Chapter 6

Common Strategies, Different Mechanisms to Infect the Host: *Anaplasma* and *Mycobacterium*

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Abstract

Intracellular bacteria such as *Anaplasma* spp. and *Mycobacterium* spp. pose a risk to human and animal populations worldwide. The main function of immune response cells is to eliminate invading pathogens. However, pathogens can deregulate host cell function and turn defense cells into suitable hosts. Intracellular bacterial have a smaller genome, compared to the host cell, thus requiring efficient mechanisms for survival and persistence within the host by inducing sustained changes in cell function and immune response. Bacterial epigenetic regulation of host cell gene transcription appears to be a general mechanism that enhances pathogen survival while altering host cell function and facilitating infection. *Anaplasma phagocytophilum* leads to modified host cell gene transcription and phenotype by epigenetically altering host chromatin. Mycobacterial infection of human cells also results in host gene silencing using a mechanism that involves HDAC complex formation and histone deacetylation. Membrane proteins are essential for cell invasion in both pathogens, and can regulate and protect the pathogen against the host response. Understanding the mechanisms employed by these bacteria to infect the host could contribute to develop effective interventions for the control of tuberculosis and anaplasmosis. This review focuses on the common strategies employed by two zoonotic pathogens, *Anaplasma* and *Mycobacterium* spp., highlighting also the different mechanisms used to infect host cells.

Keywords: *Anaplasma*, *Mycobacteria*, immunology, infection, tuberculosis

1. Introduction

Ticks and tick-borne diseases represent a growing problem for human and animal health worldwide whereas tuberculosis continues to be a global burden in both human and animal populations [1, 2]. Pathogenic organisms have evolved host mimicking properties

and manipulate host responses for their own survival and propagation. To successfully establish and maintain a bacterial infection, the pathogens subvert the host cells defense response to survive, proliferate, and persist within the infected cell. To evade host defense systems, bacterial pathogens produce a variety of virulence factors that stimulate bacterial adherence and invasion and subvert host cell signaling cascades that regulate intracellular microbial survival and trafficking. Some of these mechanisms are mediated by factors released by the bacteria, whereas others rely on hijacking host components to prevent the production of an effective immune response thus promoting their survival within the host cell [2, 3]. Intracellular bacteria from *Anaplasma* and *Mycobacterium* genera produce similar genes expression patterns in infected ruminants [4]. Pathogen and host-specific differences could contribute to disease diagnosis and treatment of tuberculosis and anaplasmosis in ruminants.

In this review, we provide an overview of some of the mechanisms employed by *Anaplasma* and *Mycobacterium* to infect the host cell and the impact on their pathogenesis.

2. *Anaplasma phagocytophilum*, an intracellular bacterium with unusual tropism

The emergence of tick-borne pathogens has been promoted by the exploitation of environmental resources and the increase in human outdoor activities, allowing the contact with tick vectors normally present in the field [5]. *Anaplasma phagocytophilum* is an obligate intracellular rickettsial pathogen transmitted mainly by *Ixodes* spp. ticks causing human granulocytic anaplasmosis (HGA), equine, and canine granulocytic anaplasmosis, and tick-borne fever (TBF) in ruminants [6]. In the vertebrate host, *A. phagocytophilum* infects neutrophils where the pathogen multiplies within a parasitophorous vacuole or morula in the cytoplasm of tick and vertebrate host cells [7, 8]. These gram-negative bacteria are grouped within the family Anaplasmataceae [3]. Complications and fatality are rare but more common in the elderly, the immunocompromised, or if proper diagnosis and/or antibiotic therapy are delayed. Fatalities are usually not directly attributed to the infection itself; pathological findings suggest defects in host defense and the presence of secondary infections [9]. However, the severity of illness and fatality rates could also be due to underlying immunosuppression.

