Tyrosine phosphorylation and bacterial virulence

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Protein phosphorylation on tyrosine has emerged as a key device in the control of numerous cellular functions in bacteria. In this article, we review the structure and function of bacterial tyrosine kinases and phosphatases. Phosphorylation is catalyzed by autophosphorylating adenosine triphosphate-dependent enzymes (bacterial tyrosine (BY) kinases) that are characterized by the presence of Walker motifs. The reverse reaction is catalyzed by three classes of enzymes: the euksrytic-like phosphatases (PTPs) and dual-specific phosphatases; the low molecular weight protein-tyrosine phosphatases (LMW-PTPs); and the polymerase-histidinol phosphatases (PHP). Many BY kinases and tyrosine phosphatases can utilize host cell proteins as substrates, thereby contributing to bacterial pathogenicity. Bacterial tyrosine phosphorylation/dephosphorylation is also involved in biofilm formation and community development. The Porphyromonas gingivalis tyrosine phosphatase Ltp1 is involved in a restraint pathway that regulates heterotypic community development with Streptococcus gordonii. Ltp1 is upregulated by contact with S. gordonii and Ltp1 activity controls adhesin expression and levels of the interspecies signal AI-2.

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INTRODUCTION
Regulation of protein activity, as orchestrated by the tightly coordinated and balanced dynamics between kinases and phosphatases, is one of the critical determinants of normal cellular growth and development. While the addition or removal of phosphoryl groups to/from serine, threonine or tyrosine residues has long been established as one of the predominant mechanisms of post-translational protein modification in eukaryotes, it was not until the 1970s that landmark studies demonstrated its importance in prokaryotes. Furthermore, protein phosphorylation has now also been shown to be prevalent in archaea. The first characterized phosphorylation systems in prokaryotic organisms were the two component systems (TCS) and the phosphotransferase system (PTS). In the basic configuration of TCS, a surface-exposed sensor kinase is first autophosphorylated in response to an external signal. The phosphoryl group is then transferred to the aspartyl residue of a response regulator, which in turn can modulate gene expression. In this manner, signal transduction is effectuated by phosphate flow. TCS are widespread in bacteria, and they control the response to a wide range of environmental stimuli. Remarkably, any one organism can possess up to 50 functionally isolated systems. In the PTS system, a phosphoryl group from phosphoenol pyruvate is transferred along a chain of proteins by reversible phosphorylation of histidine residues (although HPr is phosphorylated on histidine and serine). The final receptor for the phosphoryl group is a sugar; hence, the PTS is involved in carbohydrate uptake rather than signal transduction.

PHOSPHORYLATION OF PROTEINS IN BACTERIA
Serine and threonine phosphorylation
Bacterial serine/threonine specific phosphorylation was discovered more than 30 years ago, and this post-translational modification is now known to be ubiquitous and is involved in a diverse array of physiological processes including secondary metabolism, catabolite repression, oxidative stress responses and sporulation. Serine/threonine kinases and phosphatases are also involved in bacterial virulence, in particular through their action on host cell substrates (Table 1). For example, the YpkA/YopO kinase of Yersinia species is delivered into epithelial cells by type III secretion machinery, whereupon it disrupts actin microfilament structure. Two autophosphorylated Ser/Thr protein kinases, NleH1 and NleH2, in enterohemorrhagic Escherichia coli, and the OspG protein in Shigella flexneri, inhibit activation of the proinflammatory transcription factor NF-κB. The serine phosphatase SerB of Porphyromonas gingivalis, which is required for maximal invasion of the organisms into epithelial cells, can impact both the actin and tubulin cytoskeleton of host cells, and also attenuate NF-κB activation. The secretion of serine kinases and/or phosphatases has thus afforded bacterial pathogens the means to interfere with host signal transduction pathways.

