FEBS Letters 584 (2010) 2748–2758

FEBS Letters

journal homepage: www.FEBSLetters.org

Review

Post-translational modifications in host cells during bacterial infection

David Ribet, Pascale Cossart *

Institut Pasteur, Unité des Interactions Bactéries-Cellules, Département de Biologie Cellulaire et Infection, F-75015 Paris, France
INSERM, U604, F-75015 Paris, France
INRA, USC2020, F-75015 Paris, France

ARTICLE INFO

Article history:
Received 6 May 2010
Accepted 10 May 2010
Available online 21 May 2010

Edited by Jan Rydström

Keywords:
Rho GTPase
Cytoskeleton
Ubiquitin
MAPK
SUMO
Pathogenesis
Listeria

ABSTRACT

Post-translational modification of proteins is a widespread mechanism used by both prokaryotic and eukaryotic cells to modify the activity of key factors that plays fundamental roles in cellular physiology. This review focuses on how bacterial pathogens can interfere with host post-translational modifications to promote their own survival and replication.
© 2010 Federation of European Biochemical Societies. Published by Elsevier B.V. All rights reserved.

1. Introduction

Post-translational modifications (PTM) consist in the chemical modification of proteins after their translation, a widespread strategy used by both prokaryotic and eukaryotic cells to modify quickly, locally and specifically the activity of key factors and enable cells to respond rapidly to environmental changes. These modifications allow a diversification of the activities of proteins encoded by all organisms and add a layer of complexity between the genome and the proteome. PTMs are catalyzed by specific enzymes, which are tightly regulated and often are also substrates for modifications. More than 300 PTMs are currently known. They include the addition of chemical groups (e.g. phosphate or acetate) or more complex molecules (e.g. carbohydrates or lipids), the covalent linkage of small proteins (like ubiquitin and ubiquitin-like proteins (UBLs)) or the modification of side chain residues of specific amino acids (like deamidation or eliminylation) (Fig. 1). We also consider proteolysis, i.e. the irreversible cleavage of the peptide bond between two amino acids of a protein, as a PTM.

As PTMs play fundamental roles in cellular physiology, it is not surprising that pathogens interfere in many different ways with the PTMs of their host to promote their own survival and replication. In this review, we will describe how bacterial pathogens can interfere with (i.e. counteract or stimulate) host PTMs and what are the roles of these modifications in bacterial infection.

The impact of bacteria on specific host PTMs is mediated by a variety of bacterial effectors that are either located at the bacterial surface or secreted. These effectors can interact with plasma membrane or intracellular host proteins. This latter case is observed for intracellular bacteria and also for toxins secreted by extracellular bacteria and able to penetrate inside the host cell, or for effectors directly injected by the bacteria in the host cell via type III or IV secretion systems (T3SS, T4SS).

In this review, we will focus on the most frequent PTMs targeted by bacterial pathogens (Fig. 2). For each PTM, different situations will be discussed: (i) the direct post-translational modification of host proteins by bacterial factors displaying an enzymatic activity (Table 1); (ii) the activation or inhibition by bacterial factors of host signalling cascades involving PTMs (Table 2); (iii) the interference of bacterial effectors with host PTM machineries; (iv) the post-translational modification of bacterial factors (Table 3).

2. Phosphorylation

Phosphorylation is one of the most common PTMs of proteins and consists in the reversible attachment of a phosphate group to a specific residue of a target protein. Several types of

* Corresponding author at: Unité des Interactions Bactéries-Cellules, Institut Pasteur, 25 rue du Dr Roux, 75015 Paris, France. Fax: +33 1 45 68 87 06.
E-mail addresses: david.ribet@pasteur.fr (D. Ribet), pascale.cossart@pasteur.fr (P. Cossart).

0014-5793/$36.00 © 2010 Federation of European Biochemical Societies. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.febslet.2010.05.012

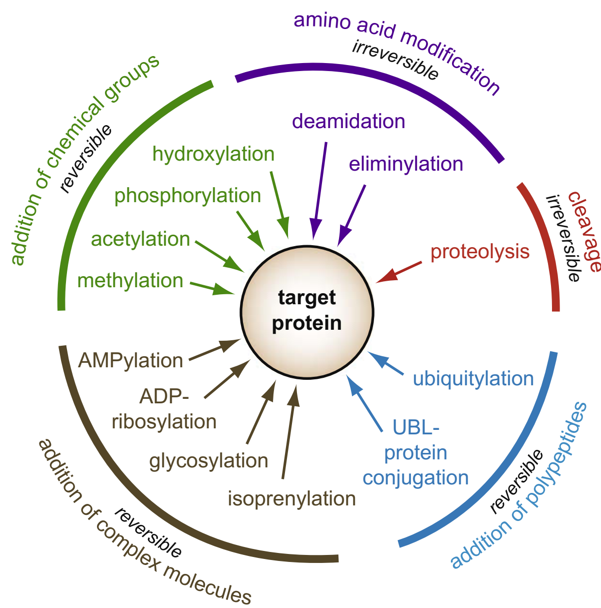

Fig. 1. Diversity of post-translational modifications. PTMs correspond to the modification of target proteins after their translation. Different classes of modifications can be distinguished: the modification of the chemical structure of amino acid side chains, the addition of chemical groups or complex molecules to specific amino acids, the covalent linkage of polypeptides, or the cleavage of the peptide bond between two amino acids, known as proteolysis. For each class, the reversibility of the modification as well as examples of PTMs are indicated.

phosphorylation have been reported, the most frequent being phosphorylation of the hydroxyl group of serine, threonine or tyrosine residues. Phosphorylation is catalyzed by kinases that transfer a phosphate group from ATP to the target protein via the establishment of a phosphoester bond. Conversely, phosphatases hydrolyze this phosphoester bond thereby releasing the phosphate group and restoring the acceptor amino acid in its unphosphorylated form. We cannot describe here all the various pathways triggered by bacterial pathogens that involve one or several phosphorylation events. We will only give examples of bacterial effectors that display kinase or phosphatase activities, as well as effectors with phosphothreonine lyase activity.

The three pathogenic *Yersinia* species (*Yersinia enterocolitica*, *Yersinia pseudotuberculosis* and *Yersinia pestis*), involved in human pathologies ranging from enteric diseases to plague, possess a virulence plasmid encoding a T3SS. This T3SS mediates the translocation of several bacterial effectors in the cytoplasm of host cells and is required for the survival and replication of *Yersinia* within host lymphoid tissues. Several of these injected factors participate into the inhibition of phagocytosis by macrophages by impairing cytoskeleton rearrangements and the subsequent engulfment of invading bacteria. YopH is a *Yersinia* T3SS effector which has a potent tyrosine phosphatase activity [1,2]. The dephosphorylation of several host proteins by YopH contributes to the inhibition of phagocytosis of *Yersinia* by macrophages as well as the impairment of *Yersinia* uptake by epithelial cells (reviewed in Ref. [3]). YopH dephosphorylates, for example, Fak (Focal adhesion kinase) and p130^{Cas} (Crk-assocaited substrate), two proteins normally involved in formation of new focal adhesion complexes and bacterial uptake [4–6]. YopH is also involved in the inhibition of the host adaptative immunity by impairing cytokines production or T-cell activation [3]. Consistently, *Yersinia* mutants defective for YopH are severely attenuated in vivo and rapidly eliminated from spleen and liver of infected mice [3].

YpkA (called YopO in *Y. enterocolitica)* is another *Yersinia* effector, with a multidomain architecture, that leads to the disruption of the actin cytoskeleton once injected into the host cell. The N-terminal domain of YpkA displays a serine/threonine kinase activity [7]. This protein targets and phosphorylates host Gαq, a subfamily of G proteins involved in signals transduction. This phosphorylation inhibits Gαq binding to GTP and thereby prevents activation of Gαq-mediated cellular responses [8]. Otubain-1, a host deubiquitylating enzyme, is also phosphorylated by YpkA [9]. However, the exact roles of the phosphorylation of Otubain-1 and Gαq in *Yersinia* infection, as well as the roles of the kinase activity of YpkA in actin cytoskeleton disruption, remain elusive [8,10,11].

Besides phosphatase and kinase activities, some bacterial factors display another enzymatic activity called phosphothreonine lyase, which irreversibly eliminates a phosphate group from phosphorylated host proteins. *Shigella flexneri*, the causative agent of bacillary dysentery, produces a protein with phosphothreonine lyase activity called OspF [12]. This T3SS effector, when translocated into the host cell, mediates the irreversible elimination of a phosphate group from phosphorylated threonine residues of host MAPKs (Mitogen Activated Protein Kinases). The enzymatic reaction catalyzed by OspF does not restore a phosphorylatable hydroxyl group, as do classical phosphatases. It generates, via a β-elimination reaction called eliminylation, a modified threonine residue which can no longer be phosphorylated [12,13]. Interestingly, other bacterial factors share the same enzymatic activity as OspF. This is the case for SpvC, a protein encoded by the intracellular pathogenic bacterium *Salmonella enterica* serovar Typhimurium (thereafter denominated *S.* Typhimurium) [12,14,15], and HopAI1, an effector of the plant pathogen *Pseudomonas syringae* [16]. The modification catalyzed by these phosphothreonine lyases irreversibly inactivates MAPKs of the infected cells and was proposed to contribute to the dampening of the host immune response during bacterial infection [12,15,16].

