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INTERACTION OF ANTIGEN PRESENTATION AND ANTIBACTERIAL IMMUNITY

Abstract. *Macrophages and dendritic cells are phagocytic antigen-presenting cells involved in the immune response to bacteria, linking the Innate and adaptive responses during bacterial infection. Antigens from bacteria are processed for presentation on MHC class II and MHG class I to stimulate* $CD4^+$ *and* $CD8^+$ *T cells, respectively. Many bacterial pathogens have developed strategies to interfere with the host's capacity to mount an immune response by interfering with antigen processing pathways or otherwise modulating the adaptive immune response. Understanding the mechanisms bacteria use to avoid immune recognition may facilitate the development of new strategies to eradicate pathogens from infected hosts.*

As discussed in this review, bacteria have different mechanisms for modulating Ag presentation and T cell activation. More information from infection models will help us to better understand the role of MΦs and DCs in different stages of the immune response to bacteria. In addition, there remains much to learn about how bacterial modulation of APC function influences the immune response in vivo.

Keywords: *immunity, macrophages, bacteria, T-cells, antigen.*

Introduction. Macrophages (MΦs) and immature dendritic cells (DCs) are phagocytic cells that not only internalize and degrade bacteria but also present bacterial peptides on MHC class I (MHC-I) and class II (MHC-II) molecules for T cell recognition. These phagocytic antigen-presenting cells (APCs) are located in peripheral tissues and are poised to interact with bacterial invaders. They are thus important in the interface between innate and adaptive immunity to bacterial infections.

MHC-II antigen (Ag) processing and presentation is largely restricted to specialized APCs, such as MΦs, DCs and B cells. Although both MΦs and DCs can process and present bacterial antigens, differences in their physiology and function suggest they have complementary roles in the immune response to bacteria. For example, immature DCs, such as those residing in peripheral tissues, have significant surface expression of MHC-II, whereas resting MΦs do not. Although the expression of MHC and co-stimulatory molecules (e.g. CD86) increases on both MΦs and DCs upon bacterial and/or inflammatory stimuli, the levels of cell surface MHC-II and CD86 are higher on bone marrow-derived DCs in comparison to the level of expression on MΦs when exposed to Salmonella [1, 2]. Moreover, the migratory

capacity of DCs from tissues into draining lymphoid tissue is well documented [3], but, MΦs do not appear to have this capacity. Finally, the ability of mature DCs to stimulate naive T cells is far superior to that of monocytes/MΦs [4]. These observations indicate that DCs are the most important APCs for priming T cell responses. However, MΦs have important roles in presenting microbial Ags to effector T cells to elicit cytokine production and other T cell effector functions at sites of infection.

Antigen processing pathways. For the adaptive immune system, Ag processing and presentation plays a central role in the induction of specific immune responses. For protein Ags, proteolytic processing generates short peptides that bind to MHC molecules. Peptide-MHC complexes are presented to T cells to generate responses that mediate and/or regulate cellular immunity and B cell responses. Presentation of protein Ag to T cells is mediated by two classes of MHC molecules, MHC-I and MHC-II, which use distinct Ag processing pathways.

Exogenous Ags, both soluble and particulate, are internalized by APCs and catabolized by vacuolar proteases in endocytic or phagocytic organelles to generate peptides. Newly synthesized MHC-II molecules' associate with the invariant chain in the endoplasmic reticulum (ER) and are transported via the trans-Golgi network to the endocytic pathway. Invariant chain is degraded by endosomal/lysosomal proteases, leaving the MHC-II molecules associated with a fragment of the invariant chain called the class-II associated invariant chain peptide (CLIP), which occupies the peptide-binding groove. Another MHC-encoded molecule, H2-DM (human leukocyte antigen [HLA]-DM in humans) then catalyzes the replacement of CLIP with an antigenic peptide derived from internalized, degraded Ag. MHC-II molecules can also bind peptides derived from proteins associated with the plasma membrane or membranes of vacuolar compartments.

