



CHALMERS
UNIVERSITY OF TECHNOLOGY

The role of protein Ser/Thr/Tyr kinases in bacteriophage infection

Downloaded from: <https://research.chalmers.se>, 2026-06-16 00:13 UTC

Citation for the original published paper (version of record):

Lei, S., Jers, C., Ji, B. et al (2026). The role of protein Ser/Thr/Tyr kinases in bacteriophage infection. *Current Opinion in Microbiology*, 91. <http://dx.doi.org/10.1016/j.mib.2026.102749>

N.B. When citing this work, cite the original published paper.

Review

The role of protein Ser/Thr/Tyr kinases in bacteriophage infection

Lei Shi¹, Carsten Jers², Boyang Ji³ and Ivan Mijakovic^{1,2}

In the evolutionary arms race between bacteria and bacteriophages, both parties have evolved diverse defense systems and counter-defense strategies. Protein phosphorylation is a ubiquitous regulatory mechanism that enables rapid cellular responses to internal and external stimuli. Accordingly, protein phosphorylation-based responses have been established in both the bacterial host and the infecting phages. This review provides an overview of protein Ser/Thr/Tyr kinases involved in bacterial defense and phage counter-defenses, with a particular focus on insights gained from mass spectrometry-based phosphoproteomic analyses of phage infections.

Addresses

¹ Systems and Synthetic Biology Division, Department of Life Sciences, Chalmers University of Technology, Gothenburg, Sweden

² The Novo Nordisk Foundation Biotechnology Research Institute for the Green Transition, Technical University of Denmark, Kongens Lyngby DK-2800, Denmark

³ Bioinnovation Institute, Copenhagen, Denmark

Corresponding authors: Shi, Lei (slei@chalmers.se), Mijakovic, Ivan (ivan.mijakovic@chalmers.se)

Current Opinion in Microbiology 2026, 91:102749

This review comes from a themed issue on **Cell regulation**

Edited by **Fabian Commichau**

Available online xxxx

<https://doi.org/10.1016/j.mib.2026.102749>

1369–5274/© 2026 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Protein phosphorylation on serine (Ser), threonine (Thr), and tyrosine (Tyr) residues plays an important regulatory role in allowing bacteria to respond and adapt to dynamic environments [1,2]. The attachment of phosphate triggers the changes in physicochemical properties of proteins, such as protein conformation, protein-protein interactions, or protein localization, hence altering the protein activity or stability [3]. Protein phosphorylation is catalyzed by protein kinases, and the reverse process

of dephosphorylation is catalyzed by cognate protein phosphatases. Thereby, phosphorylation enables cellular signaling and regulation in a rapid and reversible manner. Ser/Thr/Tyr-type phosphorylations are especially amenable to phosphoproteomic studies due to the chemical stability of their phospho-bonds. This has facilitated rapid accumulation of knowledge about Ser/Thr/Tyr-type phosphorylation using mass spectrometry (MS) proteomics [4–6].

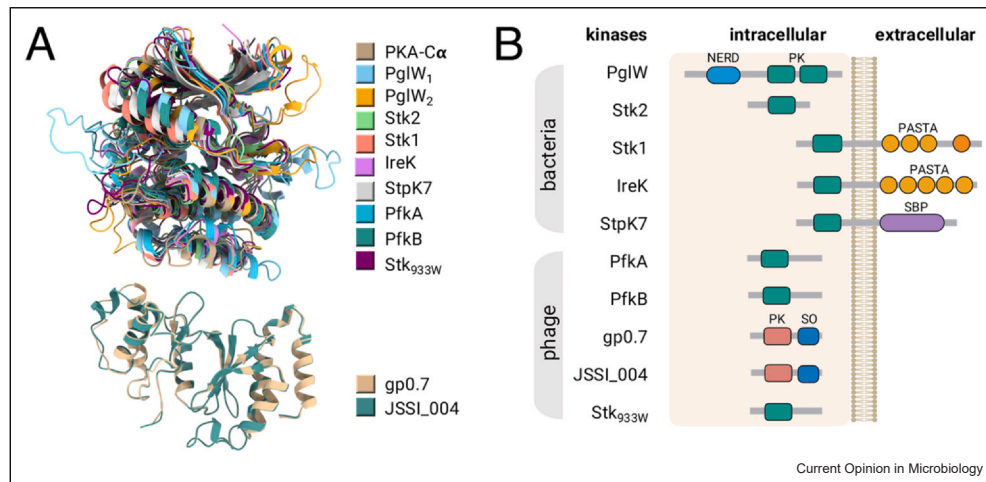
Bacteriophages (phages) are bacterial viruses that infect the host and hijack the host cell machinery to produce new virions [7,8]. Bacteria have evolved diverse strategies to restrict phage infection [9], whereas phages also have evolved counter-defenses in this evolutionary arms race [10,11]. Protein phosphorylation has been demonstrated to play crucial roles in both processes [12], and its study sheds new light on our understanding of bacteria–phage interactions.

In this review, we summarize the current knowledge on the involvement of protein Ser/Thr/Tyr kinases in phage infection, and highlight the use of MS-based phosphoproteomics methodology to analyze the dynamics of kinase-mediated protein Ser/Thr/Tyr phosphorylation events during infection.

