TLR2 in the induction of cytokines in response to *Mtb*[42].

When *Mtb* is internalized by alveolar macrophages or other innate cells, it encounters the TLRs[43,44]. TLR2 partners TLR1 or TLR6 to recognize bacterial components (of which the best studied ones are the lipoproteins) to trigger canonical NF-κB and MAPK signalling. Among its ligands are the mycobacterial 19-kDa lipoprotein, glycolipids like lipomannan (LM), 38-kDa antigen, LprG lipoprotein and phosphatidylinositol mannoside (PIM)[45]. TLR signalling is required for activation of the vitamin D receptor by 1,25-dihydroxyvitamin D3 (converted from vitamin D3 by CYP27B1) and synthesis of the antimicrobial peptide cathelicidin (or LL-37)[45]. The transcription factor NFAT5 is activated by TLR signalling and the co-infection of HIV-1 in tuberculosis accelerates an increase of viral load through expression of NFAT5 (ref. 46). TLR4 is activated by heat shock protein 60/65 and 38-kDa antigen. TLR9 recognizes unmethylated CpG motifs of mycobacterial DNA[47]. In mouse models, $TLR9^{(-/-)}$ but not $TLR2^{(-/-)}$ mice display defective mycobacteria-induced interleukin (IL)-12p40 and interferon IFN-γ responses[48]. However, neither TLR2 nor TLR9 knockout mice showed substantial changes in resistance to low dose pathogen challenge. $TLR2/9^{(-/-)}$ mice displayed markedly enhanced susceptibility to infection and altered pulmonary pathology.

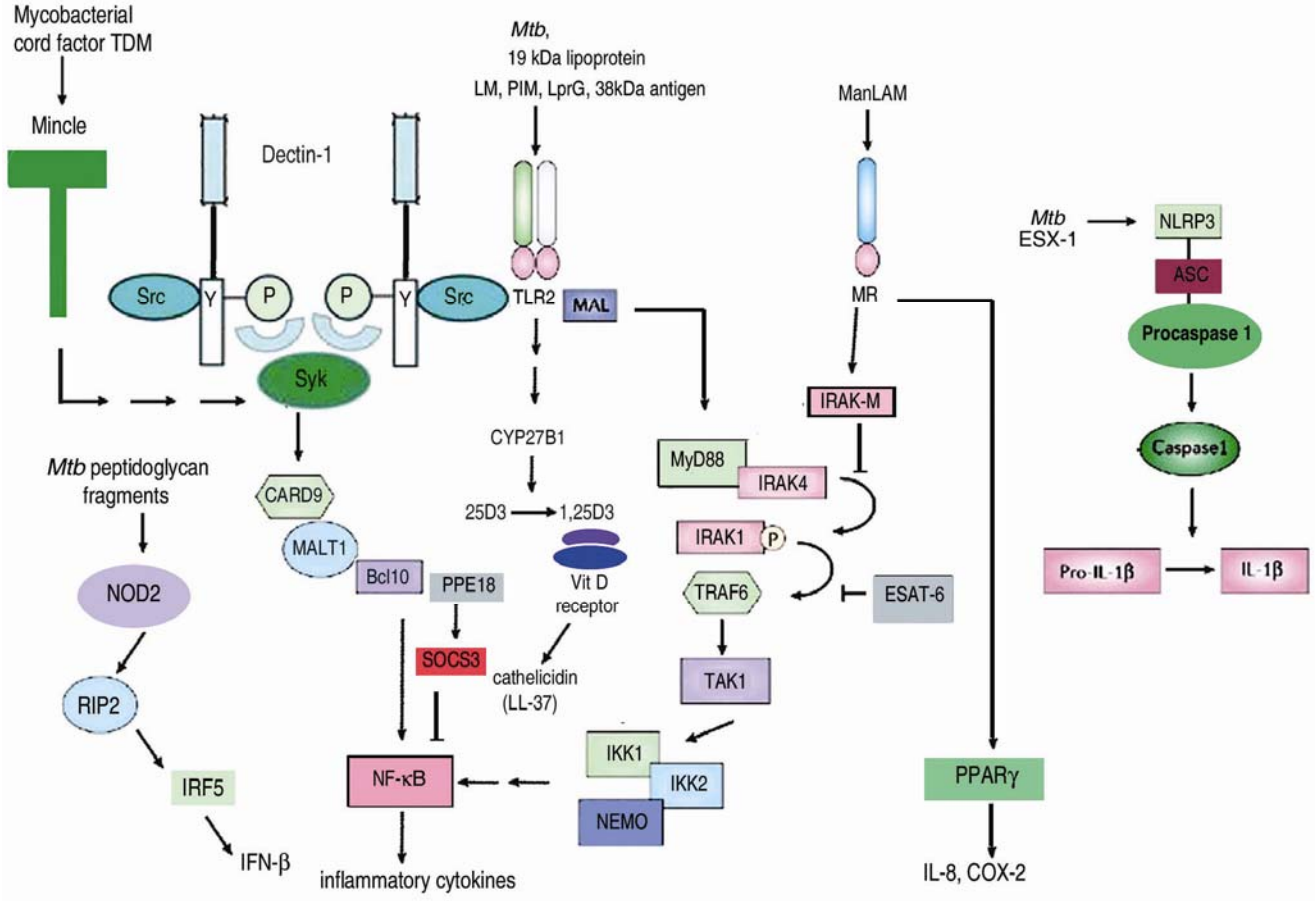

Figure 1. Overview of the regulation of macrophage signalling pathways by *M. tuberculosis* through pattern recognition receptors. Mycobacteria or its effectors bind to a variety of cell surface as well as intracellular receptors and induce signalling pathways leading to activation of transcription factors including NF-κB, PPARγ or IRF. Regulators like IRAK-M negatively regulate the activation of NF-κB in order to control time-dependent activation of cytokine release. *Mtb* also induces NLRP3 mediated activation of caspase 1 and subsequent conversion of pro-IL1β to IL-1β.

Trehalose dimycolate (TDM) an important cell surface component of *Mtb* is tethered to several receptors, including TLR2, the class A scavenger receptor MARCO, Fc receptor-γ (FcRγ) and macrophage-inducible C-type lectin (Mincle)[49–51]. TDM has been reported to trigger MARCO/TLR2/CD14-dependent signalling to produce proinflammatory cytokines[49]. It also activates macrophages and dendritic cells via FcRγ-Syk-Card9 pathway[50,51] by signalling through Mincle.