In contrast to MHC-II molecules, MHC-I molecules mainly bind peptides derived from cytosolic (endogenous) Ags, for example, tumor Ags, viral proteins, self proteins and Ags derived from bacteria or parasites that escape from the phagosome to the cytosol. Here, Ags are catabolized by proteasomes to generate peptides that are transported to the ER via the transporter associated with Ag processing (TAP). Peptides bind to MHC-I molecules docked to TAP via tapasin, and peptide-MHC-I molecules exit the ER to the cell surface for presentation to $CD8^+$ T cells.

Cells internalize solutes and particles via pinocytosis, receptor-mediated endocytosis and phagocytosis. Bacteria are phagocytosed by specialized phagocytic cells (MΦs, neutrophils and DCs) mediated by surface receptor molecules described below. Cross-linking of these receptors by ligands initiates cytoskeletal rearrangements and internalization of bacteria into the phagosome. Although it has long been thought that the phagosome is largely derived from the plasma membrane, a recent report from Desjardins and co-workers [5] suggests that the ER is a major reservoir of membrane for phagosome formation. Internalized bacteria reside in phagosomes and are primarily presented by MHC-II molecules. However, even Ags from microbes that do not escape from vacuolar compartments can be presented by MHC-I molecules by alternative MHC-I presentation pathways [6, 7]. There is now

an extensive body of evidence that establishes the ability of MHC-I molecules to present exogenous particulate Ags, and several models exist to explain these observations. Some models indicate that presentation of exogenous Ags on MHC-I occurs via vacuolar pathways, whereby peptides derived from exogenous Ags bind to MHC-I within post-Golgi vacuolar compartments or on the cell surface. By contrast, other models indicate cytosolic mechanisms of alternative processing, whereby whole organisms or Ags escape from vacuolar compartments into the cytosol, undergo cytosolic processing and bind MHC-I in the ER, as in the conventional MHC-I presentation pathway.

In addition to the recognition of peptides, T cells can recognize foreign (microbe)-derived and self-derived lipids bound to CD 1 molecules. The CD1 antigen presentation pathway has been reviewed elsewhere [8] and will not be discussed here. This review summarizes strategies used by bacteria to avoid recognition by the immune system, such as modulating the capacity of APCs to present bacterial Ags on classical MHC molecules, as well as other mechanisms that dampen the T cell response. The role of DCs and M$s during the response to bacterial infection will also be discussed on the basis of data from in vivo infection models.

Receptor-ligand interactions that influence the immune response to bacteria. The immune response to microbial pathogens relies on both innate and adaptive components. Innate immune responses utilize a variety of receptors that recognize conserved motifs on pathogens that are not found in higher eukaryotes. These motifs, referred to as pathogen-associated molecular patterns (PAMPs), bind to their cognate pattern-recognition receptors (PRRs) on host cells, allowing the host to sense the presence of microbes. A wide variety of PAMPs have been identified and include bacterial cell wall components (e.g. LPS, peptidoglycans and teichoic acids), bacterial DNA fragments (unmethylated CpG motifs), formylated peptides, and mannans in yeast cell wall. Binding of PAMPs to some PRRs, such as mannose and scavenger receptors, leads to internalization of the antigen. Pathogens are also opsonized by complement and immunoglobulins and internalized via complement and Fc receptors, respectively. Binding of PAMPs to other PRRs, for example, Toll-like receptors (TLRs), leads to signaling for the activation of innate immunity and mechanisms that influence adaptive immunity [9]. This signaling induces the expression of co-stimulatory molecules and release of cytokines that instruct the adaptive immune response.

Bacterial modulation of MHC-II antigen processing and presentation. It has long been appreciated that internalized bacteria reside in phagosomes that fuse with both endosomes and lysosomes and acquire proteases that mediate the degradation of bacterial Ags. However, it has remained unclear whether phagosomes actually mediate the formation of peptide-MHC-II complexes or just provide antigen fragments for additional processing and binding to MHC-II molecules in endocytic compartments. Recent studies have examined the processing of Ag85 of Mycobacterium tuberculosis by MΦs. M. tuberculosis phagosomes contain MHC-II and H2-DM, degrade phagosome-associated Ags and mediate the formation of Ag8S peptide-MHC-II complexes [10], as has been demonstrated with model particulate

Ags [11]. In addition, phagosomes containing particulate antigens acquire both newly synthesized and recycling MHC-II molecules, but utilize newly synthesized MHC-II molecules for phagocytic antigen processing [12].

