# Bacterial Virulence Factors

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There are several levels to influence the expression of eukaryotic genes. A first level of interference is changing of the DNA's structure on the chromatin level. Epigenetic modulation enables remodelling of the chromatin to transfer heterochromatin into euchromatin allowing transcription or vice versa. In addition, the affinity of promotors and other regulatory DNA sequences for RNA polymerases and transcription factors (TFs) can be influenced by cytosine or adenine methylation. Only a minor portion (fewer than 2%) of genes is transcribed into mRNAs, instead the majority is transferred into so called non-coding RNAs (ncRNAs). Certain long ncRNAs (lncRNAs) are also involved in epigenetic regulations. Epigenetic mechanisms are used for manipulation of gene expression in the course of several cellular processes. Here, we give an overview on the epigenetic control of gene expression by bacterial virulence factors during host cell infection.

epigenetics | gene expression | bacteria | virulence factor | histone modification | DNA methylation | lncRNA

## 1. Introduction

The expression of genes is dependent on their accessibility for RNA polymerase II (RNA Pol II) and TFs. As approximately 147 base pairs of the DNA are wrapped around histone octamers build by the subunits H2A, H2B, H3 and H4 as well as the scaffold protein H1 to form the nucleosome, those sequences are protected from transcription [1][2][3]. Therefore, the packaging of the nucleosomes defines the chromatin state into euchromatin and heterochromatin enabling transcription or blocking it. In order to react properly to a certain stimulus, the chromatin state can be remodeled to give access to the required genes, a process called nuclear remodeling or histone modification. Enzymes posttranslationally modify the amino acids at the N-termini of the histone proteins (called histone tails) by acetylation, phosphorylation, methylation and ubiquitination in a reversible manner to modify the interaction between neighbored nucleosomes favoring an open or closed chromatin state [4][5][6]. Nucleosomes are then allowed to slide along the chromatin fiber in an ATP-dependent manner, to give access to the DNA sequence. This reveals the dual function of chromatin, to provide a natural scaffold and being part of an essential regulatory signaling network processing the incoming data to create a special transient biological output [7]. On top, established posttranslational modifications (PTMs) can be maintained beyond the initial signal and cell divisions inheriting cell type specific gene expression enabling cell lineage specification and cellular identity [7][8][9].

The enzymes responsible for the modulation of the histone tails are divided into "writers," which attach the chemical units, "readers," which recognize and translate them by recruitment of activating or repressing factors and

“erasers,” which remove the modifications. The resulting “epigenetic code” is highly dynamic, as each established modification influences the addition or removement of other modifications that in turn influence the own stability and persistence. Moreover, epigenetic mechanisms represent the missing link between more or less stable gene expression and the impact of environmental factors on gene expression that can also cause diseases as cancer [1][10][11]. Therefore, these enzymes represent a central role in the regulation of immune responses as alterations in their activity and expression profiles leading to global changes in the histone modification pattern have been detected as cause of several chronic immune diseases as asthma, chronic obstructive pulmonary disease, colitis, systemic lupus erythematosus and rheumatoid arthritis [12][13].

Additionally, the DNA can be methylated at cytosine or adenosine residues converting them into methyl-cytosine or methyl-adenosine to cause transcriptional repression [14]. Hypermethylation dominantly occurs at CpG islands, cytosine-guanine rich regions at promotor regions, disrupting TFs and RNA polymerase binding to DNA or recruiting other co-repressors. A hypermethylated gene, that was not methylated before is therefore, not suitable for transcription and with the recruitment of further silencing-factors, will finally be silenced. This kind of modification is thought to provide a stable gene silencing that can be inherited to the next generation of cells [15][16].

Moving away from the old definition of epigenetics as hereditable stable changes at chromatin and DNA without changing its sequence, modern opinion changed towards a highly dynamic and reversible mechanism of gene regulation also enabling short term adaptions to changing environments [14]. As consequence, regulation through ncRNAs are also included to the epigenetic regulatory repertoire that can be classified according to their length into short ncRNAs (<200 nucleotides), which include miRNAs or long ncRNAs (>200 nucleotides) [17].

