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# **Chromatin Remodelling During Host-Bacterial Pathogen Interaction**

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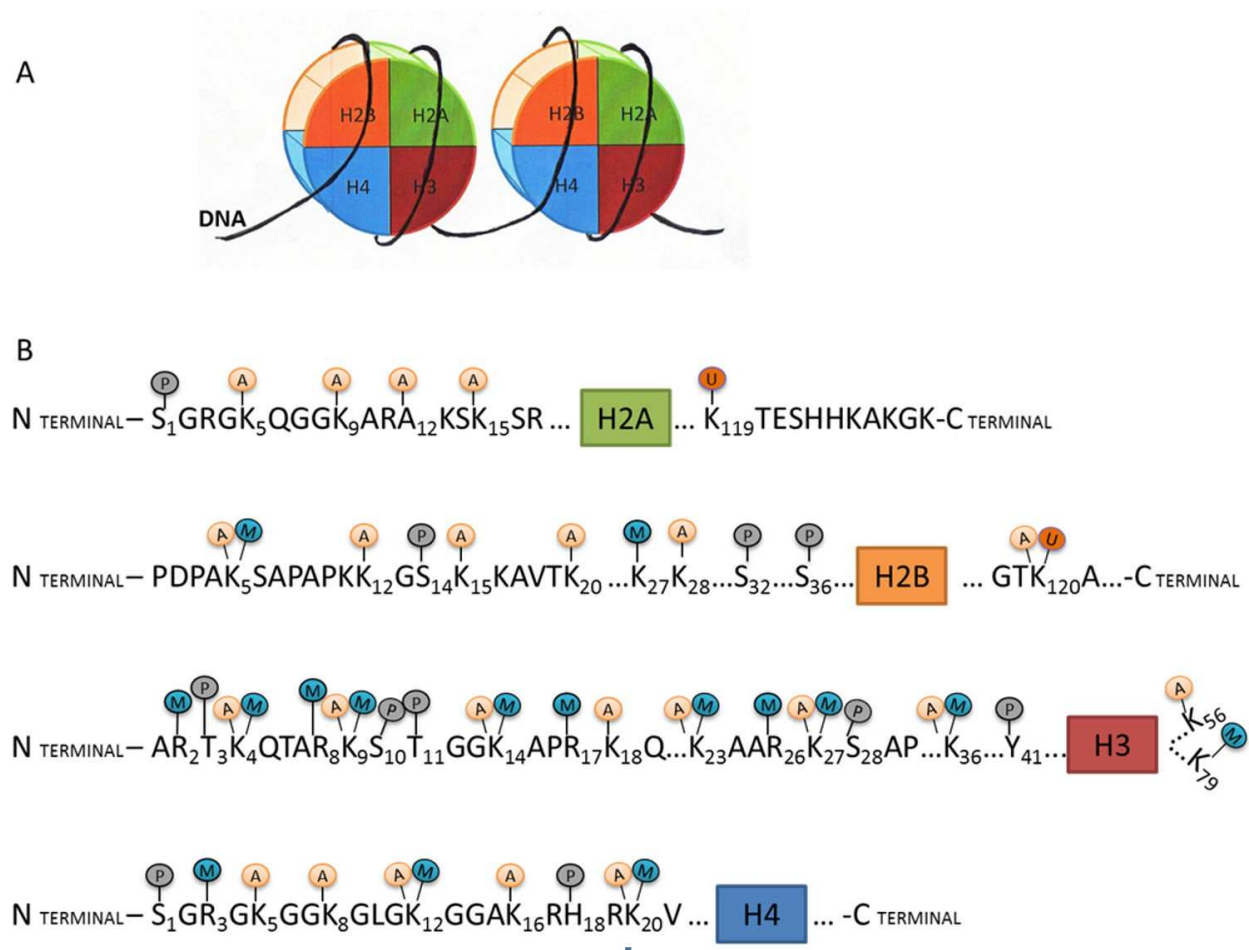
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## **1. Introduction**

Eukaryotic DNA is tightly packaged into nucleosome repeats, which form the basic unit of cellular chromatin. The nucleosome consists of an octamer core wrapped with a segment of 146 base pairs of double stranded DNA. Each octamer core is composed of two molecules of each core histone proteins H2A, H2B, H3 and H4 (Figure 1). A fifth histone protein, linker H1, binds to the nucleosomal core particle and assists in further compaction of the chromatin into higher-order structure (Lusser and Kadonaga, 2003; Roberts and Orkin, 2004). This compaction of genomic DNA into chromatin restricts access of a variety of DNA regulatory proteins to the DNA strand, which are involved in the processes of transcription, replication, DNA repair and recombination machinery. To overcome these barriers, eukaryotic cells possess a number of multi-protein complexes which can alter the chromatin structure and make DNA more accessible. These complexes can be divided into two groups, histone-modifying enzymes and ATP-dependent chromatin remodelling complexes. The histone-modifying enzymes post-translationally modify the N-terminal tails of histone proteins through acetylation, phosphorylation, ubiquitination, ADP-ribosylation and methylation. On the other hand, ATP-dependent chromatin remodelling complexes use the energy of ATP hydrolysis to disrupt the contact between DNA and histones, move nucleosomes along DNA, and remove or exchange nucleosomes (Kallin and Zhang, 2004; Lusser and Kadonaga, 2003; Roberts and Orkin, 2004). The importance of chromatin structure and its functional role in genome regulation and development is becoming increasingly evident, especially in diseases such as cancer.



**Figure 1. Schematic representation of a nucleosome (A) and major histone modifications (B).** Modifications on histones are described in text. The major modifications shown include acetylation (A), methylation (M), phosphorylation (P) and ubiquitination (U). Histone modifications mainly occur on the N-terminal tails of histones but also on the C-terminal tails and globular domains, for example, ubiquitination of the C-terminal tails of H2A and H2B and acetylation and methylation of the globular domain of H3 at K56 and K79, respectively.

Intracellular pathogens, through a long-standing coexistence with host cells, have evolved mechanisms that provide pathogens with the amazing capacity to adapt and survive in the variable and often hostile environments of their hosts (Galan and Cossart, 2005). The concept of chromatin modification as a mechanism by which pathogens affect host immune responses to facilitate infection has emerged in recent years. For example, listeriolysin O (LLO), secreted by *Listeria monocytogenes*, induces a dramatic dephosphorylation of histone H3 at serine 10 and deacetylation of histone H4, and these modifications are associated with changes in host gene expression during early stages of infection (Hamon *et al.*, 2007). Arbibe and colleagues also indicate that *Shigella flexneri* effector OspF dephosphorylates ERK and p38 mitogen-activated protein kinase (MAPK) in the nucleus; this subsequently prevents histone H3 phosphorylation at Ser10 at the promoters of a specific subset of genes, which blocks the activation of nuclear factor  $\kappa$ B (NF- $\kappa$ B)- responsive genes leading to a compromised inflammation in the infected tissue (Arbibe *et al.*, 2007). These results suggest a strategy developed by microbial pathogens

to manipulate the host cellular function through histone modification and subversion of host innate immune responses for their survival or to infect the host.