Tyrosine phosphorylation
The first definitive evidence of protein tyrosine kinase activity in bacteria was discovered in E. coli with the identification of phosphotyrosine in partial acid hydrolysates of proteins. Protein tyrosine phosphorylation subsequently was shown to direct many essential
cellular processes, such as capsule production, growth, proliferation, migration, flagellin export, adaptation to stress and production of secondary metabolites (Table 2). Moreover, the addition of a bulky, negatively charged phosphoryl group to a protein can influence both cellular location and the overall protein interactome. A number of global phosphoproteome studies have now been conducted in bacteria, including *E. coli*, *Helicobacter pylori*, *Bacillus subtilis*, *Streptomyces coelicolor*, *Mycobacteria*, *Campylobacter jejuni* and *Pseudomonas* species. These databases have shown an increasing number of bacterial proteins that are phosphorylated on Ser/Thr/Tyr residues; and, moreover, these proteins are involved

### Table 1 Bacterial kinases and phosphatases involved in virulence through interaction with host cell proteins

| Organism            | Enzyme | Activity          | Impact on host cell function                                    | References |
|---------------------|--------|-------------------|-----------------------------------------------------------------|------------|
| *Coxiella burnetii* | Acp    | Tyrosine phosphatase | Inhibition of human neutrophils                                  | 55–56      |
| *Enterohemorrhagic* | NleH1, NleH2 | Ser/Thr kinase     | Inhibit activation of NF-kB                                     | 6          |
| *Escherichia coli*  | NleH1, NleH2 | Ser/Thr kinase     | Inhibit activation of NF-kB                                     | 6          |
| *Listeria monocytogenes* | LipA | Tyrosine phosphatase | Actin cytoskeleton disruption                                   | 39         |
| *Mycobacterium tuberculosis* | MPTpA and B | Tyrosine phosphatase | Phagoctosis actin polymerization in macrophages                 | 35, 57     |
| *Porphromonas gingivalis* | PknG | Ser/Thr kinase | Inhibition of phagosome-lysosome fusion                          | 58         |
| *Salmonella typhi*   | StpA   | Tyrosine phosphatase | Host cytoskeleton disruption                                    | 59         |
| *Salmonella typhimurium* | SpG | Tyrosine phosphatase | Actin rearrangements                                            | 60         |
| *Shigella flexneri*  | OspG   | Ser/Thr kinase     | Inhibit NF-κB activation                                        | 6          |
| *Yersinia enterocolitica* | YopO | Ser/Thr kinase | Disruption of actin; inhibition of phagocytosis                 | 62         |
| *Yersinia pseudotuberculosis* | YopH | Tyrosine phosphatase | Cytoskeletal rearrangements; inhibition of phagocytosis          | 28         |
| *Yersinia pseudotuberculosis* | YpkA | Ser/Thr kinase | Disruption of actin; inhibition of phagocytosis                 | 5          |
| *Yersinia pestis*    | YpkA   | Ser/Thr kinase     | Disruption of actin; inhibition of phagocytosis                 | 5          |