## 2. Manipulation at the Level of Histone Modifications

After recognition of bacterial presence by PRRs, signaling cascades activate proinflammatory cytokine expression. To improve accessibility of TFs, such as NF-κB, to the promoters of inflammatory response genes, an activating histone modification as phosphorylation of Serine 10 on histone H3 (H3S10) is established, which itself is mediated by MAPK signalling. It has been shown, that the virulence factor LPS alone is able to induce a global increase of H3S10 leading to promotion of gene expression proving the high sensitivity of the immune reaction [18].

Recent studies revealed that bacteria directly interfere with a host’s histone modifications to dampen the expression of proinflammatory cytokines by the secretion of effectors. Presence of *Listeria monocytogenes* induces phosphorylation of H3S10 but the bacterium is able to remove this activating phosphorylation within short time [19][20][21][22]. The secreted virulence factor Listeriolysin (LLO) mediates this mechanism and is also responsible for a global deacetylation of H3 and H4. Other bacteria, as *Clostridium perfringens* or *Streptococcus pneumoniae*, produce toxins, such as perfringolysin and pneumolysin, respectively, that belong to the same family as LLO and show also a similar effect on H3S10 phosphorylation [20]. The decreased levels of phosphorylated H3S10 and acetylated H4 at proinflammatory genes resulted in transcriptional downregulation thereby damping the immune response. As this observation is only dependent on the membrane-binding ability of LLO, it is most likely that LLO modulates the signal transduction to induce alterations in the histone modification pattern [20].

Like *L. monocytogenes*, *Shigella flexneri* is also able to inhibit H3S10 phosphorylation by secretion of phosphothreonine lyase effector OspF, which dephosphorylates MAPKs as p38 or ERK resulting in attenuated NF-κB binding at promotors of inflammatory genes [23]. Together with OspB, another effector of *Shigella,* OspF, interacts with the human retinoblastoma protein Rb that is capable of binding several chromatin-remodeling factors [24][25]. In this constellation, *Shigella* adjusts the chromatin structure at specific genes to downregulate host innate immunity.

*L. monocytogenes* owns another effector, which induces deacetylation on lysine 18 of histone H3 (H3K18). Thereby, Internalin B (InlB) activates the host histone deacetylase sirtuin 2 (SIRT 2), leading to repression of transcriptional start sites through occupation by SIRT 2 and following downregulation of the immune response, which could be attenuated by SIRT 2 inhibition [26]. The listerial virulence factor LntA enters the nucleus after infection of epithelial cells targeting the chromatin silencing complex component BAHD1. Together with heterochromatin protein 1 (HP1), methylated DNA-binding protein 1 (MBD1), histone deacetylases (HDAC1/2) and the KRAB-associated protein 1 (KAP1/TRIM28) that are involved in heterochromatin formation, BADH1 targets interferon-stimulated genes (ISG) for silencing by binding to their promotors [27][28]. This is inhibited by LntA, which is thought to promote chromatin-unwinding and as consequence upregulation of ISG by histone H3 acetylation. The exact mechanisms, how BAHD1 is recruited to its targets and how LntA interferes with this process has still to be investigated [29].