Protein Ser/Thr/Tyr kinases in bacteria–phage interaction

Both bacteria-encoded kinases and phage-encoded kinases have been reported to be involved in phage infection [12]. Figure 1 summarizes protein kinases with experimental validations of their involvement in phage infection. Structural alignment of the kinase domains indicates most of them belong to the super-family of Hanks-type kinases, while gp0.7 and its homolog JSS1_004 are classified as a special T7-type kinase (Figure 1a). Hanks-type kinases are widely distributed in bacteria, archaea, and eukaryotes and are evolutionarily conserved [13]. A typical Hanks-type kinase consists of a highly conserved cytosolic kinase domain and a diverse extracellular sensing domain, enabling the alteration of the kinase activity by sensing different extracellular signaling ligands. Hanks-type kinases superfamily includes two main subdivisions, the Ser/Thr kinases and the Tyr kinases, but some of the members exhibit both Ser/Thr and Tyr kinase activity and are defined as dual-specificity protein kinases [14]. Hanks-type kinases play essential roles in eukaryotic immune

Figure 1



Overview of the protein Ser/Thr/Tyr kinases that have been reported to be involved in phage infection **(a)** Protein structure alignment of kinase domains. Upper: alignment of kinase domains of PKA-C α (the alpha catalytic subunit of protein kinase A from mouse), a typical Hanks-type kinase as a control, and the other kinase domains in this review. PglW contains two kinase domains, which are indicated as PglW₁ and PglW₂. Lower: alignment of kinase domains of gp0.7 and JSS1_004. Protein models were created by AlphaFold 3 [50], and alignment was performed using UCSF ChimeraX [60]. **(b)** Schematic representation of the domain organization of kinases. Hanks-type kinase domain is indicated by green and T7-type kinase domain is indicated by red. NERD: nuclease-related domain; PK: protein kinase domain; PASTA: for penicillin-binding protein and Ser/Thr kinase associated domain; SBP: bacterial extracellular solute binding domain; SO: shutoff domain.

responses. They act as signaling regulatory relay in both innate and adaptive immune responses to assist the host against virus infection [15,16], but also can be hijacked by the virus to facilitate the pathogenesis [17,18], and have therefore been established as an antiviral drug target [19]. T7-type kinase consists of an N-terminal kinase domain and a C-terminal shutoff (SO) domain that allows temporal regulation of kinase autophosphorylation [20]. As shown in Figure 1b, Stk1, StpK7, and IreK represent the domain organization as a typical Hanks-type kinase, suggesting a potential capability for extracellular signal sensing, while the cytosolic kinases are expected to be activated by intracellular signals. The signals that activate these Ser/Thr/Tyr kinases and the role of each kinase are outlined in the following sections (Figure 2).

Bacterial kinase provides bacterial defense against phage

Bacteria-encoded kinases are often found to provide bacterial defense against phage infection.

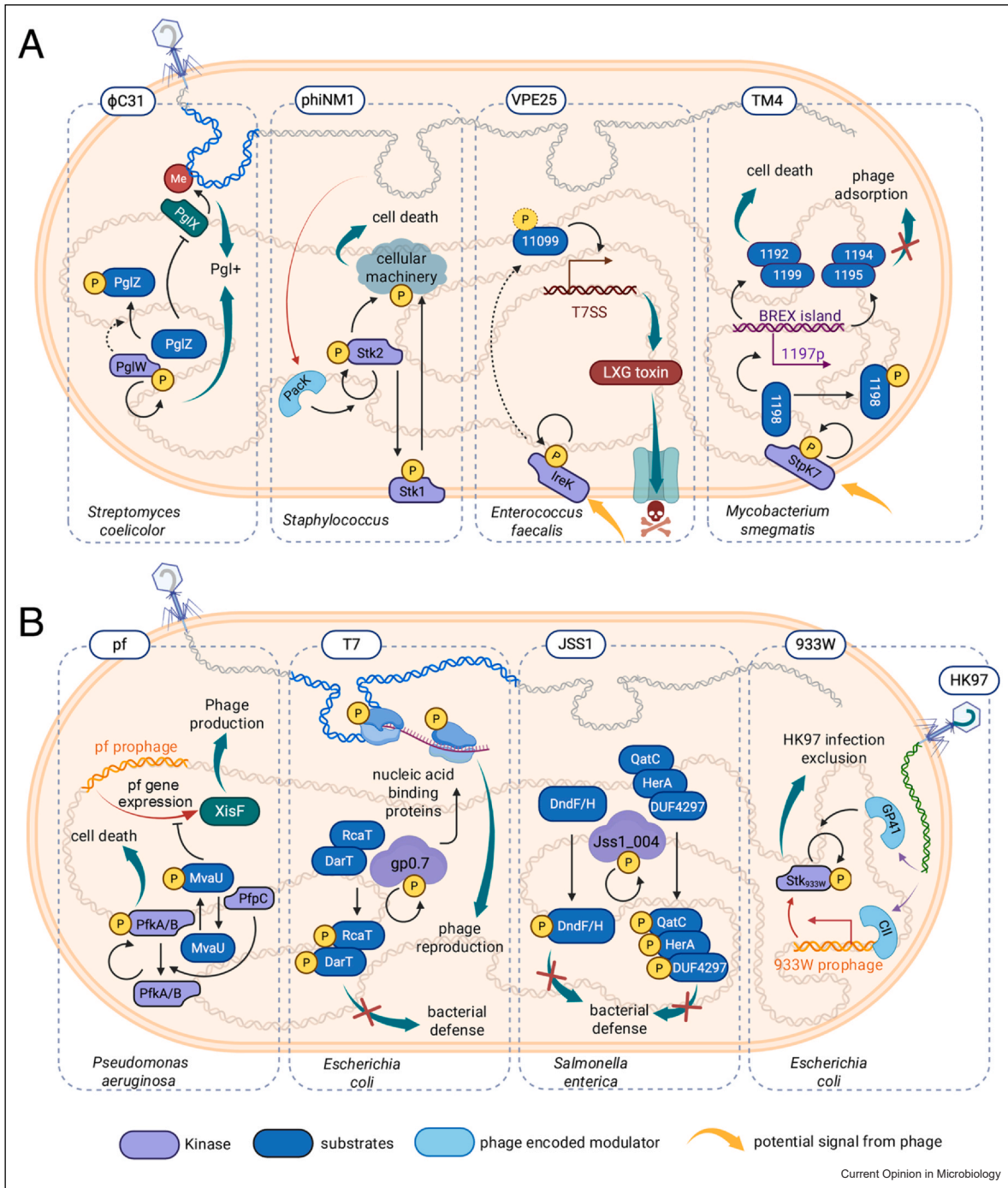
PglW from *Streptomyces coelicolor* plays a crucial role in the phage growth limitation (Pgl) system against phage ϕ C31 [21,22]. During the initial round of infection, PglW is found to be autophosphorylated and suspected to regulate PglZ through phosphorylation, which releases PglZ from the DNA methyltransferase PglX [23], thereby enabling methylation of the phage DNA. Although the burst of the infected phage is normal for this

round, the progeny phages are modified, rendering them attenuated for the subsequent round of infection of Pgl⁺ hosts. However, the phosphorylation sites and phosphorylation-dependent regulation of PglZ by PglW remain unclear.

