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Review

Histone Modifications and Chromatin Remodeling during Bacterial Infections

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The link between bacteria and host chromatin remodeling is an emerging topic. The exciting recent discoveries on bacterial impact on host epigenetics, as discussed in this Review, highlight yet another strategy used by bacterial pathogens to interfere with key cellular processes. The study of how pathogens provoke host chromatin changes will also provide new insights into host epigenetic regulation mechanisms.

Introduction

The long coexistence of bacterial pathogens with their eukaryotic hosts, and their coevolution, have provided pathogens with an amazing capacity to exploit host cell functions for survival, replication inside or outside cells, and escape from early innate immune responses. The fact that bacteria are so well adapted to their host has been of great benefit for cell biologists who are increasingly using them to study fundamental cell processes. In this Review, we will discuss the emergence of chromatin modification as a mechanism by which bacteria affect their host. Similar to viruses, bacteria provoke histone modifications and chromatin remodeling in infected cells, thereby altering the host's transcriptional program and in most cases dampening the host innate immune response. We will review our present knowledge of the effects of lipopolysaccharide (LPS), *Mycobacteria*, *Shigella*, *Listeria*, and *Helicobacter* on histones and chromatin. The particular case of tolerance to LPS is discussed. In addition, we report on bacterial homologs of eukaryotic chromatin-binding proteins, whose activity on eukaryotic targets are yet to be demonstrated.

Chromatin, Nucleosomes, and the Histone Code

Eukaryotic cells are faced with the challenge of packaging large amounts of DNA into the confined space of the nucleus, without compromising the crucial properties of DNA in various processes such as replication, repair, transcription, and also chromosome segregation. This important requirement is achieved by two classes of proteins, histones and chromatin-remodeling proteins, which compact DNA into a highly organized structure called chromatin. The first step in chromatin formation is the wrapping of 147 nucleotide pairs of DNA (1.7 turns) around an octamer of four core histones—H2A, H2B, H3, and H4 (Figure 1A). This structure, the nucleosome, defines the basic unit of chromatin and repeats at intervals of approximately 200 base pairs. Another histone, H1, stabilizes the DNA around the core histones and further compacts DNA by looping of nucleosomes on top of each other. During mitosis, DNA becomes further compacted into mitotic chromosomes, allowing for proper segregation of the replicated chromosomes. However, the precise folded and looped structure of the DNA in the nucleus in vivo is still a matter of debate, probably because this structure is very dynamic, constantly undergoing remodeling allowing for transcription, repair, or cell division to take place (Tremethick, 2007).

The interphase DNA is organized into two chromatin states—the heterochromatin and the euchromatin, which differ in their level of compaction. It is believed that the position of a gene in either hetero- or euchromatin will define its expression state. Indeed, heterochromatin is the denser of the two states, with most of the DNA present in this structure being silent. In fact, heterochromatin is found at centromeres, which are gene-poor regions, in the inactive X chromosome, at repeats dispersed throughout the chromosomes, and at cell type specific genes silenced during development. In contrast, euchromatin is much less condensed, and DNA in this state is poised for transcription. Yet, the two chromatin states are not static, and many factors contribute to chromatin dynamics.

Chromatin dynamics is orchestrated by chromatin-remodeling complexes and histone-modifying enzymes. Chromatin-remodeling complexes utilize ATP hydrolysis to unwind DNA and/or reposition nucleosomes allowing for the underlying DNA to become accessible or inaccessible for processes such as gene expression, DNA replication, repair, or recombination. Currently, remodeling complexes are organized into four classes defined by their ATPase subunit: SWI/SNF, ISWI, Mi-2, and Ino80. Each of these complexes interact with sequence-specific DNA-binding factors at the targeted genes and can have both a positive and a negative role on transcription (reviewed in Mohrmann and Verrijzer, 2005).

Histone-modifying enzymes are also crucial for conferring the dynamic nature of chromatin. Indeed, core histones are subject to a vast array of covalent modifications, including phosphorylation, acetylation, methylation, and ubiquitylation, which occur mostly on the N-terminal tails, but also occur in the histone core (Figure 1B). These modifications are dynamic and reversible, and enzymes that either induce or remove the modifications have been identified. Histone modifications regulate transcription either by affecting the chromatin structure directly, i.e., by changing the interactions of histones with DNA, and/or by recruiting nonhistone proteins such as transcription factors (Kouzarides, 2007). Therefore, the combination of different histone modifications, which has been called the "histone code," adds an additional level of transcriptional regulation besides regulation by activators or repressors at the promoter level (Strahl and Allis, 2000).