Histone acetylation/deacetylation is a key epigenetic regulator of chromatin structure and gene expression, in combination with other posttranslational modifications. These patterns of histone modification are maintained by histone modifying enzymes such as histone acetyltransferases (HATs) and histone deacetylases (HDACs). While HATs acetylate histones, conferring an "open" chromatin structure that allows transcriptional activation, HDACs have the opposite effect resulting in transcriptional repression by closing chromatin structure. Global HDAC-mediated transcriptional changes can have a concomitant effect on cell function – an epigenetic mechanism often exploited by viruses to promote infection (Punga and Akusjarvi, 2000; Radkov *et al.*, 1999; Valls *et al.*, 2007). Recent reports also show that intracellular bacteria manipulate host cell epigenetics to facilitate infection (Arbibe *et al.*, 2007; Hamon *et al.*, 2007; Hamon and Cossart, 2008). Disruption of HDAC activity with inhibitors or by siRNA affects gene expression profiling in different cell types (Glaser *et al.*, 2003a; Glaser *et al.*, 2003b; Lee *et al.*, 2004; Zupkovitz *et al.*, 2006). The potential of HDAC inhibitors in treatment of infection has been studied.

In this chapter, the chromatin modifications in host cells induced by bacterial pathogens and their effects on host gene expression and infection will be reviewed. Furthermore, the potential role of HDAC inhibitors, as a therapeutic immunomodulator, in treatment of infections will also be discussed.

## 2. Chromatin structure in transcription regulation

The packaging of DNA into chromatin does not only simply facilitate the compaction of eukaryotic DNA genomes into the cell nucleus but also plays a profound and ubiquitous role in almost all DNA-related cellular processes such as DNA replication, repair, recombination and transcription (Clapier and Cairns, 2009; Li *et al.*, 2007a). Chromatin structure is not a simple static unit. It possesses dynamic properties that are orchestrated by ATP-dependent chromatin-remodeling complexes and histone-modifying enzymes. In conjunction with other co-regulators, these chromatin remodelers modify histone-DNA interaction and regulate transcription at specific genomic loci.

### 2.1. Histone modifications and transcription

Histone sequences are highly conserved. A core histone protein typically consists of an unstructured N-terminal tail, a globular core including a central histone-fold domain, and a conformationally mobile C-terminal tail (Garcia *et al.*, 2007b; Mersfelder and Parthun, 2006). Both N-terminal tails and globular domains are subject to a variety of posttranslational modifications (Kouzarides, 2007, 128:693-705) (Figure 1). At least fourteen different types of posttranslational (or covalent) modifications involving more than 60 different residues on histones have been reported to date including acetylation, methylation, phosphorylation, ubiquitination, poly-ADP ribosylation, sumoylation, butyrylation, formylation, deimination,

citrullination, isomerisation, O-GlcNAcylation, crotonylation and hydroxylation (Martin and Zhang, 2007; Ruthenburg *et al.*, 2007; Sakabe *et al.*, 2010; Tan *et al.*, 2011). The majority of known histone modifications are located within the N-terminal tails of core histones. These modifications play an important role in the control of chromatin dynamics and its availability for transcription (Kouzarides, 2007). It has been suggested that all these modifications are combinatorial and interdependent and therefore may constitute a “histone code” (Jenuwein and Allis, 2001; Strahl and Allis, 2000). According to this hypothesis, the “histone code” is read by effector proteins (readers) which recognize and bind to modifications via specific domains and result in distinct and consistent cellular processes, such as replication, transcription, DNA repair and chromosome condensation (Kouzarides, 2007; Shi and Whetstine, 2007). Specific histone modifications are essential for partitioning the genome into functional domains, such as transcriptionally silent heterochromatin and transcriptionally active euchromatin (Martin and Zhang, 2005).

There are two major mechanisms underlying the function of histone modifications (Kouzarides, 2007; Ruthenburg *et al.*, 2007). The first is the modulation of chromatin structure either by altering DNA-nucleosome interaction or by altering nucleosome-nucleosome interactions via changing the histone charges or by addition of physical entities. For example, histone acetylation, a modification associated with transcriptional activation, has been proposed to unfold chromatin structure via neutralization of the basic charges of lysines (Kouzarides, 2007). Indeed, *in vitro* studies using recombinant nucleosomal arrays have demonstrated that acetylation of H4K16 restricts the formation of a 30-nanometer fiber and the generation of higher-order structures (Shogren-Knaak *et al.*, 2006; Shogren-Knaak and Peterson, 2006). Secondly, histone modifications provide docking sites for the recruitment of specific binding proteins, which recognize and interact with modified histones via specialized domains such as bromo-, chromo- and PHD (plant homeodomain) domains, thereby influence chromatin dynamics and function (Wysocka *et al.*, 2005; Wysocka *et al.*, 2006b; Zeng and Zhou, 2002). A number of proteins have been identified that are recruited to specific modifications. For example, methylation of H3K4, H3K9 and H3K27 can be recognized by inhibitor of growth (ING) proteins, heterochromatin protein 1 (HP1) and polycomb proteins, respectively. It has been shown that histone modification binding proteins can tether, directly or indirectly, an enzyme to chromatin. The activity of this recruited enzyme can be regulated (Pena *et al.*, 2006; Shi *et al.*, 2006; Wysocka *et al.*, 2006b). BPTF, a component of the NURF chromatin remodelling complex, binds to H3K4me3 via a PHD domain and tethers the SNF2L ATPase to H0XC8 gene and activates the expression of the latter (Wysocka *et al.*, 2006b). JMJD2A and CHD1, two other H3K4me-binding proteins, possess enzymatic activities themselves and can directly deliver enzymatic activities to chromatin when recruited (Huang *et al.*, 2006; Pray-Grant *et al.*, 2005; Sims, III *et al.*, 2005).