Stk2 from *Staphylococcus* [24], triggering phosphorylation on Ser/Thr, provides bacterial defense against phage ϕ INM1 by inducing abortive infection (Abi) [25,26]. Stk2 is activated by the phage DNA packaging protein PacK, resulting in the phosphorylation of numerous host proteins involved in DNA repair, RNA transcription, protein translation, and cell cycle. Consequently, the growth of the host cell is arrested, and the cell is committed to death. Moreover, another Ser/Thr kinase Stk1 [27] is involved in the Stk2-mediated Abi phenotype, by a phosphorylation cascade-like mechanism in which Stk2 activates Stk1 to provoke secondary phosphorylation events [25,28]. Interestingly, Stk2 was found to be activated also by other phage proteins AVT76_GP14 (43% identity to PacK) from phage ϕ INM2 and ST85ORF023 (no identity to PacK) from phage 85. It has been shown that 23% of Staphylococcal phages carry homologs of PacK, and 13% carry homologs of ST85ORF023, but only in Siphoviridae [25], which suggests that the bacterial defense mediated by Stk2 in *Staphylococcus* could be broad-spectrum for Siphoviridae.

IreK from *Enterococcus faecalis* [29,30], triggers a type VII secretion system (T7SS) antibacterial response against phage VPE25. The induced T7SS inhibits the growth of

Figure 2



Protein Ser/Thr/Tyr kinase-mediated regulatory responses in phage infection. The phage is indicated in a white oval at the top of a dashed rectangle, and the corresponding bacterial host is indicated at the bottom. **(a)** Bacteria-encoded kinases. In phage infection, kinase PglW controls PglZ by phosphorylation, and thereby relieves the inhibition of PglZ on PglX, enabling PglX-mediated phage DNA methylation, thereby reducing the subsequent infectivity of progeny phage in Pgl⁺ hosts. Kinase Stk2 is activated by phage-encoded modulator PacK and triggers phosphorylation events, including that of another kinase Stk1, leading to arrested cell growth. Kinase IreK is autophosphorylated and activates the type VII secretion system (T7SS) via the phosphorylation of OG1RF_11099, and thereby inhibits the growth of non-susceptible neighboring cells. The autophosphorylation of kinase StpK7 inhibits the defense island BREX by phosphorylation of transcriptional factor MSMEG_1198. The phosphorylated MSMEG_1198 is incapable of promoting the expression of genes involved in restriction of phage infection. **(b)** Phage/prophage encoded kinases. The pf prophage KKP (kinase-kinase-phosphatase, PfkA/B, PfpC) module enables lysogeny-lytic control via the phosphorylation level of PfkA/B and MvaU. Phosphorylated MvaU inhibits the expression of Pf gene expression, including Pf excisionase encoding gene *xisF*, and thereby prevents phage production. Kinase gp0.7 extensively phosphorylates host nucleic acid-binding proteins to hijack the cell machinery for virion production, and also abolishes the bacterial defense. Kinase JSS1_004 abolishes the bacterial defense system via phosphorylation on key proteins. Kinase Stk933W is upregulated by phage HK97-encoded CII and further activated by HK97-encoded modulator GP41, thereby leading to the exclusion of the HK97 infection.

non-susceptible neighboring cells and consequently restricts the phage production [31]. IreK is activated by membrane damage in lytic phage infection and hereafter controls transcription factor OG1RF_11099 to promote gene expression of the T7SS cluster, including the LXXG toxin encoding gene OG1RF_11121. However, it remains unclear how IreK regulates OG1RF_11099. Notably, T7SS-mediated antagonism influences distantly related bacterial species among Gram-positive bacteria, which allows growth inhibition to occur in a diverse range of non-susceptible cells during phage infection. However, the phosphorylation sites of OG1RF_11099 and the mechanism by which IreK controls OG1RF_11099 remain unknown.

Bacterial kinase seized by phage to abolish bacterial defense

Interestingly, bacteria-encoded kinases can also be hijacked by phage to abolish bacterial defense. StpK7 (MSMEG_1200) from *Mycobacterium smegmatis*, phosphorylated on Thr, helps mycobacteriophage TM4 escape the bacterial defense [32]. StpK7 is located within a bacteriophage exclusion (BREX)-like gene island (MSMEG_1191 to MSMEG_1200) in the host genome [33]. Phage infection activates StpK7, which thereafter phosphorylates the transcription factor MSMEG_1198 and abolishes its capability to upregulate another transcription factor MSMEG_1197. MSMEG_1197 positively regulates two phosphatidylglycerol production genes, MSMEG_1194 and MSMEG_1195. Thereby, StpK7 forces the host cells to maintain lipid homeostasis for phage adsorption. In addition, StpK7 abolishes the expression of two lethal genes MSMEG_1192 and MSMEG_1199, and thus prevents cell suicide, ultimately allowing phage production. StpK7 provides a unique example of how a bacterial defense system is hacked by a phage to revoke host counter-defense.

Phage kinase restricts bacterial defense

Most of the phage-encoded kinases are demonstrated to restrict bacterial defense.

The kinase-kinase-phosphatase (KKP) component (PfkA-PfkB-PfpC) from Pf prophage phosphorylates on Ser/Thr residues and plays a dual role in that it regulates both Pf production and counter-defense in *Pseudomonas aeruginosa* [34]. In planktonic cells, *pfkA* is highly expressed and maintains the phosphorylation level of MvaU, which inhibits the expression of Pf genes, including the Pf excisionase encoding gene *xisF*, and consequently abolishes the production of Pf phage (Figure 2b). In biofilms, *pfpC* expression is upregulated and leads to MvaU dephosphorylation and therefore relieves the repression of prophage genes. The KKP module also functions as a tripartite toxin-antitoxin system in bacterial defense [35], in which PfkA/B restrict cell growth and viability, while PfpC relieves the repression. Notably, a bioinformatic analysis identified more than 1200 putative KKP gene clusters across Gram-negative bacteria, with the majority encoded within prophage regions, suggesting that this phosphorylation-based mechanism may be widespread [34].