Another prominent histone modification is the methylation or demethylation of lysine residues, mediated by histone N-lysine methyltransferase (HKMT) or histone demethylases (HDM), respectively. Several bacteria express HKMT effectors, which enable them to directly interfere with host gene regulation as they are mimics of host chromatin modifiers. As there are many HKMT homologues in the repertoire of bacterial effectors described this mechanism seems to be a successful strategy to subvert host gene expression [30]. The nuclear effector (NUE), is secreted by *Chlamydia trachomatis* via a type III secretion system (T3SS) to enable its localization to the nucleus, where it might methylate H2B, H3 and H4. The homologous effectors RomA and LegAS4 secreted by *Legionella pneumophila Paris* and *L. pneumophila Philadelphia Lp02* strains, respectively, methylate H3 to alter host transcription but target different residues [30][31]. RomA represses global transcription by methylation of histone 3 lysine 14 (H3K14), a modification that is known to compete with the activating acetylation of H3K14 [31]. Contrary to RomA, LegAS4 increases transcription of ribosomal RNA genes (rRNA) through methylation of histone 3 lysine 4 (H3K4) but if this modification is mediated by LegAS4 alone it is not clear yet [30]. Interestingly all described bacterial methyltransferases own a conserved SET (Suppressor of variegation, Enhancer of zeste and Trithorax) domain, which uses a S-adenosyl-l-methionine (SAM) methyl donor to catalyze methyl group attachment to lysine residues [30][32]. One example is the effector BtSET, secreted by *Burkholderia thailandensis* that localizes to the nucleolus to methylate histone H3K4 promoting transcription of rRNA genes. Some effectors are capable of more unusual modifications, for example, the effector BaSET identified in *Bacillus anthracis* trimethylates histone H1 but none of the core histones. This effector represses the expression of NF-κB target genes after transient overexpression in mammalian cells and its deletion results in the loss of virulence [30][31][32].

Another modification, which differs from the known mechanisms of histone modification, is represented by dimethylation of histone 3 on arginine 42 (H3R42me2), a residue critical for DNA entry/exit from the nucleosome and not located at the histone N-termini. This modification is involved in the regulation of ROS (reactive oxygen species) production, which represents a crucial host defense mechanism against bacterial pathogens [33]. *Mycobacterium tuberculosis* represses genes involved in ROS production by secreting Rv1988, a methytransferase able to establish H3R42me2 to increase survival in host macrophages [33]. An overview of bacteria and their effectors that are secreted to induce histone modifications is given in Table 1.

**Table 1.** Histone modifications established by bacterial effectors.

| Target | Modification | Bacterium | Effector | Mediator | Cellular Function | References |
|---|---|---|---|---|---|---|
| H3S10 | de-phosphorylation | *L. monocytogenes* | LLO | unknown | Reduced expression of important immune regulators | [20] |
| H3S10 | de-phosphorylation | *S. flexneri* | OspF | MAPK | | [23][34][35] |
| H3S10 | de-phosphorylation | *Clostridium perfringens* | perifringo-lysin | unknown | unknown | [20] |
| H3S10 | de-phosphorylation | *Streptococcus pneumoniae* | pneumolysin | unknown | unknown | [20] |
| H3K18 | deacetylation | *L. monocytogenes* | InlB | c-Met induced SIRT2 recruitment PI3K/AKT | Reduced expression of important immune regulators | [20] |
| H3K4 | methylation | *L. pneumophila Philadelphia LP02* | LegAS4 | direct | Transcriptional activation of ribosomal genes | [34] |
| H3K4 | methylation | *B. thaliandensis* | BtSET | direct/NF-κB | Transcription of rRNA genes | [30][32] |
| H3K9 | acetylation | *M. tuberculosis* | Rv3423.1 | maybe direct | | [36] |
| H3K14 | methylation | *L. pneumophila Paris* | RomA | direct | Transcriptional repression | [31] |
| | acteylation | *M. tuberculosis* | Rv3423.1 | maybe direct | | [36] |

| Target | Modification | Bacterium | Effector | Mediator | Cellular Function | References |
|---|---|---|---|---|---|---|
| H3K23 | Global deacetylation | *H. pylori* | | H3S10 dephosphorylation | Differential c-Jun and HSP70 expression | [37] |
| H1 | trimethylation | *B. anthracis* | BaSET | direct/NF-κB | Transcriptional repression of NF-κB target genes | [32] |
| H2B, H3, H4 | methylation | *C. trachomatis* | NUE | direct | Transcriptional repression | [38] |
| H3, H4 | acetylation | *P. gingivivalis* | SCAFs, LPS | unknown | unknown | |
| H3 | deacetylation | *M. tuberculosis* | unknown | HDAC1 | Silencing of inteleukin-12β, suppression of T-helper1 response | [39] |
| H4 | deacetylation | *L. monocytogenes* | LLO | H3S10 de-phosphory-lation | unknown | [20] |
| H4 | deacetylation | *M. tuberculosis* | unknown | HDAC complex containing mammalian co-repressor Sin3A | Inhibition of interferon-γ-dependent HLA-DR gene expression | [40] |