The link between histone modifications and transcriptional regulation has been widely studied. It has been found that a specific modification can be associated with transcriptional activation or repression. Among the histone modifications, methylation and acetylation of H3 and H4 play a major role in the regulation of transcriptional activity (Berger, 2007; Jenuwein and Allis, 2001; Li *et al.*, 2007a; Shahbazian and Grunstein, 2007). Methylation, which occurs on



either a lysine or an arginine residue, is catalyzed by three different classes of methyltransferases: SET domain-containing histone methyltransferases (HMTs), non-SET domain-containing lysine methyltransferases as well as protein arginine methyltransferase (PRMT). Methylation is implicated in both activation and repression of transcription depending on the methylation site and the type of methyltransferase involved (Shilatifard, 2006; Wysocka *et al.*, 2006a). For example, methylation of lysine 4, 36 or 79 of H3 correlates with activation of transcription whereas methylation of lysine 9, 27 of H3 or lysine 20 of H4 is usually linked to transcriptional repression (Pawlak and Deckert, 2007). Type I PRMT, such as CARM1 (cofactor associated arginine methyltransferase 1), PRMT1 and PRMT2, catalyze the formation of monomethyl- and asymmetric dimethyl-arginine derivatives and is involved in transcriptional activation. Type II PRMT, such as PRMT5, catalyzes the formation of monomethyl- and symmetric dimethyl-arginine derivatives and is involved in transcriptional repression. In addition, a lysine can be mono-, di- or trimethylated with different effect on gene transcription (Santos-Rosa *et al.*, 2002; Schneider *et al.*, 2005). Both lysine and arginine methylations can be reversed by histone demethylases, which had been discovered many years after the discovery of HMTs. LSD1 was the first histone demethylase discovered in 2004 and was shown to demethylate H3K4 and to repress transcription (Shi *et al.*, 2004). However, LSD1 was also shown to demethylate H3K9 and activate transcription when present in a complex with the androgen receptor (Metzger *et al.*, 2005). Following the discovery of LSD1, a number of other related enzymes were subsequently discovered. Among them, Jumonji domain-containing 6 protein (JMJD6) is the only direct arginine demethylase reported to date shown to demethylate H3 at arginine 2 and H4 at arginine 3 (Chang *et al.*, 2007). In addition, human peptidylarginine deiminase 4 protein (Pad4) can regulate histone arginine methylation by converting monomethylated arginine into citrulline via demethyliminium or deimination (Cuthbert *et al.*, 2004; Wang *et al.*, 2004). Histone methylation may affect the binding of other histone-modifying enzymes to the chromatin, which then mediates other posttranscriptional modifications, such as histone phosphorylation and DNA methylation (Mosammaparast and Shi, 2010; Pedersen and Helin, 2010).

Acetylation, another well-characterized modification, occurs on lysine residues mainly in the N-terminal tail of core histones. However, a lysine 56 within the globular domain of H3 (H3K56) has been found to be acetylated in yeast. Yeast protein SPT10, a putative histone acetyltransferase (HAT), was shown to mediate the H3K56 acetylation of histone genes at their promoter regions. H3K56 acetylation allows the recruitment of Snf5, an essential component of SWI/SNF chromatin remodeling complex and subsequently regulating transcription (Xu *et al.*, 2005). Compared with the SPT10, the Rtt109 acetyltransferase mediates H3K56 acetylation more globally (Driscoll *et al.*, 2007; Han *et al.*, 2007; Schneider *et al.*, 2006). The acetylation level correlates with transcriptional activation (Davie, 2003; Legube and Trouche, 2003). The level of acetylation is balanced by HATs and HDACs. Generally, increased levels of histone acetylation by HATs enhance chromatin decondensation and DNA accessibility for transcription factors to activate gene expression. In contrast to acetylation, deacetylation of histones catalyzed by HDACs leads to chromatin condensation and gene silencing (Berger, 2007; Li *et al.*, 2007a). The relationship between histone

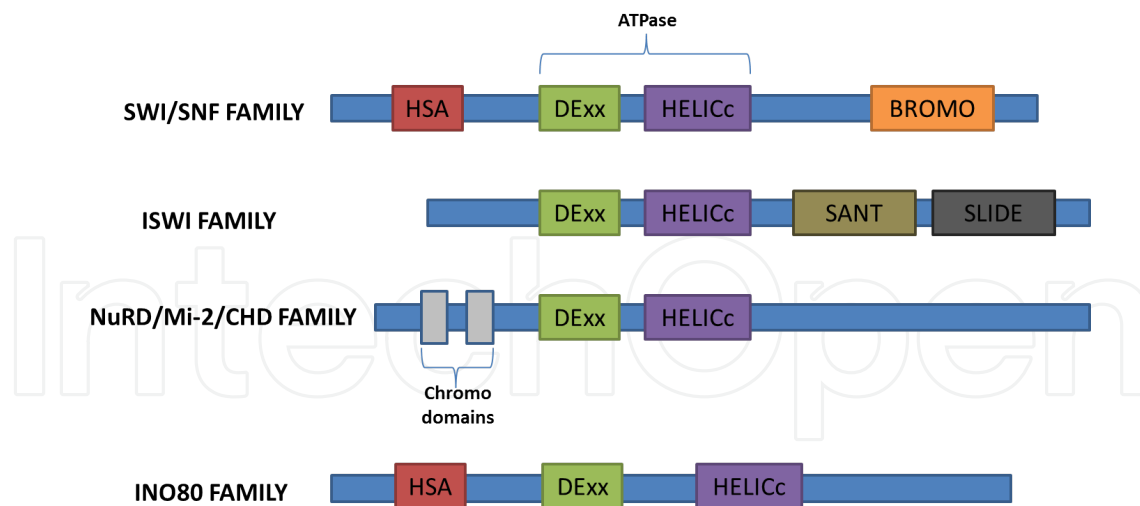
acetylation and gene expression has been well documented (Verdone *et al.*, 2006). HATs can also acetylate non-histone proteins, such as transcription factors and nuclear receptors to facilitate gene expression (Bannister and Miska, 2000; Masumi, 2011)

Other histone modifications, such as phosphorylation, ubiquitylation and sumoylation, have also been shown to be involved in transcriptional regulation. For example, H3S10 phosphorylation has been demonstrated to be involved in the activation of NF- $\kappa$ B-regulated genes as well as “immediate early” genes, such as c-fos and c-jun (Macdonald *et al.*, 2005). Ubiquitination of H2AK119 and H2BK120 are associated with transcriptional repression and activation, respectively (Wang *et al.*, 2006; Zhu *et al.*, 2005).