The kinase gp0.7 (gene 0.7) from bacteriophage T7 [36], also known as TK7, triggers phosphorylation on Ser/Thr/Tyr residues and enables the phage to hijack its host *Escherichia coli* [20,37]. During the early infection stage, gp0.7 hyper-phosphorylates the host proteins. Through its C-terminal nucleic acid-binding domain, gp0.7 binds DNA, resulting in preferential phosphorylation of nearby nucleic acid-associated proteins. Those proteins are involved in transcription, translation, and nucleic acid processing [38–40], and hence the phage is allowed to hijack the related cellular processes for reproduction. Those proteins are also involved in bacterial defense [20]. Phosphorylation of RcaT, a toxic effector in Retron-Eco9 system [41], leads to its inactivation and thereby abolishment of the corresponding Abi defense. Phosphorylation on DarT, a toxin in the DarTG1 prevalent toxin-antitoxin system [42], affects its conformation and/or stability, and thereby leads to the abolishment of the DarTG1 system.

JSS1_004 from *Salmonella* phage JSS1, phosphorylates on Ser/Thr/Tyr residues and enables the phage to

counteract multiple bacterial defense systems during its infection of *S. enterica* [43]. To abolish the phosphorothioate (PT)-based DNA degradation (Dnd) defense system [44], JSS1_004 phosphorylates DndF and DnH, which alters the conformation and thereby activity of the DndFGH complex, leading to diminished discrimination and cleavage of non-PT modified foreign DNA. Additional phosphorylation events targeting other bacterial defense modules, such as clustered regularly interspaced short palindromic repeats-Cas system SIR2+HerA, QatABCD, and DUF4297+HerA, were also observed, suggesting that the JSS1_004 functions as a broad-spectrum effector to neutralize diverse host defense mechanisms [43].

Prophage kinase excludes infection by unrelated phages

However, there is also a prophage-encoded kinase that protects the host against infection by unrelated phages. Stk_{933W} from prophage 933W [45], phosphorylates Thr residues and provides its host, *E. coli*, protection from infection by the unrelated phage HK97 [46]. HK97 CII protein promotes the expression of Stk_{933W}, and HK97 Orf41 triggers the autophosphorylation of Stk_{933W}. Stk_{933W} phosphorylation results in cell death and hence prevents HK97 phage production, thereby protecting the bacterial community. However, the substrates of Stk_{933W} remain unclear, as does the mechanism of cell death resulting from the Stk_{933W}-mediated phosphorylation.

Global analysis of the kinase-mediated protein Ser/Thr/Tyr phosphorylation events during phage infection

Our understanding of protein phosphorylation during phage infection has evolved in parallel with advances in proteomics methodology (Table 1). This methodological progression is particularly well illustrated by studies of phage T7 infection of *E. coli*, which now serves as a paradigm for phosphorylation-based phage counter-defense. Initial work using one-dimensional gels demonstrated that T7 infection induces phosphorylation of numerous host proteins in a manner dependent on an early phage-encoded protein kinase, later identified as gp0.7 [37,47,48]. Subsequent two-dimensional gel studies refined these observations, revealing that gp0.7 targets specific host proteins, including translation initiation factors and ribosomal proteins, and that the resulting phosphorylation contributes to efficient phage growth under certain conditions, although it is not strictly essential for infection [38,39]. In contrast, recent LC-MS/MS-based phosphoproteomic analysis has revealed a far broader and more dramatic impact of T7 kinase activity on the host cell [20]. This study demonstrated that activation of gp0.7 leads to a rapid and pervasive surge in host protein phosphorylation, with > 12 000 phosphopeptides detected and close to complete, highly stoichiometric

Table 1
Evolution of Ser/Thr/Tyr phosphorylation detection during phage infection.

Bacterial host	Phage	Method	Kinase involvement	Scale of detected phosphorylation	Representative substrates	Reference
<i>E. coli</i>	T7	1D SDS-PAGE + ³² P	gp0.7	~10–20 host protein bands	RNAP β', RNAP β	[32,43]
<i>E. coli</i>	T7	2D IEF/NEPHGE + ³² P	gp0.7	~50–100 proteins	IF1, IF2, IF3, S1, EF-G, RNase III	[31,33]
<i>E. coli</i>	T7	LC-MS/MS	gp0.7	> 12,000 phosphosites; ~80 high-stoichiometry proteins	RcaT, RNAP β'	[15]
<i>S. enterica</i>	JSS1	phosphoproteomics LC-MS/MS	JSS1_004	480 phosphosites in 333 proteins; 120 phosphosites in 27 proteins upregulated (WT vs ΔJSS1_4)	DndF, DndH	[38]
<i>P. aeruginosa</i>	Pf prophage	LC-MS/MS + Grad-seq	KKP module	2170 phosphosites	MvaU	[29]
<i>S. aureus</i>	φNM1 / CNPx	LC-MS/MS (TiO ₂ enrichment)	Stk2	32 proteins	FtsZ, SigA	[20]

phosphorylation of at least ~80 host proteins. Notably, this wave of phosphorylation is transient and confined to the early phase of infection, consistent with autophosphorylation-mediated inactivation of gp0.7 [49]. Time-resolved MS-based phosphoproteomics captured this early phosphorylation burst at the proteome-wide and site-resolved scale. Functional characterization of selected targets showed that phosphorylation can directly inactivate bacterial defense effectors, allowing us to expand our knowledge of gp0.7 from a regulator of a small number of specific pathways to function as a broad-spectrum counter-defense kinase [20].

A similar phosphorylation-based counter-defense strategy has recently been described for JSS1_004, a homolog of gp0.7. Global phosphoproteomic analysis revealed extensive remodeling of the host phosphoproteome during JSS1 infection, with 480 phosphosites identified in 333 proteins involved in multiple cellular metabolic pathways. It also includes multiple components of bacterial defense systems. Moreover, 120 phosphosites and 27 phosphoproteins were found to be upregulated in Δ JSS1_4 [43].