### Table 2 Bacterial protein tyrosine kinases and phosphatases and their functional roles

| Organism                                      | Tyrosine Kinase | Tyrosine Phosphatase | Substrate(s)                  | Function                                    | References |
|-----------------------------------------------|-----------------|----------------------|-------------------------------|---------------------------------------------|------------|
| *Acinetobacter johnsonii*                     | Ptk             | Ptp                  | Ptp uses Ptk as endogenous substrate | Phosphorelay reactions of inner membrane proteins | 63         |
| *Acinetobacter lwoffii*                       | Wzc             | Wzb                  | Wzb uses Wzc as endogenous substrate | Emulsan production                          | 46         |
| *Bacillus subtilis*                           | YwqD, PtkA, PtkB, McsB | YwqE, YfkI, YwIE, PtpZ | TuaD, Ugd, SsbA, McsA, CtsR, YpoA, YnfE, TxyG, YorK, Asd, YwpH | Exopolysaccharide synthesis, teichuronic acid production, DNA metabolism, heat shock response | 64–65      |
| *Caulobacter crescentus*                      | DivL            | —                   | —                             | Cell division                               | 66         |
| *Erwinia amylovora*                           | AmsA            | AmsI                 | Lipid carrier di-/monophosphates | Amylovoran production                        | 67         |
| *Escherichia coli* K-12                       | Wzc,CA          | Wzb                  | Ugd; Wzb uses Wzc as endogenous substrate | Colonoc acid synthesis                       | 40, 68     |
| *Escherichia coli* K-12/K-30                  | Etk             | —                   | —                             | Exopolysaccharide production                | 69         |
| *Escherichia coli* K-30                       | Wzc,CA          | Wzb                  | Ugd                            | Group 1 capsule assembly                     | 44         |
| *Klebsiella pneumonia*                        | YocD, Wzc       | YorS, YorZ           | Yor5 uses YocD as endogenous substrate | Capsule synthesis                           | 18, 70     |
| *Myxococcus xanthus*                          | MasK            | —                   | —                             | Aggregation, sporulation, motility, development | 71         |
| *Porphyromonas gingivalis*                    | LtpO            | —                   | —                             | Exopolysaccharide production, heterotypic community development | 49         |
| *Pseudomonas aeruginosa*                      | WaiP            | —                   | —                             | Lipopolysaccharide synthesis                | 72         |
| *Pseudomonas aeruginosa*                      | 42k             | —                   | —                             | Flagellin export                            | 73         |
| *Pseudomonas aeruginosa*                      | TbpA            | —                   | Flagellin a and b proteins; Diguanylate cyclase                | Exopolysaccharide production, biofilm development | 47         |
| *Ralstonia solanacearum*                      | EpsB            | EpsP                 | PSC                           | Exopolysaccharide transport                  | 74–75      |
| *Salmonella typhimurium*                      | PutA            | —                   | —                             | Proline metabolism                          | 76         |
| *Sinorhizobium meliloti*                      | ExoP            | —                   | Succinoglycan production                          | 77         |
| *Staphylococcus aureus*                       | Cap5B2          | CapC, PtpA, PtpB     | Cap50 (UDP-acetyl-mannosamine dehydrogenase) | Capsule synthesis                          | 78         |
| *Streptococcus agalactiae*                    | CpsD            | CpsB                 | —                             | Polysaccharide chain length                  | 79         |
| *Streptococcus pneumoniae*                    | CpsD            | CpsB                 | —                             | Capsule synthesis                            | 80         |
| *Streptococcus thermophilus*                  | EpsD            | EpsB                 | EpsE                           | Exopolysaccharide biosynthesis               | 81         |
| *Streptomyces coelicolor* A3(2)               | AfsK            | —                   | —                             | Antibiotic production                        | 82–84      |
|                                               | SCO5717          |                      |                               | Cell growth                                 |            |
Bacterial tyrosine phosphorylation
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BACTERIAL TYROSINE KINASES
Structure
The bacterial tyrosine (BY) kinase family comprises the major group of bacterial enzymes endowed with tyrosine kinase activity. In most cases, BY kinases possess a transmembrane domain that can function both as an anchor and a sensor, as well as an intracellular catalytic domain. The catalytic domain lacks the distinctive eukaryotic kinase motifs, and is defined by the presence of Walker A (P-loop) and B motifs (Figure 1). In addition, some BY kinases also contain a Walker A’ motif. BY kinases autophosphorylate at a tyrosine rich cluster in the C-terminal region using adenosine triphosphate as a phosphoryl donor, and the degree of phosphorylation in this region determines the interaction strength with other proteins. Some BY kinases also autophosphorylate on a tyrosine residue in close proximity to the Walker A’ box. Recent studies have identified other bacterial tyrosine kinases including those that closely resemble eukaryotic-like kinases, and those that utilize guaadin-phosphotransferase domains. Additionally, in some cases, tyrosine can substitute for histidine in TCS.

Function
The majority of genes encoding BY kinases reside in operons responsible for regulating the synthesis and secretion of polysaccharides. The autophosphorylation state of the BY kinases exerts control over this process through phosphorylation, and activation, of UDP-sugar dehydrogenases and glucosyltransferases. As bacterial regulatory networks are extensively interconnected, the phosphotransfer reactions can modulate a myriad of physiological processes that include resistance to cationic peptides and polymixin, along with heat shock responses. A greater appreciation for the role of tyrosine kinases in prokaryotes has emerged from the application of global phosphoproteome technologies. For example, the PtkA BY kinase of Bacillus subtilis can phosphorylate at least nine different protein substrates. Several of these substrates, most notably single-stranded DNA exonuclease YorK and aspartate semialdehyde dehydrogenase Asd, are activated via phosphorylation. Yet, the activity of many others, such as enolase, YjoA, YnfE, TvyG, Ugd and SsbA, remains unaffected by phosphorylation, and rather the cellular localization of these proteins is governed by phosphorylation status. Hence, BY action can not only regulate the activity of substrates, but also ensure the correct cellular localization of specific protein targets.