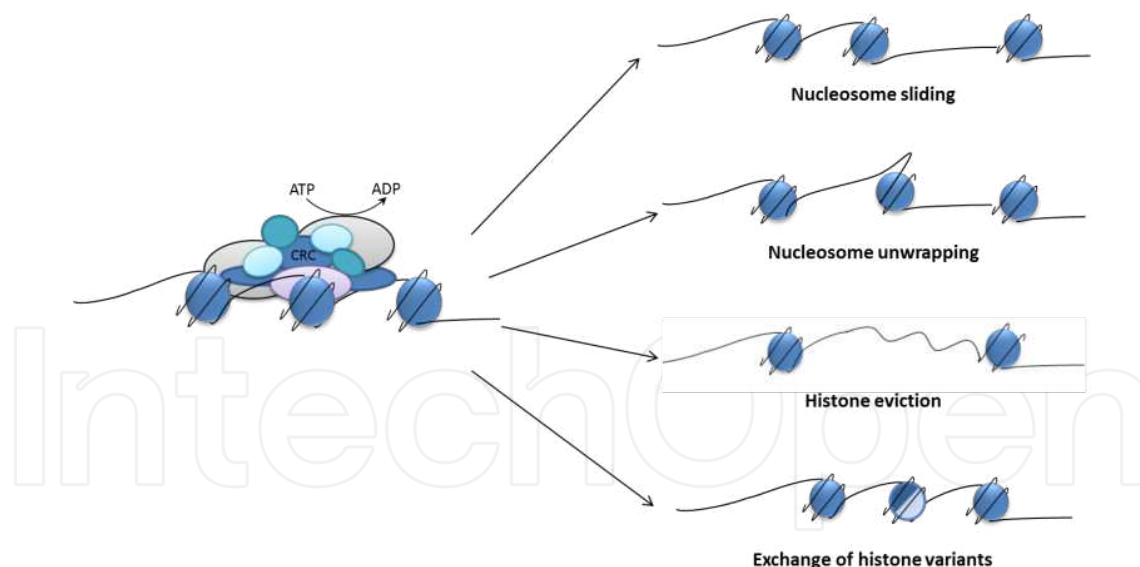
## 2.2. Chromatin remodelling complex and transcription

The second major class of chromatin-modifying factors are the protein complexes that use energy from ATP hydrolysis to alter nucleosomal structure and DNA accessibility and hence are generally referred to as chromatin remodeling complex (Flaus and Owen-Hughes, 2004; Saha *et al.*, 2006). Each ATP-dependent chromatin-remodeling complex characterized to date contains a highly conserved ATPase subunit that belongs to the SNF2 ATPase superfamily (Marfella CGA, Mutate Res, 2007). Based on the similarities of their ATPase subunits and the presence of other conserved domains, these complexes can be classified into at least four different families (Figure 2): the SWI/SNF (mating type switching /sucrose non-fermenting) family; the ISWI (imitation switch) family; the NuRD/Mi-2/CHD (chromodomain helicase DNA-binding) family and INO80 (inositol requiring 80) family (Farrants, 2008; Saha *et al.*, 2006). The ATPase subunits of the SWI/SNF family members, including yeast Snf2 and Sth1, *Drosophila melanogaster* brahma (BRM) and mammalian BRM and BRG1 (brahma-related gene 1), contain an C-terminal bromodomains which recognize and binds to acetylated histone tails (Hassan *et al.*, 2002; Marfella and Imbalzano, 2007). The members of ISWI family, such as yeast homologues ISW1 and ISW2, and mammalian homologues SNF2H and SNF2L, each contains an ATPase subunit with homology to *Drosophila* ISWI protein and has nucleosome-stimulated ATPase activity. These enzymes are characterized by the presence of a SANT (SWI3-ADA2-NCoR-TFIIB) domain, which functions as a histone-tail-binding module (Boyer *et al.*, 2004; de la Serna *et al.*, 2006). SANT domain has been found in a number of transcriptional regulatory proteins and is therefore thought to play a role in transcriptional regulation (Aasland *et al.*, 1996; Boyer *et al.*, 2002). The NuRD/Mi-2/CHD family members include a number of proteins that are highly conserved from yeast to humans and are characterized by the presence of two N-terminal chromodomains involved in the remodeling of chromatin structure and regulation of transcription (Brehm *et al.*, 2004; Eisenberg, 2001; Jones *et al.*, 2000). The INO80 family contains the INO80 remodeling complex (INO80.com) and the SWR1 remodeling complex (SWR1.com), which are distinguished by the split ATPase domains and the presence of two RuvB-like proteins, Rvb1 and Rvb2 (Bao and Shen, 2007).

ATP-dependent chromatin remodelers can reposition (slide, twist, or loop) nucleosomes along the DNA, evict histones from DNA or facilitate exchange of histone variants, and thus creating nucleosome-free regions for gene activation (Figure 3) (Wang *et al.*, 2007).



**Figure 2. ATPase subunits of the four main families of ATP-dependent chromatin remodeling complexes.** The ATPase subunit of each ATP-dependent chromatin-remodeling complex belongs to the SNF2 ATPase superfamily, whose ATPase domain comprises an N-terminal DExx and a C-terminal HELICc subdomain, separated by an insert region. The SWI/SNF family contains an HSA domain for actin binding, and a bromodomain which recognizes and binds to the acetylated histone tails. The ISWI family contains the SANT and SLIDE domains, important for histone binding. The CHD/NURD/Mi-2 family is characterized by the presence of two N-terminal chromodomains that is involved in the remodeling of chromatin structure and the transcriptional regulation of genes. The INO80 family, like the SWI/SNF family, also contains an HSA domain, however the insert region between the DExx and the HELICc subdomains is three times longer than that of other three families.



**Figure 3. Mechanisms of ATP-dependent chromatin remodeling activity to alter the accessibility of nucleosomal DNA.** Upon utilization of the energy from ATP hydrolysis, the nucleosomal structure is altered to make protected region of chromatin available to DNA binding protein complexes, such as transcription factors, which involves mobilization of nucleosome position(sliding), dissociation of DNA-histone contact (unwrapping), and eviction of histones (histone eviction). In some cases ATP dependent remodeling complexes can use the energy from ATP hydrolysis to introduce histone variants into the nucleosome (exchange of histone variants), such as H2A–H2B or H2A variants (H2Avar)–H2B dimers.



### 3. The role of chromatin remodelling in the regulation of inflammatory gene expression

The inflammatory response is a defense mechanism developed in higher organisms to protect themselves from infection with pathogens. It demands rapid and coordinated regulation of expression of multiple inflammatory genes in immune cells, including macrophages. It has increasingly become clear that alterations of chromatin architecture orchestrated by histone modifications and ATP-dependent chromatin remodeling complexes play a key role in controlling of inflammatory response genes (Medzhitov and Horng, 2009; Smale, 2010).