Anaplasma is a highly antigenically variant bacterial pathogen that displays a diversity of mechanisms to create the structural and antigenic variation necessary to escape the immune response and allows long-term persistence in the host thus being able to act as a reservoir for transmission. *A. phagocytophilum* strategies to infect vertebrate host cells include, among others, remodeling of the cytoskeleton, inhibition of cell apoptosis, manipulation of the immune response and modification of cell epigenetics and metabolism [10]. Hosts respond to infection by activating alternative pathways to regulate cell apoptosis, immunity, metabolism and stress response mediated by heat-shock proteins (Hsps) [1]. Unlike other bacteria, *A. phagocytophilum* is aflagellated and does not have a type III secretion system (T3SS) [11, 12].

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Pathogens subvert cellular immune response to favor infection and multiplication. Host cell transcriptome and proteome studies have demonstrated an effect of *A. phagocytophilum* infection on the inhibition of cell innate immunity [13–15]. They employ a variety of mechanisms to create the structural and antigenic variation needed to subvert the host immune system and long-term persistence [3]. *A. phagocytophilum* also employs a type IV secretion system (T4SS) to deliver proteins or DNA into eukaryotic cells [16]. It also inhibits host cell apoptosis to allow the bacteria sufficient time to develop morulae [17].

Adaptation to a life in eukaryotic cells and transmission between hosts has been assisted by the deletion of many genes that are present in the genomes of free-living bacteria, including genes required for the biosynthesis of lipopolysaccharide and peptidoglycan that are involved in the activation of host leukocytes [18].

P44 (also known as MSP2) is a highly variable immunodominant surface protein that facilitates adherence to granulocytes [19]. The genome of *Anaplasma* consists of more than 100 *msp2(p44)* paralogs [20]. Antibodies specific to P44 inhibit *A. phagocytophilum* infection in mice and HL-60 cells, which suggests that antigenic variation of P44 proteins may help *A. phagocytophilum* to escape host immune surveillance [3]. Some *Anaplasma* strains are naturally persistent in lambs and can be used to analyze the mechanisms of persistence in the vertebrate host. Variation of the outer membrane protein MSP2(P44) is believed to play a key role in persistence of the organism [21].

A. phagocytophilum can avoid killing by innate immunity but it also induces some innate immune responses, such as the production of IFN-γ, that contribute to tissue injury and disease [22]. Signal transducer and activator of transcription 1 (Stat1) is important in host innate and adaptive immune responses to intracellular pathogens, including intracellular bacteria [23]. It mediates most of the biological functions of both type I interferon (IFNα/β) and type II IFN (IFNγ). *A. phagocytophilum* infection-induced IFNγ signaling leads to phosphorylation of Stat1 in mice and is critical for the generation of protection [24]. Experimental infections with mice have demonstrated that the absence of Stat1 converts the subclinical infection to a severe one [22] suggesting that Stat1 plays an important role in controlling the response to bacterial infections. Stat1 also participates in the IFN-γ signaling of mycobacterial immunity. IFN-γ signaling provides positive feedback to both macrophages and CD4+ T-cells, which amplifies the Th1 response [25]. Suppressor of cytokine signaling (SOCS) expression has been implicated in intracellular survival of *A. phagocytophilum* in neutrophils where expression of IFN-γ receptor alpha-chain CD119 is diminished leading to reduced Stat1 dimerization and signaling [26].

In neutrophils, the genes most downregulated in response to *A. phagocytophilum* infection include those coding for proteins involved in bacterial killing such as myeloperoxidase, transferrin, bactericidal/permeability-increasing protein and cell protection (mucin 12). Immune-system-related genes encoding interferons, cytokines, chemokines, and their receptors are upregulated in response to infection [13–15]. This suggests that pathogens have developed mechanisms to subvert the innate immune protective mechanisms in vertebrate hosts. However, some species can activate innate immune protective mechanisms to control

infection and appear to play a minor role as reservoir hosts for the pathogen [27]. For instance, pigs naturally and experimentally infected with *A. phagocytophilum* control bacterial infection through activation of innate immune responses, phagocytosis, and autophagy [28] resulting in low infection levels or infection clearance.