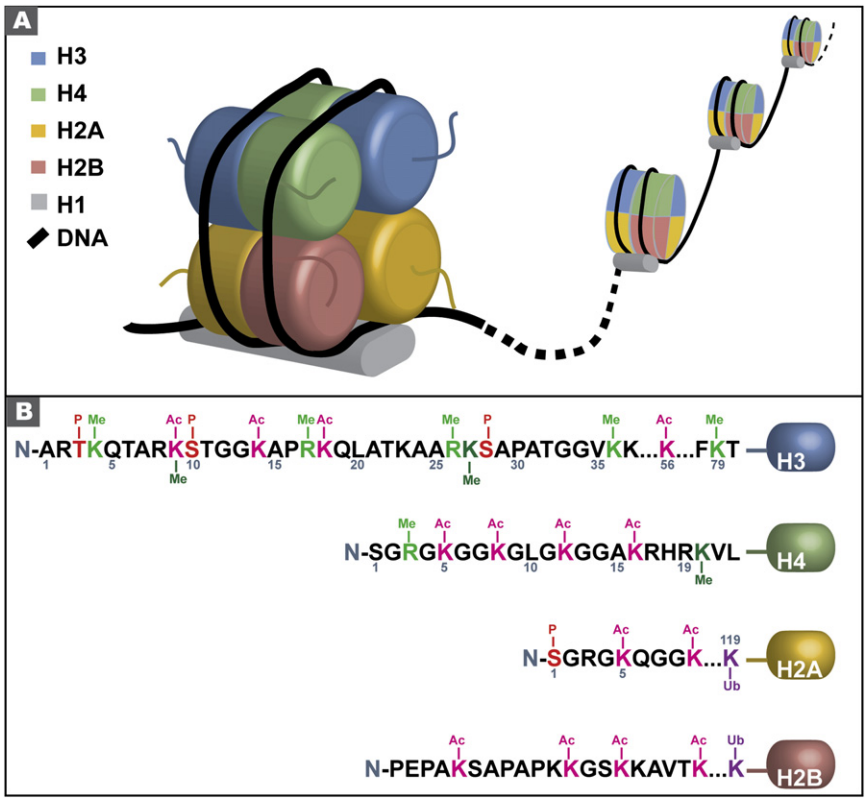

Figure 1. Nucleosome Structure and Histone Tail Modifications

(A) The arrangement of the eight histone proteins in the nucleosome is shown schematically. One hundred and forty-seven base pairs of DNA are wrapped around the histone core. Histone H1 seals the nucleosome separating each nucleosome unit from each other.

(B) Covalent modifications of histone tails as listed per histone. The sequences of the N-terminal tails of histones are shown with amino acid position indicated in gray underneath. Modifications shown above the sequence are associated with an activation of transcription and those indicated beneath are associated with transcriptional repression.

The histone code has only just started to be unraveled, and it is now possible to associate a specific modification with a transcriptional state. Methylation, which can occur on either a lysine or an arginine residue, is the best-characterized modification to date (reviewed in Shilatifard, 2006). Methylation is associated with either transcriptional activation or repression depending on the lysyl residue modified and whether this residue is mono-, di-, or trimethylated. For instance, trimethylation (and not mono- or di-) of histone H3 on lysine 9 (H3K9) is associated with repression, heterochromatin formation, and DNA methylation. The repression by H3K9 also involves the recruitment of the heterochromatin protein 1 (HP1), a protein responsible for forming and propagating heterochromatin. Interestingly, many of the proteins identified as histone methyltransferases also methylate a variety of nonhistone substrates, implicating these proteins in signaling cascades and processes independent of transcriptional regulation (Rathert et al., 2008, and references within). Another well-described mark, acetylation, which is also a modification found on lysine residues, has been mostly shown associated with active transcription. It is thought that acetylation renders chromosomal domains more accessible to the transcription machinery. However, a direct role for histone acetylation in recruiting the transcription machinery has not been shown, and it remains possible that this mark arises as a consequence of active transcription rather than as a prerequisite for transcriptional activation. Furthermore, similarly to methyltransferases, histone acetyltransferases can modify lysines on various histones and nonhistone proteins (reviewed in Kouzarides, 2000).

A list of histone modifications and their correlation with transcriptional activation or repression is shown in Figure 1B and is reviewed in Kouzarides (2007). However, many recent studies show that any given modification has the potential to both activate or repress transcription, and it is the context in which they are found—i.e., the surrounding modifications—that is important for determining their function.

Not only is the meaning of the histone code becoming clear but also the mechanisms by which histone modifications appear. Cellular stimuli are integrated through signal-transduction pathways, culminating in activation of histone modifying enzymes and modification of histones. Among them, the best- characterized link between a stimulus and its effect on histones is the MAPK (mitogen-activated protein kinase) cascade, which upon activation leads to phosphorylation of histone H3 on serine 10 (H3S10). Three MAP kinase cascades have been defined according to the MAP kinase that is activated: the ERK pathway, the JNK/SAPK pathway, and the p38 kinase pathway, each responding to a different stimulus (including stress, growth factor, and differentiation factor signals). Both the ERK and p38 kinases have been shown to activate effector kinases, MSK1 and MSK2, which will directly phosphorylate H3S10 at the promoter of activated genes (Clayton and Mahadevan, 2003; Mahadevan et al., 1991; Thomson et al., 1999). The time course of H3 phosphorylation closely correlates with the timing of gene activation, suggesting a link between this modification and transcriptional activation; however, the exact role of this modification in gene expression remains unclear. The current hypothesis is that phosphorylation of H3S10 is a predisposing mark for acetylation, itself a mark for active transcription (Cheung et al., 2000). It should be noted that, independently of its role in transcription, H3S10 has also been shown to be important for mitotic chromatin condensation (Cheung et al., 2000) (Figure 2). How this single modification can lead to unwinding of DNA for transcription and condensation for mitosis remains to be elucidated.

Phosphorylation of H3S10, upon activation of MAPKs, was shown to occur in a promoter-specific manner, targeting only a subset of genes (Clayton and Mahadevan, 2003). This specificity of histone modifications to subsets of promoters has long been puzzling. Recently, reports have shown data supporting a model in which MAPKs present in chromatin-modifying and

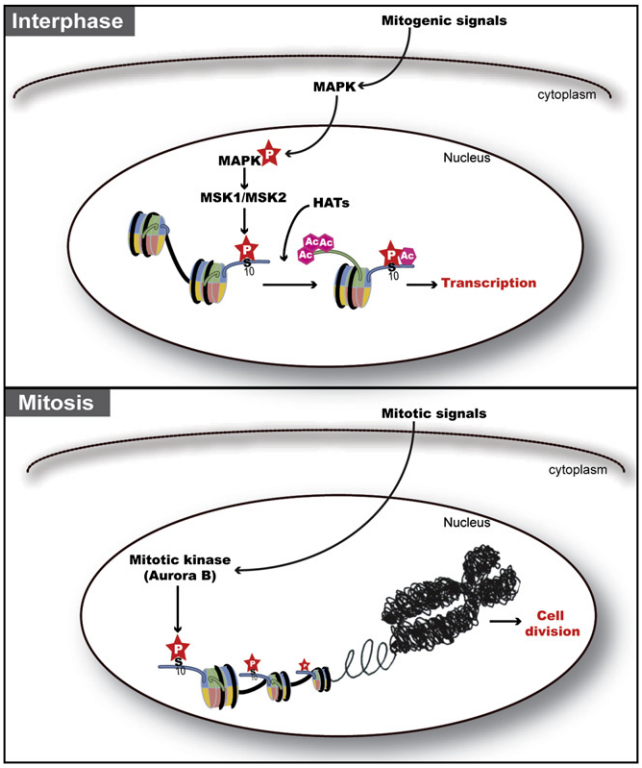

Figure 2. Dual Role of Phosphorylated Serine 10 on Histone H3 in Transcription and in Mitosis

During interphase, mitogenic signals (which include stress, growth factor, and developmental factor signals) activate MAPK signaling culminating in translocation of the MAPKs to the nucleus, where they activate a downstream kinase (MSK1 or MSK2) leading to phosphorylation of H3S10. This mark is thought to be a predisposing mark for acetylation and transcriptional activation.