#### 3.1. LPS-induced chromatin modification and target gene expression

LPS, a large molecule consisting of a lipid and a polysaccharide joined by a covalent bond, is the major component of the outer membrane of gram-negative bacteria and is one of the best-characterized agonist of host inflammatory response. LPS is recognized by Toll-like receptor 4 (TLR4) and activates the downstream signaling pathways, including the NF- $\kappa$ B signaling cascades, MAPK cascades and interferon regulatory factor (IRF) signaling cascades and induce the transcription of proinflammatory cytokine genes such as interleukin-6 (IL-6), IL-12 and tumor necrosis factor (TNF) (Akira and Takeda, 2004; Takeda *et al.*, 2003). The first evidence of the involvement of chromatin remodeling in LPS-induced gene expression dates back to 1999, when it was observed that nucleosome remodeling appears to contribute to the rapid induction of p40 subunit of IL-12 (IL-12p40). Upon activation by LPS, a positioned nucleosome, which spans the IL-12p40 gene promoter, is rapidly and selectively repositioned prior to initiation of transcription process (Weinmann *et al.*, 1999). Further studies demonstrated that the nucleosome remodeling by LPS requires TLR4 signaling but is independent of c-Rel, one of the NF- $\kappa$ B subunits required for transcription of integrated IL-12p40 promoter (Weinmann *et al.*, 2001). In the year 2000, Sacconi and colleagues (Sacconi *et al.*, 2002) revealed that upon LPS stimulation, H3 phosphorylation at serine 10 (H3S10) occurs selectively on the IL-12p40 promoter as well as promoters of a subset of other NF- $\kappa$ B-responsive proinflammatory genes such as IL-6, IL-8, and CC-chemokine ligand 2 (CCL2) but not TNF- $\alpha$ , MIP-1 $\alpha$  and CCL3. This phosphorylation event was shown to be dependent on the activation of p38 MAPK signaling pathway by LPS, and specific inhibition of p38 activation blocks H3S10 phosphorylation, recruitment of NF- $\kappa$ B to the selective promoters and gene expression (Sacconi *et al.*, 2002). Therefore, it is postulated that phosphorylation of H3S10 via the p38 MAPK signaling pathway promotes the loosening of chromatin at certain selective promoters, thereby permitting accessibility to NF- $\kappa$ B and allowing transcription to occur. There are some evidence that link H3S10 mark with transcriptional activation. Serine to alanine substitution at position 10 of H3 or deletion of Snf1, a histone H3 kinase which phosphorylates the serine 10, abrogates transcriptional activation of LPS-inducible genes (Lo *et al.*, 2001; Lo *et al.*, 2000).

LPS activates TLR-dependent signaling to produce inflammatory cytokines and chemokines, which contribute to the efficient control and clearance of invading pathogens. However, production of these inflammatory mediators is tightly regulated because excessive production results in amplified inflammatory response and fatal illness characteristic of severe septic

shock. Therefore, the host has readily available mechanisms in place which allow to dampen the response to LPS or even confer unresponsiveness to successive stimuli with LPS, a phenomenon named LPS or endotoxin tolerance (Cavaillon and Adib-Conquy, 2006; Cavaillon *et al.*, 2003). The mechanisms underlying endotoxin tolerance are not completely understood, but are characterized by impaired TLR-mediated activation of both NF- $\kappa$ B- and MAPK-dependent genes (Adib-Conquy *et al.*, 2006; Adib-Conquy *et al.*, 2000). Endotoxin tolerance has been shown to be associated with chromatin remodeling in the promoter regions of several tolerizable genes (Chan *et al.*, 2005; El *et al.*, 2007). Chang and colleagues have demonstrated that chromatin remodeling and NF- $\kappa$ B p65 recruitment at the IL-1 $\beta$  gene promoter are altered in LPS-tolerant THP-1 cells, when compared to normal THP-1 cells (Chan *et al.*, 2005). Upon LPS treatment, increased phosphorylation of H3S10 and demethylation of H3K9 are observed in normal THP-1 cells, which represent an “open” chromatin state; however, these modifications are impaired in LPS-tolerant cells. Concomitantly, recruitment of NF- $\kappa$ B p65 but not NF- $\kappa$ B p50 to the IL-1 gene promoter is impaired in LPS-tolerant cells despite that the activation and nuclear accumulation of NF- $\kappa$ B is not changed. Similar histone modifications and NF- $\kappa$ B binding were also observed at the TNF- $\alpha$  promoter during endotoxin tolerance (El *et al.*, 2007). Interestingly, LPS tolerance negatively regulates expression of proinflammatory mediators without affecting antimicrobial effectors. Using microarrays and real-time PCR, Foster and colleagues (Foster *et al.*, 2007) identified two classes of genes based on their responsiveness to re-stimulation with LPS: so called tolerizable genes, which include proinflammatory mediators, and non-tolerizable genes, which include antimicrobial effectors. Induction of tolerance to LPS inhibits expression of the proinflammatory genes, while the other group of genes remain inducible. Both classes of gene promoters show H4 acetylation and H3K4 tri-methylation, which mark an “open” chromatin state, upon initial stimulation with LPS; however, this kind of “open” chromatin state and recruitment of Brg1 are lost in tolerizable genes upon LPS re-stimulation. In contrast, these epigenetic marks are maintained in the genes that remain inducible. Aung and colleagues reported that HDACs are transiently repressed then induced to express in murine bone marrow-derived macrophages when treated with LPS. HDACs are recruited to different gene promoters to regulate the expression of the latter.

### 3.2. Manipulation of host chromatin remodelling process by bacteria to facilitate infection

Interestingly, intracellular pathogens, such as *Listeria monocytogenes*, *Shigella flexneri*, and *Helicobacter pylori*, affecting the expression of host defense gene via modulation of chromatin structure has also been reported in recent years. *Listeria monocytogenes* is a gram positive bacterium that causes listeriosis. Two different mechanisms have been reported to be used by *L. monocytogenes* to modify histones during the course of infection. In endothelial cells, *L. monocytogenes* has been shown to selectively induce serine 10 phosphorylation and lysine 14 acetylation of H3 and lysine 8 acetylation of H4 at the IL-8 but not the Interferon- $\gamma$  (IFN- $\gamma$ ) gene promoter through the activation of p38 and ERK MAPK pathway. A subsequent study showed that activation of p38 MAPK signaling pathway and NF- $\kappa$ B by *L. monocytogenes* depends on nucleotide-binding oligomerization domain-containing protein 1 (NOD1). NOD1 is critical for *L. monocytogenes* induced secretion of IL-8. Interestingly, only invasive bacteria which can enter into the host cell cytoplasm induce IL-8 production in endothelial cells (Opitz

*et al.*, 2006). In another study, *L. monocytogenes* has been found to induce a dramatic H3 dephosphorylation at serine 10 (H3S10) as well as a deacetylation of H4 during early phase of infection (Hamon *et al.*, 2007). In contrast to the report described as above, entry of bacteria into the host cells is not required for these histone modifications. The LLO released by *L. monocytogenes* is a member of CDC (cholesterol-dependent cytolysin) toxin family, which is identified as a major effector sufficient for induction of H3S10 dephosphorylation and H4 deacetylation. LLO-induced H3S10 dephosphorylation specifically occurs in the case of genes whose expression is regulated by LLO, a number of which are involved in immunity. Interestingly, other members of the large family of CDC toxins, such as PFO and PLY secreted by *Clostridium perfringens* and *Streptococcus pneumoniae*, respectively, dephosphorylate H3S10 through a mechanism analogous to that of LLO (Hamon *et al.*, 2007), suggesting that different bacteria may subvert immune response through a similar mechanism.