BACTERIAL TYROSINE PHOSPHATASES
Structure
Bacterial tyrosine phosphatases catalyze the dephosphorylation of tyrosyl phosphorylated proteins, which in turn can result in either the propagation or inhibition of phospho-dependent signaling. Bacterial tyrosine phosphatases can be categorized into three distinct families: (i) the eukaryotic-like phosphatases (PTPs) and dual-specific phosphatases that also display activity against phosphoserine and phosphothreonine; (ii) the low molecular weight protein-tyrosine phosphatases (LMW-PTPs), a family of small acidic enzymes also found in eukaryotes; and (iii) the polymerase–histidinol phosphatases (PHP), a family of phosphoesterases commonly found in gram-positive bacteria. The PTP, dual-specific phosphatase and LMW-PTP enzymes utilize a common catalytic mechanism that involves the conserved signature C(X)₅R motif in the phosphate binding loop where cysteine, functioning as a nucleophile, attacks the phosphorus atom of the phosphotyrosine residue of the substrate. The arginine residue interacts with the phosphate moiety of the phosphotyrosine.

Function
While bacterial tyrosine phosphatases can be intimately involved in a number of cellular processes, two major themes have become apparent: involvement in polysaccharide production; and as secreted effector proteins with the potential for manipulation of host cell signal transduction pathways. Polysaccharide production, encompassing both exopolysaccharides and capsular polysaccharides, is also a key virulence determinant in many organisms and thus tyrosine phosphatase activity is emerging as a central player in the information flow that controls pathogenic activity.

The YopH protein tyrosine phosphatase of Yersinia, a member of the PTP family, is an essential virulence factor that is injected into epithelial cells by type III secretion machinery. YopH can uncouple multiple signal transduction pathways, and in human epithelial cells YopH dephosphorylates several focal adhesion proteins, including p130Cas (Cas), focal adhesion kinase and paxillin. Similarly, Salmonella ‘typhimurium’ translocates the PTP tyrosine phosphatase SptP into epithelial cells where it is involved in reversing mitogen-activated protein kinase activation. SptP is required for full virulence in murine models of disease. Shigella flexneri produces a dually specific phosphatase, OsPF, that dephosphorylates mitogen-activated protein kinase, which consequently prevents histone H3 phosphorylation.

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A reduction in the level of histone 3 phosphorylation impedes access of the transcription factor NF-kB to the chromosome and hence transcription of NF-xB responsive genes such as IL-8 is reduced. Thus, OspF activity allows S. flexneri to modulate host cell epigenetic information as a strategy for repressing innate immunity. Mycobacterium tuberculosis secretes two LMW-PTPs, PtpA and PtpB. The predicted lack of tyrosine kinases in the M. tuberculosis genome suggests a dedicated role for these phosphatases in regulation of host cell functions. Expression of ptpA in M. tuberculosis is upregulated within monocytes, and a ptpB mutant is impaired in its ability to grow in human macrophages and survive in a guinea pig model. These phosphatases appear to function by impacting actin polymerization within macrophages and thereby affecting phagocytosis of the organism. A recently identified phosphatase, LipA, in L. monocytogenes has a predicted structure bearing a remarkable resemblance to the PtpB phosphatase. Moreover, both LipA and PtpB share a unique feature whereby they possess dual-function activities as phospho-tyrosine and phosphoinositide phosphatases, and both harbor the potential to play pivotal roles in bacterial virulence.