Similar themes are beginning to emerge from phosphoproteomic studies of other phage-host systems. KKP module from *P. aeruginosa* was shown to trigger widespread phosphorylation when PfkA was overexpressed, and phosphoproteomic analysis identified 2170 phosphosites, belonging to proteins in essential cellular metabolic pathways [34]. Although the precise functional consequences of most of these phosphorylation events remain to be defined, these data suggest that large-scale phosphorylation may also underlie prophage-mediated counter-defense and lysogeny control. Phosphoproteomics has also shed additional light on host-encoded kinase systems that function in bacterial defense. In *Staphylococcus* species, activation of the Ser/Thr kinase Stk2 by PacK triggers 32 phosphopeptides, including proteins related to transcription, translation, cell-cycle control, and stress response [25].

Altogether, these studies illustrated how the application of increasingly powerful phosphoproteomic methodologies has shifted the view of phosphorylation during phage infection from isolated, pathway-specific modifications to a system-level regulatory strategy, underscoring that extensive phosphorylation can be deployed both by phages and by bacterial hosts, albeit with opposite outcomes.

Perspective

Despite the extensive presence of Ser/Thr/Tyr kinase genes in bacterial genomes, only a few kinases were identified as phage-infection-related. Changes in protein phosphorylation during phage infection are drastic, and it is not certain that all those phosphorylation events can be ascribed to the known protein kinases. Therefore, one

important question in the field is whether we are aware of all protein kinases involved in phage infection. Today, the advances of deep-learning techniques present unique advantages in data processing and protein structure prediction, in particular, with the release of AlphaFold [50]. We expect these techniques to accelerate the identification of novel protein kinases that could be dedicated to the phage-infection response. Longin et al. proposed such a pipeline for artificial intelligence (AI)-driven enzyme discovery [51]. The pipeline starts with enzyme discovery through deep-learning-driven genome mining and genomic context analysis. Although it has been revealed that most of the bacterial defense system genes are often clustered as a defense island in the bacterial genome [52–54], and the presence of PglW in the Pgl system in such defense islands [52] has been demonstrated, our understanding of the presence of Ser/Thr/Tyr kinase genes in defense islands is still limited. The pipeline proposed by Longin et al. may lead to a significant expansion of our knowledge of protein phosphorylation in phage infection response. Moreover, by integrating the sequence and structural information with the evolutionary context, such AI-based techniques may provide insights into the determinants of protein kinases' catalytic specificities and kinetics.

Another major challenge in the field is the quantification and functional characterization of the rapidly growing dataset of phosphosites reported from MS analyses. The Ser/Thr/Tyr kinases are known to exhibit promiscuity toward substrates [55,56], which is also demonstrated by the studies of gp0.7, JSS1_004, and PfkA/PfkB. This indicates that phage- or host-encoded kinases can rapidly rewire large portions of the cellular proteome, either to disable host defenses or to trigger abortive infection, rather than fine-tuning individual processes. However, the mechanism underlying the hyper-phosphorylation events and reconstruction of the phosphorylation-driven cellular response network remains to be fully elucidated.

Regarding the signals that activate these kinases, our knowledge is severely limited. There is a hypothesis that cell membrane damage or related stress response triggered by phage infection could lead to kinase activation, but the particular signals are still undiscovered. Furthermore, one cannot exclude the existence of eukaryotic-like phosphorylation cascades in bacteria–phage interactions, in light of the kinases being cytosolic and lacking the typical signal-sensing domain. For example, Stk1 was thought to be activated also by Stk2, and such potential kinase cross-talk events in *Bacillus subtilis* have been indicated by previous studies [57].

Therefore, a systematic view of the phosphorylation landscape and longitudinal dynamics is needed. The combination of AI-driven kinase discovery, time-resolved MS-based phosphoproteomics, and high-throughput functional characterization of protein phosphorylation, together

with prediction of protein-ligand and protein-protein interactions and subsequent experimental validation [58,59], could begin to fill our knowledge gaps concerning the regulatory mechanisms underlying bacterial defense and phage counter-defense.

CRedit authorship contribution statement

Lei Shi: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Carsten Jers:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Boyang Ji:** Visualization, Writing – review & editing. **Ivan Mijakovic:** Funding acquisition, Project administration, Writing – review & editing.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

We claim there is no conflict of interest in this study.