A. phagocytophilum, a pathogen lacking the T3SS and flagellin, activates the NLRC4 inflammasome (a component of the innate immune system) and secretion of IL-1β [29]. IL-18 release mediated by the NLRC4 inflammasome regulates IFN-γ production by $CD4^+$ T cells upon *A. phagocytophilum* infection [30]. The receptor-interacting serine/threonine-protein kinase 2 (RIPK2) appears to be a major regulator of the immune response against *A. phagocytophilum*. *Ripk2*−/− immune cells exhibit a defect in activation for the nuclear factor (NF)-κB and the NLRC4 inflammasome pathways [29]. Furthermore, experimental mice lacking *COX2* (*cyclo-oxygenase 2*) are more susceptible to *A. phagocytophilum*, they do not secrete IL-18 and exhibit splenomegaly and damage to the splenic architecture [29].

A. phagocytophilum transiently infects bone-marrow derived macrophages (BMDMs) [31] and clinical features in animal models and infected patients suggest classical macrophage activation [32]. Deep sequencing analysis of experimentally infected macrophages indicated that the transcription of genes that encode for phospholipase A2 (*pla2g12a*, *pla2g5* and *pla2g2e*), *COX2* and *PGE* synthase (ptges) was increased upon *A. phagocytophilum* infection [29].

A. phagocytophilum use heat shock proteins (Hsps) for infection of vertebrate host cells [33, 34]. Host cells can also activate Hsps in response to infection [35–37]. The mammalian immune response against pathogen Hsps to control infection may trigger a detrimental autoimmune response to host Hsps [35, 36, 38]. However, recent evidence suggests that hosts may benefit from induction of Hsps in response to pathogen infection [1]. A mutant strain of *Mycobacterium tuberculosis*, that constitutively over produced Hsp70 proteins, was fully virulent in the initial stage of infection, but its survival was reduced in the chronic phase. This suggests that induction of microbial genes encoding Hsps might provide a novel strategy to boost the immune response of individuals with latent infections [39].

How *A. phagocytophilum* interacts with the mammalian immune system is still unclear. Both T and B cells have been shown to play important roles in the control and clearance of *A. phagocytophilum* [40, 41]. CD4+ T cells and T-helper 1 (Th1) play a key role in the immune response to the infection of *A. phagocytophilum* [30, 42]. IFNγ, IL-12, and IL-18 also play important roles in the early clearance of *A. phagocytophilum* [30, 43]. Well-known anti-bacterial innate immune detection system such as TLR2, TLR4, and their adaptor MyD88 appear to play no role in the immune response to *A. phagocytophilum* infection [41]. Some studies suggest that signaling through the Nod Like Receptor (NLR) family member IPAF (NLRC4), its adaptor ASC, and Caspase-1 is critical for the control of *A. phagocytophilum* infection during the early phase of infection [30].

Rip2 has been previously shown to play an essential role in the immunity against various intracellular pathogens including *Mycobacterium tuberculosis* [44]. Rip2 also plays an

important role in the control of *A. phagocytophilum* infection [44]. *A. phagocytophilum* infection upregulates Rip2, the adaptor molecule of the cytoplasmic pattern recognition receptor Nod1 and 2 in immune cells [45]. Following peptidoglycan detection, Nod1/Nod2 recruit and associate with the adaptor protein Rip2, triggering proinflammatory signaling pathways via NF-κB and the mitogen-activated protein (MAP) kinases p38, JNK, and ERK [46]. IL-8, a major inflammatory chemokine, is heavily induced during *A. phagocytophilum* infection in humans [47]. Trafficking of neutrophils to the sites of infection is induced by this chemokine and Rip2, which appears to play an important role in neutrophil recruitment *in vivo* [48]. IFN-γ, another inflammatory cytokine, plays a major role in the immune pathology and early clearance of *A. phagocytophilum* infection [43]. It is also known that an adaptive CD4+ T cell mediated response is critical for the complete clearance of *A. phagocytophilum* infection [42]. Previous reports have shown the importance of natural killer (NK) cells, NKT cells [49] and CD4 + T cells [42] in the IFNγ production and host defense to *A. phagocytophilum* infection (**Figure 1**).

Using oligonucleotide array technology [50], it was observed that genes involved in the immune response were modulated in neutrophils infected with *A. phagocytophilum*. Among the genes that were most upregulated in the early transcriptional response to infection in neutrophils were cytokines, chemokines, and their receptors (e.g., *CCL3*, *CCL3L3*, *IL-8*, *IL-1β*, and *CXCR4*).