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*Anaplasma phagocytophilum*, an intracellular pathogen causing human granulocytic anaplasmosis, causes upregulation of HDAC1 leading to a globally increased HDAC activity [41]. The recruitment of HDAC1 to AT-rich chromatin sites in promotors of host defense genes is mediated by the effector ankyrin A (AnkA) resulting in the reduction of histone H3 acetylation and the suppression of target genes such as *CYBB* that encodes Cytochrome b-245, beta polypeptide. As this element of the phagocyte NADPH oxidase is involved in the clearance of the pathogen by neutrophils, it is preferentially targeted [42][43][44][45]. Furthermore, AnkA functionally mimics SATB1, a protein able to bind AT-rich sequences distributed across distinct chromosomes at attachment regions of the nuclear matrix. Proteins with this ability are involved in nuclear matrix attachment, spatial organization of chromatin and large-scale transcriptional regulation [44][46][47][48]. AnkA could also perform as global organizer of the neutrophil genome, thereby acting locally (*cis*) and at a distance (*trans*) to a target gene. Moreover, pathogens as *Chlamydia psittaci* secrete nucleomodulins (SinC) that could act like AnkA and influence anchoring factors and lamins that control the dynamics of chromatin looping and organization, as the inner nuclear membrane proteins MAN1 and LAP1 [49].

**Table 2.** Bacteria targeting histone modifying enzymes.

| Target | Modification | Bacterium | Effector | Cellular function | References |
|---|---|---|---|---|---|
| **HDAC1** | induction | *A. phagocytophilum* | Ankyrin A | suppression of target genes as CYBB that encodes cytochrome b-245, beta polypeptide | [41] |
| **HDAC1** | induction | *P. aeruginosa* | 2-Amnoacetophenone | reduced expression of inflammatory cytokines and chemokines | [50] |
| **HDAC1** | induction | *M. tuberculosis* | unknown | Silencing of inteleukin-12β, suppression of T helper1 response | [40] |
| **HDAC2** | repression | *P. gingivalis* | SCAFs | Activation of genes | [51][52][53][54][55] |
| **P300** | repression | *E. coli* | Proteinase NleC | decreased IL-8 production | [56] |
| **HKMT** | repression | *P. gingivalis* | SCAFs | Inhibition of heterochromatin marks | [53][54][55] |

*Pseudomonas aeruginosa*, an opportunistic pathogen that infects and colonizes inflamed airways and burn wounds, induces HDAC1 expression in human THP-1 monocytes with the help of a molecule usually used for quorum sensing, 2-aminoacetophenone [50][57]. This is followed by global histone H3K18 hypoacetylation and reduced expression of inflammatory cytokines and chemokines (e.g., TNF, IL-1b and MCP-1) resulting in dampened host defense against the bacterium.

Considering that this effect was also dampened by knockdown or inhibition of class I HDACs and the evidence that besides *A. phagocytophilum* and *P. aeruginosa* also *Porphyromonas gingivalis* modulates HDAC1 during infections, HDAC1 family members might play a central role in development of an epigenetic mediated tolerance against the pathogens [58]. In patients with chronic periodontitis, mRNA and protein levels of HDAC1 expression were globally increased compared to healthy individuals and colocalized with TNF expressing cells and tissues. Interestingly, epigenetic regulation mediated by *P. gingivalis* seems to be cell-type specific, since HDAC1 and HDAC2 are downregulated in gingival epithelial cells *in vitro*, while levels of acetylated histone H3 were increased in murine epithelial cells of the gingival tissue [51][59]. In addition, the host acetylation system is also often influenced by short chain fatty acids (SCAFs) produced by commensals or pathogenic bacteria as *P. gingivalis* (for recent reviews please refer to References [60] and [61]).