3. Ubiquitylation

3.1. The ubiquitin system

Ubiquitin is a small protein of ~9 kDa present in all eukaryotes. Ubiquitylation, i.e. the covalent addition of one or several ubiquitins on a target protein, is an essential post-translational modification of eukaryotic cells. The conjugation of ubiquitin on a target protein requires different enzymes: E1 activating enzymes, E2 conjugation enzymes and E3 ubiquitin ligases (Fig. 3). E3 ubiquitin ligases control substrates specificity by directly interacting with the targeted proteins. All eukaryotes encode several E2s and E3s enzymes (up to several dozens of E2s and hundreds of E3s), allowing the modification of many different proteins often under a strict temporal and spatial control. Ubiquitylation is a reversible modification as specific proteases, called deubiquitylating enzymes (DUBs), can remove ubiquitin from a target protein (Fig. 3). The conjugation of ubiquitin occurs most frequently on lysine residues of target proteins, although linkages on cysteine, serine or threonine residues or on the N-terminal amino group of target proteins have also been reported. The addition of one or several ubiquitins modifies the localization and/or the activity of the targeted protein. Monoubiquitylation is involved in many cellular functions including membrane-protein trafficking, endocytosis, signal transduction, DNA repair and transcription regulation. In the case of polyubiquitylation, the lysine side chain of a ubiquitin moiety is used as a target for the addition of another ubiquitin moiety. Ubiquitin contains seven lysine residues, all of which can contribute to such linkage. The topology of the ubiquitin chains formed influence the fate of the modified substrate proteins. Lys-48-linked chains are most commonly associated with proteasome binding and degradation of the polyubiquitylated protein whereas Lys-63-linked

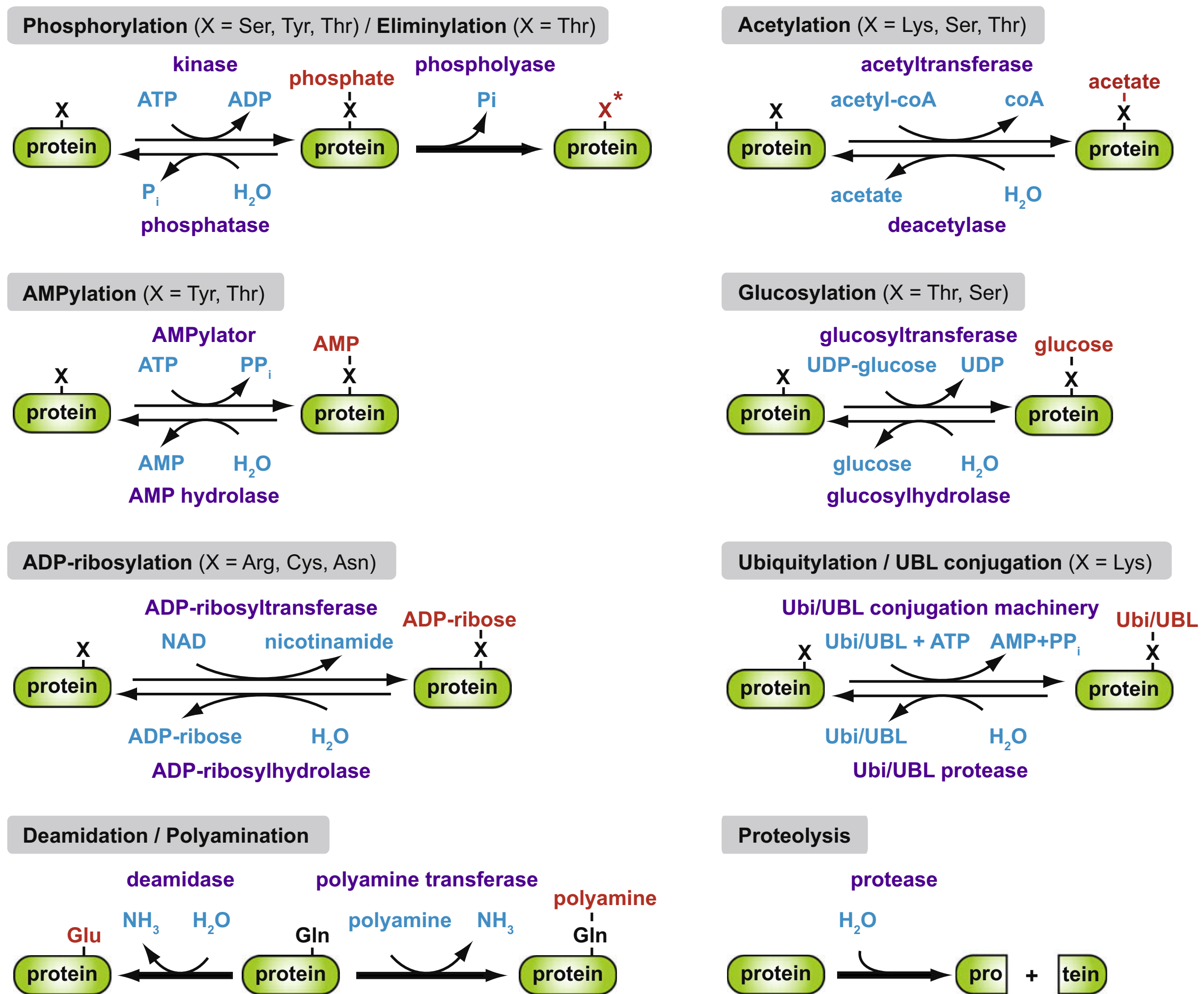

Fig. 2. Post-translational modifications regulated by bacterial pathogens. Bacterial pathogens interfere with many different host PTMs to promote their own survival and replication. The major PTMs regulated by bacteria are described in the figure. For each PTM, the nature of the amino acid most frequently modified (X) is indicated in the title, as well as the enzymes catalyzing the modification (in purple), the cofactors potentially involved (in blue) and the group added to the target protein (in red). X^*, unphosphorylatable amino acid; P_i, inorganic phosphate; PP_i, inorganic pyrophosphate; NAD, nicotinamide adenine dinucleotide; coA, coenzyme A; Ubi, ubiquitin.

chains participate in signal transduction, vesicular trafficking or DNA repair (reviewed in [17]).

Not surprisingly, there are many examples of pathogens interfering with ubiquitylation of the host cell.

3.2. Ubiquitylation of bacterial effectors

In some cases, bacterial pathogens hijack host ubiquitylation to trigger the degradation of their own effectors. This is the case for two effectors of *S.* Typhimurium: SopE and SptP, that exhibit opposing activities on host cell Rho GTPases. Rho GTPases act as "molecular switches" in many different signalling pathways and, in particular, in the actin cytoskeleton dynamics. SopE display a GEF-like activity (Guanine nucleotide Exchange Factor) that activates host Rho GTPases, resulting in actin cytoskeleton rearrangements, membrane ruffling and subsequent bacterial uptake [18]. SptP, which is codelivered with SopE, deactivates Rho GTPases and allows the recovery of the actin cytoskeleton's normal architecture, a few hours after infection [19]. It has been shown that SopE and SptP have different half-lives: SopE undergoes a rapid polyubiquitylation and degradation after translocation in the host cytoplasm, while SptP exhibits a much slower degradation kinetics [20]. In this example, ubiquitylation is controlling the transient activation of Rho GTPases and allows a temporal regulation of cytoskeleton rearrangements, required for successful infection. *Listeria monocytogenes* is another pathogenic bacterium that interacts in several instances with host ubiquitylation. *Listeria* is a facultative intracellular bacterium responsible for listeriosis, a food-borne disease. After induction of its own uptake into a host cell, *Listeria* is able to escape from its internalization vacuole to reach the cytoplasm and replicate therein (Fig. 4). Escape from the vacuole requires a toxin secreted by the bacterium, named Listeriolysin O (LLO), which has a pore-forming activity and facilitates the disruption of the vacuolar membrane [21]. As this pore-forming toxin may damage the host-cell plasma membrane and lead to cytotoxicity, a tight restriction of LLO activity to the vacuolar membrane is required to ensure bacterial intracellular lifestyle and avoid direct exposure to the immune system. It has been reported that once *Listeria* has reached the cytoplasm, LLO produced by the bacteria is phosphorylated and polyubiquitylated and then targeted to the proteasome for degradation [22]. However, inhibition of proteasome does not increase the cytotoxicity of LLO in infected cells and the exact role of LLO-proteasomal degradation in *L. monocytogenes* intracellular growth or virulence thus remains unclear [22,23].

Table 1
Bacterial effectors catalyzing post-translational modifications.

Bacteria	Effector	Bacterial effector activity	PTM	Host targets	Reference(s)
Yersinia	YopH	Tyrosine phosphatase	Dephosphorylation	Fak, p130^{Cas}, others	[1–6]
Yersinia	YpkA/YopO	Kinase	Phosphorylation	Gαq, Otubain-1	[7–11]
Shigella	OspF	Phosphothreonine lyase	Eliminylation	MAPK	[12,13]
S. Typhimurium	SpvC	Phosphothreonine lyase	Eliminylation	MAPK	[12–15]
P. syringae	HopAI1	Phosphothreonine lyase	Eliminylation	MAPK	[13,16]
Shigella	IpaH9.8	E3-ubiquitin ligase	Ubiquitylation	IKKγ/NEMO	[36,37,46]
S. Typhimurium	SopA	E3-ubiquitin ligase	Ubiquitylation	Unknown	[38,39,46]
L. pneumophila	LubX	E3-ubiquitin ligase	Ubiquitylation	Clk1	[40,46]
P. syringae	AvrPtoB	E3-ubiquitin ligase	Ubiquitylation	Fen	[43–46]
S. Typhimurium	SseL	Deubiquitylase	Deubiquitylation	Unknown	[51,52]
C. trachomatis	ChlaDUB1, 2	Deubiquitylase/deneddylase	Deubiquitylation/deneddylation	Unknown	[53]
X. campestris	XopD	DeSUMOylase	DeSUMOylation	Unknown	[60–62]
X. campestris	AvrXv4	DeSUMOylase	DeSUMOylation	Unknown	[63]
V. parahaemolyticus	VopS	AMPylator	AMPylation	Rho GTPases	[70,72]
H. somni	IbpA	AMPylator	AMPylation	Rho GTPases	[71,72]
C. botulinum	C3 exoenzyme	ADP-ribosyl transferase	ADP-ribosylation	Rho GTPases	[73,74,77]
B. cereus	C3 transferase	ADP-ribosyl transferase	ADP-ribosylation	Rho GTPases	[75,77]
S. aureus	EDIN toxins	ADP-ribosyl transferase	ADP-ribosylation	Rho GTPases	[76,77]
C. botulinum	C2 toxin	ADP-ribosyl transferase	ADP-ribosylation	Actin	[78,79]
C. perfringens	Iota toxin	ADP-ribosyl transferase	ADP-ribosylation	Actin	[79]
S. Typhimurium	SpvB	ADP-ribosyl transferase	ADP-ribosylation	Actin	[80]
P. luminescens	TccC3	ADP-ribosyl transferase	ADP-ribosylation	Actin	[81]
V. cholerae	Cholera toxin	ADP-ribosyl transferase	ADP-ribosylation	G proteins	[82]
B. pertussis	Pertussis toxin	ADP-ribosyl transferase	ADP-ribosylation	G proteins	[83]
E. coli	Heat-labile LT enterotoxin	ADP-ribosyl transferase	ADP-ribosylation	G proteins	[84]
P. aeruginosa	Exotoxin A	ADP-ribosyl transferase	ADP-ribosylation	EF2	[85]
C. diphtheriae	Diphtheria toxin	ADP-ribosyl transferase	ADP-ribosylation	EF2	[86]
P. aeruginosa	Cytotoxin ExoS	ADP-ribosyl transferase	ADP-ribosylation	ERMs, Ras	[87,88]
P. aeruginosa	Cytotoxin ExoT	ADP-ribosyl transferase	ADP-ribosylation	Crk	[89]
Yersinia	YopJ/YopP	Acetyltransferase	Acetylation	MAPK kinases, IKKα, IKKβ	[49,50]
V. parahaemolyticus	VopA	Acetyltransferase	Acetylation	MAPK kinases	[90]
C. difficile	Toxin A and B	Glucosyltransferase	Glucosylation	Rho GTPases	[95,96]
C. sordelli	Hemorrhagic and lethal toxins	Glucosyltransferase	Glucosylation	Rho GTPases	[97,98]
C. novyi	α-toxin	N-acetyl-glucosamine transferase	N-acetyl-glucosamination	Rho GTPases	[99]
L. pneumophila	Lgt1, 2, 3	Glucosyltransferase	Glucosylation	eEF1A	[100,101]
E. coli	CNF1	Deamidase	Deamidation	Rho GTPases	[102,103]
Bordetella	DNT	Deamidase/polyamine transferase	Deamidation/polyamination	Rho GTPases	[104,105]
Y. enterocolitica	YopT	Protease	Proteolysis	Rho GTPases	[106,107]
B. fragilis	BFT	Protease	Proteolysis	E-cadherin	[108]
C. histolyticum	Collagenase	Collagenase	Proteolysis	Collagen, gelatin	[109]
B. anthracis	Anthrax LF	Metalloprotease	Proteolysis	MAPK kinases	[110]
C. botulinum	Botulinum toxins	Protease	Proteolysis	SNARE	[109]
C. tetani	Tetanus toxin	Protease	Proteolysis	SNARE	[109]