During mitosis, H3S10 becomes phosphorylated by specific mitotic kinases, leading to chromosomal condensation and proper cell division.

transcription complexes can be activated in the nucleus (Edmunds and Mahadevan, 2004; Pokholok et al., 2006; Simone et al., 2004). Genome occupancy by MAPK thus constitutes a new perception of how these signaling cascades work with the consequence that regulation occurs at the targeted genes themselves and in a gene-specific manner.

It has increasingly become clear that histone modifications and chromatin structure are key regulators of eukaryotic transcription and, thus, good targets for pathogens during an infection. In fact, viruses have long been described as able to manipulate the host chromatin to impose a transcriptional program beneficial for the maintenance of infection (Lieberman, 2006). Recent reports show that bacterial pathogens are also able to induce chromatin remodeling, thereby imposing a specific transcriptional profile. We review here the first reports on this emerging field of study, which highlight novel aspects of host-pathogen interactions.

Histone Modifications and Chromatin Remodeling Provoked by Bacteria

Various bacterial products or secreted factors may induce chromatin/histone modifications, involving different host signaling cascades (Figures 3 and 4).

A. LPS, Tolerance, and TLR-Induced Chromatin Modification (Figure 3)

Innate immunity is the first line of defense against a bacterial infection, and most organisms are able to mount an efficient early, nonspecific response leading to the recruitment of cellular effectors and inflammation. Microbial components that elicit an inflammatory response have been called microbial associated molecular patterns (MAMPs) and include LPS, bacterial flagellin, lipoteichoic acid, peptidoglycan, and nucleic acids. Host cells recognize MAMPs through pattern recognition receptors (PRRs) present either at the cell surface and/or on endosomes, for Toll-like receptors (TLRs), or in the cytoplasm, for nucleotide-binding oligomerization domain proteins (NODs) and NOD-like receptors (NLRs). These receptors activate signaling cascades leading to transcriptional activation of immunity genes such as cytokine genes (reviewed in Akira and Takeda, 2004; Kanneganti et al., 2007).

LPS is the major component of the outer membrane of Gram-negative bacteria and is one of the best-characterized agonist of host inflammatory signaling responses. LPS is recognized by TLR4, and downstream signaling includes activation of the nuclear factor-κB signaling cascade (NF-κB), activation of all three MAPK cascades, and increased transcription of genes for proinflammatory cytokines such as interleukin-12 (IL-12), IL-6, and tumor-necrosis factor (TNF) (Akira and Takeda, 2004).

The first link between LPS stimulation and chromatin remodeling has been established through the study of a gene activated by LPS, the IL-12 cytokine gene. This cytokine is produced by activated macrophages and dendritic cells and is required for the activation of T cells. It has been shown that a nucleosome spans the promoter of the IL-12 gene, which is displaced upon LPS stimulation, thereby allowing transcription to occur (Weinmann et al., 1999). Nucleosome repositioning by LPS occurred in a TLR4-dependent manner and correlated with histone H3 and H4 acetylation at the IL-12 promoter (Weinmann et al., 2001). From these data, it was first suggested that LPS stimulation of TLR4 induces histone acetylation and nucleosome remodeling, allowing for NF-κB to gain access to the IL-12 promoter. One year later, another group elucidated the mechanism underlying chromatin remodeling and NF-κB accessibility at the IL-12 promoter and other NF-κB-dependent promoters (Saccani et al., 2002). The authors showed that activation of the p38 MAPK pathway upon LPS stimulation of TLR4 induced phosphorylation of H3S10 and phosphorylation/acetylation (S10/K14) of H3 (phosphorylation at serine 10 and acetylation on lysine 14 of the same histone tail), which were crucial modifications for recruiting NF-κB to the promoter of certain genes, such as IL-12. Therefore, the current model is that some NF-κB-activated genes require phosphorylation of H3S10 and phosphoacetylation of H3S10K14 via the p38 MAPK pathway so that their promoters become accessible to NF-κB, allowing transcription to occur. However, Saccani et al. also identified MAPK-independent mechanisms of phosphorylation of H3S10 and p38- and phosphorylated H3S10-independent mechanisms of gene activation, suggesting that there are at least two other modes of NF-κB-dependent gene activation (Saccani et al., 2002).

LPS induction of TLR4 and expression of inflammatory cytokines and chemokines is of great importance for the host to clear