Another strategy followed by bacteria during host infection and manipulation of the epigenetic regulatory mechanisms is to proteolytically degrade histone acetyl transferase (HAT) family members. One example of

bacteria using this strategy are enteropathogenic and enterohaemorrhagic *Escherichia coli*, which secrete the effector protein NleC, a zinc-dependent metalloproteinase targeting intracellular signaling to dampen the host inflammatory response [56]. The protein specifically binds and degrades the host HAT p300 in infected cells leading to decreased IL-8 production, an effect that can be restored by p300 overexpression. Thus, HATs and HDACs can both be targeted by pathogenic bacteria to modulate epigenetics and inflammatory gene expression in their benefit.

## 3. How to Control Host DNA Methylation

DNA methylation is another way to control gene expression. There are several enzymes called DNA-(cytosine C5)-methyltransferases (DNMTs), which establish methyl residues to cytosine or adenosine residues, respectively [61]. In contrast, the removement of DNA methylation patterns is more complex, as the modified nucleotides or DNA sequences have to be exchanged by DNA-repair mechanisms or the methylation has to be oxidized to form 5-Hydroxymethylcytosine, which can be removed by enzymes [62]. DNA methylation patterns at promotors of tumor suppressor genes had already been discovered, when first hints pointed towards an influence of bacterial inflammation on mechanisms establishing DNA-methylation patterns after *Helicobacter pylori* infection. In this context, among others, genes associated with cell growth (*apc, p14 (ARF), p16 (INK4a)*), cell adherence (*cdh1, flnc, hand1, lox, hrasis, thbd, p14ARC*) and DNA-repair (*brca1, mgmt., hMLH1*) are influenced [37][63][64][65]. Similar observations of altered DNA-methylation patterns during inflammation were made following uropathogenic *E. coli, Campylobacter rectus* and *Mycobacterium leprae* infections [66][67][68]. Still, the questions if DNA-methylation is directly induced by bacteria or is a secondary reaction by the host due to persistent inflammations, as well as the underlying mechanisms, are not completely answered yet [69].

However, several *Mycoplasma* species to encode mammalian DNMTs like equivalents that target cytosine-phosphate-guanine (CpG) dinucleotides to establish methylation patterns in the bacterial genome [70][71][72]. Moreover, their expression in human cells results in their translocation to the nucleus, where they set up unusual methylation patterns on the host DNA. This was shown for the DNMTs Mhy1, Mhy2 and Mhy3 expressed by *Mycoplasma hyorhinis* in combination with up- and downregulation of certain genes resulting in activation of proliferation specific pathways, a process that might contribute to tumor progression [70][73].

*Mycobacterium tuberculosis* owns an effector called Rv2699 that can enter the nucleus of THP1 cells (a monocytic cell line derived from a patient with acute monocytic leukemia) and methylate cytosines outside CpG dinucleotides. Notably, Rv2699 prefers cytosine-phosphate-adenine or cytosine-phosphate-thymine sites to generate a type of methylation that is, with few exceptions, normally not present in mammalian adult differentiated cells [74][75]. However, non-CpG methylation could lead to a more stable type of modification that persists longer in the genome of infected nondividing macrophages, offering an advantage for *M tuberculosis* by establishing an intracellular environment for persistence [75]. A follow up study revealed that THP1 macrophages infected with *M. tuberculosis* strain H37Rv created genome-wide *de novo* methylation patterns at non-CpG dinucleotides that included hyper- and hypomethylated regions [75][76]. Additionally, clinical isolates infecting THP1 cells may downregulate IL-6 receptor expression by hypermethylation of CpG-dinucleotides at the promoter of the IL-6 receptor gene. Still, it

has to be mentioned, that the observations of *M. tuberculosis* induced DNA-methylation patterns depend on the infected cell type.

Another interesting bacterial induced modification of gene expression is represented by differentiated Swann cells that adapt the phenotype of progenitor stem-like cells after *M. leprae* infection. This is probably induced by silencing of the *Sox10* gene after bacterial methylation [67]. In contrast to the decreased expression of Sox10, other genes involved in epithelial–mesenchymal transition (EMT) were demethylated and transcribed leading to the transformation of Swann cells into myofibers or smooth muscles in vitro and in vivo [77].