Table 2
Bacterial effectors indirectly triggering host protein post-translational modifications.

Bacteria	Effector	Host targets	Modification	Reference(s)
B. anthracis	Anthrax toxin	TEM8, CMG2	Ubiquitylation	[27,28]
L. monocytogenes	InlB	Met	Phosphorylation/ubiquitylation	[29–31]
L. monocytogenes	InlA	E-cadherin	Phosphorylation/ubiquitylation	[32]
R. conorii	rOmpB	Ku70	Ubiquitylation	[33]
E. coli	CNF1	Rho GTPases	Polyubiquitylation/degradation	[34]
Shigella	OspG	IκBα	Inhibition of ubiquitylation	[35]
L. monocytogenes	LLO	Histones	Deacetylation/dephosphorylation	[93]
L. monocytogenes	LLO	SUMOylated proteins	DeSUMOylation/degradation	[64]

It should be noted that the restriction of LLO activity to vacuolar compartments is also due to pH regulation as this toxin is quickly denatured and inactivated in compartments with neutral pH such as cytoplasm [24].

In other cases, bacterial factors can hijack the host ubiquitylation machinery to modify their localization in the host cell. This is the case for SopB, a phosphoinositide phosphatase of *S.* Typhimurium injected via a T3SS inside the host cell during infection. This bacterial enzyme acts either at the plasma membrane, where it modulates actin-mediated bacterial invasion or at the level of *Salmonella* Containing Vacuole (SCV), a membrane-bound compartment where bacteria reside and where SopB regulates vesicular trafficking and bacterial intracellular growth. SopB was shown to be multi-monoubiquitylated. These modifications are required both for the regulation of SopB activity at the plasma membrane and for the correct targeting of SopB to SCV compartment [25,26].

3.3. Bacterial induced ubiquitylation of host proteins

Some bacterial effectors trigger pathways involving ubiquitylation of host proteins. This is the case for some bacterial toxins, like the tripartite anthrax toxin of *Bacillus anthracis*, which exploits ubiquitylation to mediate its endocytosis into the host cell. The

Table 3
Bacterial effectors post-translationally modified upon infection.

Bacteria	Effector	Modification	Reference(s)
L. monocytogenes	SOD	Phosphorylation	[115]
L. monocytogenes	ActA	Phosphorylation	[116]
Shigella	OspG	Autophosphorylation	[35]
L. monocytogenes	LLO	Phosphorylation/polyubiquitylation/degradation	[22,23]
S. Typhimurium	SopE, SptP	Polyubiquitylation/degradation	[20]
S. Typhimurium	SopB	Ubiquitylation	[25,26]

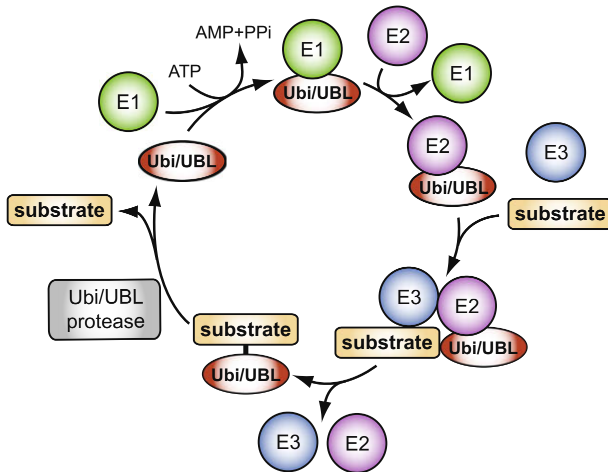

Fig. 3. Ubiquitin and ubiquitin-like proteins conjugation machineries. Ubiquitin (Ubi) and UBLs are small polypeptides that can be attached to substrate proteins via related enzymatic pathways. These polypeptides are first activated by an E1 enzyme in an ATP-dependent manner, then transferred to an E2 conjugating enzyme and eventually conjugated to a substrate protein with the help of E3 ligases. The set of E1, E2 and E3 enzymes involved is specific of each Ubi/UBL protein. Ubiquitin and UBLs can be deconjugated from target proteins by the action of specific proteases.

Anthrax Protective Antigen (PA) component of this toxin enables cell binding, endocytosis and injection of the two enzymatic components, i.e. Anthrax Lethal Factor and Edema Factor, into the cytoplasm of the intoxicated cell. PA can bind two cell surface receptors: TEM8 (Tumor Endothelial Marker 8) or CMG2 (Capillary Morphogenesis Gene 2). These receptors are subsequently ubiquitylated by the host E3 ubiquitin ligase Cbl, which triggers the internalization of the toxin complex into early endosomes by a clathrin-dependent endocytosis [27,28]. This ubiquitylation is thus essential for the intracellular activity of this toxin. Interestingly, some bacteria, like *L. monocytogenes*, also exploit ubiquitin-dependent endocytosis machinery to mediate their internalization. *Listeria* uses the surface protein InlB to invade a variety of cell types. This protein interacts with and triggers the autophosphorylation of Met, the hepatocyte growth factor receptor [29]. Met is then monoubiquitylated by the E3 ligase Cbl which leads to the recruitment of the endocytic machinery [30] (Fig. 4). This ubiquitin-dependent recruitment of the endocytic machinery, and in particular the recruitment of clathrin, is required for InlB-mediated invasion of cells by *Listeria* [30,31]. In addition to InlB, *Listeria* can invade epithelial cells using the InlA surface protein that interacts with the junctional protein E-cadherin. InlA induces two successive post-translational modifications on E-cadherin: a Src-mediated tyrosine phosphorylation and an ubiquitylation by the Hakai E3 ubiquitin ligase (Fig. 4). Again, this ubiquitylation of E-cadherin is required for the recruitment of the endocytic machinery and optimal bacterial internalization [32]. Finally, invasion of eukaryotic cells by *Rickettsia conorii*, an obligate intracellular bacteria responsible for spotted fever, also requires the Cbl-mediated ubiquitylation of Ku70, a receptor for this bacteria [33].

Toxins secreted by bacteria, can target host factors to polyubiquitylation and degradation. CNF1 (Cytotoxic Necrotizing Factor-1) is a toxin encoded by uropathogenic *Escherichia coli* that, once translocated in the host cell, catalyzes the permanent activation of host Rho GTPases via deamidation of these proteins (see below). However, this effect is only transient as the host cell triggers in response the polyubiquitylation of deamidated Rho GTPases leading to their proteasomal degradation [34]. Thus, CNF1 induces only a transient activation of Rho GTPases, as subsequent recruitment of the host cell ubiquitylation machinery leads to Rho GTPases degradation.

3.4. Targeting of the host ubiquitylation machinery by bacterial effectors

Bacterial effectors can target components of the ubiquitylation machinery of the host cell, thereby altering ubiquitylation of host proteins. This is the case for OspG, a T3SS effector of *S. flexneri*. This effector binds to various E2 ubiquitin-conjugating enzymes of the host cell. Among them, UbcH5 is an E2 enzyme involved in the ubiquitylation and degradation of IκBα, an essential inhibitor of the NF-κB pathway [35]. NF-κB has a pivotal role in many cellular processes, including the inflammatory and immune responses and, therefore, is tightly regulated. Activation of the NF-κB pathway proceeds via the activation of the IκB kinase (IKK) complex, leading to the phosphorylation of IκBα, an inhibitor of this pathway sequestrating NF-κB in the cytoplasm. Phosphorylated IκBα is then recognized by the host ubiquitylation machinery, polyubiquitylated and finally degraded by the proteasome. This allows the release and translocation of NF-κB in the nucleus where it acts as a transcription factor on a large set of genes, including genes of the immune response. OspG, by interacting with specific E2 ubiquitin conjugating enzymes, interferes with the ubiquitylation of IκBα [35], prevents it degradation and thus impairs NF-κB activation induced by TNFα stimulation. OspG thereby negatively regulates the NF-κB-mediated inflammatory response upon invasion of the intestinal epithelium. Consistently, a *Shigella* strain defective for OspG induces a stronger inflammatory response than the wild type strain during infection of rabbit ileal loops [35].