In addition to physical protection, exopolysaccharide such as capsule is often poorly immunogenic and can mask protein antigens and receptors for complement and phagocytic cells. In many cases, dephosphorylation of tyrosine kinases increases the level of polysaccharide synthesis, as evidenced by the activity of the E. coli K-12 BY kinase Wzc-ca, which is regulated by its cognate LMW-PTP, Wzb. In this system, production of the capsular exopolysaccharide colonic acid is maximal when Wzc-ca is dephosphorylated by Wzb. Similarly, in Streptococcus pneumoniae autophosphorylation of the CpsD kinase, when in the presence of its cognate partner, CpsC, results in the autophosphorylation of the CpsD kinase, as well as a reduction in the level of encapsulation via a negative feedback regulatory loop. Consequently, the PHP family phosphatase CpsB can control capsule production via dephosphorylation of CpsD which functions as a reversible switch. The converse situation also exists. In clinical isolates of S. pneumoniae, phosphorylation of CpsD increases capsule production under anaerobic conditions, and in E. coli K30 the assembly of group I capsular polysaccharides is elevated by phosphorylation of Wzc-cps. Undoubtedly, the interplay among tyrosine kinases, phosphatases and exopolysaccharide is of a nuanced and subtle nature that may be reconfigured according to environmental conditions. Indeed, metabolic activity is one factor that has been shown to influence kinase to phosphatase ratios.

Role in biofilms
A recent study in Pseudomonas aeruginosa demonstrated that tyrosine phosphatase activity is a unifying element that amalgamates polysaccharide production and biofilm formation with quorum sensing. The PTP family tyrosine phosphatase, TphA, is a negative regulator of 3,5-cyclic diguanylic acid (c-di-GMP), an important second messenger which suppresses transcription across the pel operon that encodes for extracellular matrix polysaccharide. Lower levels of exopolysaccharide in turn lead to reduced biofilm formation. In addition, TphA responds to acyl homoserine lactone, and TphA is regulated positively by the LasR transcriptional regulator. TphA also regulates cell lysis as a means to control extracellular DNA that is used for complex biofilm maturation. These findings also reveal a previously unrecognized ability for phospho-dependent signaling to intersect with other important cellular second messenger systems.

Tyrosine phosphatases can also control heterotypic biofilm formation among oral organisms. P. gingivalis accumulates into heterotypic communities with the antecedent oral biofilm colonizer S. gordonii (Figure 2). Maeda et al. identified a LMW-PTP, Ltp1, in P. gingivalis which functions as a negative regulator of EPS production, as well as community formation with S. gordonii. Transcription of ltp1 is increased following contact with S. gordonii and Ltp1 is a component of a signaling pathway that converges on the LuxR family transcriptional regulator CdhR. The expression of P. gingivalis Mfa fimbriae and of LuxS, both of which contribute to community development with S. gordonii, are negatively regulated by CdhR (Figure 3). Thus, in both P. aeruginosa and P. gingivalis, tyrosine phosphatase activity results in arrested community development which may maintain optimal biofilm architecture.

CONCLUSION
It is sobering to reflect that until fairly recently, post-translational modification of tyrosine residues by phosphorylation was believed to be an indicator of the sophisticated regulatory networks characteristic of eukaryotic systems. Since then, research on bacterial tyrosine kinases and phosphatases has proceeded apace and they are now considered key contributors to bacterial cell homeostasis, virulence and even cell survival in all domains of life. Future genomics and proteomics research will decipher and dissect the underlying mechanisms of tyrosine phosphotransfer cascades in bacteria and their functional roles. Accumulating evidence reaffirms the notion that bacterial tyrosine kinases and phosphatases display exquisite substrate specificity; nevertheless, they are still capable of utilizing multiple protein substrates, both endogenous and exogenous, thereby providing versatility in phosphorelay signaling networks. Ongoing studies reveal increasing instances where bacterial kinases/phosphatases are capable of inducing post-translational modifications of host proteins and are a crucial facet of the dynamic host-pathogen relationship. Moreover, as BY kinases differ from their eukaryotic counterparts in significant biochemical and structural aspects, they provide attractive targets for specific antibacterial drugs. The crystal structures of the CapB kinase of Staphylococcus aureus and the Etk kinase of E. coli have been determined and they exhibit a high degree of structural similarity. The availability of structural and biochemical information will facilitate the rational design of compounds that can inhibit BY kinases, while concomitantly avoiding any eukaryotic kinases.

Figure 2. Porphyromonas gingivalis (green) accumulates into a mixed species community on a substratum of Streptococcus gordonii (red). Image courtesy of Dr Christopher Wright.
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