Acknowledgement

We acknowledge the funding from the Swedish Research Council Vetenskapsrådet, grant number 2020-03176 and 2025-05786, and Novo Nordisk Foundation grant number NNF20CC0035580 and NNF24SA0100980, to IM. Illustration was created with the assistance of BioRender. Shi, L. (2026) <https://BioRender.com/vu9xdhn>. Molecular graphics and analyses performed with UCSF ChimeraX, developed by the Resource for Biocomputing, Visualization, and Informatics at the University of California, San Francisco, with support from National Institutes of Health R01-GM129325 and the Office of Cyber Infrastructure and Computational Biology, National Institute of Allergy and Infectious Diseases.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Macek B, Forchhammer K, Hardouin J, Weber-Ban E, Grangeasse C, Mijakovic I: **Protein post-translational modifications in bacteria.** *Nat Rev Microbiol* 2019, **17**:651-664, <https://doi.org/10.1038/s41579-019-0243-0>
2. Saier MH: **Introduction: protein phosphorylation and signal transduction in bacteria.** *J Cell Biochem* 2004, **51**:1-6, <https://doi.org/10.1002/jcb.240510102>
3. Cousin C, Derouiche A, Shi L, Pagot Y, Poncet S, Mijakovic I: **Protein-serine/threonine/tyrosine kinases in bacterial signaling and regulation.** *FEMS Microbiol Lett* 2013, **346**:11-19, <https://doi.org/10.1111/1574-6968.12189>
4. Macek B, Mann M, Olsen JV: **Global and site-specific quantitative phosphoproteomics: principles and applications.** *Annu Rev Pharmacol Toxicol* 2009, **49**:199-221, <https://doi.org/10.1146/annurev.pharmtox.011008.145606>
5. Zittlau K, Nashier P, Cavarischia-Rega C, Macek B, Spät P, Nalpas N: **Recent progress in quantitative phosphoproteomics.** *Expert Rev Proteom* 2023, **20**:469-482, <https://doi.org/10.1080/14789450.2023.2295872>
6. White FM, Wolf-Yadlin A: **Methods for the analysis of protein phosphorylation-mediated cellular signaling networks.** *Annu Rev Anal Chem* 2016, **9**:295-315, <https://doi.org/10.1146/annurev-anchem-071015-041542>
7. Clokie MRJ, Millard AD, Letarov AV, Heaphy S: **Phages in nature.** *Bacteriophage* 2014, **1**:31-45, <https://doi.org/10.4161/bact.1.1.14942>
8. Koskella B, Hernandez CA, Wheatley RM: **Understanding the impacts of bacteriophage viruses: from laboratory evolution to natural ecosystems.** *Annu Rev Virol* 2022, **9**:57-78, <https://doi.org/10.1146/annurev-virology-091919-075914>
9. Georjon H, Bernheim A: **Publisher correction: the highly diverse antiphage defence systems of bacteria.** *Nat Rev Microbiol* 2023, **21**:833, <https://doi.org/10.1038/s41579-023-00987-y>
10. Nialut T, van Houte S, Westra E, Swarts DC: **Evolution and ecology of anti-defence systems in phages and plasmids.** *Curr Biol* 2025, **35**:R32-R44, <https://doi.org/10.1016/j.cub.2024.11.033>. The authors describe the diverse strategies of phage counter-defense, and explore the evolutionary origins of counter-defense systems.
11. Hampton HG, Watson BNJ, Fineran PC: **The arms race between bacteria and their phage foes.** *Nature* 2020, **577**:327-336, <https://doi.org/10.1038/s41586-019-1894-8>
12. Zhang YE: **Protein kinases in mediating phage-bacteria interactions.** *Kinases Phosphatases* 2025, **3**:14. This publication summarizes the roles of histidine kinases and serine/threonine kinases in bacterial defense and phage counter-defense.
13. Stancik IA, Sestak MS, Ji B, Axelson-Fisk M, Franjevic D, Jers C, Domazet-Loso T, Mijakovic I: **Serine/threonine protein kinases from bacteria, archaea and eukarya share a common evolutionary origin deeply rooted in the tree of life.** *J Mol Biol* 2018, **430**:27-32, <https://doi.org/10.1016/j.jmb.2017.11.004>
14. Hanks SK, Hunter T: **Protein kinases 6. The eukaryotic protein kinase superfamily: kinase (catalytic) domain structure and classification.** *FASEB J* 1995, **9**:576-596.
15. Zhang YL, Dong C: **MAP kinases in immune responses.** *Cell Mol Immunol* 2005, **2**:20-27.
16. Villarino AV, Kanno Y, Ferdinand JR, O'Shea JJ: **Mechanisms of Jak/STAT signaling in immunity and disease.** *J Immunol* 2015, **194**:21-27, <https://doi.org/10.4049/jimmunol.1401867>
17. Sodhi A, Montaner S, Gutkind JS: **Viral hijacking of G-protein-coupled-receptor signalling networks.** *Nat Rev Mol Cell Biol* 2004, **5**:998-1012, <https://doi.org/10.1038/nrm1529>
18. Feng L, Luo X, Huang L, Zhang Y, Li F, Li S, Zhang Z, Yang X, Wang X, OuYang X, et al.: **A viral protein activates the MAPK pathway to promote viral infection by downregulating callose deposition in plants.** *Nat Commun* 2024, **15**:10548, <https://doi.org/10.1038/s41467-024-54467-9>. This publication presents that the mitogen-activated protein kinase cascade within the plant *Nicotiana benthamiana* is activated by a viral protein during infection by the positive-strand RNA virus tomato chlorosis virus, and hereafter promotes the viral spread.
19. Yángüez E, Hunziker A, Dobay MP, Yildiz S, Schading S, Elshina E, Karakus U, Gehrig P, Grossmann J, Dijkman R, et al.: **Phosphoproteomic-based kinase profiling early in influenza virus infection identifies GRK2 as antiviral drug target.** *Nat Commun* 2018, **9**:3679, <https://doi.org/10.1038/s41467-018-06119-y>
20. T.BartolecK.MitoschC.PotelF.CoronaA.L.J.YangM.L.BurtscherA. •• Koumoutsil.BecherJ.BobonisN.Karcher, et al.: **Pervasive Phosphorylation by Phage T7 Kinase Disarms Bacterial Defenses;** 2024. (<https://doi.org/10.1101/2024.12.20.629319>).. This publication outlines the promiscuity of phage-encoded protein kinase gp0.7 (T7K), which triggered massive phosphorylation events in phage infection. Importantly, the phosphorylation-mediated abolishment of bacterial defense is also presented.
21. Hoskisson PA, Sumbly P, Smith MCM: **The phage growth limitation system in *Streptomyces coelicolor* A(3)2 is a toxin/antitoxin system, comprising enzymes with DNA methyltransferase, protein kinase and ATPase activity.** *Virology* 2015, **477**:100-109, <https://doi.org/10.1016/j.viro.2014.12.036>
22. Sumbly P, Smith MCM: **Genetics of the phage growth limitation (Pgl) system of *Streptomyces coelicolor* A3(2).** *Mol Microbiol* 2002, **44**:489-500, <https://doi.org/10.1046/j.1365-2958.2002.02896.x>