3.5. Bacterial effectors mimicking components of the host ubiquitylation machinery

Bacterial effectors can directly mimic enzymes of the host ubiquitylation machinery, like E3 ubiquitin ligases or DUBs. IpaH9.8, a *S. flexneri* T3SS effector, displays an E3 ubiquitin ligase activity and dampens the NF-κB-mediated inflammatory response to bacterial infection [36,37]. IpaH9.8 is indeed able to mediate the polyubiquitylation of the NEMO/IKKγ protein, a component of the IKK complex, which then undergoes proteasome-dependent degradation thereby perturbing NF-κB activation [37]. SopA, a T3SS effector of *S.* Thyphimurium, is another example of a bacterial factor with E3 ubiquitin ligase activity, which is involved in the host inflammatory response against *Salmonella* [38,39]. *Legionella pneumophila*, the etiological agent of pneumonia Legionnaire's disease, also

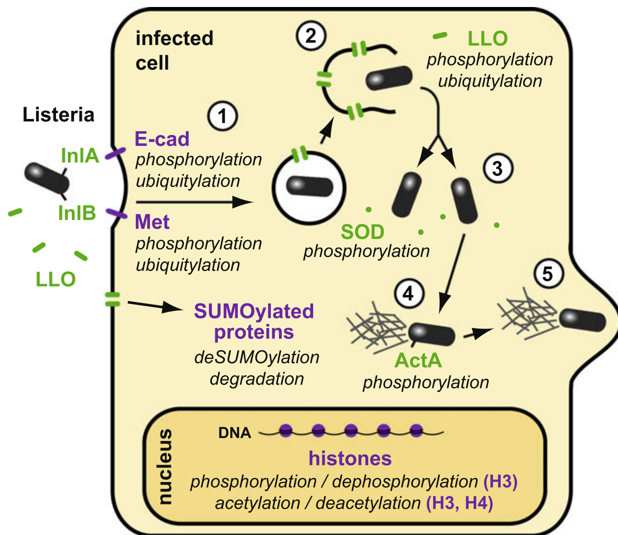

Fig. 4. Post-translational modifications occurring during *Listeria* infection. After entry into a host cell, *Listeria monocytogenes* is entrapped in an intracellular vacuole (1). The membrane of this vacuole is disrupted by the secretion of two bacterial phospholipases and the pore-forming toxin Listeriolysin O (LLO) (2). This allows the escape of bacteria into the cytoplasm where they replicate (3) and start to polymerize actin, leading to the formation of the so-called actin comet tails (4). Actin polymerization allows bacteria to move in the host cell cytoplasm and to pass into a neighbouring cell by forming protrusions in the plasma membrane (5). During *Listeria* infectious process, several host proteins (in purple) are post-translationally modified, including E-cadherin (E-cad), Met receptor, histones H3 and H4. Bacterial effectors (in green) such as LLO, SOD (SuperOxide Dismutase) or ActA, can also been post-translationally modified. In addition, *Listeria* can counteract some host proteins PTMs such as SUMOylation, acetylation or phosphorylation.

codes for different factors mimicking eukaryotic E3 ubiquitin ligase, including LubX, a *Legionella* effector mediating in vitro the ubiquitylation of the host protein Clk1 (Cdc2-like kinase 1) [40–42]. Factors with E3 ubiquitin ligase activity can also be encoded by plant pathogens. *P. syringae* factor AvrPtoB, for example, is able to bind a plant E2 ubiquitin conjugating enzyme (AtUBC8) and possesses E3 ubiquitin ligase activity. This factor is essential for inhibition of host programmed cell death defences in susceptible plants, and enabling of bacterial growth [43–45]. Of note, SopA, LubX and AvrPtoB share sequence and structural homologies with the two major classes of eukaryotic E3 ubiquitin ligases (i.e. HECT and RING E3 ligases, respectively) and may have been acquired through horizontal gene transfer from a eukaryotic host. In contrast, some bacterial E3 ubiquitin ligases, including IpaH9.8, have interestingly evolved a novel structure to functionally mimic the activity of eukaryotic E3 ubiquitin ligases [46].

The first bacterial factor displaying deubiquitylase activities was identified in *Yersinia*. It is a T3SS effector named YopJ (YopP in *Y. enterocolitica)* that plays an important role in the inhibition of the NF-κB-mediated inflammatory response and the induction of apoptosis in macrophages. This protein shares structural homologies with cysteine proteases and was initially proposed to act as a deSUMOylating enzyme by removing SUMO, an ubiquitin-like protein, from its target proteins [47]. However, subsequent studies have shown that YopJ displays deubiquitylase rather than deSUMOylase activity [48] although the exact roles of this activity in the inhibiton of the NF-κB pathway remain unclear. Furthermore, YopJ was shown to have also an acetyltransferase activity and to acetylate MKKs (MAPK Kinases) on critical serine or threonine residues thereby preventing MKKs activation [49,50] (see below). In addition to YopJ, SseL, a *S.* Thyphimurium effector, also shares structural homologies with cysteine proteases and displays deubiquitylating activity in vitro [51,52]. Consistently, infection of epithelial cells and macrophages with an *sseL* mutant strain of *Salmonella* leads to the accumulation of host or bacterial ubiquitylated proteins at, or in vicinity of SCV membranes [51]. *SseL* mutant strains do not display replication defect but are defective for late-stage cytotoxic effect on macrophages and are attenuated for virulence in the systemic phase of infection in mice. SseL was shown to inhibit IκBα ubiquitylation in response to TNFα, suggesting that it may act directly on K48-linked chains that targets IκBα to proteasomal degradation. This is in agreement with the observed in vivo activation of the NF-κB pathway induced by SseL-deficient bacteria [52]. Finally, *Chlamydia trachomatis*, an obligate intracellular bacterium, also encodes two proteases (*Chla*DUB1 and 2) that were shown to have deubiquitylating activities in vitro [53]. However, the roles of these bacterial proteases in *Chlamydia* infection remain to be established [53].

4. SUMOylation and conjugation of other ubiquitin-like proteins

Besides ubiquitin, a whole family of small proteins can be covalently linked to protein substrates (Fig. 3). These ubiquitin-like proteins share a common three-dimensional structure. SUMO (Small Ubiquitin-like MOdifier) is a ∼10 kDa polypeptide belonging to UBLs and found ubiquitously in the eukaryotic kingdom. The human genome encodes three functional SUMO proteins that can be linked to distinct and overlapping sets of proteins [54]. SUMOylation, i.e. the covalent linkage of SUMO on a lysine residue of a substrate protein, requires a set of different enzymes, in a fashion analogous to ubiquitylation. In humans, the SUMOylation machinery is composed of an E1 SUMO enzyme (the SAE1/SAE2 heterodimer), an E2 SUMO enzyme (Ubc9), and E3 SUMO enzymes that enhance SUMO conjugation of specific targets. SUMOylation, as ubiquitylation, is essential for many different cellular functions. Several hundreds of SUMO targets have now been identified, involved in transcription regulation, maintenance of genome integrity, intracellular transport, stress responses, protein stability and many other biological processes [55,56].

Consistent with the essential role of SUMOylation in the host cell, it has been shown that pathogens can interfere with this post-translational modification. Proteins from pathogens can either be substrate for SUMOylation or alter the SUMOylation of some host proteins. Such mechanisms were first documented with viruses for which several viral proteins were shown to be SUMOylated during infection. There are also some examples of viral proteins which either impair SUMOylation of some specific host targets or modify the SUMOylation machinery itself [57]. Among these viral proteins, Gam1, an avian adenoviral protein, targets the E1 SUMO enzyme by inducing the recruitment of an ubiquitin ligase complex on the SAE1/SAE2 heterodimer leading to the proteasomal degradation of SAE1 [58,59]. This blockade of the SUMOylation machinery leads to a global deSUMOylation of host proteins. The precise biological role of the interference of viruses on the SUMOylation of the host cell remains, however, often elusive [57].

In contrast to viruses, little is known concerning the putative link between pathogenic bacteria and SUMOylation. XopD is a T3SS effector of the plant pathogen *Xanthomonas campestris* pathovar *vesicatoria* that promotes bacterial growth and suppresses host defence and pathogen-induced cell death [60]. XopD displays a cysteine protease activity with a strong specificity for plant SUMO substrates. It triggers a global deSUMOylation of host proteins when expressed in plant cells [61,62]. The exact roles of these deSUMOylations in the repression of transcription of host

genes during infection, as well as the targets of this protease, remain to be characterized [60]. *Xanthomonas* possesses another T3SS effector, named AvrXv4, that shares structural homologies with known deSUMOylases. This factor, when expressed in plant cells, leads to a reduction of host SUMO-conjugated proteins. However, its contribution in *Xanthomonas* virulence remains to be determined [63].

The first putative link between SUMOylation and a human bacterial pathogen was reported in the case of the *Yersinia* YopJ effector (see above). This protein, which shares structural homologies with the yeast ubiquitin-like protease 1 (Ulp1), was proposed to target SUMOylated proteins of the host cell [47]. However, as aforementioned, this protein displays instead deubiquitylase and/or acetyltransferase activities [48–50].

A recent study that focused on *L. monocytogenes* has revealed that this pathogenic bacterium can directly target the SUMOylation machinery [64] (Fig. 4). Listeriolysin O (LLO), the pore-forming toxin secreted by *Listeria,* was shown to trigger the degradation of Ubc9 (the human E2 SUMO enzyme) in infected cells. As there is only one E2 SUMO enzyme in humans, in contrast to the situation for the ubiquitylation machinery in which dozens of E2 enzyme are found, degradation of Ubc9 leads to a blockade of SUMOylation and a global deSUMOylation of host proteins in infected cells. In addition, LLO was also shown to induce the degradation of some host SUMOylated proteins. This loss of SUMO-conjugated proteins was shown to be beneficial for efficient infection by *Listeria*. Interestingly, other pore-forming toxins closely related to Listeriolysin O were also shown to induce Ubc9 degradation, indicating that inhibition of SUMOylation by pathogens may be a widespread phenomenon [64].

Besides SUMO, there are many other ubiquitin-like proteins encoded in the human genome including NEDD8 or ISG15 (reviewed in [65]). The roles of these ubiquitin-like modifications in bacterial infection remain to be established. In the case of NEDD8, it was reported that non-pathogenic commensal bacteria act on the neddylation (i.e. the covalent linkage to NEDD8) of some host factors. Indeed, bacterial fermentation products, like butyrate or other short-chained fatty acids, can induce the local production of reactive oxygen species in intestinal epithelial cells. This induces the inactivation of redox-sensitive proteins such as Ubc12, the NEDD8 E2 enzyme, and thus blocks the neddylation machinery. This inactivation leads, in particular, in the alteration of Cullin-1 neddylation and in suppressive effects on the NF-κB pathway [66–68]. It has been proposed that this mechanism may participate to the inflammatory tolerance of the mammalian intestinal epithelium towards commensal bacteria [66]. In addition to these commensal bacteria, the aforementioned *Chla*DUB1 and 2 proteases from *C. trachomatis* that possess deubiquitylase activities in vitro were also reported to have deneddylating activities [53]. Again, the roles of these bacterial proteases in *Chlamydia* infection remain unknown. In the case of ISG15, an interferon-stimulated gene, there is no reported link between this UBL and bacterial pathogens. However, this issue is to be explored as this protein is well-known for its antiviral functions (reviewed in [69]).

In conclusion, the study of these other ubiquitin-like modifications and their roles in bacterial infection might provide insights into unknown mechanisms used by pathogens to manipulate activities of key host proteins.