Other than the activating signals arising out of ligation of TLRs, *Mtb* is endowed with the ability to dampen TLR signals using a variety of mechanisms. ManLAM suppresses TLR4-driven IL-12p40 induction by virtue of its ability to induce IRAK-M, a kinase-dead variant of the IRAK family which negatively regulates the classical NF-κB pathway[52]. Basu and coworkers have demonstrated that exogenous ESAT-6 downregulates MyD88-dependent TLR signalling[53]. ESAT-6 and CFP-10 also downregulate LPS-induced ROS production[54]. The zinc metalloprotease Zmp1[55] and the cell envelope-associated serine hydrolase Hip1 dampen activation of the inflammosome[56]. These are a few of the examples of mycobacterial effectors that dampen proinflammatory signalling. An overview of mycobacterial regulation of some innate immune signalling pathways through PRRs is summarized in Figure 1.

The mycobacterial genome is characterized by the presence of the unique PE/PPE family of proteins which have highly conserved proline–glutamate (PE) and proline–proline–glutamate (PPE) residues near the N-termini[57,58]. The *pe*/*ppe* families have coevolved with the *esx* genes. Several of these proteins are surface-localized and could also be localized to the cell envelope as part of a secretory system. It is likely that the surface localized PE/PPE proteins interact directly with macrophages. For example, Rv1759c has fibronectin-binding properties. Other members of the family, Rv1818c, Rv1787 and Rv3018 influence virulence and survival of *Mtb* in macrophages. Some of the PE/PPE family members elicit B- and T-cell responses[59–61]. The PPE18 protein signals through TLR2 to activate IL-10 production and dampen NF-κB signalling by upregulating SOCS3[62]. It is likely that many more members of the family fulfill varied roles in mycobacterial pathogenesis.

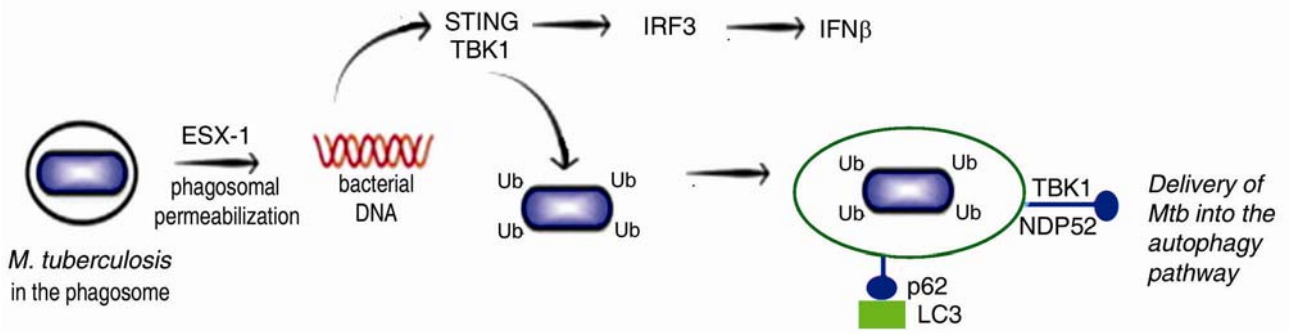

Figure 2. The role of cytosolic escape of *M. tuberculosis* in IFN-β induction and autophagy. The ESX-1 secretion system facilitates escape of *Mtb* from the cytosol. Bacterial DNA subsequently stimulates the STING/TBK1/IRF3 axis to promote the induction of IFN-β. STING also links the bacterium to the autophagy pathway with the p62 and NDP52 proteins involved in formation of a phagophore around the bacilli, and eventual delivery of engulfed bacteria to the lysosomes.

The NOD-like receptors (NLRs) and RIG-like receptors (RLRs) cooperate with the TLRs in innate immunity[63]. The NLRs NOD1 and NOD2 respond to peptidoglycan fragments to activate NF-κB[63]. The NLRs NLRP1 and NLRP3 respond to bacterial products to activate caspase-1. The RLRs detect viral nucleic acid and activate interferon-regulated factor (IRF) family members. Type II IFNs (IFN-α and IFN-β) negatively regulate host resistance to *Mtb* in mice[64,65]. The transcription factor IRF3 which is activated by phosphorylation by TBK1 is required for IFN-β induction. The Cox group suggests that the ESX-1 secretion system promotes escape of *Mtb* from the cytosol, followed by recognition of bacterial DNA by IFI204 (ref. 66). This stimulates the sting/TBK1/IRF3 signalling axis leading to IFN-β induction. These results are in conflict with the findings of Pandey *et al.*[67] which suggest that the type I interferon response depends on the recognition of mycobacterial peptidoglycan by NOD2 and NOD2/RIP2/IRF5 signalling. The role of DNA-dependent activation of STING/TBK1 signalling is shown in Figure 2.

Brooks *et al.*[68] have shown that pre-treatment of human monocyte-derived and alveolar macrophages with the NOD2 ligand muramyl dipeptide enhances production of TNF-α and IL-1β in response to *Mtb* and BCG in a RIP2-dependent fashion. NOD2 controls the growth of both *Mtb* and BCG in human macrophages. Using a high-throughput shRNA-based screen NLRs and CARDs important for IL-1β secretion upon *Mtb* infection have been identified[69]. NLRP3, ASC and caspase-1 form an infection-inducible inflammasome complex that is dependent on ESAT-6.

The protein CARD9 is important for NOD2-mediated activation of p38 and JNK[40]. Macrophages from CARD9-deficient mice activate NF-κB normally in response to MDP, but p38 and JNK activation is inhibited[70]. Card9$^{(-/-)}$ mice succumb early after aerosol infection[71].

In vivo studies showed somewhat discordant results in susceptibility of mice deficient in several TLR-related genes, including TLR2, TLR4, TLR6 or MyD88, in *Mtb* infection[72–74]. However, genetic studies suggest a link between TLR signalling and susceptibility to disease in humans. I602S is a frequent single-nucleotide polymorphism of human TLR1 that greatly inhibits cell surface trafficking, confers hyporesponsiveness to TLR1 agonists and protects against leprosy and tuberculosis[75]. rs352139, an SNP located in the intron of TLR9, is associated with tuberculosis susceptibility in Indonesian and Vietnamese populations[76]. The TLR2 variant R753Q influences the progression of infection to TB disease in children[77]. A reported role of the nonsynonymous SNP S180L (975C/T) in TIRAP[78] in protection against TB results from attenuation of TLR2 signal transduction. Another polymorphic variant (558C/T) in TIRAP, discovered in the Vietnamese population, showed an association with TB meningitis but not pulmonary TB[79]. An association of TLR8 with pulmonary TB has also been suggested[80]. These associations strengthen the role of TLRs in innate immunity against TB.