The major adipocyte lipid droplet-associated phosphoprotein perilipin (PLIN) is upregulated in HL60 infected cells. Both protein and mRNA levels were higher in infected cells and the over expression of *PLIN* was parallel with bacterial infection levels [51]. Furthermore, *PLIN* knockdown resulted in a reduction of *A. phagocytophilum* infection in HL60 cells, suggesting the bacteria modulate host lipid metabolism to infect and multiply in the host cell [51].

In THP-1 cells, *A, phagocytophilum* infection displays an upregulation of histone deacetylates 1 and 2 (*HDAC1* and *HDAC2)*, while protein levels exhibit a similar kinetic pattern for both HDACs. Moreover, pharmacological inhibition of HDAC and *HDAC1* silencing reduced the level of bacterial infection in THP-1 cells [52]. Mycobacterial infection of THP-1 cells specifically inhibits HLA-DR gene expression by a pathway involving HDAC complex formation at the HLA-DR promoter, resulting in histone deacetylation and gene silencing [53].

Proteins secreted by bacteria are involved in many important tasks and they account for many of the virulence factors of pathogens. Outer membrane protein A (OmpA), also known as peptidoglycan-associated lipoprotein, is conserved among most Gram-negative bacteria and interacts with peptidoglycan to maintain outer membrane integrity [54]. The expression of *OmpA* increases in the early stages of infection. OmpA is presented on the pathogen's surface and is upregulated during invasion of HL-60 cells. Sera from HGA patients and experimentally infected mice recognize recombinant OmpA. Pretreatment of *A. phagocytophilum* organisms with OmpA antiserum reduces their ability to infect HL-60 cells [54].