5. AMPylation

AMPylation is a recently discovered post-translational modification triggered by bacteria. Indeed, two virulence factors encoded by two different pathogenic bacteria, namely VopS from *Vibrio parahaemolyticus* and IbpA from *Histophilus somni*, use ATP to covalently add an adenosine monophosphate (AMP) moiety to threonine or tyrosine residues of some Rho GTPases [70,71]. This activity involves a conserved domain of VopS and IbpA called fic domain (for filamentation induced by cAMP domain), which is also found in eukaryotic proteins [70–72]. The addition of AMP to Rho GTPases prevents their interaction with downstream effectors leading to the disruption of host actin cytoskeleton in the infected cells. Although firstly described as a modification triggered by bacterial effectors, AMPylation has now been shown to be naturally occurring in eukaryotic cells [70–72].

6. ADP-ribosylation

ADP-ribosylation is a post-translational modification catalyzed by many different bacterial toxins and has been described more than four decades ago. These toxins transfer the ADP-ribose group from NAD (Nicotinamide Adenine Dinucleotide) to Arg, Cys and Asn residues of various host target proteins to alter their function and, subsequently, key metabolic processes.

Clostridium botulinum C3 exoenzyme, as well as other C3-like exoenzymes (like *Bacillus cereus* C3 transferase or *Staphylococcus aureus* EDIN toxins), mediates the ADP-ribosylation of Rho GTPases [73–76]. This modification blocks the Rho GTPases activation by GEFs, leading to major changes in the signalling pathways regulated by these proteins and, in particular, to actin polymerization (reviewed in [77]). In addition to Rho GTPases, actin can also be ADP-ribosylated by several bacterial toxins thereby deregulating the host cell cytoskeleton. *C. botulinum* C2 toxin was the first discovered toxin with such an activity [78]. *C. perfringens* iota toxin, *Salmonella* SpvB toxin and *Photorhabdus luminescens* TccC3 toxin are other examples of bacterial proteins that all mediate ADP-ribosylation of actin [79–81].

Another important class of host proteins ADP-ribosylated by bacterial toxins are G proteins, which are targeted by cholera toxin (*Vibrio cholerae*), pertussis toxin (*Bordetella pertussis)* and heat-labile LT enterotoxins (*E. coli)* [82–84]. Other cellular targets that can be ADP-ribosylated include Elongation Factor 2 modified by *Pseudomonas aeruginosa* Exotoxin A and *Corynebacterium diphtheriae* diphtheria toxin (DT) [85,86], ERMs (for Ezrin, Radixin and Moesin) and Ras, modified by *P. aeruginosa* cytotoxin ExoS [87,88], and Crk proteins, modified by *P. aeruginosa* cytotoxin ExoT [89].

7. Acetylation

Extensive studies on the inhibition of MAPK and NF-κB signalling by the *Yersinia* YopJ effector have led to the discovery that this virulence factor was able to mediate acetylation of host proteins, including the MAPK kinases MEK2, MKK6 and the IKKα and β kinases of the IKK complex [49,50]. This acetylation occurs on serine and threonine residues in the activation loop of the targeted kinases and prevents the phosphorylation of these residues, a step required for kinase activation. Similarly, VopA, a YopJ-like protein encoded by *V. parahaemolyticus*, acetylates a lysine residue of MAPK kinases that blocks the binding of ATP to these enzymes and leads to inactive phosphorylated kinases [90].

Another important class of host proteins modified by acetylation, and other modifications as well, are histones [91]. The acetylation of lysine residues in histone tails is one of the many modifications that can affect these proteins and that constitutes the so-called "histone code", which plays a fundamental role in transcription regulation. Acetylation is often associated with active transcription, probably by rendering chromosomal domains more accessible to the transcription machinery. Some bacteria modify the acetylation of histones upon infection and thereby alter the transcription of specific genes (Fig. 4). For example, *L. monocytogenes* infection of endothelial cells was linked to the

activation of p38 and ERK MAPK pathways. This activation correlates with an increase in acetylation of histone H3 and H4 (together with an increase in phosphorylation of histone H3) and the transcriptional activation of MAPK induced genes, such as IL-8 [92]. Another report demonstrated that Listeriolysin O, the pore-forming toxin produced by *Listeria*, induces a decrease in the acetylation of histone H4 in epithelial cells, together with a decrease in the phosphorylation of histone H3 [93]. A transcriptome analysis of the host genes whose expression is modulated by LLO revealed a downregulation of some genes involved in immunity, in correlation with the LLO-induced modifications of histones. In addition, infection of epithelial cells by *L. monocytogenes* leads to a decrease in the acetylation of histone H3, in an LLO-independent manner [93].

Another example of intracellular bacterium modulating acetylation of histones is *Anaplasma phagocytophilum*, a tick-transmitted *Rickettsia*. It was demonstrated that infection of macrophages by this intracellular bacterium leads to silencing of host defence gene expression. This was correlated to an increase in the activity of HDAC1 and a decrease in histone H3 acetylation on the promoters of defence genes [94].

8. Glycosylation

Two major groups of bacterial toxins have been described to possess glycosyltransferase activity. The first one is composed of toxins produced by *Clostridium* species. Toxins A and B from *C. difficile*, as well as hemorrhagic and lethal toxins from *C. sordelli*, transfer the glucose moiety from UDP-glucose to threonine residues of Rho GTPases [95–98]. This modification occurs in the so-called switch-I region of Rho GTPases, a conserved domain involved in interactions of these proteins with their effectors. Glucosylation of Rho-GTPases leads to the inhibition of effector coupling, nucleotide exchange by GEFs and membrane cycling of Rho GTPases that stay at the membrane even in their inactive form. This impairment of Rho GTPases results in extensive morphological changes by redistribution of the actin cytoskeleton and several other cellular alterations (reviewed in [77]). In addition, *C. novyi* α-toxin can modify Rho proteins by attachment of another type of sugar, N-acetyl glucosamine, which has similar consequences on Rho GTPases functions as glucosylation [99].

A second group of glycosyltransferases are toxins produced by *L. pneumophila*. These toxins glucosylate a serine residue of the GTPase domain of eEF1A (eukaryotic Elongation Factor 1A) and thereby inhibit host cell protein synthesis and induce death of target cells [100,101].

9. Deamidation and polyamination

CNF1, the lethal toxin causing tissue damage produced by some pathogenic strains of *E. coli*, induces the deamidation of a specific glutamine residue of Rho GTPases into glutamic acid. This generates "constitutively" active Rho GTPases and leads to alteration of the actin cytoskeleton dynamic [102,103]. As mentioned above, this constitutive activation of Rho GTPases is only transient as it is followed by its polyubiquitylation and subsequent degradation [34]. The dermonecrotizing toxin (DNT), produced by various *Bordetella* species, also activates Rho proteins and leads to the massive formation of actin stress fibers and focal adhesions in intoxicated cultured cells. Although DNT shares sequence homologies with CNF and is also able to deamidate Rho GTPases, the preferred reaction catalyzed by this toxin is polyamination, i.e. the attachment of polyamines, such as putrescine, spermine and spermidine, on a glutamine residue of Rho GTPases that becomes constitutively active [104,105].

10. Proteolysis

Proteolysis is an irreversible post-translational modification. It is, as other PTMs, a very common process used to regulate the activity of host factors. Proteolysis events during infection can be triggered either by host cellular proteases or by bacterial factors displaying proteolytic activities. We will focus here on the bacterial effectors that cleave host proteins and will not detail all the cellular pathways induced by pathogens that involve proteolytic events, such as induction of apoptosis via caspase proteolytic activities.

Several bacterial proteins possess proteolytic activities. YopT, an effector of *Y. enterocolitica*, displays such an activity. It triggers the cleavage of Rho GTPases at a specific site, which releases the isoprenylated C-terminal cysteine of these proteins [106]. As isoprenylation of Rho GTPases is essential for their membrane binding and proper function, YopT cleavage impairs the cellular functions of these enzymes. This results in the disruption of the actin cytoskeleton and contributes to the antiphagocytic effect induced by *Yersinia*, in addition to the effects of other effectors like YopH or YpkA/YopO (see above) [107].

Host cell surface molecules can also be targeted by bacterially encoded proteases. For example, *Bacteroides fragilis* enterotoxin (BFT) is a secreted protein with characteristics of metalloproteases found in strains of *B. fragilis* associated with diarrheal diseases. When added to tissue-cultured cells, this toxin cleaves the extracellular portion of E-cadherin, a transmembrane protein responsible for cell-cell adhesion in epithelial cells [108]. BFT thus alters tight junction function in polarized intestinal epithelial cells. *Clostridium histolyticum* collagenases are other examples of bacterial metalloproteases that specifically target collagen and gelatin, two proteins of the extracellular matrix. These bacterial enzymes play an important role in the degradation of the connective tissue observed during myonecrosis and gangrene associated with *C. histolyticum* (reviewed in [109]).

The Anthrax Lethal Factor (LF), which is a part of the Anthrax tripartite toxin encoded by *B. anthracis*, is a metalloprotease responsible for the shock-like symptoms observed in systemic anthrax infection. This toxin is translocated in the cytoplasm of targeted cells via the Anthrax Protective Antigen. Once in the cytoplasm, LF cleaves the N-terminus of MAPK kinases. This cleavage prevents the activation of downstream MAPKs, by disrupting a critical docking interaction, and functionally impairs cells of both the innate and adaptative immune systems of the host (reviewed in [110]).

C. botulinum and *C. tetani* neurotoxins constitute other examples of bacterial factors displaying proteolytic activities. Botulinum toxins are ingested through contaminated food or, in the case of an intestinal colonization by *C. botulinum*, are produced by bacteria directly in the intestine. These toxins then cross the digestive mucosa by transcytosis, target motoneuron endings, and are delivered in the cytoplasm of intoxicated neurons where they exert their proteolytic activities. Botulinum toxins trigger the cleavage of neuronal VAMP-1 (Vesicular-Associated Membrane Protein-1), SNAP25 (Soluble N-ethylmaleimide-sensitive factor Accessory Protein 25) or Syntaxin, which all belong to the family of SNARE (SNAP Receptor) proteins. These cleavages lead to the blockade of exocytosis of the neuronal neurotransmettors containing vacuoles and thus the release of acetylcholine in the neuromuscular junction, leading to flaccid paralysis. In the case of *C. tetani*, the tetanus toxin is produced in wounds colonized by the bacterium and targets all types of nervous endings, although it acts mainly on motoneurons. In contrast to botulinum toxins, tetanus toxin, once internalized in a motoneuron, follows a retrograde transport and is delivered into the cytoplasm of the upstream inhibitory interneuron. The toxin then cleaves VAMP-1 and blocks the release of glycine or GABA

from the inhibitory interneuron leading to a permanent excitation of the downstream motoneuron and muscles (reviewed in [109]). Botulinum and tetanus neurotoxins constitute striking examples of bacterial factors modifying host proteins at the post-translational level that directly play a pivotal role in the infection-associated pathogenesis.