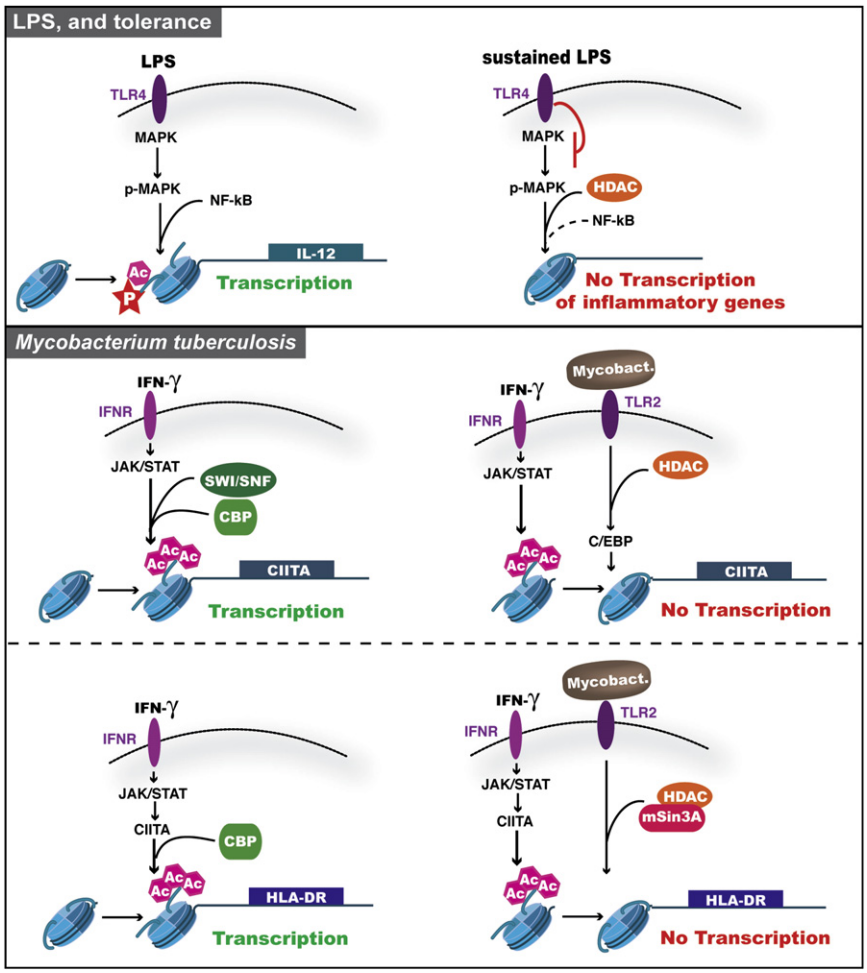

Figure 3. Schematic Representation of *Mycobacterium*-Induced Signaling as Described in the Text

a bacterial pathogen. However, prolonged expression of inflammatory factors is detrimental to surrounding tissues. Therefore, a tight downregulation of the inflammatory response occurs, with repressed expression of the proinflammatory genes, a phenomenon named LPS or endotoxin tolerance, and is associated with immunosuppression and poor prognosis (Cavaillon and Adib-Conquy, 2006). This tolerance has in two cases been shown to be controlled by epigenetic changes involving heterochromatin binding protein 1α (HP1α), methylation of H3K9, reduced phosphorylation of H3S10, and diminished binding of NF-κB at the promoter of inflammatory genes (El Gazzar et al., 2007; Chan et al., 2005). Importantly, LPS tolerance negatively affects proinflammatory mediators without inhibiting antimicrobial effectors. Interestingly, the two classes of promoters, those of proinflammatory mediator genes and those of antimicrobial effector genes, which both show histone acetylation and H3 trimethylation on lysine 4 upon initial exposure to LPS, are later distinguished by the modification of their histones (Foster et al., 2007). Indeed, with prolonged exposure, the histones at the silenced genes become deacetylated, while those at genes that remain inducible stay highly acetylated. Another report supports these findings by showing that prolonged exposure to LPS leads to transcriptional activation of multiple histone deacetylases (HDACs), each being recruited at a different promoter (Aung et al., 2006). Together, these reports suggest that inflammatory genes are regulated at a gene-specific level and not strictly by a signaling cascade-specific mechanism. This novel way of viewing signaling cascades implies that even though a large number of genes are regulated by the same signaling cascade, there are promoter-specific mechanisms that fine tune the expression of each individual gene.

B. Mycobacterium Tuberculosis, Histone Deacetylation, and Inhibition of the Normal IFN-γ-Induced Response (*Figure 3*)

Mycobacterium tuberculosis is the causative agent of tuberculosis, responsible for approximately 3 million deaths a year across the world. Most infected individuals are able to clear the infection. However, 10% of them are unable to contain it and develop an active disease, despite an apparently healthy immune system. If the *M. tuberculosis* infection is not cleared, a long-term chronic infection persists, harbored by macrophages. An important challenge in the study of *M. tuberculosis* is to understand how this bacterium avoids destruction by the immune system.

One of several immune effectors important for controlling a *M. tuberculosis* infection is IFN-γ, a cytokine secreted by activated T cells and natural killer cells, and whose major role is to induce expression of the major histocompatibility complex class II (MHC class II) on the surface of various cell types (Boehm et al., 1997). Upon binding of IFN-γ to its cell-surface receptor, the Janus tyrosine kinase (JAK) is activated, leading to phosphorylation of STAT1 (signal transducer and activator of transcription), which translocates into the nucleus and mediates transcription of several genes including that of the transactivator CIITA, itself necessary for transcription of the genes involved in the MHC class II complex formation.

Strikingly, *M. tuberculosis* is able to inhibit IFN-γ responses at the level of mRNA expression of IFN-γ-responsive genes. *M. tuberculosis* targets a subset of IFN-γ-induced genes, including CIITA, CD64, and HLA-DR, while others are unaffected, and this occurs despite normal activation of the JAK/STAT1 pathway (Kincaid and Ernst, 2003). These findings suggested promoter-specific mechanisms of transcription inhibition, which are starting to become understood. Two different mechanisms were recently identified, each having an effect on a different IFN-γ-regulated promoter and both involving histone modifications and chromatin remodeling.