Arachidonic acid metabolites and innate immunity

The arachidonic acid metabolites, eicosanoids, lipoxins and leukotrienes play crucial roles in the inflammatory response associated with mycobacteria-induced necrosis in macrophages. Prostanoids such as PGE_2 induce plasma membrane repair and prevent mitochondrial damage; promoting apoptosis rather than necrosis[81]. On the other hand, products of 5-lipoxygenase (5-LO) such as LXA_4 inhibit cyclooxygenase 2 (COX2) production, shutting down prostaglandin synthesis. 5-LO knockout mice show resistance to *Mtb* infection[82]. Activation of the 5-LO pathway inhibits *Mtb*-induced apoptosis, prevents cross-presentation of antigens by dendritic cells and therefore compromises the adaptive immune response[83].

LXA_4 a product of the 5-LO reaction, is produced by macrophages after infection with virulent *Mtb*. Tobin *et al.*[84] have shown that zebra fish lacking the leukotriene

A4 (LTA4) hydrolase enzyme show decreased transcription of TNF-α and an anti-inflammatory phenotype[84]. SNPs in the leukotriene A4 hydrolase (*lta4h*) gene are associated with protection against tuberculosis, arguing in support of a role of *lta4h* in the human disease[85].

Autophagy and *Mtb* infection

During autophagy, cytoplasmic components are sequestered by double membranous structures which subsequently fuse to lysosomes for degradation generating substrates for energy metabolism and protein synthesis[86]. Autophagy plays a role in defense against intracellular pathogens[87–92]. Autophagy can be induced exogenously via starvation, treatment with IFN-γ or vitamin D3 or genetic depletion of inhibitors of autophagy resulting in decreased bacterial replication[93–95]. A recent system-level analysis has identified the tyrosine kinase Src as a major regulatory hub which restricts phagosomal acidification and autophagy during infection[96]. The prevalent view is that *Mtb* inhibits autophagy. This has been challenged in recent times by the Cox group[97], suggesting that the ESX-1 secretion system plays a role in eliciting autophagy leading to the targeting of *Mtb* to lysosomes. Recognition of cytosolic bacterial DNA by STING leads to the LC3 binding adaptors p62 and NDP52 collaborating to form a phagophore around the bacilli, a process requiring the TBK1 kinase and ATG5. The engulfed bacteria are delivered to the lysosomes resulting in elimination of a subpopulation of the bacilli. The authors suggest that this autophagy pathway is a determinant of host resistance to *Mtb in vivo*. Jagannath *et al*.[98] suggest that induction of autophagy by administration of rapamycin, increases the potency of vaccination. Polymorphisms in the autophagy associated gene *IRGM1* have been reported to be associated with TB[99,100].

Cellular death pathways triggered by *Mtb*

Mtb can trigger both apoptotic and necrotic forms of cell death in macrophages[101–103]. Mice with resistant *sst1* (susceptibility to tuberculosis-1) locus undergo apoptosis in response to *Mtb* infection[104]. Apoptosis is associated with mycobacterial killing[105–108]. Apoptotic vesicles enhance T cell responses via the 'detour pathway' of antigen presentation[109–111]. At low multiplicities of infection (MOI), virulent *Mtb* strains undergo less apoptosis than attenuated strains[112]. An ASK1/p38 MAP kinase driven pathway regulates caspase-8 dependent apoptosis in macrophages[113]. Factors such as ManLAM[114], nuoG[115,116], secA2 (ref. 117), the OppABCD peptide transporter of *Mtb*[118] and Rv3654c-Rv3655c[119], inhibit apoptosis. There are reports in favour of apoptosis-inducing factors of *Mtb* such as ESAT-6 (ref. 120) and apoptosis induced by *Mtb* is associated with mitochondrial membrane disruption[121].

At higher MOIs, virulent *Mtb* also triggers necrosis in macrophages[122]. Chen *et al*. have proposed that cleavage of annexin-1 induced by *Mtb* leads to the inefficient formation of the apoptotic envelope and progression to necrosis[123]. Wong and Jacobs[124] have linked the ESX-1 secretion system and its substrate ESAT-6 to necrotic death in THP1 human macrophages in a process dependent on the Syk tyrosine kinase and NLRP3. At a high MOI of 10, ESAT-6 dependent, caspase-1 and cathepsin B-independent necrosis was also observed in human monocyte-derived macrophages[125].

The role of microRNAs

MicroRNAs (miRNAs) are single-stranded RNAs of 22 nucleotides that are processed from approximately 70 nucleotide precursors. Circulating miRNAs have been explored as potential biomarkers of pulmonary tuberculosis[126]. The expression profile of miRNAs under PPD challenge of peripheral blood mononuclear cells (PBMCs) isolated from active TB patients and healthy controls, showed the specific upregulation of miR-155 and miR-155* in PBMCs from active TB patients[127], again suggesting a potential diagnostic value of miRNAs in TB infection. There are at present, a handful of studies showing that miRNAs regulate the response of host macrophages to *Mtb* challenge. Rajaram *et al*.[128] present evidence that *M. tuberculosis* lipomannan signals through TLR2 to express miR-125b. miR-125b production lowers the stability of the TNF-α protein thereby limiting TNF-α production. The authors show that, in human macrophages, pathogenic mycobacteria skew the balance of miRNA production towards a high miR-125b and low miR-155 production, thereby favouring subversion of the host innate immune response. On the other hand, using the murine macrophage as a model system, Kumar *et al.*[129] presents evidence that miR-155 production is higher in the virulent *M. tuberculosis* H37Rv strain compared to *M. bovis* BCG, and that miR-155 production is dependent on the virulence factor ESAT-6. The authors argue that by suppressing the miR-155 target SHIP1 and activating Akt, the balance of signalling is tilted in favour of macrophage survival thereby preserving the intracellular niche of the pathogen. Further, miR-155 inhibits expression of the transcriptional repressor Bach1 which enhances the activation of heme oxygenase-1 thereby favouring the production of carbon monoxide which activates the DosR regulon of *Mtb*. This too augments survival of the pathogen. In addition, *Mtb* induces miR-99b in dendritic cells[130]. Inhibition of miR-99b production enhances production of IL-6, IL-12 and IL-β. Taken together, these results highlight the ability of pathogenic mycobacteria to exploit miRNAs of the host to the advantage of the pathogen. The existing literature point to a need to carefully elucidate the responses of human and murine

macrophages to challenge with virulent *Mtb*, as the balance of miRNAs may depend on the host system and the cell type being used for analysis. Previous studies have also reported the differences in the immunology of mice and humans[131]. For example, NOD2 is required to control the growth of *Mtb* in humans[68] but not in mice[132].