23. Chinenova TA, Mkrtumian NM, Lomovskaia ND: **Genetic characteristics of a new phage resistance trait in *Streptomyces coelicolor* A3(2)**. *Genetika* 1982, **18**:1945-1952.
24. Didier J-P, Cozzzone AJ, Duclos B: **Phosphorylation of the virulence regulator SarA modulates its ability to bind DNA in *Staphylococcus aureus***. *FEMS Microbiol Lett* 2010, **306**:30-36, <https://doi.org/10.1111/j.1574-6968.2010.01930.x>
25. Depardieu F, Didier JP, Bernheim A, Sherlock A, Molina H, Duclos B, Bikard D: **A eukaryotic-like serine/threonine kinase protects *Staphylococci* against phages**. *Cell Host Microbe* 2016, **20**:471-481, <https://doi.org/10.1016/j.chom.2016.08.010>
26. Forde A, Fitzgerald GF: **Bacteriophage defence systems in lactic acid bacteria**. *Antonie Van Leeuwenhoek* 1999, **76**:89-113.
27. Beltramini AM, Mukhopadhyay CD, Pancholi V: **Modulation of cell wall structure and antimicrobial susceptibility by a *Staphylococcus aureus* eukaryote-like serine/threonine kinase and phosphatase**. *Infect Immun* 2009, **77**:1406-1416, <https://doi.org/10.1128/IAI.01499-08>
28. Débarbouillé M, Dramsi S, Dussurget O, Nahori M-A, Vaganay E, Jouvion Gg, Cozzzone A, Msadek T, Duclos B: **Characterization of a serine/threonine kinase involved in virulence of *Staphylococcus aureus***. *J Bacteriol* 2009, **191**:4070-4081, <https://doi.org/10.1128/jb.01813-08>
29. Kristich CJ, Wells CL, Dunny GM: **A eukaryotic-type Ser/Thr kinase in *Enterococcus faecalis* mediates antimicrobial resistance and intestinal persistence**. *Proc Natl Acad Sci USA* 2007, **104**:3508-3513, <https://doi.org/10.1073/pnas.0608742104>
30. Labbe BD, Kristich CJ: **Growth- and stress-induced PASTA kinase phosphorylation in *Enterococcus faecalis***. *J Bacteriol* 2017, **199**, <https://doi.org/10.1128/JB.00363-17>
31. Chatterjee A, Willett JLE, Dunny GM, Duerkop BA: **Phage infection and sub-lethal antibiotic exposure mediate *Enterococcus faecalis* type VII secretion system dependent inhibition of bystander bacteria**. *PLoS Genet* 2021, **17**:e1009204, <https://doi.org/10.1371/journal.pgen.1009204>
32. Li X, Long X, Chen L, Guo X, Lu L, Hu L, He ZG: **Mycobacterial phage TM4 requires a eukaryotic-like Ser/Thr protein kinase to silence and escape anti-phage immunity**. *Cell Host Microbe* 2023, **31**:1469-1480, <https://doi.org/10.1016/j.chom.2023.07.005>
33. Goldfarb T, Sberro H, Weinstock E, Cohen O, Doron S, Charpak-Amikam Y, Afik S, Ofir G, Sorek R: **BREX is a novel phage resistance system widespread in microbial genomes**. *EMBO J* 2014, **34**:169-183, <https://doi.org/10.15252/embj.201489455>
34. Guo Y, Tang K, Sit B, Gu J, Chen R, Shao X, Lin S, Huang Z, Nie Z, Lin J, et al.: **Control of lysogeny and antiphage defense by a prophage-encoded kinase-phosphatase module**. *Nat Commun* 2024, **15**:7244, <https://doi.org/10.1038/s41467-024-51617-x>.
This publication identifies the prophage-encoded KKP (kinase-phosphatase) module and its functional involvement in the regulation of phage production and phage counter-defense.
35. LeRoux M, Laub MT: **Toxin-antitoxin systems as phage defense elements**. *Annu Rev Microbiol* 2022, **76**:21-43, <https://doi.org/10.1146/annurev-micro-020722-013730>
36. Robertson ES, Nicholson AW: **Protein kinase of bacteriophage T7 induces the phosphorylation of only a small number of proteins in the infected cell**. *Virology* 1990, **175**:525-534, [https://doi.org/10.1016/0042-6822\(90\)90437-v](https://doi.org/10.1016/0042-6822(90)90437-v)
37. Rahmsdorf HJ, Pai SH, Ponta P, Herrlich P, Roskoski R, Schweiger M, Studier FW: **Protein Kinase Induction in *Escherichia coli* by Bacteriophage T7**. *Proc Natl Acad Sci* 1974, **71**:586-589, <https://doi.org/10.1073/pnas.71.2.586>
38. Robertson ES, Aggison LA, Nicholson AW: **Phosphorylation of elongation factor G and ribosomal protein S6 in bacteriophage T7-infected *Escherichia coli***. *Mol Microbiol* 2006, **11**:1045-1057, <https://doi.org/10.1111/j.1365-2958.1994.tb00382.x>
39. Robertson ES, Nicholson AW: **Phosphorylation of *Escherichia coli* translation initiation factors by the bacteriophage T7 protein kinase**. *Biochemistry* 2002, **31**:4822-4827, <https://doi.org/10.1021/bi00135a012>
40. Severinova E, Severinov K: **Localization of the *Escherichia coli* RNA Polymerase β' Subunit Residue Phosphorylated by Bacteriophage T7 Kinase Gp0.7**. *J Bacteriol* 2006, **188**:3470-3476, <https://doi.org/10.1128/jb.188.10.3470-3476.2006>
41. Bobonis J, Mitosch K, Mateus A, Karcher N, Kritikos G, Selkrig J, Zietek M, Monzon V, Pfalz B, Garcia-Santamarina S, et al.: **Bacterial retrons encode phage-defending tripartite toxin-antitoxin systems**. *Nature* 2022, **609**:144-150, <https://doi.org/10.1038/s41586-022-05091-4>
42. LeRoux M, Srikant S, Teodoro GIC, Zhang T, Littlehale ML, Doron S, Badiie M, Leung AKL, Sorek R, Laub MT: **The DarTG toxin-antitoxin system provides phage defence by ADP-ribosylating viral DNA**. *Nat Microbiol* 2022, **7**:1028-1040, <https://doi.org/10.1038/s41564-022-01153-5>
43. Jiang S, Chen C, Huang W, He Y, Du X, Wang Y, Ou H, Deng Z, Xu C, Jiang L, et al.: **A widespread phage-encoded kinase enables evasion of multiple host antiphage defence systems**. *Nat Microbiol* 2024, **9**:3226-3239, <https://doi.org/10.1038/s41564-024-01851-2>.
This publication identifies the phage-encoded protein kinase JSS1_004 and its functional involvement in the abolishment of bacterial defense.
44. Wang L, Tang Y, Deng Z, Chen S: **DNA phosphorothioate modification systems and associated phage defense systems**. *Annu Rev Microbiol* 2024, **78**:447-462, <https://doi.org/10.1146/annurev-micro-041222-014330>.
This publication outlines the state of knowledge on DNA PT modification systems on bacterial defense in phage infection. Additionally, the application of PT systems is also presented.
45. Plunkett G, Rose DJ, Durfee TJ, Blattner FR: **Sequence of Shiga Toxin 2 Phage 933W from *Escherichia coli* O157:H7: Shiga toxin as a phage late-gene product**. *J Bacteriol* 1999, **181**:1767-1778, <https://doi.org/10.1128/jb.181.6.1767-1778.1999>
46. Friedman DI, Mozola CC, Beeri K, Ko CC, Reynolds JL: **Activation of a prophage-encoded tyrosine kinase by a heterologous infecting phage results in a self-inflicted abortive infection**. *Mol Microbiol* 2011, **82**:567-577, <https://doi.org/10.1111/j.1365-2958.2011.07847.x>
47. Rahmsdorf HJ, Herrlich P, Pai SH, Schweiger M, Wittmann HG: **Ribosomes after infection with bacteriophage T4 and T7**. *Mol Gen Genet* 1973, **127**:259-271, <https://doi.org/10.1007/bf00333766>
48. Zillig W, Fujiki H, Blum W, Janeković D, Schweiger M, Rahmsdorf H, Ponta H, Hirsch-Kauffmann M: **In vivo and in vitro phosphorylation of DNA-dependent RNA polymerase of *Escherichia coli* by bacteriophage-T7-induced protein kinase**. *Proc Natl Acad Sci* 1975, **72**:2506-2510, <https://doi.org/10.1073/pnas.72.7.2506>
49. Pai SH, Rahmsdorf HJ, Ponta H, Hirsch-Kauffmann M, Herrlich P, Schweiger M: **Protein Kinase of Bacteriophage T7**. *Eur J Biochem* 2008, **55**:305-314, <https://doi.org/10.1111/j.1432-1033.1975.tb02164.x>
50. Abramson J, Adler J, Dunger J, Evans R, Green T, Pritzel A, Ronneberger O, Willmore L, Ballard AJ, Bambrick J, et al.: **Accurate structure prediction of biomolecular interactions with AlphaFold 3**. *Nature* 2024, **630**:493-500, <https://doi.org/10.1038/s41586-024-07487-w>.
The authors present their AlphaFold 3 model and demonstrate the advantages in the prediction of protein complexes and protein-ligand interactions.
51. Longin H, Broeckeaert N, van Noort V, Lavigne R, Hendrix H: **Posttranslational modifications in bacteria during phage infection**. *Curr Opin Microbiol* 2024, **77**:eaar4120, <https://doi.org/10.1016/j.mib.2024.102425>.
The authors summarize the current knowledge on post-translational modification in phage infection, and present a three-stage pipeline (Enzyme-Target-Function) to achieve a more systematic investigation.
52. Makarova KS, Wolf YI, Snir S, Koonin EV: **Defense islands in bacterial and archaeal genomes and prediction of novel defense systems**. *J Bacteriol* 2011, **193**:6039-6056, <https://doi.org/10.1128/JB.05535-11>
53. Doron S, Melamed S, Ofir G, Leavitt A, Lopatina A, Keren M, Amitai G, Sorek R: **Systematic discovery of antiphage defense systems in the microbial pangenome**. *Science* 2018, **359**:eaar4120, <https://doi.org/10.1126/science.aar4120>