One mechanism was studied at the promoter of the gene encoding the IFN-γ-regulated gene, CIITA. In uninfected cells,

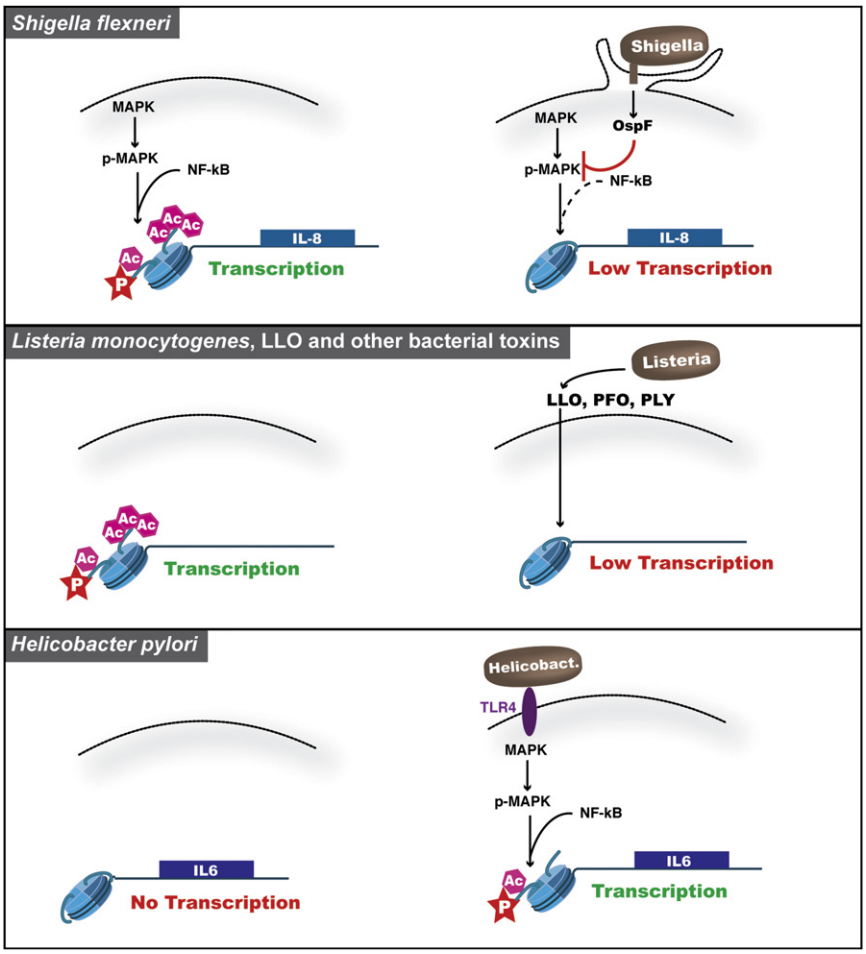

Figure 4. Schematic Representation of *Shigella*, *Listeria*, and *Helicobacter*-Induced Signaling as Described in the Text

IFN-γ induces a signaling cascade culminating in recruitment of the SWI/SNF chromatin-remodeling complex, and of CBP (CREB-binding protein), a transcriptional coactivator and histone acetyl transferase, leading to transcription of CIITA (Pattenden et al., 2002; Kretsovali et al., 1998). However, upon infection with *M. tuberculosis*, or upon incubation with the mycobacterial cell wall protein, LpqH, the IFN-γ-induced transcription of CIITA is blocked (Pennini et al., 2006 and references therein). The mechanism by which CIITA transcription is blocked occurs through inhibition of SWI/SNF binding and histone deacetylation at the CIITA promoter (Pennini et al., 2006). In correlation with inhibition of IFN-γ-induced CIITA transcription, LpqH induced binding of the C/EBP (mostly C/EBP-β LIP) transcriptional repressor to the promoter of CIITA (Pennini et al., 2007). The exact mechanism by which histone acetylation, SWI/SNF, and C/EBP control CIITA transcription has not been elucidated. One plausible hypothesis is that *M. tuberculosis* induces the recruitment of C/EBP for repression of transcription. In agreement with this hypothesis, C/EBP has previously been shown to recruit a HDAC at the promoter of an unrelated gene, thereby inhibiting transcription (Di-Poi et al., 2005).

The other report analyses the downregulation of IFN-γ-dependent HLA-DR transcription by mycobacteria (Wang et al., 2005). HLA-DR is a MHC class II surface protein. Transcriptional activation of HLA-DR requires CIITA, which functions as a transcriptional coactivator and coordinates histone acetylation at the promoter either directly through intrinsic HAT activity, or by recruiting HATs, such as CBP (Beresford and Boss, 2001; Kretsovali et al., 1998), while transcriptional shutoff requires the HDACs/mSin3A corepressor complex (Zika et al., 2003). Upon infection with *M. tuberculosis*, IFN-γ-induced histone acetylation at the HLA-DR promoter was impaired, and HLA-DR expression was inhibited (Wang et al., 2005). Although IFN-γ-dependent CIITA expression was lower in infected cells compared to noninfected cells, the concentration of CIITA was considered sufficient to induce HLA-DR expression, suggesting a promoter-specific mechanism keeping HLA-DR expression low in infected cells. Indeed, in infected cells, the mSin3A repressor was recruited to the HLA-DR promoter, with a coordinate loss of CBP binding. The authors hypothesize that mSin3A could compete with CBP for binding to the HLA-DR promoter, and depending on binding of one or the other, transcription would be activated or repressed, and histones acetylated or deacetylated. How *M. tuberculosis* induces the repressor recruitment remains to be determined.

Interestingly, both mechanisms described above were found to be TLR2 dependent, even though the link between TLR2 activation and histone deacetylation remains unknown. Pennini et al. showed that activation of the TLR2 pathway induced the p38 and ERK1/2 MAPK signaling cascades (Pennini et al., 2006). However, the well-described role of MAPKs on histones is phosphorylation, a precursor mark for acetylation (Edmunds and Mahadevan, 2004). Furthermore, activation of MAPKs leads to recruitment of HATs to specific promoters, and to an increase in the intrinsic HAT activity of certain transcription factors, such as ATF-2 (Edmunds and Mahadevan, 2004). Up to now, there has been only one report of MAPK activation leading to recruitment of HDACs, thereby having a repressive activity on gene transcription (Yang et al., 2001). Whether this repressive mechanism by MAPKs is at play during infection with *M. tuberculosis* remains to be investigated.