Concluding remarks

In conclusion, this review tries to bring into focus some of our current understanding of the interplay between *Mtb* and the macrophage and the likely outcome of this interplay on the course of infection. It touches upon some of the important findings of recent years which have shed new light on the fine tuning of the innate immune response, modulation of cellular survival or death pathways (to the benefit of either the host or the pathogen), and metabolic reprogramming of the macrophage often to the benefit of the pathogen. At this juncture it appears increasingly likely that the immune response may be manipulated in a manner that could augment existing strategies of intervention without the associated risk of developing antimicrobial resistance.

1. Russell, D. G., Barry 3rd, C. E. and Flynn, J. L., Tuberculosis: what we don't know can, and does, hurt us. *Science*, 2010, **328**, 852–856.
2. Eum, S. Y. *et al.*, Neutrophils are the predominant infected phagocytic cells in the airways of patients with active pulmonary TB. *Chest*, 2010, **137**, 122–128.
3. Russell, D. G., Who puts the tubercle in tuberculosis? *Nat. Rev. Microbiol*., 2007, **5**, 39–46.
4. Davis, J. M. and Ramakrishnan, L., The role of the granuloma in expansion and dissemination of early tuberculous infection. *Cell*, 2009, **136**, 37–49.
5. Ramakrishnan, L., Revisiting the role of the granuloma in tuberculosis. *Nat. Rev. Immunol.*, 2012, **12**, 352–366.
6. Mahairas, G. G., Sabo, P. J., Hickey, M. J., Singh, D. C. and Stover, C. K., Molecular analysis of genetic differences between *Mycobacterium bovis* BCG and virulent *M. bovis*. *J. Bacteriol*., 1996, **178**, 1274–1282.
7. Gordon, S. V., Brosch, R., Billault, Garnier, T., Eiglmeier, K. and Cole, S. T., Identification of variable regions in the genomes of tubercle bacilli using bacterial artificial chromosome arrays. *Mol. Microbiol*., 1999, **32**, 643–655.
8. Bokoch, G. M. and Zhao, T., Regulation of the phagocyte NADPH oxidase by Rac GTPase. *Antioxid. Redox. Signal.*, 2006, **8**, 1533–1548.
9. Lambeth, J., NOX enzymes and the biology of reactive oxygen. *Nat. Rev. Immunol*., 2004, **4**, 181–189.
10. Spagnolo, L. *et al.*, Unique features of the sodC encoded superoxide dismutase from *Mycobacterium tuberculosis*, a fully functional copper-containing enzyme lacking zinc in the active site. *J. Biol. Chem*., 2004, **279**, 33447–33455.
11. Piddington, D. L., Fang, F. C., Laessig, T., Cooper, A. M., Orme, I. M. and Buchmeier, N. A., Cu, Zn superoxide dismutase of *Mycobacterium tuberculosis* contributes to survival in activated macrophages that are generating an oxidative burst. *Infect. Immun*., 2001, **69**, 4980–4987.
12. Chan, J. *et al.*, Microbial glycolipids: possible virulence factors that scavenge oxygen radicals. *Proc. Natl. Acad. Sci. USA*, 1989, **86**, 2453–2457.
13. Yang, C.-T., Cambier, C. J., Davis, J. M., Hall, C. J., Crosier, P. S. and Ramakrishnan, L., Neutrophils exert protection in the early tuberculous granuloma by oxidative killing of mycobacteria phagocytosed from infected macrophages. *Cell Host Microbe*, 2012, **12**, 301–312.
14. Idh, J. *et al.*, Nitric oxide production in the exhaled air of patients with pulmonary tuberculosis in relation to HIV co-infection. *BMC Infect. Dis*., 2008, **8**, 148.
15. El Kasmi, K. C. *et al.*, Toll-like receptor-induced arginase 1 in macrophages thwarts effective immunity against intracellular pathogens. *Nat. Immunol*., 2008, **9**, 1399–1406.
16. Schreiber, T. *et al.*, Autocrine IL 10 induces hallmarks of alternative activation in macrophages. *J. Immunol*., 2009, **183**, 1301–1312.
17. Qualls, J. E. *et al.*, Arginase usage in mycobacteria-infected macrophages depends on autocrine-paracrine cytokine signalling. *Sci. Signal.*, 2010, **3**, ra62.
18. Mishra, B. B., Rathinam, V. A. K., Martens, G. W., Martinot, A. J., Kornfeld, H., Fitzgerald, K. A. and Sassetti, C. M., Nitric oxide controls the immunopathology of tuberculosis by inhibiting NLRP3 inflammasome-dependent processing of IL-1β. *Nat. Immunol*., 2013, **14**, 52–60.
19. Shui, W. *et al.*, Organelle membrane proteomics reveals differential influence of mycobacterial lipoglycans on macrophage phagosome maturation and autophagosome accumulation. *J. Proteome Res*., 2011, **10**, 339–348.
20. Welin, A., Winberg, M. E., Abdalla, H., Sarndahl, E., Rasmusson, B., Stendahl, O. and Lerm, M., Incorporation of *Mycobacterium tuberculosis* lipoarabinomannan into macrophage membrane rafts is a prerequisite for the phagosomal maturation block. *Infect. Immun*., 2008, **76**, 2882–2887.
21. Fratti, R. A., Chua, J., Vergne, I. and Deretic, V., *Mycobacterium tuberculosis* glycosylated phosphatidylinositol causes phagosome maturation arrest. *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 5437–5442.
22. Fratti, R. A., Backer, J. M., Gruenberg, J., Corvera, S. and Deretic, V., Role of phosphatidylinositol 3-kinase and Rab5 effectors in phagosomal biogenesis and mycobacterial phagosome maturation arrest. *J. Cell Biol*., 2001, **154**, 631–644.
23. Simonsen, A., Wurmser, A. E., Emr, S. D. and Stenmark, H., The role of phosphoinositides in membrane transport. *Curr. Opin. Cell Biol*., 2001, **13**, 485–492.
24. Vergne, I., Chua, J. and Deretic, V., Tuberculosis toxin blocking phagosome maturation inhibits a novel Ca^{2+}/calmodulin-PI3K hVPS34 cascade. *J. Exp. Med*., 2003, **198**, 653–659.
25. Welin, A., Raffetseder, J., Eklund, D., Stendahl, O. and Lerm, M., Importance of phagosomal functionality for growth restriction of *M. tuberculosis* in primary human macrophages. *J. Innate Immun*., 2011, **3**, 508–518.
26. Koszycki, S. *et al.*, Lack of acidification in *Mycobacterium* phagosomes produced by exclusion of the vesicular proton-ATPase. *Science*, 1994, **263**, 678–681.
27. van der Wel, N. *et al.*, *M. tuberculosis* and *M. leprae* translocate from the phagolysosome to the cytosol in myeloid cells. *Cell*, 2007, **129**, 1287–1298.
28. Houben, D. *et al.*, ESX-1-mediated translocation to the cytosol controls virulence of mycobacteria. *Cell. Microbiol*., 2012, **14**, 1287–1298.
29. Welin, A. and Lerm, M., Inside or outside the phagosome? The controversy of the intracellular localization of *Mycobacterium tuberculosis*. *Tuberculosis*, 2012, **92**, 113–120.
30. Bruns, H. *et al.*, Abelson tyrosine kinase controls phagosomal acidification required for killing of *Mycobacterium tuberculosis* in human macrophages. *J. Immunol*., 2012, **189**, 4069–4078.
31. Napier, R. J. *et al.*, Imatinib-sensitive tyrosine kinases regulate mycobacterial pathogenesis and represent therapeutic targets against tuberculosis. *Cell Host Microbe*., 2011, **10**, 475–478.