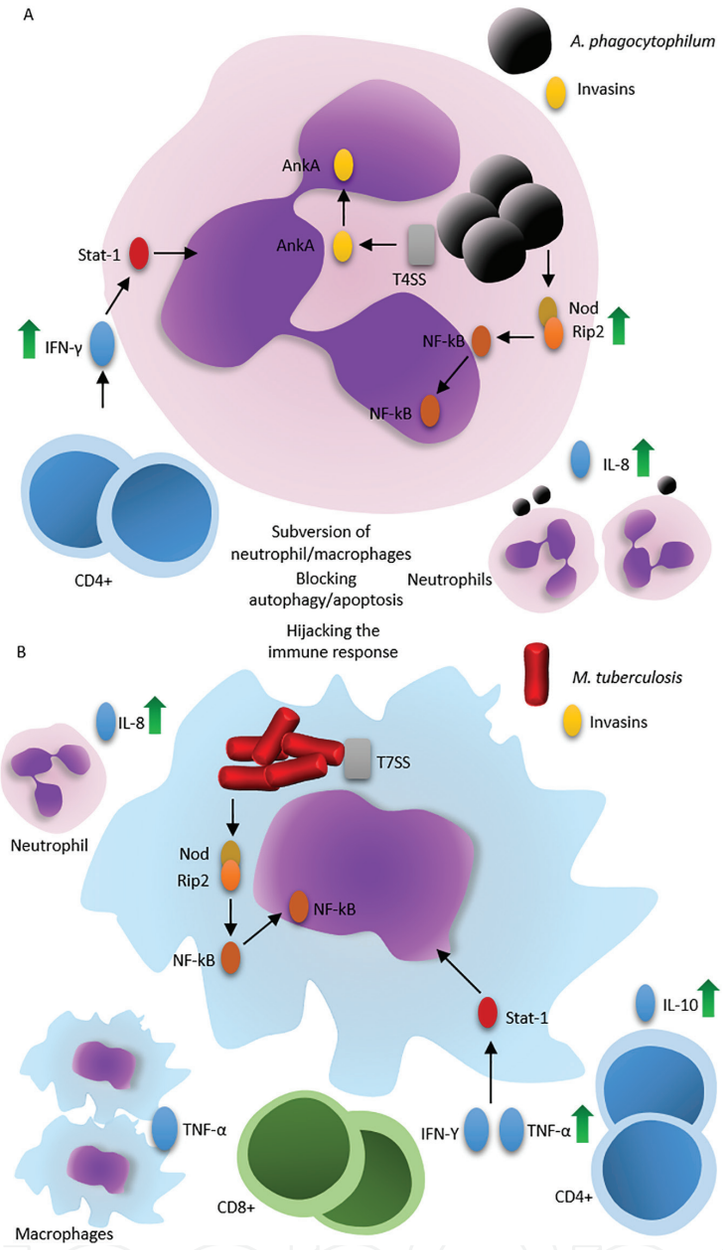

Figure 1. *A. phagocytophilum* and *M. tuberculosis* employ common strategies but different mechanisms to infect host cells: Nod proteins activate NF-κB through the serine–threonine kinase Rip2. NF-κB is translocated to the nucleus and stimulates cytokine expression. Secretion of IL-8 stimulates neutrophil and T cell migration. Stat1 participates in the IFN-γ signaling of intracellular bacteria. (A). Neutrophil infected with *A. phagocytophilum*: IFN-γ contributes to tissue injury and disease. AnkA is secreted by the bacteria and translocates to the nucleus of infected cells regulating host cell transcription facilitating intracellular bacterial survival and growth. (B). Macrophage infected with *M. tuberculosis*: IFN-γ activates macrophage phagocytosis killing intracellular bacteria. TNF-α attracts macrophages and lymphocytes at the site of infection and promotes granuloma formation thus resulting in limited antigen presentation.

A. phagocytophilum uses surface proteins invasins OmpA, Asp14, and AipA to bind and infect mammalian hosts [55, 56]. OmpA interacts with α1,3-fucose, which is critical for the bacteria to bind host cell surfaces and invade them. OmpA, Asp14, and AipA play essential roles in the *A. phagocytophilum* lifecycle [54, 55, 57]. Directing the immune response to their binding domains could enhance protective efficacy. It has been observed that an antibody cocktail

specific for the OmpA, Asp14, and AipA binding domains blocked *A. phagocytophilum* infection of host cells [56]. This finding could help the development of an anti-multi-invasin vaccine to protect against human and veterinary granulocytic anaplasmosis or even against other obligate intracellular pathogens such as *Mycobacterium* spp. since they also use multiple invasins to enter host cells [58].

MSP1a and MSP1b from *Anaplasma marginale* have been shown to be adhesins for host cells [59]. Studies on the immunogenicity of recombinant BCG expressing the MSP1a antigen suggested that the immune responses were influenced by the level of antigen expression [60]. These results indicated that recombinant *M. bovis* BCG expressing MSP1a could be used to test for protective antibody production for the control of anaplasmosis.

The *A. phagocytophilum* genome encodes a type four secretion system (T4SS) that may facilitate intracellular survival by translocation of virulence factors that appear to be important for the manipulation of the host cell. Ankirin A (AnkA) is a translocated virulence factor that is tyrosine-phosphorylated by host cell kinases upon translocation into the host cell early during infection [16, 61].

Anaplasma translocation substrate 1 (Ats-1) protein belongs to T4SS of *Anaplasma*, which is secreted and localizes into the mitochondria of human neutrophils and HL60 cells. Ats-1 translocates to the host cell mitochondria matrix via the translocase of the outer mitochondrial membrane (TOM) complex. Transfection assays with RF/6A and yeast cells demonstrated that Ats-1 inhibits etoposide and Bax-induced apoptosis respectively [62] thus facilitating pathogen survival.

In mammalian cells, *A. phagocytophilum* activates extracellular signal-regulated kinase (Erk)1/2, a key protein of the MAP kinase pathway [50, 63]. AptA (*Anaplasma phagocytophilum* toxin A, formerly named APH_0233) stimulates Erk1/2 phosphorylation in HL60 and HEK293 cells [64]. Furthermore, AptA interacts with vimentin, and gene silencing and inhibitory enzymatic assays in HL60 cells and neutrophils respectively, demonstrated that vimentin is necessary for Erk1/2 activation and *Anaplasma* infection [64].