C. Shigella flexneri and inhibition of the p38 MAPK (Figure 4)

Shigella flexneri is the causative agent of bacillary dysentery, which causes more than a million deaths a year, mostly in children of the developing world. This facultative intracellular pathogen is able to induce its own uptake into colonic epithelial cells through a type III secretion system, and survive inside

macrophages. Both infected epithelial cells and macrophages mount an important innate immune response crucial for clearance of *S. flexneri*.

In a recent publication a new mechanism of host subversion by *S. flexneri* has been identified: alteration of the chromatin structure leading to modulation of the host transcriptional response (Arbibe et al., 2007). During a *S. flexneri* infection, the type III secretion effector OspF migrated to the nucleus of the host cell where it specifically targeted the ERK and p38 MAPKs for dephosphorylation, but not the JNK MAPK. As a consequence, OspF prevented MAPK-dependent phosphorylation of H3S10 at the promoter of a specific subset of genes. It has been known that H3 phosphorylation by MAPK signaling results not only in activation of MAPK-regulated gene transcription, but also in chromatin remodeling allowing for NF-κB to access certain promoters (for activation of the p38 MAPK) (Saccani et al., 2002). Consistent with this knowledge, the OspF-induced block of MAPK induced H3 phosphorylation, correlated with impaired recruitment of NF-κB to the promoter of the inflammatory cytokine IL-8. Therefore, by inactivating ERK and p38, OspF blocked phosphorylation of H3 and inhibited transcriptional activation of important immunity genes, such as IL-8.

Given that OspF was shown to dephosphorylate ERK and p38, a primary assumption was made that OspF was a dual specificity phosphatase (Arbibe et al., 2007). However, a recent report using mass spectrometry showed that OspF was responsible for dehydration of phophorylated ERK, as well as dephosphorylation (Li et al., 2007). This result, along with a detailed analysis of the OspF sequence, ruled out OspF as a classical protein phosphatase. Further biochemical experiments demonstrated that purified OspF has phosphothreonine lyase activity, a unique activity that has not previously been described for any protein (Li et al., 2007; Zhu et al., 2007). This new enzymatic activity chemically modifies carbon bonds of the substrate, leading to irreversible inactivation of the ERK kinase and rendering ERK non rephosphorylatable. This finding, in combination with the role of OspF on transcription, suggests that OspF would block IL-8 gene activation irreversibly. However, at 2 hr of infection with wild-type *S. flexneri*, there is a 300-fold increase in IL-8 expression compared to noninfected cells (Pedron et al., 2003), suggesting that other mechanisms are involved in IL-8 regulation. Two hypotheses can be proposed to reconcile these data: either (1) IL-8 expression is only induced in cells in which OspF is not translocated or expressed; or (2) OspF expression is transient during infection, and other signaling cascades overcome the activity of OspF and induce expression of important immunity genes. Interestingly, type III secretion effectors of *Salmonella typhimurium* (SpvC) and *Pseudomonas syringae* (HopA1) were also shown to have the same phosphothreonine lyase activity as OspF (Li et al., 2007; Zhu et al., 2007; Chen et al., 2008; Zhang et al., 2007), suggesting that *Salmonella* might also have a similar effect on host cell histones and gene expression.

D. *Listeria monocytogenes*, LLO, and Other Bacterial Toxins (*Figure 4*)

Listeria monocytogenes is the causative agent of the foodborne infection, listeriosis, which mainly affects immunocompromised individuals, pregnant women, and newborns. Characteristic manifestations of listeriosis are gastroenteritis, meningitis, encephalitis, mother-to-fetus infections, and septicaemia, resulting in death of 25%–30% of patients. During infection, *L. monocytogenes* is adapted to cross the intestinal barrier and gain access to internal organs. In severe infections, *L. monocytogenes* is able to cross the blood-brain barrier, and in pregnant women, the fetoplacental barrier, leading to infection of the brain and fetus respectively.

L. monocytogenes has emerged as a multifaceted model, which has led to important breakthroughs in host immunity, cell biology, and cellular microbiology (Hamon et al., 2006). Recently, two reports have described two different mechanisms by which *L. monocytogenes* modifies histones during infection (Schmeck et al., 2005; Hamon et al., 2007).

In one of the reports, *L. monocytogenes* was shown to activate p38 and ERK MAPK pathways after 30 min of infection in endothelial cells (Schmeck et al., 2005). Correspondingly, this MAPK activation correlated with an increase in lysine 8 acetylation on H4 and serine 10 phosphorylation/lysine 14 acetylation of H3, and transcriptional activation of MAPK induced genes, such as IL-8 after 2 hr of infection. Genes that were not regulated by MAPK, such as the IFN-γ gene, showed no change in the level of modified histone at their promoter, demonstrating that histone modification is specific to MAPK-induced genes. Interestingly, a followup study done by the same group demonstrated that IL-8 activation only occurred when bacteria had entered the host cytoplasm and that the NOD-1 protein was critical in *L. monocytogenes* dependent secretion of IL-8 (Opitz et al., 2006). These studies therefore show that in the cytoplasm, NOD-1 activation by *L. monocytogenes* leads to histone modifications. Whether NOD-1 activation by other pathogens can also lead to histone modifications, or whether this response is specific *to L. monocytogenes* remains to be determined. Interestingly, this was the first report that suggested a link between NOD activation and histone modifications.