11. Conclusion

Interference with the host PTMs by bacterial pathogens is a widely used strategy allowing modification of host or bacterial key factor activities involved in infection.

Interestingly, some host proteins seem to be preferential targets for bacterial-induced PTMs. This is the case for example of Rho GTPases that are targeted by a wide variety of modifications, leading either to their constitutive activation (via their deamidation or polyamination), their inactivation (via their AMPylation, ADP-ribosylation, glucosylation or proteolysis) or their degradation (via their polyubiquitylation). Rho GTPases constitute central molecular switches of eukaryotic cells. Targeting these regulators might thus be an efficient strategy developed by pathogens to modify the activity of many different proteins of a given pathway, and thus trigger a coordinated response of the host cell, by targeting only one factor. Targeting of Rho GTPases also reflects the well established pivotal roles of the remodelling of host cell cytoskeleton in many aspects of bacterial infection. Consistently, many other components of the cell cytoskeleton have been reported to be post-translationally modified by bacterial pathogens. However, targeting of Rho GTPases by pathogens probably go beyond the alteration of cytoskeleton as these proteins are involved in many other pathways and, in particular, in the innate and adaptative immune response.

Other central pathways involved in the host immune response, like the MAPK or the NF-κB signalling pathways, are also preferential targets for pathogens. Interestingly, there has also been a recent emergence in the number of reports of bacterial effectors manipulating histones PTMs. These modifications, constituting the "histone code", allow a finely tuned regulation of host genes transcription. Histone modifications and chromatin remodelling induced by bacterial pathogens constitute a new exciting field of study of host-pathogen interactions [111].

One very interesting aspect of PTM is the possibility of cross talks between different types of modifications. The first situation corresponds to competition between different PTMs. This occurs in particular when two PTMs target the same residue (or closeby residues) in a substrate protein. SUMOylation, for example, can compete with ubiquitylation and proteasome degradation [55]. Acetylation was also shown to compete with phosphorylation [49,50]. The other case corresponds to synergies between different PTMs. For example, some studies have highlighted that ubiquitin can interact with SUMO to trigger proteasomal degradation of proteins. This interaction requires SUMO-dependent ubiquitin ligases, that specifically mediate the polyubiquitylation and degradation of polySUMOylated proteins (reviewed in [112]). In addition, phosphorylation, when localized downstream of a SUMOylation site, can increase the SUMOylation level of a protein by increasing the binding of Ubc9 on the target protein [113]. PTMs are thus organized in very complex networks.

Of note, "post-synthesis" modifications can occur on other molecules than proteins. Indeed, there are many examples of modifications of lipids (by phosphorylation, glycosylation) or nucleic acid (by methylation, ADP-ribosylation) that play fundamental roles in the biology of the cell. Pathogens also interfere with the modifications of these other cellular components as they do with proteins in the context of infection. This is the case for example with phosphoinositides lipids, with which pathogens can interfere in many different ways [114].

We have in this review focused on the major PTMs regulated by bacteria. However, there are many other types of modifications that may modulate infection like nitrosylation, addition of lipids or even disulfide bond formation/disruption. It is very likely that the number of cellular proteins reported to be post-translationally modified by bacterial pathogens will increase in the near future, as well as the diversity of the involved PTMs. Interestingly, some eukaryotic PTM, like AMPylation, were discovered through the study of bacterial pathogens. Future research in this domain will thus undoubtedly lead to exciting new discoveries into the field of host-pathogen interactions and the biology of mammalian cells.

Acknowledgements

Work in P.C. laboratory receive financial support from Institut Pasteur, Inserm, INRA, ERC (advanced Grant 233348) and the Foundation le Roch Les Mousquetaires. D.R. is supported by a fellowship from the Association pour la Recherche sur le Cancer. P.C. is an international research scholar of the Howard Hughes Medical Institute.

References

[1] Guan, K.L. and Dixon, J.E. (1990) Protein tyrosine phosphatase activity of an essential virulence determinant in Yersinia. Science 249, 553–556.
[2] Bliska, J.B., Guan, K.L., Dixon, J.E. and Falkow, S. (1991) Tyrosine phosphate hydrolysis of host proteins by an essential Yersinia virulence determinant. Proc. Natl. Acad. Sci. USA 88, 1187–1191.
[3] Viboud, G.I. and Bliska, J.B. (2005) Yersinia outer proteins: role in modulation of host cell signaling responses and pathogenesis. Annu. Rev. Microbiol. 59, 69–89.
[4] Persson, C., Carballeira, N., Wolf-Watz, H. and Fallman, M. (1997) The PTPase YopH inhibits uptake of Yersinia, tyrosine phosphorylation of p130Cas and FAK, and the associated accumulation of these proteins in peripheral focal adhesions. EMBO J. 16, 2307–2318.
[5] Black, D.S. and Bliska, J.B. (1997) Identification of p130Cas as a substrate of Yersinia YopH (Yop51), a bacterial protein tyrosine phosphatase that translocates into mammalian cells and targets focal adhesions. EMBO J. 16, 2730–2744.
[6] Bruce-Staskal, P.J., Weidow, C.L., Gibson, J.J. and Bouton, A.H. (2002) Cas, Fak and Pyk2 function in diverse signaling cascades to promote Yersinia uptake. J. Cell. Sci. 115, 2689–2700.
[7] Galyov, E.E., Hakansson, S., Forsberg, A. and Wolf-Watz, H. (1993) A secreted protein kinase of *Yersinia pseudotuberculosis* is an indispensable virulence determinant. Nature 361, 730–732.
[8] Navarro, L., Koller, A., Nordfelth, R., Wolf-Watz, H., Taylor, S. and Dixon, J.E. (2007) Identification of a molecular target for the Yersinia protein kinase A. Mol. Cell 26, 465–477.
[9] Juris, S.J., Shah, K., Shokat, K., Dixon, J.E. and Vacratsis, P.O. (2006) Identification of otubain 1 as a novel substrate for the Yersinia protein kinase using chemical genetics and mass spectrometry. FEBS Lett. 580, 179–183.
[10] Juris, S.J., Rudolph, A.E., Huddler, D., Orth, K. and Dixon, J.E. (2000) A distinctive role for the Yersinia protein kinase: actin binding, kinase activation, and cytoskeleton disruption. Proc. Natl. Acad. Sci. USA 97, 9431–9436.
[11] Prehna, G., Ivanov, M.I., Bliska, J.B. and Stebbins, C.E. (2006) Yersinia virulence depends on mimicry of host Rho-family nucleotide dissociation inhibitors. Cell 126, 869–880.
[12] Li, H. et al. (2007) The phosphothreonine lyase activity of a bacterial type III effector family. Science 315, 1000–1003.
[13] Brennan, D.F. and Barford, D. (2009) Eliminylation: a post-translational modification catalyzed by phosphothreonine lyases. Trends Biochem. Sci. 34, 108–114.
[14] Zhu, Y. et al. (2007) Structural insights into the enzymatic mechanism of the pathogenic MAPK phosphothreonine lyase. Mol. Cell 28, 899–913.
[15] Mazurkiewicz, P., Thomas, J., Thompson, J.A., Liu, M., Arbibe, L., Sansonetti, P. and Holden, D.W. (2008) SpvC is a Salmonella effector with phosphothreonine lyase activity on host mitogen-activated protein kinases. Mol. Microbiol. 67, 1371–1383.
[16] Zhang, J. et al. (2007) A *Pseudomonas syringae* effector inactivates MAPKs to suppress PAMP-induced immunity in plants. Cell Host Microbe 1, 175–185.
[17] Hochstrasser, M. (2009) Origin and function of ubiquitin-like proteins. Nature 458, 422–429.
[18] Hardt, W.D., Chen, L.M., Schuebel, K.E., Bustelo, X.R. and Galan, J.E. (1998) *S. typhimurium* encodes an activator of Rho GTPases that induces membrane ruffling and nuclear responses in host cells. Cell 93, 815–826.

[19] Fu, Y. and Galan, J.E. (1999) A salmonella protein antagonizes Rac-1 and Cdc42 to mediate host-cell recovery after bacterial invasion. Nature 401, 293–297.

[20] Kubori, T. and Galan, J.E. (2003) Temporal regulation of salmonella virulence effector function by proteasome-dependent protein degradation. Cell 115, 333–342.

[21] Schnupf, P. and Portnoy, D.A. (2007) Listeriolysin O: a phagosome-specific lysin. Microbes Infect. 9, 1176–1187.

[22] Schnupf, P., Portnoy, D.A. and Decatur, A.L. (2006) Phosphorylation, ubiquitination and degradation of listeriolysin O in mammalian cells: role of the PEST-like sequence. Cell Microbiol. 8, 353–364.

[23] Schnupf, P., Zhou, J., Varshavsky, A. and Portnoy, D.A. (2007) Listeriolysin O secreted by *Listeria monocytogenes* into the host cell cytosol is degraded by the N-end rule pathway. Infect. Immun. 75, 5135–5147.

[24] Schuerch, D.W., Wilson-Kubalek, E.M. and Tweten, R.K. (2005) Molecular basis of listeriolysin O pH dependence. Proc. Natl. Acad. Sci. USA 102, 12537–12542.

[25] Patel, J.C., Hueffer, K., Lam, T.T. and Galan, J.E. (2009) Diversification of a Salmonella virulence protein function by ubiquitin-dependent differential localization. Cell 137, 283–294.

[26] Knodler, L.A., Winfree, S., Drecktrah, D., Ireland, R. and Steele-Mortimer, O. (2009) Ubiquitination of the bacterial inositol phosphatase, SopB, regulates its biological activity at the plasma membrane. Cell Microbiol. 11, 1652–1670.

[27] Abrami, L., Liu, S., Cosson, P., Leppla, S.H. and van der Goot, F.G. (2003) Anthrax toxin triggers endocytosis of its receptor via a lipid raft-mediated clathrin-dependent process. J. Cell Biol. 160, 321–328.

[28] Abrami, L., Leppla, S.H. and van der Goot, F.G. (2006) Receptor palmitoylation and ubiquitination regulate anthrax toxin endocytosis. J. Cell Biol. 172, 309–320.