Anaplasma inclusions have a double-lipid bilayer membrane, and induce autophagosome formation in the host cell. Also, beclin 1 and light chain 3 (LC3) proteins that play a central role in autophagy are colocalized bacterial replicative inclusions. Furthermore, assays of inhibition and induction of this catabolic mechanism in HL60 infected cells demonstrated that autophagy benefits infection, rather than elimination [65]. Ref. [66] described that induction of autophagy in host cells is mediated trough beclin 1 (Becn1) that binds Ats-1 to supply nutrients for pathogen growth. Additionally, gene silencing of *Becn1* inhibits infection in mammalian cells [66].

3. The *Mycobacterium tuberculosis* complex, a global burden for human and animal health

Macrophages play a central role in the first line of defense against pathogenic microorganisms, however, they are also the key target cells for mycobacteria. The bacteria can live and

replicate inside the macrophages, thus evading the innate immune response against infection of the host through immunosuppression and immune evasion [53]. Co-evolution of *M. tuberculosis* with its hosts has enabled the pathogen to develop host immune evasion strategies that interfere with both innate and adaptive immunity. These include the manipulation of their phagosome within host macrophages, the avoidance of pattern recognition receptors, the modulation of host cytokine production, and the manipulation of antigen presentation to prevent or alter the quality of T-cell responses [67]. Other mechanisms include interference with phagosomal acidification and trafficking, blocking autophagy and apoptosis-mediated killing, perturbing calcium signaling, and inhibiting the inflammasome activation in order to modulate the host immune responses. Manipulation of these host pathways is achieved by bacterial components such as cell wall lipids, serine threonine kinases, phosphatases and proteases, and using specialized secretion systems.

The outcome of infection with *Mycobacterium tuberculosis* depends on the ability of the immune response to clear or contain the infection. When this fails, the bacterium replicates, disseminates within the host, and elicits a pathologic inflammatory response. Individuals infected with *M. tuberculosis* develop mainly CD4 T cell responses to protein components of *M. tuberculosis*, an immune response that can persist for years. Infections with mycobacteria are characterized by their chronic course and, even with an adequate immune response, they can persist inside macrophages. Progression to active disease is possible even decades after exposure [68] and is typically triggered by immune compromise. Although the bacteria are concealed within the infected macrophage, B cells and antibodies also play a role on the immune response to intracellular bacteria and are likely to be important in the control of *M. tuberculosis* [69]. In addition, B cells are a major cellular component of the granuloma (an important mechanism of host defense against tuberculosis) where they can process and present antigen to T cells, secrete antibodies, and modulate inflammation through the production of IL-10 [70]. *In vitro* human B cells have been shown to ingest mycobacteria, produce IgM, and upregulate the expression of the costimulatory molecules *CD80* and *CD86* and the chemokine *CXCL10* [71]. The human CD4 T cell response exhibits Th1-response characteristics [72].

Mycobacteria have a distinct secretion system, named type VII (T7SS or ESX), which is associated with virulence and pathogenesis, including growth in macrophages [73] and antigen presentation. This system is encoded by a locus that is deleted in attenuated strains of *M. bovis* (bacille Calmette–Guérin (BCG) strains), which are used to vaccinate against tuberculosis [74].

IL-8 is a chemokine with a significant role in regulating leukocyte influx in TB. *In vivo* studies have shown that pre-treatment with anti-IL-8 alone inhibits mycobacterial granuloma formation [75]. IL-8 is involved in attracting neutrophils and T cells and in monocyte recruitment [76]. Targeting IL-8 secretion during inflammation could be the subject for new therapeutic approaches [77].

Mycobacterial components can activate MAP kinase signaling cascades but this activation varies depending on the species of *Mycobacterium*. For instance, it appears to be diminished in macrophages infected with pathogenic strains of *M. avium* [78].

IFN-γ is a Th1 cytokine that plays a vital role in the protective immune response against *M. tuberculosis* infection [2]. In cattle, IFN-γ is produced predominately by activated CD4 T cells following presentation of *M. bovis* antigens on the surface of antigen presenting cells (APCs) [79]. IL-10 is released following phagocytosis of pathogenic mycobacteria [80] and has been shown to inhibit the pro-inflammatory cytokine response through down regulation of IL-12 and IFN-γ [81, 82]. Increased IL-10 levels appear to correlate with progression of infection in a bovine tuberculosis model [83] (**Figure 1**).