Bacteria can modulate the MHC-II pathway by a variety of mechanisms that include altering phagosome-lysosome fusion or biosynthesis, intracellular trafficking and surface expression of MHC-II (Table 1; [10, 13-17, 18,19-21]). Certain bacteria, such as mycobacteria, *Chlamydia* and *Legionella*, inhibit fusion between phagosomes and lysosomes (i.e. they inhibit “phagosome maturation”). Inhibition of phagosome maturation by live *M. tuberculosis* [20, 21] may inhibit MHC-II processing of M. tuberculosis antigens [10]. Mycobacteria also prevent acidification of their phagosomes by excluding H^+-ATPase [22] and they alter phagosome protein composition to promote their survival [15]. These mechanisms may influence the degradation of bacteria and prevent the generation of bacterial peptide-MHC-II complexes and T cell responses to bacterial Ags.

Salmonella typhimurium remains enclosed in spacious phagosomes following infection of mouse MΦs. Maintenance of these spacious phagosomes correlates with survival and pathogenicity of *Salmonella* [23-25] and appears to depend on the expression of genes in the *pho*P regulatory locus. *Salmonella* that constitutively express *pho*P are processed very inefficiently by MΦs for MHC-II presentation [26]. In addition, *pro*P-regulated gene expression influences processing of antigen phagocytosed independently of the bacteria, demonstrating that *pro*P-regulated gene products decrease the processing capacity of infected MΦs [26]. An influence of *pho*P on MHC-II presentation of *Salmonella* antigens by immature DCs is also apparent when antigen-specific $CD4^+$ T cell stimulation is quantitated shortly after exposure to the bacteria [1]. However, this influence of *pho*P is not apparent when T cell stimulation is quantitated after longer, processing times [1, 27], and the *pho*P locus does not influence the capacity of immature DCs to process *Salmonella*, for MHC-I presentation [1].

Recent reports have shown that several types of bacteria, including mycobacteria, *Escherichia coli* and *Chlamydia*, can decrease MHC-II expression in infected cells, inhibiting Ag processing and presentation to support their survival (Table 1; [17, 18,19, 28, 29]). Inhibition of MHC-II expression and Ag processing by *M. tuberculosis* is mediated by the 19 kDa lipoprotein of *M. tuberculosis*, which signals via TLR2 [18]. Other studies with *M. tuberculosis* suggest that live bacilli may impair the transport of newly synthesized MHC-II through endocytic processing compartments, inhibiting the production of peptide-loaded MHC-II heterodimers without affecting MHC-II synthesis [14]. Phagocytosis of mycobacteria by THP-1, a human monocytic cell line, decreased cell surface MHC-II levels for 2-3 days [30]. MHC-II expression was also inhibited in *E.* coli infected THP-1 cells and human monocytes [28, 30].

Some studies have addressed the signaling and gene transcription mechanisms involved in inhibition of MHC-II expression and Ag processing by bacteria. Infection of human MΦs with *E. coli* decreased MHC-II expression and subsequent antigen presentation by down regulating transcription of the class II transcriptional activator,

GIITA [28]. Infection of MΦs with *M. tuberculosis* or exposure to the 19 kDa lipoprotein also decreases expression of CIITA, apparently by interfering with IFN-γ signaling and IFN-γ-dependent CIITA induction (RK Pai, M (Convery. TA Hamilton etal., unpublished data). Dalpke et al. [31] showed that, suppressor of cytokine signaling (SOCS)-l and -3 were induced by GpG DNA and suggested that CpG DNA-mediated inhibition of cytokine synthesis and IFN-γ-induced MHC-II expression was caused by SOCS-1, which is proposed to inhibit JAK-mediated phosphorylation of STAT-1 in some systems. However, induction of SOCS-1 may not be central to inhibition of MHC-II expression and Ag processing by PAMPs, as recent studies show that IFN-γ-induced phosphorylation of STAT-1 proceeds normally in MOs after treatment with CpG DNA and *M. tuberculosis* 19 kDa lipoprotein (contrary to the predicted effects of SOCS-1), and inhibition is still produced in SOCS-1 knockout MΦs (RK Pai, M Convery, TA Hamflton *et al.,* unpublished data). In addition Ting *et al.* [32] demonstrated that STAT-1 signaling is unaffected by whole *M. tuberculosis*. Another novel mechanism of MHC-II downregulation has been observed following the infection of host cells with *Chlamidia*. This bacterium suppresses MHC-II expression by secreting protease-like factors that degrade host transcription factors required for MHC expression [19, 33].