[29] Shen, Y., Naujokas, M., Park, M. and Ireton, K. (2000) InIB-dependent internalization of Listeria is mediated by the Met receptor tyrosine kinase. Cell 103, 501–510.

[30] Veiga, E. and Cossart, P. (2005) Listeria hijacks the clathrin-dependent endocytic machinery to invade mammalian cells. Nat. Cell Biol. 7, 894–900.

[31] Veiga, E. et al. (2007) Invasive and adherent bacterial pathogens co-Opt host clathrin for infection. Cell Host Microbe 2, 340–351.

[32] Bonazzi, M., Veiga, E., Cerda, J.P. and Cossart, P. (2008) Successive post-translational modifications of E-cadherin are required for InlA-mediated internalisation of *Listeria monocytogenes*. Cell Microbiol. 10, 2208–2222.

[33] Martinez, J.J., Seveau, S., Veiga, E., Matsuyama, S. and Cossart, P. (2005) Ku70, a component of DNA-dependent protein kinase, is a mammalian receptor for *Rickettsia conorii*. Cell 123, 1013–1023.

[34] Doye, A. et al. (2002) CNF1 exploits the ubiquitin-proteasome machinery to restrict Rho GTPase activation for bacterial host cell invasion. Cell 111, 553–564.

[35] Kim, D.W., Lenzen, G., Page, A.L., Legrain, P., Sansonetti, P.J. and Parsot, C. (2005) The *Shigella flexneri* effector OspG interferes with innate immune responses by targeting ubiquitin-conjugating enzymes. Proc. Natl. Acad. Sci. USA 102, 14046–14051.

[36] Rohde, J.R., Breitkreutz, A., Chenal, A., Sansonetti, P.J. and Parsot, C. (2007) Type III secretion effectors of the IpaH family are E3 ubiquitin ligases. Cell Host Microbe 1, 77–83.

[37] Ashida, H., Kim, M., Schmidt-Supprian, M., Ma, A., Ogawa, M. and Sasakawa, C. (2010) A bacterial E3 ubiquitin ligase IpaH9.8 targets NEMO/IKKgamma to dampen the host NF- kappaB-mediated inflammatory response. Nat. Cell Biol. 12, 66–73.

[38] Zhang, Y., Higashide, W.M., McCormick, B.A., Chen, J. and Zhou, D. (2006) The inflammation-associated Salmonella SopA is a HECT-like E3 ubiquitin ligase. Mol. Microbiol. 62, 786–793.

[39] Diao, J., Zhang, Y., Huibregtse, J.M., Zhou, D. and Chen, J. (2008) Crystal structure of SopA, a Salmonella effector protein mimicking a eukaryotic ubiquitin ligase. Nat. Struct. Mol. Biol. 15, 65–70.

[40] Kubori, T., Hyakutake, A. and Nagai, H. (2008) Legionella translocates an E3 ubiquitin ligase that has multiple U-boxes with distinct functions. Mol. Microbiol 67, 1307–1319.

[41] Lomma, M. et al. (2010) The Legionella pneumophila F-box protein Lpp2082 (AnkB) modulates ubiquitination of the host protein parvin B and promotes intracellular replication. Cell Microbiol. (e-pub).

[42] Price, C.T., Al-Khodor, S., Al-Quadan, T., Santic, M., Habyarimana, F., Kalia, A. and Kwaik, Y.A. (2009) Molecular mimicry by an F-box effector of Legionella pneumophila hijacks a conserved polyubiquitination machinery within macrophages and protozoa. PLoS Pathog. 5, e1000704.

[43] Abramovitch, R.B., Janjusevic, R., Stebbins, C.E. and Martin, G.B. (2006) Type III effector AvrPtoB requires intrinsic E3 ubiquitin ligase activity to suppress plant cell death and immunity. Proc. Natl. Acad. Sci. USA 103, 2851–2856.

[44] Janjusevic, R., Abramovitch, R.B., Martin, G.B. and Stebbins, C.E. (2006) A bacterial inhibitor of host programmed cell death defenses is an E3 ubiquitin ligase. Science 311, 222–226.

[45] Rosebrock, T.R., Zeng, L., Brady, J.J., Abramovitch, R.B., Xiao, F. and Martin, G.B. (2007) A bacterial E3 ubiquitin ligase targets a host protein kinase to disrupt plant immunity. Nature 448, 370–374.

[46] Hicks, S.W. and Galan, J.E. (2010) Hijacking the host ubiquitin pathway: structural strategies of bacterial E3 ubiquitin ligases. Curr. Opin. Microbiol. 13, 41–46.

[47] Orth, K. et al. (2000) Disruption of signaling by Yersinia effector YopJ, a ubiquitin-like protein protease. Science 290, 1594–1597.

[48] Zhou, H., Monack, D.M., Kayagaki, N., Wertz, I., Yin, J., Wolf, B. and Dixit, V.M. (2005) Yersinia virulence factor YopJ acts as a deubiquitinase to inhibit NF-kappa B activation. J. Exp. Med. 202, 1327–1332.

[49] Mukherjee, S., Keitany, G., Li, Y., Wang, Y., Ball, H.L., Goldsmith, E.J. and Orth, K. (2006) Yersinia YopJ acetylates and inhibits kinase activation by blocking phosphorylation. Science 312, 1211–1214.

[50] Mittal, R., Peak-Chew, S.Y. and McMahon, H.T. (2006) Acetylation of MEK2 and I kappa B kinase (IKK) activation loop residues by YopJ inhibits signaling. Proc. Natl. Acad. Sci. USA 103, 18574–18579.

[51] Rytkonen, A. et al. (2007) SseL, a Salmonella deubiquitinase required for macrophage killing and virulence. Proc. Natl. Acad. Sci. USA 104, 3502–3507.

[52] Le Negrate, G. et al. (2008) Salmonella secreted factor L deubiquitinase of *Salmonella typhimurium* inhibits NF-kappaB, suppresses IkappaBalpha ubiquitination and modulates innate immune responses. J. Immunol. 180, 5045–5056.

[53] Misaghi, S., Balsara, Z.R., Catic, A., Spooner, E., Ploegh, H.L. and Starnbach, M.N. (2006) *Chlamydia trachomatis*-derived deubiquitinating enzymes in mammalian cells during infection. Mol. Microbiol. 61, 142–150.

[54] Vertegaal, A.C., Andersen, J.S., Ogg, S.C., Hay, R.T., Mann, M. and Lamond, A.I. (2006) Distinct and overlapping sets of SUMO-1 and SUMO-2 target proteins revealed by quantitative proteomics. Mol. Cell. Proteomics 5, 2298–2310.

[55] Geiss-Friedlander, R. and Melchior, F. (2007) Concepts in sumoylation: a decade on. Nat. Rev. Mol. Cell Biol. 8, 947–956.

[56] Zhao, J. (2007) Sumoylation regulates diverse biological processes. Cell. Mol. Life Sci. 64, 3017–3033.

[57] Boggio, R. and Chiocca, S. (2006) Viruses and sumoylation: recent highlights. Curr. Opin. Microbiol. 9, 430–436.

[58] Boggio, R., Colombo, R., Hay, R.T., Draetta, G.F. and Chiocca, S. (2004) A mechanism for inhibiting the SUMO pathway. Mol. Cell 16, 549–561.

[59] Boggio, R., Passafaro, A. and Chiocca, S. (2007) Targeting SUMO E1 to ubiquitin ligases: a viral strategy to counteract sumoylation. J. Biol. Chem. 282, 15376–15382.

[60] Kim, J.G., Taylor, K.W., Hotson, A., Keegan, M., Schmelz, E.A. and Mudgett, M.B. (2008) XopD SUMO protease affects host transcription, promotes pathogen growth, and delays symptom development in xanthomonas-infected tomato leaves. Plant Cell 20, 1915–1929.

[61] Hotson, A., Chosed, R., Shu, H., Orth, K. and Mudgett, M.B. (2003) Xanthomonas type III effector XopD targets SUMO-conjugated proteins in planta. Mol. Microbiol. 50, 377–389.

[62] Chosed, R., Tomchick, D.R., Brautigam, C.A., Mukherjee, S., Negi, V.S., Machius, M. and Orth, K. (2007) Structural analysis of Xanthomonas XopD provides insights into substrate specificity of ubiquitin-like protein proteases. J. Biol. Chem. 282, 6773–6782.

[63] Roden, J., Eardley, L., Hotson, A., Cao, Y. and Mudgett, M.B. (2004) Characterization of the Xanthomonas AvrXv4 effector, a SUMO protease translocated into plant cells. Mol. Plant Microbe Interact. 17, 633–643.

[64] Ribet, D. et al. (2010) *Listeria monocytogenes* impairs SUMOylation for efficient infection. Nature 464, 1192–1195.

[65] Kerscher, O., Felberbaum, R. and Hochstrasser, M. (2006) Modification of proteins by ubiquitin and ubiquitin-like proteins. Annu. Rev. Cell Dev. Biol. 22, 159–180.

[66] Collier-Hyams, L.S., Sloane, V., Batten, B.C. and Neish, A.S. (2005) Cutting edge: bacterial modulation of epithelial signaling via changes in neddylation of cullin-1. J. Immunol. 175, 4194–4198.

[67] Kumar, A. et al. (2007) Commensal bacteria modulate cullin-dependent signaling via generation of reactive oxygen species. EMBO J. 26, 4457–4466.

[68] Kumar, A., Wu, H., Collier-Hyams, L.S., Kwon, Y.M., Hanson, J.M. and Neish, A.S. (2009) The bacterial fermentation product butyrate influences epithelial signaling via reactive oxygen species-mediated changes in cullin-1 neddylation. J. Immunol. 182, 538–546.

[69] Sadler, A.J. and Williams, B.R. (2008) Interferon-inducible antiviral effectors. Nat. Rev. Immunol. 8, 559–568.

[70] Yarbrough, M.L., Li, Y., Kinch, L.N., Grishin, N.V., Ball, H.L. and Orth, K. (2009) AMPylation of Rho GTPases by Vibrio VopS disrupts effector binding and downstream signaling. Science 323, 269–272.

[71] Worby, C.A. et al. (2009) The fic domain: regulation of cell signaling by adenylylation. Mol. Cell 34, 93–103.

[72] Kinch, L.N., Yarbrough, M.L., Orth, K. and Grishin, N.V. (2009) Fido, a novel AMPylation domain common to fic, doc, and AvrB. PLoS One 4, e5818.

[73] Aktories, K., Weller, U. and Chhatwal, G.S. (1987) *Clostridium botulinum* type C produces a novel ADP-ribosyltransferase distinct from botulinum C2 toxin. FEBS Lett. 212, 109–113.