32. Russell, D. G., Cardona, P. J., Kim, M. J., Allain, S. and Altare, F., Foamy macrophages and the progression of the human tuberculosis granuloma. *Nat. Immunol*., 2009, **10**, 943–948.
33. Peyron, P. *et al.*, Foamy macrophages from tuberculous patients' granulomas constitute a nutrient-rich reservoir for *M. tuberculosis* persistence. *PLoS Pathog*., 2008, **4**, e1000204.
34. Daniel, J., Maamar, H., Deb, C., Sirakova, T. D. and Kolattukudy, P. E., *Mycobacterium tuberculosis* uses host triacylglycerol to accumulate lipid droplets and acquires a dormancy-like phenotype in lipid-loaded macrophages. *PLoS Pathog.*, 2011, **7**, e1002093.
35. Podinovskala, M., Lee, W., Caldwell, S. and Russell, D. G., Infection of macrophages with *Mycobacterium tuberculosis* induces global modifications to phagosomal function. *Cell. Microbiol*., 2013, Article published online 9 January 2013.
36. Singh, V., Jamwal, S., Jain, R., Verma, P., Gokhale, R. and Rao, K. V. S., *Mycobacterium tuberculosis*-driven targeted recalibration of macrophage lipid homeostasis promotes the foamy phenotype. *Cell Host Microbe*., 2012, **12**, 669–681.
37. Lee, W., VanderVen, B. C., Fahey, R. J. and Russell, D. G., Intracellular *Mycobacterium tuberculosis* exploits host-derived fatty acids to limit metabolic stress. *J. Biol. Chem*., 2013, **288**, 6788–6880.
38. Jo, E. K., Mycobacterial interaction with innate receptors: TLRs, C-type lectins, and NLRs. *Cur. Opin. Infect. Dis.*, 2008, **21**, 279–286.
39. Sasindran, J. and Torrelles, J. B., *Mycobacterium tuberculosis* infection and inflammation: what is beneficial for the host and for the bacterium? *Front. Microbiol*., 2011, **2**, 2.
40. Underhill, D. M., Collaboration between the innate immune receptors dectin-1, TLRs, and Nods. *Immunol. Rev*., 2007, **219**, 75–87.
41. Rajaram, M. V. S., Brooks, M. N., Jessica, D. M., Torrelles, J. B., Azad, A. K. and Schlesinger, L. S., *Mycobacterium tuberculosis* activates human macrophage peroxisome proliferator-activated receptor gamma linking mannose receptor recognition to regulation of immune responses. *J. Immunol*., 2010, **185**, 929–942.
42. Yadav, M. and Schorey, J. S., The {beta}-glucan receptor Dectin-1 functions together with TLR2 to mediate macrophage activation by mycobacteria. *Blood*, 2006, **108**, 3168–3175.
43. Akira, S. and Takeda, K., Toll-like receptor signalling. *Nat. Rev. Immunol*., 2004, **4**, 499–511.
44. Basu, J., Shin, D. M. and Jo, E. K., Mycobacterial signaling through toll-like receptors. *Front. Cell. Infect. Microbiol*., 2012, **2**, 145.
45. Liu, P. T. *et al*., Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science*, 2006, **311**, 1770–1773.
46. Ranjbar, S., Jasenosky, L. D., Chow, N. and Goldfeld, A. E., Regulation of *Mycobacterium tuberculosis*-dependent HIV-1 transcription reveals a new role for NFAT5 in the toll-like receptor pathway. *PLoS Pathog*., 2012, **8**, e1002620.
47. Jo, E. K., Yang, C. S., Choi, C. H. and Harding, C. V., Intracellular signalling cascades regulating innate immune responses to Mycobacteria: branching out from Toll-like receptors. *Cell. Microbiol.*, 2007, **9**, 1087–1098.
48. Bafica, A., Scanga, C. A., Feng, C. G., Leifer, C., Cheever, A. and Sher, A., TLR9 regulates Th1 responses and cooperates with TLR2 in mediating optimal resistance to *Mycobacterium tuberculosis. J. Exp. Med*., 2005, **19**, 1715–1724.
49. Bowdish, D. M. E. *et al*., MARCO, TLR2, and CD14 are required for macrophage cytokine responses to mycobacterial trehalose dimycolate and *Mycobacterium tuberculosis*. *PLoS Pathog*., 2009, **5**, e1000474.
50. Werninghaus, K. *et al*., Adjuvanticity of a synthetic cord factor analogue for subunit *Mycobacterium tuberculosis* vaccination requires FcRgamma-Syk-Card9-dependent innate immune activation. *J. Exp. Med*., 2009, **206**, 89–97.
51. Ishikawa. E. *et al.*, Direct recognition of the mycobacterial glycolipid, trehalose dimycolate, by C-type lectin Mincle. *J. Exp. Med*., 2009, **206**, 2879–2888.
52. Pathak, S. K., Basu, S., Bhattacharyya, A., Pathak, S., Kundu, M. and Basu J., *Mycobacterium tuberculosis* lipoarabinomannan-mediated irak-M induction negatively regulates Toll-like receptor-dependent interleukin-12 p40 production in macrophages. *J. Biol. Chem*., 2005, **280**, 42794–42800.
53. Pathak, S. K. *et al*., Direct extracellular interaction between the early secreted antigen ESAT-6 of *Mycobacterium tuberculosis* and TLR2 inhibits TLR signaling in macrophages. *Nat. Immunol*., 2007, **8**, 610–618.
54. Ganguly, N. *et al*., *Mycobacterium tuberculosis* secretory proteins CFP-10, ESAT-6 and CFP10:ESAT-6 complex inhibit lipopolysaccharide-induced NF-κB transactivation by downregulation of reactive oxidative species (ROS) production. *Immunol. Cell Biol*., 2008, **86**, 98e106.
55. Master, S. S. *et al.*, *Mycobacterium tuberculosis* prevents inflammasome activation. *Cell Host Microbe*, 2008, **3**, 224–232.
56. Madan-Lala, R., Peixoto, K. V., Re, F. and Rengarajan, J., *Mycobacterium tuberculosis* Hip1 dampens macrophage proinflammatory responses by limiting Toll-Like receptor 2 activation. *Infect. Immun*., 2011, **79**, 4828–4838.
57. Mukhopadhyay, S. and Balaji, K., The PE and PPE proteins of *Mycobacterium tuberculosis*. *Tuberculosis*, 2011, **91**, 441–447.
58. Akhter, Y., Ehebauer, M. T. and Mukhopadhyay, S. E., The *PE/PPE* multigene family codes for virulence factors and is a possible source of mycobacterial antigenic variation: Perhaps more? *Biochmie*, 2012, **94**, 110–116.
59. Dheenadhayalan, V., Delogu, G. and Brennan, M. J., Expression of the PE-PGRS 33 protein in *Mycobacterium smegmatis*, triggers necrosis in macrophages and enhanced mycobacterial survival. *Microbes Infect*., 2006, **8**, 262–272.
60. Li, Y., Miltner, E., Wu, M., Petrofsky, M. and Bermudez, L. E., A *Mycobacterium avium* PPE gene is associated with the ability of the bacterium to grow in macrophages and virulence in mice. *Cell. Microbiol*., 2005, **4**, 539–548.
61. Camacho, L. R., Ensergueix, D., Perez, E., Gicquel, B. and Guilhot, C., Identification of a virulence gene cluster of *Mycobacterium tuberculosis* by signature-tagged transposon mutagenesis. *Mol. Microbiol*., 1999, **34**, 257–267.
62. Nair, S., Pandey, A. D. and Mukhopadhyay, S., The PPE18 protein of *Mycobacterium tuberculosis* inhibits NF-κB/rel-mediated proinflammatory cytokine production by upregulating and phosphorylating suppressor of cytokine signaling 3 protein. *J. Immunol*., 2011, **186**, 5413–5424.
63. Creach, E. M. and O'Neill, L. A. J., TLRs, NLRs and RLRs: a trinity of pathogen sensors that co-operate in innate immunity. *Trends Immunol*., 2006, **27**, 352–357.
64. Manca, C. *et al.*, Virulence of a *Mycobacterium tuberculosis* clinical isolate in mice is determined by failure to induces Th1 type immunity and is associated with induction of IFN-α/β. *Proc. Natl. Acad. Sci. USA*, 2001, **98**, 5752–5757.
65. Leber, J. H., Crimmins, G. T., Raghavan, S., Meyer-Morse, N. P., Cox, J. S. and Portnoy, D. A., Distinct TLR- and NLR-mediated transcriptional responses to an intracellular pathogen. *PLoS Pathog*., 2008, **4**, e6.
66. Manzanillo, P. S., Shiloh, M. U., Portnoy, D. A. and Cox, J. S., *Mycobacterium tuberculosis* activates the DNA-dependent cytosolic surveillance pathway within macrophages. *Cell Host Microbe*, 2012, **11**, 469–480.
67. Pandey, A. K. *et al*., NOD2, RIP2 and IRF5 play a critical role in the Type I interferon response to *Mycobacterium tuberculosis*. *PLoS Pathog.*, 2009, **57**, e1000500.