Certain toxins, including cholera toxin and the related heat-labile toxin of *E. coli*, impair MHC-II processing of bacterial Ags by MΦs. These toxins may interfere with MHC-II trafficking, as they do not effect the presentation of previously processed Ag [34, 35]. The enzymatically active suburms of these toxins have been linked with this inhibition [34, 35]. Recent evidence suggests that the β subunits of cholera and *E. coli* toxins may also contribute to impaired Ag processing by altering the progression of exogenous Ag along the endocytic processing pathway in the murine MΦ cell line J774.2, preventing or delaying efficient epitope presentation and T cell stimulation [36] Despite these inhibitory effects, cholera toxin and heat-labile toxin of *E. coli* are effective adjuvants. They also induce maturation of DCs [37]. Their divergent effects on different APCs or their ability to induce co-stimulatory or other accessory molecules [38] may override their inhibitory effects on MΦ Ag processing to promote T cell responses.

Bacterial modulation of the MHC-I presentation pathway. Similar to the inhibition of MHC-II expression described above, *Chlamidia* also downmodulates surface factors [33, 39]. However, other bacteria, including mycobacteria and E. coli, do not inhibit MHC-I expression by MΦs [14, 30]. For example, Tobian *et al.* (AAR Tobian, NS Potter, L Ramachandra et al., unpublished data) found that MHC-I expression was unchanged or slightly increased following infection of IFN-γ-activated bone marrow MΦs with M. tuberculosis or exposure to the M. tuberculosis 19 kDa lipoprotein (conditions that downregulate MHC-II expression; AAR Tobian, NS Potter, L Ramachandra *et al.,* unpublished data). Nonetheles, M. tuberculosis and the 19 kDa lipoprotein inhibit alternative MHC-I Ag processing, apparently by interfering with phagosome maturation and antigen proteolysis (AAR Tobian, NS Potter, L Ramachandra *et al.,* unpublished data).

Huang et al. [40] described a novel mechanism by which incubation of two HLA-B27 transfected cell lines (one derived from B lymphocytes and the other from the monocyte lineage) with invasive, but not noninvasive, *Salmonella* or *Yersinia* led to alternative splicing of the pre-mRNA of HLA-B27 and decreased MHC-I expression. This could result from misfolding and subsequent degradation of HLA-B27 molecules. Moreover, peripheral blood mononuclear cells infected with *Salmonella*, *Yersinia* or *Klebsiella* also downregulate cell surface expression of MHC-I, predominantly in patients with HLA-B27 genotype [41], apparently as a consequence of intracellular retention of MHC-I. Wuorela et al. [42] also demonstrate that infection of human monocytes with arrtritogenic *Yersinia enterocolitica* serotype O:3 reduced synthesis of HLA-B27 molecules. Thus, modulation of cell surface MHC expression, both MHC-I and MHC-II, is a means that several bacteria use to influence that presentation of bacterial antigens.

A few studies have examined alterations in the peptide repertoire bound to MHC-I following exposure to invasive bacteria. Invasion of HLA-B27 transfected HeLa cells by *S. typhimurium* increased transcription for the LMP2, LMP7, and MECL proteasome subunit genes, as well as the proteasomal activator PA28α and β genes, and increased expression of the LMP2 protein [43]. Modulation of LMP2 subunit expression and proteasome activity were accompanied by significant quantificative and qualitative changes in the peptide repertoire bound to HLA-B27. Wuorella *et al.* [42] observed alterations in the repertoire of peptides presented by the HLA-B27 molecules on human monocytes infected with *Y. enterocolitica* serotype O:3.