[74] Braun, U., Habermann, B., Just, I., Aktories, K. and Vandekerckhove, J. (1989) Purification of the 22 kDa protein substrate of botulinum ADP-ribosyltransferase C3 from porcine brain cytosol and its characterization as a GTP-binding protein highly homologous to the rho gene product. FEBS Lett. 243, 70–76.

[75] Just, I., Selzer, J., Jung, M., van Damme, J., Vandekerckhove, J. and Aktories, K. (1995) Rho-ADP-ribosylating exoenzyme from *Bacillus cereus*. Purification, characterization, and identification of the NAD-binding site. Biochemistry 34, 334–340.

[76] Sugai, M. et al. (1992) Epidermal cell differentiation inhibitor ADP-ribosylates small GTP-binding proteins and induces hyperplasia of epidermis. J. Biol. Chem. 267, 2600–2604.

[77] Aktories, K. and Barbieri, J.T. (2005) Bacterial cytotoxins: targeting eukaryotic switches. Nat. Rev. Microbiol. 3, 397–410.
[78] Aktories, K., Barmann, M., Ohishi, I., Tsuyama, S., Jakobs, K.H. and Habermann, E. (1986) Botulinum C2 toxin ADP-ribosylates actin. Nature 322, 390–392.
[79] Mauss, S., Chaponnier, C., Just, I., Aktories, K. and Gabbiani, G. (1990) ADP-ribosylation of actin isoforms by *Clostridium botulinum* C2 toxin and Clostridium perfringens iota toxin. Eur. J. Biochem. 194, 237–241.
[80] Tezcan-Merdol, D., Nyman, T., Lindberg, U., Haag, F., Koch-Nolte, F. and Rhen, M. (2001) Actin is ADP-ribosylated by the *Salmonella enterica* virulence-associated protein SpvB. Mol. Microbiol. 39, 606–619.
[81] Lang, A.E., Schmidt, G., Schlosser, A., Hey, T.D., Larrinua, I.M., Sheets, J.J., Mannherz, H.G. and Aktories, K. (2010) *Photorhabdus luminescens* toxins ADP-ribosylate actin and RhoA to force actin clustering. Science 327, 1139–1142.
[82] Moss, J., Manganiello, V.C. and Vaughan, M. (1976) Hydrolysis of nicotinamide adenine dinucleotide by choleragen and its A promoter: possible role in the activation of adenylate cyclase. Proc. Natl. Acad. Sci. USA 73, 4424–4427.
[83] Katada, T. and Ui, M. (1982) Direct modification of the membrane adenylate cyclase system by islet-activating protein due to ADP-ribosylation of a membrane protein. Proc. Natl. Acad. Sci. USA 79, 3129–3133.
[84] Moss, J. and Richardson, S.H. (1978) Activation of adenylate cyclase by heat-labile *Escherichia coli* enterotoxin. Evidence for ADP-ribosyltransferase activity similar to that of choleragen. J. Clin. Invest. 62, 281–285.
[85] Iglewski, B.H. and Kabat, D. (1975) NAD-dependent inhibition of protein synthesis by *Pseudomonas aeruginosa* toxin. Proc. Natl. Acad. Sci. USA 72, 2284–2288.
[86] Collier, R.J. and Cole, H.A. (1969) Diphtheria toxin subunit active in vitro. Science 164, 1179–1181.
[87] Maresso, A.W., Baldwin, M.R. and Barbieri, J.T. (2004) Ezrin/radixin/moesin proteins are high affinity targets for ADP-ribosylation by *Pseudomonas aeruginosa* ExoS. J. Biol. Chem. 279, 38402–38408.
[88] Ganesan, A.K., Frank, D.W., Misra, R.P., Schmidt, G. and Barbieri, J.T. (1998) *Pseudomonas aeruginosa* exoenzyme S ADP-ribosylates Ras at multiple sites. J. Biol. Chem. 273, 7332–7337.
[89] Sun, J. and Barbieri, J.T. (2003) *Pseudomonas aeruginosa* ExoT ADP-ribosylates CT10 regulator of kinase (Crk) proteins. J. Biol. Chem. 278, 32794–32800.
[90] Trosky, J.E., Li, Y., Mukherjee, S., Keitany, G., Ball, H. and Orth, K. (2007) VopA inhibits ATP binding by acetylating the catalytic loop of MAPK kinases. J. Biol. Chem. 282, 34299–342305.
[91] Kouzarides, T. (2007) Chromatin modifications and their function. Cell 128, 693–705.
[92] Schmeck, B. et al. (2005) Intracellular bacteria differentially regulated endothelial cytokine release by MAPK-dependent histone modification. J. Immunol. 175, 2843–2850.
[93] Hamon, M.A., Batsche, E., Regnault, B., Tham, T.N., Seveau, S., Muchardt, C. and Cossart, P. (2007) Histone modifications induced by a family of bacterial toxins. Proc. Natl. Acad. Sci. USA 104, 13467–13472.
[94] Garcia-Garcia, J.C., Barat, N.C., Trembley, S.J. and Dumler, J.S. (2009) Epigenetic silencing of host cell defense genes enhances intracellular survival of the rickettsial pathogen *Anaplasma phagocytophilum*. PLoS Pathog. 5, e1000488.
[95] Just, I., Selzer, J., Wilm, M., von Eichel-Streiber, C., Mann, M. and Aktories, K. (1995) Glucosylation of Rho proteins by *Clostridium difficile* toxin B. Nature 375, 500–503.
[96] Just, I., Wilm, M., Selzer, J., Rex, G., von Eichel-Streiber, C., Mann, M. and Aktories, K. (1995) The enterotoxin from *Clostridium difficile* (ToxA) monoglucosylates the Rho proteins. J. Biol. Chem. 270, 13932–13936.
[97] Just, I., Selzer, J., Hofrnann, F., Green, G.A. and Aktories, K. (1996) Inactivation of Ras by *Clostridium sordellii* lethal toxin-catalyzed glucosylation. J. Biol. Chem. 271, 10149–10153.
[98] Genth, H., Hofmann, F., Selzer, J., Rex, G., Aktories, K. and Just, I. (1996) Difference in protein substrate specificity between hemorrhagic toxin and lethal toxin from *Clostridium sordellii*. Biochem. Biophys. Res. Commun. 229, 370–374.
[99] Selzer, J., Hofmann, F., Rex, G., Wilm, M., Mann, M., Just, I. and Aktories, K. (1996) Clostridium novyi alpha-toxin-catalyzed incorporation of GlcNAc into Rho subfamily proteins. J. Biol. Chem. 271, 25173–25177.
[100] Belyi, Y., Niggeweg, R., Opitz, B., Vogelsgesang, M., Hippenstiel, S., Wilm, M. and Aktories, K. (2006) Legionella pneumophila glucosyltransferase inhibits host elongation factor 1 A. Proc. Natl. Acad. Sci. USA 103, 16953–16958.
[101] Belyi, Y., Tabakova, I., Stahl, M. and Aktories, K. (2008) Lgt: a family of cytotoxic glucosyltransferases produced by *Legionella pneumophila*. J. Bacteriol. 190, 3026–3035.
[102] Schmidt, G., Sehr, P., Wilm, M., Selzer, J., Mann, M. and Aktories, K. (1997) Gln 63 of Rho is deamidated by *Escherichia coli* cytotoxic necrotizing factor-1. Nature 387, 725–729.
[103] Flatau, G., Lemichez, E., Gauthier, M., Chardin, P., Paris, S., Fiorentini, C. and Boquet, P. (1997) Toxin-induced activation of the G protein p21 Rho by deamidation of glutamine. Nature 387, 729–733.
[104] Masuda, M., Betancourt, L., Matsuzawa, T., Kashimoto, T., Takao, T., Shimonishi, Y. and Horiguchi, Y. (2000) Activation of rho through a cross-link with polyamines catalyzed by Bordetella dermonecrotizing toxin. EMBO J. 19, 521–530.
[105] Horiguchi, Y., Inoue, N., Masuda, M., Kashimoto, T., Katahira, J., Sugimoto, N. and Matsuda, M. (1997) Bordetella bronchiseptica dermonecrotizing toxin induces reorganization of actin stress fibers through deamidation of Gln-63 of the GTP-binding protein Rho. Proc. Natl. Acad. Sci. USA 94, 11623–11626.
[106] Shao, F., Merritt, P.M., Bao, Z., Innes, R.W. and Dixon, J.E. (2002) A Yersinia effector and a Pseudomonas avirulence protein define a family of cysteine proteases functioning in bacterial pathogenesis. Cell 109, 575–588.
[107] Trosky, J.E., Liverman, A.D. and Orth, K. (2008) Yersinia outer proteins: Yops. Cell Microbiol. 10, 557–565.
[108] Wu, S., Lim, K.C., Huang, J., Saidi, R.F. and Sears, C.L. (1998) *Bacteroides fragilis* enterotoxin cleaves the zonula adherens protein, E-cadherin. Proc. Natl. Acad. Sci. USA 95, 14979–14984.
[109] Popoff, M.R. and Bouvet, P. (2009) Clostridial toxins. Future Microbiol. 4, 1021–1064.
[110] Turk, B.E. (2007) Manipulation of host signalling pathways by anthrax toxins. Biochem. J. 402, 405–417.
[111] Hamon, M.A. and Cossart, P. (2008) Histone modifications and chromatin remodeling during bacterial infections. Cell Host Microbe 4, 100–109.
[112] Geoffroy, M.C. and Hay, R.T. (2009) An additional role for SUMO in ubiquitin-mediated proteolysis. Nat. Rev. Mol. Cell Biol. 10, 564–568.
[113] Hietakangas, V., Anckar, J., Blomster, H.A., Fujimoto, M., Palvimo, J.J., Nakai, A. and Sistonen, L. (2006) PDSM, a motif for phosphorylation-dependent SUMO modification. Proc. Natl. Acad. Sci. USA 103, 45–50.
[114] Pizarro-Cerda, J. and Cossart, P. (2004) Subversion of phosphoinositide metabolism by intracellular bacterial pathogens. Nat. Cell Biol. 6, 1026–1033.
[115] Archambaud, C., Nahori, M.A., Pizarro-Cerda, J., Cossart, P. and Dussurget, O. (2006) Control of Listeria superoxide dismutase by phosphorylation. J. Biol. Chem. 281, 31812–31822.
[116] Chong, R., Swiss, R., Briones, G., Stone, K.L., Guicicek, E.E. and Agaisse, H. (2009) Regulatory mimicry in *Listeria monocytogenes* actin-based motility. Cell Host Microbe 6, 268–278.