68. Brooks, M. N. *et al.*, NOD2 controls the nature of the inflammatory response and subsequent fate of *Mycobacterium tuberculosis* and *M. bovis* BCG in human macrophages. *Cell. Microbiol.*, 2011, **13**, 402–418.
69. Mishra, B. B., Moura-Alves, P., Sonawane, A., Hacohen, N., Griffiths, G., Moita, L. F. and Anes, E., *Mycobacterium tuberculosis* protein ESAT-6 is a potent activator of the NLRP3/ASC inflammasome. *Cell. Microbiol.*, 2010, **12**, 1046–1063.
70. Hsu, Y. M. *et al.*, The adaptor protein CARD9 is required for innate immune responses to intracellular pathogens. *Nat. Immunol*., 2007, **8**, 198–205.
71. Dorhoi, A. *et al.*, The adaptor molecule CARD9 is essential for tuberculosis control. *J. Exp. Med*., 2010, **207**, 777–792.
72. Doherty, T. M. and Arditi, M., TB, or not TB: that is the question – does TLR signaling hold the answer? *J. Clin. Invest*., 2004, **114**, 1699–1703.
73. Quesniaux, V. J. *et al.*, Toll-Like Receptor 2 (TLR2)-dependent-positive and TLR2-independent-negative regulation of proinflammatory cytokines by mycobacterial lipomannans. *J. Immunol*., 2004, **172**, 4425–4434.
74. Hölscher, C. *et al.*, Containment of aerogenic *Mycobacterium tuberculosis* infection in mice does not require MyD88 adaptor function for TLR2, -4 and -9. *Eur. J. Immunol.*, 2008, **38**, 680–694.
75. Hart, B. E. and Tapping, R. I., Differential trafficking of TLR1 I602S underlies host protection against pathogenic mycobacteria. *J. Immunol*., 2012, **189**, 5347–5355.
76. Kobayashi, K. *et al.*, Association of TLR polymorphisms with development of tuberculosis in Indonesian females. *Tissue Antigens*, 2012, **79,** 190–197.
77. Dalgic, N. *et al.*, Arg753Gln polymorphism of the human Toll-like receptor 2 gene from infection to disease in pediatric tuberculosis. *Hum. Immunol*., 2011, **72**, 440–445.
78. Khor, C. C. *et al.*, A mal functional variant is associated with protection against invasive pneumococcal disease, bacteremia, malaria and tuberculosis. *Nat. Genet*., 2007, **39**, 523–528.
79. Hawn, T. R. *et al.*, A polymorphism in Toll-interleukin 1 receptor domain containing adaptor protein is associated with susceptibility to meningeal tuberculosis. *J. Infect. Dis*., 2006, **194**, 1127–1134.
80. Davila, S. *et al.*, Genetic association and expression studies indicate a role of toll-like receptor 8 in pulmonary tuberculosis. *PLoS Genet*., 2008, **4**, e1000218.
81. Chen, M. *et al.*, Lipid mediators in innate immunity against tuberculosis: opposing roles of PGE2 and LXA4 in the induction of macrophage death. *J. Exp. Med*., 2008, **205**, 2791–801.
82. Bafica, A., Scanga, C. A., Serhan, C., Machadom F., White, S., Sher, A. and Aliberti, J., Host control of *Mycobacterium tuberculosis* is regulated by 5-lipoxygenase-dependent lipoxin production. *J. Clin. Invest*., 2005, **115**, 1601–1606.
83. Divangahi, M., Desjardins, D., Nunes-Alves, C., Remold, H. G. and Behar, S. M., Eicosanoid pathways regulate adaptive immunity to *Mycobacterium tuberculosis*. *Nat Immunol*., 2010, **11**, 751–758.
84. Tobin, D. M. *et al.*, lta4h locus modulates susceptibility to mycobacterial infection in zebrafish and humans. *Cell*, 2010, **140**, 717–730.
85. Tobin, D. M. *et al.*, Host genotype-specific therapies can optimize the inflammatory response to mycobacterial infections. *Cell*, 2012, **148**, 434–446.
86. Deretic, V. and Levine, B., Autophagy, immunity, and microbial adaptations. *Cell Host Microbe*, 2009, **5**, 527–549.
87. Thurston, T. L., Ryzhakov, G., Bloor, S., von Muhlinen, N. and Randow, F., The TBK1adaptor and autophagy receptor NDP52 restricts the proliferation of ubiquitin-coated bacteria. *Nat. Immunol*., 2009, **10**, 1215–1221.
88. Zheng, Y. T., Shahnazari, S., Brech, A., Lamark, T., Johansen, T. and Brumell, J. H., The adaptor protein p62/SQSTM1 targets invading bacteria to the autophagy pathway. *J. Immunol*., 2009, **183**, 5909–5916.