Inhibitory effects on *T* cell responses mediated by bacteria-induced cytokine production by antigen-presenting cells. Another mechanism used by some bacteria to interfere with host immune responses involves the triggering of APCs to produce cytokines with immunosuppressive activities (Table 1). For sample, *Mycobacterium-infected* MΦs produce IL-6, IL-10 and TGF-p [44-47], whereas *Y. enterocolitica* infection stimulates IL-10 production by MΦs [48]. These cytokines inhibit T cell responses by several mechanisms, including compromising the am gel presentation capacity of APCs. Moreover, Bordetella pertussis induces IL-10 production by infected DCs, and these cells direct the differentiation of native T cells into IL-10-producmg regulatory T cells [49]. *Yersinia* also impairs pro-inflammatory responses by interfering with nuclear factor (NF)-κB signaling [50]. Virulence factors of Yersinia pseudotuberculosis and Neisseria gonorrhoeae also impair lymphocyte activation [51, 52].

Activating effects of bacteria on macrophages and dendritic cells. Despite the mechanisms used by bacteria to dampen an immune response, bacteria also activate APCs to enhance their T cell stimulatory capacity. This is particularly true for DCs, where bacteria or bacterial components, such as LPS **or** CPG DNA, are well-known inducers of DC maturation [1, 53-56]. For example, several parameters of DCs that influence antigen presentation and T cell stimulation are influenced by maturation induced by bacteria or bacterial products [54, 55, 57, 58, 59, 60]. Gram-negative bacteria and LPS also increase the cell surface expression of MHC-I, MHC-

II, CD40 and CD86 on MΦs [2, 61], particularly in the presence of IFN-γ; however, long-term stimulation of MΦs with PAMPs leads to downregulation of MHC-II expression and Ag processing. For example, long-term stimulation with CpG DNA decreases MHC-II synthesis and Ag processing by MΦs [62], in contrast to the ability of CpG DNA to enhance DC maturation and Ag presentation [55, 56, 63, 64]. Thus, it is important to note that PAMPs can have varying effects on different APCs and at different time points in their action- on a particular APC.

The role of macrophages and dendritic cells during bacterial infection. Emerging data from in vivo studies are providing insight into the role of MΦs and DCs during bacterial infection. For example, murine infection models have shown that quantitative and in situ changes occur in both MΦs and DCs during bacterial infection [65-69], and also that DCs, MΦs and neutrophils harbor bacteria during infection [66, 68, 70]. Moreover, the examination of APCs from infected mice also showed that MΦs increase MHC-II expression during Salmonella infection, and MΦs from bacille Calmette-Guerin (BCG)-infected mice undergo other functional transitions to facilitate eradication of the bacteria [67, 69]. MΦs from Listeria-infected mice also increase MHC-II expression in addition to increasing co-stimulatory molecule expression, and can stimulate Listeria-specific $CD4^+$ T cell lines ex vivo, albeit less efficiently than DCs [71]. By contrast, a BCG infection model showed that DCs but not MΦs become activated shortly after infection and, likewise, DCs but not MΦs present bacterial antigens to $CD4^+$ T cells ex vivo [66]. DCs from Salmonella-infected mice can also stimulate antigen-specific $CD4^+$ and $CD8^+$ T cells *ex vivo*. [72]. Although the capacity of MΦs from Salmonella-infected mice to directly present bacterial antigens to T cells is not known, their depletion does not appear to influence the generation of Salmonella-specific $CD8^+$ T cells [73]. Moreover, a murine model whereby DCs can be deleted by administering diphtheria toxin has shown that DCs are critical to priming $CD8^+$ T cells to the intracellular bacterium *Listeria monocytogenes* [74].

Conclusions

DCs and MΦs appear to have complementary roles in anti-bacterial immunity. Although DCs are critical for priming naive $CD8^+$ T cells to intracellular pathogens [74], MΦs are probably important in presenting bacterial antigens to effector T cells at infected tissue sites, producing and eliciting cytokines, and controlling bacterial replication. However, further studies are required to understand the relative contributions of MΦs and DCs during different stages of the immune response with Respect to antigen presentation, cytokine production, and how bacterial immune evasion mechanisms alter the host/pathogen balance. Moreover, the relative contribution of direct presentation of bacterial antigens to T cells versus indirect (or cross-) presentation is an issue that remains to be answered. Although cross-presentation of bacterial antigens to $CD4^+$ and $CD8^+$ T cells has been shown to occur in vitro [71, 75], the contribution of cross-presentation of bacterial antigens in generating T cells during infection has not been directly assessed.

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