Nod proteins and their adaptor molecule Rip2 are key components of a family of cytosolic innate immune pattern recognition receptors [84]. Nod2 triggers cytokine production by dendritic cells in response to live *M. tuberculosis*, but is not essential to control infection [85].

M. tuberculosis can use the TLR2 pathway to modify the host environment [86]. The adaptor molecule myeloid differentiation factor-88 (MyD88) appears to play a significant role in the pathogenesis of *Mycobacterium*. Mice lacking MyD88 are highly susceptible to *M. tuberculosis* infection, with a mean time to death of approximately 42 days.

Glycolipids are one of the most common cell surface components of macrophages and dendritic cells. They interact with intracellular bacteria, estimulating the host immune response [87]. LprG (Rv1411c), a cell membrane lipoprotein essential for *M. tuberculosis* virulence, binds to the acyl groups of lipoglycan [88]. In murine macrophage cells (RAW 264.7), LprG is essential for macrophage entry and inhibition of phagosome—lysosome fusion. Also, it has been described that LprG has a significant role in the production of lipoglycan lipoarabinomannan (LAM), one of the major cell surface components of *M. tuberculosis* [87, 89]. LprI is another lipoprotein used by *M. tuberculosis* to bind and inhibit the lytic activity of lysosomes [90].

Mycolic acids are major components of the outer membrane of *M. tuberculosis*. HadC (Rv0637) contributes to mycolic acids biosynthesis and its mutation or silencing is directly related to the loss of *M. tuberculosis* virulence [91].

M. tuberculosis encodes the serine protease Rv2224c (Hip1) that is present on the cellular membrane [92]. In primary macrophages, silencing of *Hip1* notably decreased mycobacterial growth compared to the wild type bacteria. Moreover, levels of cytokines (TNF-α, IL-1β, IL-6) were increased in macrophages infected with wild-type *M. tuberculosis* compared to the mutant *Hip1 M. tuberculosis* [93]. The stress-induced protein GroEL2 is a substrate for Hip1 [92]. Hip1 appears to limits dendritic cells cytokine secretion and through under modulation of CD40 and CD86, it could affect dendritic cell maturation, and decrease antigen presentation to CD4 T cells [94].

Transcriptional assays have shown that *M. tuberculosis* infection of human monocytes activate the MAPK pathway to promote over expression of IL-23, that is involved in the modulation of Th1/Th17 cells [95]. In addition, it has been reported that the bacteria may suppress the differentiation of monocytes into dendritic cells through the release of IL-10 [96].

Intracellular bacteria can manipulate host gene expression through epigenetic modifications to help infection and survival inside the host cell. Ghorpade et al. [97] described that *M. bovis* bacillus Calmette-Guérin (BCG) modify epigenetically nitric oxide and KLF4 to restrain the class II

transactivator (CIITA) and MHC-II expression thereby eluding immune surveillance. Evidence supports that *M. tuberculosis* infection in THP1 cells induces overexpression of *HDAC1*, which is implicated in the downregulation of IL-12B that plays a key role in the Th1 response [98].

Lsr2 is a *M. tuberculosis* protein with histone-like features, including the ability to regulate a variety of transcriptional responses in mycobacteria. Lsr2 protects mycobacteria against reactive oxygen intermediates (ROI) *in vitro* and during macrophage infection shielding bacterial DNA by binding to it [99] suggesting it could be a good candidate as a drug target.

4. Conclusions

Intracellular bacteria such as *Anaplasm*a and *Mycobacterium* use similar mechanisms to infect vertebrate host cells. These strategies include manipulation of the immune response, subversion of phagocyte cells and the use of proteins for infection and manipulation of host gene expression. Nevertheless, different pathogens have evolved specific strategies when infecting their hosts. Abundantly expressed proteins are often the primary targets of research, however, less prominently expressed antigens may have equally good or even superior vaccine potential. Research into the antigen catalog available for immune recognition of infected cells could provide new directions for antigen discovery and vaccine development.

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