89. Delgado, M. A., Elmaoued, R. A., Davis, A. S., Kyei, G. and Deretic, V., Toll-like receptors control autophagy. *EMBO J*., 2008, **27**, 1110–1121.
90. Lee, H. K., Lund, J. M., Ramanathan, B., Mizushima, N. and Iwasaki, A., Autophagy-dependent viral recognition by plasmacytoid dendritic cells. *Science*, 2007, **315**, 1398–1401.
91. Sanjuan, M. A. *et al.*, Toll-like receptor signalling in macrophages links the autophagy pathway to phagocytosis. *Nature*, 2007, **450**, 1253–1257.
92. Xu, Y., Jagannath, C., Liu, X. D., Sharafkhaneh, A., Kolodziejska, K. E. and Eissa, N. T., Toll-like receptor 4 is a sensor for autophagy associated with innate immunity. *Immunity*, 2007, **27**, 135–144.
93. Gutierrez, M. G. *et al*., Autophagy is a defense mechanism inhibiting BCG and *Mycobacterium tuberculosis* survival in infected macrophages. *Cell*, 2004, **119**, 753–766.
94. Kumar, D. *et al*., Genome-wide analysis of the host intracellular network that regulates survival of *Mycobacterium tuberculosis*. *Cell*, 2010, **140**, 731–743.
95. Yuk, J. M. *et al*., Vitamin D3 induces autophagy in human monocytes/macrophages via cathelicidin. *Cell Host Microbe.*, 2009, **6**, 231–243.
96. Karim, A. F., Chandra, P., Chopra, A., Siddiqui, Z., Bhaskar, A., Singh, A. and Kumar, D., Src as the major regulatory hub discriminating the responses between wild-type and attenuated Mtb infection. *J. Biol. Chem*., 2011, **286**, 40307–40319.
97. Watson, R. O., Manzanillo, P. S. and Cox, J. S., Extracellular *M. tuberculosis* DNA targets bacteria for autophagy by activating the host DNA-sensing pathway. *Cell*, 2012, **150**, 803–815.
98. Jagannath, C., Lindsey, D. R., Dhandayuthapani, S., Xu, Y., Hunter Jr, R. L. and Eissa, N. T., Autophagy enhances the efficacy of BCG vaccine by increasing peptide presentation in mouse dendritic cells. *Nat. Med*., 2009, **15**, 267–276.
99. Intemann, C. D. *et al*., Autophagy gene variant IRGM-261T contributes to protection from tuberculosis caused by *Mycobacterium tuberculosis* but not by *M. africanum* strains. *PLoS Pathog.*, 2009, **5**, e1000577.
100. King, K. Y. *et al*., Polymorphic allele of human IRGM1 is associated with susceptibility to tuberculosis in African Americans. *PLoS One*, 2011, **6**, e16317.
101. Keane, J., Balcewicz-Sablinska, M. K., Remold, H. G., Chupp, G. L., Meek, B. B., Fenton, M. J. and Kornfeld, H., Infection by *Mycobacterium tuberculosis* promotes human alveolar macrophage apoptosis. *Infect. Immun*., 1997, **65**, 298–304.
102. Abebe, M. *et al.*, Modulation of cell death by *M. tuberculosis* as a strategy for pathogen survival. *Clin. Develop. Immun*., 2011, Article ID 678570, p. 11; doi:10.1155/2011/678570.
103. Volker, B., and Jessica, L. M., Living on the edge: inhibition of host cell apoptosis by *Mycobacterium tuberculosis. Future Microbiol*., 2008, **3**, 415–422.
104. Pan, H. *et al.*, *Ipr1* gene mediates innate immunity to tuberculosis. *Nature*, 2005, **434**, 767–72.
105. Lopez, M., Sly, L. M., Luu, Y., Young. D., Cooper. H. and Reiner, N. E., The 19-kDa *Mycobacterium tuberculosis* protein induces macrophage apoptosis through Toll-like receptor-2. *J. Immunol*., 2003, **170**, 2409–2416.
106. Oddo, M., Renno, T., Attinger, A., Bakker, T., MacDonald, H. R. and Meylan, P. R., Fas ligand-induced apoptosis of infected human macrophages reduces the viability of intracellular *Mycobacterium tuberculosis. J. Immunol*., 1998, **160**, 5448–5454.
107. Lammas, D. A., Stober, C., Harvey, C. J., Kendrick, N., Panchalingam, S. and Kumararatne, D. S., ATP-induced killing of mycobacteria by human macrophages is mediated by purinergic P2Z(P2X7) receptors. *Immunity*, 1997, **7**, 433–444.
108. Molloy, A., Laochumroonvorapong, P. and Kaplan, G., Apoptosis, but not necrosis, of infected monocytes is coupled with