In another report, *L. monocytogenes* was found to induce a dramatic decrease in the level of phosphorylated H3S10 and acetylated H4 in epithelial cells early on during infection, and in contrast with the previously described report, did not require entry of *L. monocytogenes* into host cells (Hamon et al., 2007). In fact, the secreted virulence factor listeriolysin O (LLO) was identified as a main effector and was sufficient for decreasing the level of modified histones. LLO is an important toxin for lysis of the vacuole, in which the bacterium is found once it has entered the host cell, but additional potent signaling activities, independent of its pore forming activity, have also been described for this protein (Hamon et al., 2006). Since LLO inserts itself into the membrane and is rapidly degraded in the cytoplasm of the host (Schnupf and Portnoy, 2007), LLO probably affects host histones through a signaling cascade. The signaling cascade activated by LLO to induce histone modifications has not yet been identified, as none of the signaling cascades known to be activated by LLO seem to be involved in this effect (Hamon et al., 2007). Furthermore, a transcriptome analysis of the host genes whose expression is modulated by LLO did not reveal the role for another signaling cascade. However, a number of LLO-downregulated genes are involved in immunity, suggesting that *L. monocytogenes*, through LLO, also has a chromatin-dependent mechanism of altering immune gene expression. Strikingly, this mechanism was not restricted to *L. monocytogenes*, and

other toxins of the same family as LLO, but secreted by unrelated and extracellular bacteria, were found to have the same effect on decreasing phosphorylated H3S10. For example, *Clostridium perfringens*, through its toxin PFO, and *Streptococcus pneumoniae*, through PLY, could also modify host histones during infection. The molecular mechanism by which these toxins induce the dramatic decrease in phosphorylated H3S10 will prove to be interesting, as very few stimuli have been described as having such an effect on histones (Hamon et al., 2007).

E. Helicobacter pylori *and Expression of IL-6 (**Figure 4**)*

Helicobacter pylori is a Gram-negative bacterium that colonizes the human gastric mucosa. Infection by this bacterium occurs through an oral-oral or fecal-oral mode, and usually persists throughout the life of the patient. Chronic inflammation caused by *H. pylori* infection results in chronic gastritis and peptic ulcers.

IL-6 is one of the cytokines that is responsible for *H. pylori* induced tissue invasion by macrophages, leading to inflammation, and is overexpressed in the mucosa at the margin of gastric ulcers. Recently, Pathak et al. identified a *H. pylori* factor, HP0175, responsible for IL-6 expression and that has an effect on histone modifications (Pathak et al., 2006). The authors showed that HP0175, a TLR-4 interacting protein (Basak et al., 2005), induced NF-κB, ERK, and p38 MAPK activation, which were all necessary for IL-6 expression. Furthermore, IL-6 expression correlated with phosphorylation of H3S10 at the IL-6 promoter, which required induction of ERK and p38 to in turn activate MSK1, a serine kinase responsible for phosphorylating H3S10. This modification was shown to be required for NF-κB-dependent IL-6 expression upon TLR4 activation by HP0175. Although MAPK-induced histone modifications allowing for NF-κB binding had previously been described for TLR4 activation by LPS (see LPS section of this Review), this is the first report linking an *H. pylori* protein to histone modifications.

F. The commensal Bacteroides Vulgatus

Bacteroides vulgatus is a nonpathogenic commensal bacterium that is part of the normal flora of healthy individuals. Resident flora has been shown to have a crucial role in autoimmune disorders such as inflammatory bowel disease. In these disorders, the body mounts an immune response to the microbial community colonizing the host intestine, while in healthy individuals, it is "silent." These observations show that commensal bacteria have the ability to induce an immune response under certain conditions, although they normally are maintained silent without eliciting any response from the host.

Interestingly, a report has shown that normal intestinal homeostasis between the commensal, *B. vulgatus*, and intestinal epithelial cells involves chromatin modifications (Haller et al., 2003). The authors demonstrated that commensals, including *B. vulgatus*, have the potential to induce an inflammatory response in vivo in intestinal epithelial cells by activating the NF-κB pathway. However, *B. vulgatus* also activates the TGF-β1 signaling pathway, which is an important downregulator of host immune response to microorganisms. In fact, in vitro, TGF-β1 inhibited *B. vulgatus* induced expression of the proinflammatory cytokine IL-6. The mechanism by which this occurred was through inhibiting *B. vulgatus*-induced histone H3 phosphorylation/acetylation (S10/K9), leading to a decrease in recruitment of NF-κB to the IL-6 promoter. Therefore, there seems to be a tight balance between activation of IL-6 by NF-κB and inhibition by TGF-β1 to maintain homeostasis.

Bacterial Proteins Able to Interact with Host Histones

Although it is becoming clear that modulation of host histones and chromatin by bacterial pathogens is a widely spread mechanism, there is little, if any evidence that bacterial proteins directly interact with host chromatin. Interestingly, homologs of histone modification enzymes are quite common in bacteria, but their in vivo function in most cases remains unknown. In the next section we will describe the current knowledge on such homologs.

A. An Agrobacterium *Protein with Histone Chaperone-like Activity*

To date there has been only one report showing a direct interaction between a bacterial protein, the *Agrobacterium tumefaciens* 6b protein, and eukaryotic chromatin resulting in chromatin remodeling (Terakura et al., 2007). *Agrobacterium tumefaciens* is a plant pathogen that induces the formation of tumors in its host by injecting a plasmid, the Ti plasmid, which is integrated into the host genome. Encoded on this plasmid is protein 6b, which plays an important role in proliferation of plant cells, leading to tumor formation. Protein 6b interacts with histone H3 both in vitro and in vivo. Furthermore, 6b appears to contribute to nucleosome formation, suggesting that it has histone chaperone-like activity. A transcriptome analysis identified genes differentially regulated in transgenic plants expressing 6b compared to control plants, suggesting also a role for 6b in transcriptional regulation. Despite these results, the exact role of protein 6b remains to be determined, as no change in histone modification was observed at the promoter of the genes identified as differentially regulated.

B. In Vitro Activity of Bacterial Homologs of Histone-Modifying Enzymes

Homologs of histone deacetylases (HDACs), acetyl transferases (HATs), and methyltransferases have been found in bacteria and are proposed to be the ancestors of their eukaryotic homologs. However, as these enzymes have been shown in eukaryotes to have other targets, it is possible that the bacterial homologs have activities on other factors (see below). Interestingly, although histone-like proteins have been described in bacteria these proteins do not appear to be the precursors of eukaryotic histones. Indeed, these proteins have only superficial similarity to eukaryotic histones. They bear only similarities in DNA-binding activity, molecular mass, and electrostatic charge. Furthermore, so far, no covalent modification has been found associated with these proteins suggesting that histone-like proteins are not the substrates of the bacterial HDAC, HAT, or methyltransferase homologs.