*Shigella flexneri* is a human intestinal pathogen, causing dysentery by invading the epithelium of the colon and is responsible, worldwide, for more than one million deaths per year. Arbibe and colleagues have shown that *S. flexneri* infection abrogates phosphorylation of H3S10 at the promoters of a specific subset of genes, such as IL-8 and CCL-20. The underlying mechanism is that the type III effector protein, OspF, secreted by *S. flexneri* enters into the nucleus and specifically dephosphorylates ERK and p38 MAPKs and then blocks MAPK-dependent phosphorylation of H3S10. This occurs in a gene-selective way, and renders selected gene promoter sites inaccessible to NF- $\kappa$ B, thereby reducing the expression of a subset of NF- $\kappa$ B-responsive genes, including IL8 (Arbibe *et al.*, 2007). This specificity might be a consequence of OspF's ability to inactivate MAPKs, thereby preventing them from entering into nucleus. Once activated, MAPKs translocate into nucleus and are recruited to the chromatin covering their target genes, where they regulate the phosphorylation of transcription factors, histones and chromatin-remodeling enzymes (Chow and Davis, 2006). It has been shown that OspF-induced down-regulation of inflammatory response is accomplished through the interaction of OspF with host retinoblastoma (Rb) protein, which has been linked to histone modification (Zurawski *et al.*, 2009). OspF also has the phosphothreonine lyase activity, a unique activity that has been found in a family of conserved effectors secreted by type III secretion system including OspF, SpvC from nontyphoid *Salmonella* species, and HopAI1 from the plant pathogen *Pseudomonas syringae* (Kramer *et al.*, 2007; Li *et al.*, 2007b; Zhang *et al.*, 2007). These effectors specifically inactivate their host MAPK pathway by carrying out a  $\beta$  elimination reaction to irreversibly remove the phosphate moiety from the phosphothreonine in phosphorylated MAPKs. Inhibition of MAPK signaling by OspF attenuates the recruitment of polymorphonuclear leukocytes to *Shigella* infection sites by suppressing the activation of a portion of NF- $\kappa$ B-responsive genes in mice (Arbibe *et al.*, 2007), thereby contributing to the survival and persistent infection of the pathogens.

*Helicobacter pylori* is a Gram-negative bacterium that colonizes the human gastric mucosa. The chronic infection generates a state of inflammation which may develop toward chronic gastritis, peptic ulcers and gastric malignancies (Peek, Jr. and Crabtree, 2006). The virulence factors of *Helicobacter pylori* have been suggested to play a crucial role in the development of inflammation and in affecting the host immune system (Gebert *et al.*, 2003; Lu *et al.*, 2005). For example, in

mouse macrophage, *H. pylori* peptidyl prolyl cis-, trans-isomerase (HP0175) has been shown to induce H3S10 phosphorylation at the IL-6 promoter resulting in increased IL-6 gene transcription and protein expression (Pathak *et al.*, 2006). HP0175-induced IL-6 gene transcription is dependent on the TLR4 –dependent activation of ERK and p38 MAPKs, which subsequently activate mitogen- and stress-activated protein kinase 1 (MSK1), a serine kinase responsible for H3S10 phosphorylation. This modification allows for recruitment of NF- $\kappa$ B to the IL-6 promoter and activation of gene transactivation. Interestingly, *H. pylori* infection has also been shown to dephosphorylate H3S10 and deacetylate H3K23 in a time- and dose- dependent manner in gastric epithelial cells (Ding *et al.*, 2010). Therefore, the effect of a specific histone modification in host cells appears to be cell type specific and gene promoter specific. Further studies demonstrate that *cag* pathogenicity island (PAI) is responsible for the dephosphorylation of H3S10 and this modification is independent of ERK and p38 signaling pathways as well as IFN signaling. In addition, H3S10 dephosphorylation is associated with changes in the host gene expression, which contributes to bacterial infection and pathogenesis (Ding *et al.*, 2010). Treatment of gastric epithelial cells with TSA, a general inhibitor of HDACs which non-specifically increases histone H3 and H4 acetylation at multiple sites results in altered gene transcription pattern in both *IL-8* and *c-fos* genes upon *H. pylori* infection. TSA reduces *IL-8* but increases *c-fos* gene transcription in the presence of *H. pylori* infection (Ding *et al.*, 2010). *H. pylori* has also been shown to regulate the cell cycle controlled protein p21(WAF), which is associated with the release of HDAC-1 from the promoter and histone H4 acetylation (Xia *et al.*, 2008).

#### 4. Chromatin remodeling and IFN- $\gamma$ -induced transcriptional response

IFN- $\gamma$  is a cytokine secreted by activated T cells and natural killer cells. IFN- $\gamma$  can induce expression of the major histocompatibility complex class II (MHC-II) on the cell surface (Boehm *et al.*, 1997), which presents antigens to CD4<sup>+</sup> T cells and plays a crucial role in normal immune response. IFN- $\gamma$  activates gene expression mainly via the activation of JAK (Janus tyrosine kinase)/STAT1 (signal transducer and activator of transcription) signaling pathway, leading to the translocation of active STAT1 homodimers into the nucleus. The STAT1 homodimers then bind to the IFN- $\gamma$  -activated sites (GAS) present in the promoters of IFN- $\gamma$  -responsive genes thereby mediating the transcription of these genes, including class II transactivator (CIITA), which is necessary for both constitutive and inducible expression of MHC-II (Schroder *et al.*, 2004).