killing of intracellular bacillus Calmette-Guerin. *J. Exp. Med.*, 1994, **180**, 1499–1509.
109. Schaible, U. E. *et al.*, Apoptosis facilitates antigen presentation to T lymphocytes through MHC-I and CD1 in tuberculosis. *Nat. Med*., 2003, **9**, 1039–1046.
110. Winau, F., Kaufmann, S. H. and Schaible, U. E., Apoptosis paves the detour path for CD8 T cell activation against intracellular bacteria. *Cell. Microbiol*., 2004, **6**, 599–607.
111. Winau, F. *et al.*, Apoptotic vesicles crossprime CD8 T cells and protect against tuberculosis. *Immunity*, 2006, **24**, 105–117.
112. Keane, J., Remold, H. G. and Kornfeld, H., Virulent *Mycobacterium tuberculosis* strains evade apoptosis of infected alveolar macrophages. *J. Immunol*., 2000, **164**, 2016–2020.
113. Kundu, M. *et al.*, A tumor necrosis factor- and c-Cbl-dependent FLIPs degradation pathway and its role in *Mycobacterium tuberculosis*-induced macrophage apoptosis. *Nat. Immunol*., 2009, **10**, 918–925.
114. Maiti, D., Bhattacharyya, A. and Basu, J., Lipoarabinomannan from *Mycobacterium tuberculosis* promotes macrophage survival by phosphorylating Bad through a phosphatidylinositol 3-kinase/Akt pathway. *J. Biol. Chem.*, 2001, **276**, 329–333.
115. Velmurugan, K. *et al.*, *Mycobacterium tuberculosis* nuoG is a virulence gene that inhibits apoptosis of infected host cells. *PLoS Pathog*., 2007, **3**, e110.
116. Miller, J. L., Velmurugan, K., Cowan, M. J. and Briken, V., The Type I NADH dehydrogenase of *Mycobacterium tuberculosis* counters phagosomal NOX2 activity to inhibit TNF-α-mediated host cell apoptosis. *PLoS Pathog*., 2010, **64**, e1000864.
117. Hinchey, J. *et al.*, Enhanced priming of adaptive immunity by a proapoptotic mutant of *Mycobacterium tuberculosis*. *J. Clin. Invest*., 2007, **117**, 2279–2288.
118. Dasgupta, A. *et al.*, An oligopeptide transporter of *Mycobacterium tuberculosis* regulates cytokine release and apoptosis of infected macrophages. *PLoS One*, 2010, **5**, e12225.
119. Danelishvili, L., Yamazaki, Y., Selker, J. and Bermudez, L. E., Secreted *Mycobacterium tuberculosis* Rv3654c and Rv3655c proteins participate in the suppression of macrophage apoptosis. *PLoS One*, 2010, **5**, e10474.
120. Derrick, S. C. and Morris, S. L., The ESAT6 protein of *Mycobacterium tuberculosis* induces apoptosis of macrophages by activating caspase expression. *Cell. Microbiol*., 2007, **120**, 1547–1555.
121. Santucci, M. B. *et al.*, *Mycobacterium tuberculosis*-induced apoptosis in monocytes/macrophages: early membrane modifications and intracellular mycobacterial viability. *J. Infect. Dis*., 2000, **181**, 1506–1509.
122. Chen, M., Gan, H. and Remold, H. G., A mechanism of virulence: virulent *Mycobacterium tuberculosis* strain H37Rv, but not attenuated H37Ra, causes significant mitochondrial inner membrane disruption in macrophages leading to necrosis. *J. Immunol*., 2006, **176**, 3707–3716.
123. Gan, H., Lee, J., Ren, F., Chen, M., Kornfeld, H. and Remold, H. G., *Mycobacterium tuberculosis* blocks crosslinking of annexin-1 and apoptotic envelope formation on infected macrophages to maintain virulence. *Nat. Immunol*., 2008, **9**, 1189–1197.
124. Wong, K. W. and Jacobs, W. R., Critical role for NLRP3 in necrotic death triggered by *Mycobacterium tuberculosis*. *Cell. Microbiol*., 2011, **13**, 1371–1384.
125. Welin, A., Eklund, D., Stendahl, O. and Lerm, M., Human macrophages infected with a high burden of ESAT-6-expressing *M. tuberculosis* undergo caspase-1- and cathepsin B-independent necrosis. *PLoS One*, 2011, **65**, e20302.
126. Fu, Y., Yi, Z., Wu, X., Li, J. and Xu, F., Circulating microRNAs in patients with active pulmonary tuberculosis. *J. Clin. Microbiol.*, 2011, **49**, 4246–4251.
127. Wu, J. *et al.*, Analysis of microRNA expression profiling identifies miR-155 and miR-155* as potential diagnostic markers for active tuberculosis: a preliminary study. *Human Immunol.*, 2012, **73**, 31–37.
128. Rajaram, M. V. *et al.*, *Mycobacterium tuberculosis* lipomannan blocks TNF biosynthesis by regulating macrophage MAPK-activated protein kinase 2 (MK2) and microRNA miR-125b. *Proc. Natl. Acad. Sci. USA*, 2011, **108**, 17048–17413.
129. Kumar, R. *et al.*, Identification of a novel role of ESAT-6-dependent miR-155 induction during infection of macrophages with *Mycobacterium tuberculosis*. *Cell. Microbiol*., 2012, **14**, 1620–1631.
130. Singh, Y. *et al.*, *Mycobacterium tuberculosis* controls microRNA-99b (miR-99b) expression in infected murine dendritic cells to modulate host immunity. *J. Biol. Chem*., 2013, **288**, 5056–5061.
131. Mestas, J. and Hughes, C. C., Of mice and not men: NOD2 control of mycobacteria in human macrophages 417 differences between mouse and human immunology. *J Immunol*., 2004, **172**, 2731–2738.
132. Gandotra, S., Jang, S., Murray, P. J., Salgame, P. and Ehrt, S., Nucleotide-binding oligomerization domain protein 2-deficient mice control infection with *Mycobacterium tuberculosis*. *Infect Immun*., 2007, **75**, 5127–5134.

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