- HDAC Bacterial Homologs

Phylogenetic analyses show that bacterial HDACs precede not only their eukaryotic counterparts, but histone proteins themselves, inferring that the primary activity of bacterial HDAC are directed against nonhistone substrates (Finnin et al., 1999; Nielsen et al., 2005). In fact, in eukaryotes HATs and HDACs have recently been shown to have other substrates besides histones, which include DNA-binding proteins (transcription factors), nonnuclear proteins (tubulin), and proteins that

shuttle between the nucleus and the cytoplasm (nuclear import factors) (Kouzarides, 2000). Therefore, acetylation is emerging as a regulatory mark similar to phosphorylation, which not only controls transcription, but can also modify protein stability and protein interactions through mechanisms not well understood (Kouzarides, 2000). Bacterial homologs of eukaryotic HATs and HDACs have been very useful for understanding the structure and function of their eukaryotic homologs, and could also be useful for deciphering this new and not well-understood modification.

Bacterial homologs of all four classes of HDACs have been found and are called acetylpolyamine amidohydrolases (APAH), acetoin utilization proteins, or simply HDAC-like proteins. These homologs have been used as model systems to study the molecular mechanism by which HDAC proteins work. The first crystal structures of HDAC proteins were obtained using bacterial homologs to human HDAC. HDAC-like proteins of the hyperthermophilic bacterium *Aquifex aeolicus* was used as a class 1 human HDAC representative, and that of the bacterial pathogen *Bordetella*, the causative agent of whooping cough, as a class 2 representative (Finnin et al., 1999; Nielsen et al., 2005). Both of these crystal structures were solved in a complex with a HDAC inhibitor, thereby identifying the binding pocket and the residues important for catalytic activity. To date the endogenous substrate(s) of the two HDAC-homologs remain unknown; however, in vitro experiments show that they can acetylate histones (Finnin et al., 1999; Nielsen et al., 2005). These findings raise the possibility that if in contact with host histones, or other acetylated eukaryotic protein, these enzymes could have important regulatory roles.

- HAT Bacterial Homologs

The relationship between bacterial acetyl transferases and eukaryotic HATs is less clear than for HDACs, as there seems to be less homology between these families of proteins (Bradshaw et al., 1998). However, the three-dimensional structure of the *Salmonella enterica* acetyltransferase, AAC(6′)-ly, places this enzyme in the acetyltransferase superfamily in which HATs are present, suggesting that it might be the bacterial ancestor of eukaryotic HATs (Vetting et al., 2004). In vitro studies show that AAC(6′)-ly can acetylate histone proteins and demonstrated the chemical mechanism for the reaction, which was thus far unknown. However, similarly to HDACs, the substrate for bacterial HATs, such as AAC(6′)-ly, remains unknown, and one could hypothesize that if secreted and targeted to the host nucleus these proteins could have important implications on transcriptional regulation. Alternatively, a regulatory function on other host substrates could also be very interesting and would constitute a new mechanism of bacterial induced modification.

- Methyltransferase Bacterial Homologs

Methyltransferases that act on histones are part of a class of methyltransferases with a characteristic SET domain. This SET domain, which is the catalytic domain, differs widely in structure from classical methyltransferases that act on a large variety of other proteins (Aravind and Iyer, 2003). Phylogenetic analyses of SET domain proteins show that, although these proteins have homologs in bacteria and archaea, the occurrence is so rare that it is quite unlikely for the last common ancestor to have had such a protein. Additionally, the SET domains found in bacteria are mostly found in pathogens that are in close contact with eukaryotic hosts. The hypothesis then is that bacteria would have acquired these proteins from a lateral transfer from the eukaryotic host (Aravind and Iyer, 2003). However, a recent report identifies SET domain proteins in nonpathogenic bacteria, and phylogenetic trees of SET domain proteins do no cluster eukaryotic SETs with prokaryotic SETs, arguing against the hypothesis of horizontal gene transfer from the host to the pathogen. Interestingly, a chlamydial SET protein that bears 30% identity in the catalytic domain to many eukaryotic SET domains, was shown to methylate chlamydial histone-like proteins, and murine histone H3 (Murata et al., 2007). However, as the authors were only able to detect the SET protein within the chlamydial cells and not in the host, the in vivo substrate of this protein remains unknown.

Perspectives

Modulation of host transcription by pathogens is a well-accepted concept but how specific programs are controlled by pathogens remains elusive. The fact that, as detailed above, histones can be modified at specific promoters during infection starts to shed light on this important issue. The challenge that lies ahead is to determine the molecular mechanisms involved in bacterially provoked histone modifications. Indeed, to date, many studies remain at the correlative level. Whether changes in histone modification are specifically induced by the bacterium to subvert normal host responses or are the normal host responses to this pathogen will have to be determined. Many questions remain unanswered, such as the following: Do bacterial proteins known/predicted to associate with or modify chromatin or histones really do so? Do all bacterial factors interacting with TLR4 induce histone modifications at the promoters of the same genes as those described for LPS? Do all bacteria that activate TLR2 have the same effect as *Mycobacteria* on CIITA and HLA-DR? Similarly, can other bacteria that block MAPK cascades, such as *Yersinia*, have a similar inhibitory effect on immunity genes as *Shigella*? The likely scenario is that multiple signaling cascades converge on the promoters of the affected genes, and the contribution of each one of them will need to be determined in future studies.

It is important to note that in addition to the bacterial proteins described in this Review, a growing category of bacterial proteins are targeted to the nucleus. For example, cyclomodulins affect the host cell cycle (Oswald et al., 2005), and a bacterial effector of a plant pathogen, *Xanthomonas*, acts as a transcription factor in its host (Kay et al., 2007; also see the accompanying Minireview by Saijo and Schulze-Lefert [2008] on page 96). Whether or not these nuclear targeted effectors also modify host chromatin remains to be explored.

In conclusion, histone modification and chromatin remodeling provoked by bacterial pathogens is an emerging and exciting field of study. Future work will determine how widespread this phenomenon is and the diversity of mechanisms at work.

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