*P. gingivalis* was shown to increase the methylation of the TLR-2 promotor in gingival epithelial cells (GECs) reducing innate immunity activation and causing hyposensibility [59][78]. Besides, coinfection with *Filifactor alocis*, another pathogen associated with periodontitis is suggested to influence the whole cell transcriptome through impact on the nucleosome structure by reduced expression of H1 family members [53][54]. Other histone modifications induced by LPS or short chain fatty acids (SCFAs) produced by *P. gingivalis* are summarized in Table 1 and Table 2.

Still, there is not much known about the relation of DNA-methylation and infection and the underlying causalities [61][69]. Considering that many of these modifications are observed in the context of cancer initiation and progression, further investigation may contribute to new therapeutic agents and cancer prophylaxis.

## 4. Regulation of Host Gene Expression via lncRNAs

The role of lncRNAs during modulation of gene expression has been discovered in the recent years. Similar to mRNAs, lncRNAs are transcribed by RNA polymerase II or III, followed by splicing, 5′capping and in some cases polyadenylation at the 3′end. Contrary to mRNAs, the expression of lncRNAs is much lower and in a cell-, tissue- and developmental stage-specific manner [79].

Dependent on of their position relative to the neighboring protein-coding gene, lncRNAs are classified as sense, antisense, bidirectional, intronic or intergenic and, despite their enormous number, they were previously considered as “dark matter” or “junk” in the genome [80]. *Au contraire*, lncRNAs are now respected as important physiological regulators during cell homeostasis, growth, differentiation and anti-viral responses [81][82][83][84]. In addition, gene imprinting, regulation of the p53 pathway, stem cell self-renewal and differentiation and DNA damage response were reported as lncRNA controlled mechanisms [85][86][87][88].

The functionality of lncRNAs is not restricted to the neighbored protein-coding gene (*in cis*), in contrast they are also able to act *in trans* to regulate gene expression across chromosomes. In this context, lncRNAs regulate different processes as chromatin remodeling, transcription and post-transcriptional regulation via their capacity as signals, decoys, guides and scaffolds [89][90]. Interestingly, another origin of lncRNAs is the expression of pseudogenes and gaining Influence over the expression of pseudogenes could, therefore, provide a possibility to control infectious responses [91].

Immune regulation through lncRNAs has already been known after viral infections but recent research indicates its involvement also whilst fighting bacteria [92]. In that context, 76 enhancer RNAs (eRNAs), 40 canonical lncRNAs, 65 antisense lncRNAs and 35 regions of bidirectional transcription are differentially expressed in human monocytes after LPS stimulation [93]. LPS stimulation alone induces a differential expression of about 27 lncRNAs leading to histone trimethylation or acetylation of neighboring genes after de-regulation, pointing towards their regulatory influence during the innate-immune response [94]. The observation, that 44% of total lncRNAs varied in their expression after *Salmonella* infection in HeLa cells could foster these results and substantiate them by a function in the early phase of infection as sensitive markers for pathogen activity [95]. In line with this, the lncRNA HOTAIR that contributes to transcriptional repression of HOX genes also promotes inflammation in mice cardiomyocytes by TNF-α production mediated through phosphorylation of p65 protein and NF-κB activation after LPS induced sepsis [96][97].

Long intergenic non-coding RNAs (lincRNAs) are a subtype of lncRNAs, as they are expressed from intergenic regions. In response to an LPS stimulus, bone-marrow dendritic cells expressed about 20 lincRNAs with the majority being dependent on NF-κB activity, including lincRNA-Cox2, which is also upregulated in bone marrow-derived macrophages following *L. monocytognes* infection [98][99]. Additionally, bacteria sabotage lncRNA activity, as BCG (attenuated strain *M. bovis* bacillus Calmette-Guérin BCG) infected macrophages repress the expression of 11 lncRNAs that are not dampened by infection with heat activated bacteria [100]. Still, possible subversion of lncRNA-mediated inflammatory regulation needs to be further investigated.

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