54. Hochhauser D, Millman A, Sorek R: **The defense island repertoire of the *Escherichia coli* pan-genome.** *PLoS Genet* 2023, **19**:e1010694, <https://doi.org/10.1371/journal.pgen.1010694>
55. Ravikumar V, Shi L, Krug K, Derouiche A, Jers C, Cousin C, Kobir A, Mijakovic I, Macek B: **Quantitative phosphoproteome analysis of *Bacillus subtilis* reveals novel substrates of the kinase PrkC and phosphatase PrpC.** *Mol Cell Proteom* 2014, **13**:1965-1978, <https://doi.org/10.1074/mcp.M113.035949>
56. Shi L, Pigeonneau N, Ventroux M, Derouiche A, Bidnenko V, Mijakovic I, Noirot-Gros M-Fo: **Protein-tyrosine phosphorylation interaction network in *Bacillus subtilis* reveals new substrates, kinase activators and kinase cross-talk.** *Front Microbiol* 2014, **5**:538, <https://doi.org/10.3389/fmicb.2014.00538>
57. Shi L, Pigeonneau N, Ravikumar V, Dobrinic P, Macek B, Franjevic D, Noirot-Gros M-F, Mijakovic I: **Cross-phosphorylation of bacterial serine/threonine and tyrosine protein kinases on key regulatory residues.** *Front Microbiol* 2014, **5**:495, <https://doi.org/10.3389/fmicb.2014.00495>
58. Viéitez C, Busby BP, Ochoa D, Mateus A, Memon D, Galardini M, Yildiz U, Trovato M, Jawed A, Geiger AG, et al.: **High-throughput functional characterization of protein phosphorylation sites in yeast.** *Nat Biotechnol* 2021, **40**:382-390, <https://doi.org/10.1038/s41587-021-01051-x>
59. Derouiche A, Cousin C, Mijakovic I: **Protein phosphorylation from the perspective of systems biology.** *Curr Opin Biotechnol* 2012, **23**:585-590, <https://doi.org/10.1016/j.copbio.2011.11.008>
60. Meng EC, Goddard TD, Pettersen EF, Couch GS, Pearson ZJ, Morris JH, Ferrin TE: **UCSF ChimeraX: tools for structure building and analysis.** *Protein Sci* 2023, **32**:e4792, <https://doi.org/10.1002/pro.4792>