Chromatin remodeling, mediated by ATP-dependent chromatin remodeling complex and or histone-modifying enzymes, has also been shown to be involved in the activation of IFN- $\gamma$  -responsive genes, such as CIITA and HLA-DR (Ni *et al.*, 2005; Pattenden *et al.*, 2002; Zika *et al.*, 2003). SWI/SNF complex often cooperates with histone-modifying enzymes to regulate transcription of genes, including those which are induced by IFN- $\gamma$  (Chi, 2004; Wright and Ting, 2006). Studies have demonstrated that the SWI/SNF complex and CREB-binding protein (CBP), a transcriptional co-activator with histone acetyltransferase activity, are recruited to CIITA promoter in an IFN- $\gamma$ -inducible fashion, leading to transcriptional



activation of CIITA (Kretsovali *et al.*, 1998; Pattenden *et al.*, 2002). HLA-DR is a MHC-II surface molecule whose transcriptional activation is tightly associated with CIITA. However, forced expression of CIITA in BRG1- and BRM-deficient SW13 cells cannot activate expression of the MHC-II genes (Mudhasani and Fontes, 2002). BRG1 or BRM represent the catalytic subunit of mammalian SWI/SNF chromatin remodeling complex, suggesting that the SWI/SNF complex, which contains BRG1 might play additional roles in MHC-II expression. Further studies have indicated that BRG1 is recruited by CIITA to the MHC-II gene promoters and this recruitment is essential for activation of MHC-II gene expression (Mudhasani and Fontes, 2002). Interestingly, CIITA itself has intrinsic HAT activity, which can bind not only BRG1 but also HATs, such as CBP and/or p300 (Ting and Trowsdale, 2002). Furthermore, CIITA is associated with increased acetylation modifications of H3 and H4 at MHC-II promoter mediated directly through its intrinsic HAT activity or by the recruitment of HATs, such as CBP (Beresford and Boss, 2001; Kretsovali *et al.*, 1998). IFN- $\gamma$  induced transactivation of CIITA and expression of MHC-II is inhibited by HDACs/mSin3A corepressor complex whereas enhanced by TSA, a general inhibitor of HDAC. Co-immunoprecipitation assay revealed that CIITA interacts strongly with HDAC1 and weakly with HDAC2 (Zika *et al.*, 2003). All these data suggest that CIITA may act as a modulator to coordinate functions of chromatin remodeling complex, HATs and HDACs.

In the context of host-pathogen interaction, intracellular pathogens have been shown to subvert the host immune response by affecting the macrophage responsiveness to IFN- $\gamma$  but the underlying mechanism remains unclear. Intracellular pathogens may affect IFN- $\gamma$  response via different ways. For example, *Leishmania donovani* inhibited IFN- $\gamma$  response through down-regulation of IFN- $\gamma$  receptor expression or interfering with the JAK/STAT1 signaling pathway (Nandan and Reiner, 1995; Ray *et al.*, 2000). By contrast, mycobacteria such as *Mycobacterium avium* and *Mycobacterium tuberculosis* impair IFN- $\gamma$  response through inhibition of IFN- $\gamma$  -responsive gene expression without interfering with the JAK/STAT1 signaling pathway (Kincaid *et al.*, J Immunol, 2003, 171:2042-2049). Interestingly, only a subset of IFN- $\gamma$  responsive genes get affected, including CIITA, HLA-DR and CD64, while others remained unaffected (Pennini *et al.*, 2006; Wang *et al.*, 2005). Further studies showed that infection with *M. tuberculosis* affects the chromatin remodeling on CIITA gene since IFN- $\gamma$  -induced histone acetylation and recruitment of BRG1 were both impaired (Pennini *et al.*, 2006). Additionally, LpqH, a mycobacterial cell wall protein, induces binding of the C/EBP transcriptional repressor to the CIITA promoter and inhibits IFN- $\gamma$  -induced CIITA transcription (Pennini *et al.*, 2007). It has been shown that C/EBP can recruit HDAC-1-containing transcriptional repressor complex to the promoter of peroxisome proliferator-activated receptor beta thereby inhibiting its transcription (Di-Poi *et al.*, 2005). Therefore, *M. tuberculosis* might induce the recruitment of C/EBP resulting in transcriptional repression. The exact molecular mechanism by which *M. tuberculosis* inhibits IFN- $\gamma$  -induced CIITA transcription remains to be elucidated. Similarly to CIITA, IFN- $\gamma$  -induced histone acetylation gets impaired at the HLA-DR promoter and HLA-DR transcription becomes inhibited when the cells get infected with *M. tuberculosis*. Furthermore, inhibition of HDAC



activities rescues histone acetylation, suggesting a role of HDACs in the transcriptional repression induced by *M. tuberculosis* (Wang *et al.*, 2005). Indeed, Mycobacterial infection increases the expression of mSin3A (a co-repressor associated HDACs), enabling competition with CBP for binding to the HLA-DR promoter.

A recent study has demonstrated that infection with *Toxoplasma gondii* renders murine macrophages globally unresponsive to IFN- $\gamma$  stimulation without affecting the nuclear translocation of STAT1 triggered by IFN- $\gamma$  in infected macrophages. However, the binding of STAT1 to the STAT1-responsive promoters is aberrant. A number of genes, which were induced by IFN- $\gamma$  in uninfected macrophages, were not induced in the *T. gondii*-infected cells. Among them, there are several genes previously shown to be repressed by *T. gondii*, such as CIITA, MHC class II molecule H2-E $\alpha$ , and interferon- regulatory factor 1 (IRF-1) (Lang *et al.*, 2012). By analyzing the underlying mechanism, the authors revealed that assembly of chromatin remodeling complex and histone acetylation at the IFN- $\gamma$  -responsive promoters are impaired upon infection with *T. gondii*. Treatment with HDAC inhibitor restores the responsiveness of *T. gondii*-infected macrophages to IFN- $\gamma$ , leading to an increase in the expression of IFN- $\gamma$ -inducible genes, such as CIITA and H2-A/E.

## 5. The potential role of HDAC inhibitors in treatment of infection

HDAC inhibitors have been developed clinically for cancer therapy due to their abilities to induce cell-cycle arrest and apoptosis (Adcock, 2007). Studies have demonstrated that HDAC inhibitors can exert anti-inflammatory effects via the suppression of cytokine and nitric oxide production (Blanchard and Chipoy, 2005; Dinarello *et al.*, 2011), suggesting their therapeutic potential in inflammatory diseases including infectious diseases. For example, HDAC inhibitors have been examined for the treatment of HIV infection and the current results are exciting and encouraging (Wightman *et al.*, 2012). Couple of other studies have demonstrated that HDAC inhibitors, TSA and apicidin, can inhibit the growth of *Plasmodium falciparum*, the main parasite causing malaria in humans (Colletti *et al.*, 2001a; Colletti *et al.*, 2001b). Similarly, azelaic bishydroxamic acid and suberohydroxamic acid, two other HDAC inhibitors, also show anti-malarial activity against *P. falciparum* (Andrews *et al.*, 2000). The potential of HDAC inhibitors as anti-bacterial agents has also been investigated; however, the results are contradictory.

### 5.1. Inhibition of infection by targeting histone modifying enzymes in the pathogen

*Candida albicans* is an opportunistic pathogen that is normally found in the gut microflora of healthy individuals; however, *C. albicans* can cause severe and life-threatening diseases in immunosuppressed patients such as HIV infected, organ transplant and cancer chemotherapy patients (Tzung *et al.*, 2001). There is a very high rate of mortality from systemic candidiasis, ranging between 14 and 90% and averaging between 30 to 40%, depending on the disease group studied (Blot *et al.*, 2003). For patients with *Candida* infections, antifungal drug resistance

is a major clinical problem. H3K56 acetylation is mediated by HAT Rtt109 and seems to be much more abundant in yeasts than in mammals (Garcia *et al.*, 2007a; Xie *et al.*, 2009), and close homologues of Rtt109 have not yet been detected in mammals (Bazan, 2008). Therefore, it is expected that Rtt109 might be a unique target for antifungal therapeutics. Indeed, Wurtele and colleagues demonstrated that modulation of the acetylation of H3K56 exhibits potential as an anti-fungal therapy (Wurtele *et al.*, 2010). Interestingly, similar results have been found in a study by Lopes da Rosa *et al.* (Lopes da Rosa *et al.*, 2010). Wurtele and colleagues showed that deleting Rtt109, an acetyltransferase of H3K56, leads to increased sensitivity to some anti-fungal drugs. Both teams also demonstrated that Rtt109 mutants are considerably less virulent in a mouse model infected with *C. albicans*. Wurtele and colleagues further investigated how the growth of *C. albicans* is affected by chemical modification of H3 *in vitro* and *in vivo*. They have observed that the growth of *C. albicans* is greatly inhibited when HST3, the H3 deacetylase acting on lysine 56, is inhibited by nicotinamide (a form of Vitamin B3 and product of the NAD<sup>+</sup>-dependent deacetylation reaction). Furthermore, modulation of H3K56 acetylation reduces the virulence of wild-type *C. albicans* in mice when nicotinamide was given in the drinking water of mice to repress HST3 (Wurtele *et al.*, 2010). These results, together with the study by Lopes da Rosa and colleagues, provide basis for targeting H3 modifying enzymes to fight fungal infections. Although important catalytic residues in Rtt109 are much different from those in mammalian homologues, it is still a challenge to find suitable fungal-specific inhibitors of H3 modifying enzymes in the future.

## 5.2. Effects of HDAC inhibitors on host defense against bacterial infection

In a mouse model of septic shock induced by LPS, administration of suberoylanilide hydroxamic acid (SAHA) (50mg/kg intraperitoneally), improves long-term survival rates of mice whether given before or post a lethal dose of LPS, which may be due to the down-regulation of MyD88-dependent pathway and decreased expression of proinflammatory mediators such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 (Li *et al.*, 2010; Li *et al.*, 2009). Further studies demonstrated that treatment with SAHA increases anti-inflammatory IL-10 levels while decreasing proinflammatory IL-6 and MAP kinase production in the liver of septic shock mice (Finkelstein *et al.*, 2010). In contrast, it has also been shown that treatment with HDAC inhibitors lead to impaired host defense against bacterial infections. Studies have shown that HDAC inhibitors, TSA, SAHA, and VPA, can impair innate immune responses to TLR agonists by down-regulating the expression of genes involved in microbial sensing, such as C-type lectins and adhesion molecules, as well as genes involved in host defense, such as cytokines and chemokines, thereby increasing susceptibility to infection (Roger *et al.*, 2011). Interestingly, while LPS-induced IFN- $\beta$  production is enhanced by HDAC inhibitors, the expression of a number of IFN- $\beta$  /STAT1-dependent genes is strongly inhibited by TSA and VPA, suggesting that increased IFN- $\beta$  production cannot overcome the potent inhibitory effects of HDAC inhibitors. Surprisingly, VPA was shown to increase the mortality of mice infected with *C. albicans* or *K. pneumonia*, but protect mice from toxic shock and severe sepsis in mouse models (Roger *et al.*, 2011). When murine macrophages were treated with TSA and VPA, their ability to kill *Escherichia coli* and *Staphylococcus aureus* was attenuated, with impaired phagocytosis and production of reactive oxygen and nitrogen species (Mombelli *et al.*, 2011). Together, these

data reveal the complex effector mechanisms of HDAC inhibitors and suggest that more studies are required to fully understand this complex process.

## 6. Concluding remarks

The activation and suppression of innate immunity are central principles of host-pathogen interaction and need to be very well controlled. To establish persistent infection, intracellular pathogens must acquire efficient mechanisms to evade the host immune response. Interference with host posttranscriptional modifications by bacterial pathogens is a strategy widely used by the pathogens to promote survival and replication during the course of infection. MAPK, IFN- $\gamma$  and transcription factor NF- $\kappa$ B signaling pathways are common targets for bacteria-induced posttranscriptional modifications (Ribet and Cossart, 2010). Interestingly, in the past few years, evidence has accumulated that targeting of histone modifications and chromatin remodeling, and subsequently subverting the host immune response, is a new and exciting field in the study of host-pathogen interaction. Phosphorylation of H3 and acetylation of H3 and/or H4 at lysine residues are frequently associated with transactivation. Conversely, dephosphorylation and methylation of histones are more often associated with gene suppression (Berger, 2002; Kouzarides, 2007; Verdone *et al.*, 2006). Several strains of bacteria, including *L. monocytogenes*, *C. perfringens*, *S. pneumonia* and *H. pylori*, induce the same dephosphorylation of H3S10, while *S. flexneri* blocks phosphorylation of H3S10; all of which lead to decreased phosphorylation of H3S10 and are associated with altered host immune response.

The molecular mechanisms by which bacterial infection induces histone modification and chromatin remodeling remain to be understood. For many pathogens, it is very difficult to hypothesize about the extent or the mechanics of epigenetic change they might induce. Currently available data largely provide snapshots of what is happening to the usual host genes studied in an infection model. More comprehensive global studies, such as ChIP-on-chip (chromatin immunoprecipitation coupled with expression microarray technology) for mapping global chromatin modifications, are now necessary and possible. This might provide fundamental clues to better understand the role and mechanism of chromatin regulation in the control of immune gene expression in inflammatory and infectious diseases.

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