Veterinary Microbiology 153 (2011) 82–88

Contents lists available at ScienceDirect

Veterinary Microbiology

journal homepage: www.elsevier.com/locate/vetmic

Review

The Pho regulon and the pathogenesis of *Escherichia coli*

Sébastien Crépin [a,b], Samuel-Mohammed Chekabab [b,c,1], Guillaume Le Bihan [b,c,1], Nicolas Bertrand [c], Charles M. Dozois [a,b,c], Josée Harel [b,c,*]

[a] *INRS-Institut Armand-Frappier, 531 Boul. des Prairies, Laval, Québec, Canada H7V 1B7*
[b] *Centre de Recherche en Infectiologie Porcine (CRIP), Université de Montréal, Faculté de Médecine Vétérinaire, C.P. 5000, Saint-Hyacinthe, Québec, Canada J2S 7C6*
[c] *Groupe de Recherche sur les Maladies Infectieuses du Porc (GREMIP), Université de Montréal, Faculté de Médecine Vétérinaire, C.P. 5000, Saint-Hyacinthe, Québec, Canada J2S 7C6*

ARTICLE INFO

Article history:
Received 23 December 2010
Received in revised form 18 May 2011
Accepted 25 May 2011

Keywords:
Pho regulon
Pathogenic *Escherichia coli*
Two-component regulatory system
Stress response

ABSTRACT

During the course of infection, bacteria must coordinately regulate gene expression in response to environmental stimuli. The phosphate (Pho) regulon is controlled by the two component-regulatory system PhoBR. PhoBR is activated during starvation and regulates genes involved in phosphate homeostasis. Several studies have highlighted the importance of the Pho regulon in bacterial pathogenesis, showing how induction of PhoBR, in addition to regulating genes participating in phosphate metabolism, leads to modulation of many cellular processes. The pleiotropic effects of Pho regulon activation include attenuated virulence and alteration of many virulence traits, including adhesion to host cells and resistance to cationic antimicrobial peptides, acidity and oxidative stresses. This review provides an overview of the relationship between the Pho regulon and virulence in *Escherichia coli* and illustrates that, in addition to regulating phosphate homeostasis, the Pho regulon plays a key role in regulating stress responses and virulence.

Contents

* Corresponding author at: Groupe de Recherche sur les Maladies Infectieuses du Porc (GREMIP), Université de Montréal, Faculté de Médecine Vétérinaire, C.P. 5000, Saint-Hyacinthe, Québec, Canada J2S 7C6. Tel.: +1 450 773 8521x8233; fax: +1 450 778 8108.
E-mail address: josee.harel@umontreal.ca (J. Harel).
[1] These authors contributed equally to this work.

0378-1135/$ – see front matter
doi:10.1016/j.vetmic.2011.05.043

1. Introduction

To adapt and survive in different microenvironments, bacteria must sense and respond to extracellular signals. The adaptive response to environmental stimuli can be transduced by two-component regulatory systems (Gao and Stock, 2009), which are involved in the regulation of chemotaxis, osmoregulation, metabolism and transport (Mizuno, 1997). A typical two-component regulatory system (TCRS) is composed of an inner-membrane histidine kinase (HK) sensor protein and a response regulator (RR) that acts as a DNA-binding protein, activating or repressing gene expression (West and Stock, 2001).

Phosphorus, in terms of cellular content, is the third most abundant element. It is found in several molecules, including membrane lipids, complex sugars and nucleic acids. Phosphate is also involved in energy metabolism and in signal transduction, which is mediated by a TCRS (Wanner, 1996). The extracellular concentration of phosphate is sensed by the two-component regulatory system PhoBR, in which PhoR encodes the HK and PhoB the RR. PhoBR responds to phosphate limitation, when the extracellular phosphate concentration falls below 4 μM. In phosphate-limiting conditions, PhoBR induces genes belonging to the Pho (phosphate) regulon, which includes genes involved in acquisition and metabolism of different phosphate groups (Hsieh and Wanner, 2010; Lamarche et al., 2008b; Wanner, 1996). The control of the Pho regulon and transmembrane signal transduction by environmental inorganic phosphate (P_i) has been extensively studied in *Escherichia coli* and *Bacillus subtilis.* In *E. coli* K-12, the Pho regulon comprises 31 genes (Hsieh and Wanner, 2010) and, in addition to being involved in phosphate homeostasis, is also connected to bacterial virulence as its induction results in attenuated pathogens.

Host–pathogen interactions are dynamic processes responding to the diverse environmental conditions encountered by invading pathogens. Survival of a pathogen in different sites in the host requires an adaptive response capable of reacting to different stimuli in its immediate environment. The specialised regulatory systems that control the expression of virulence factors are essential for survival and necessarily complex, with interconnections between regulatory systems at many levels. Although the presence of pathogen-specific genes may dictate the pathogenic lifestyle and virulence potential of pathogenic *E. coli*, products encoded by conserved or "core" genes undoubtedly contribute to functional metabolism, physiology and adaptation to environmental changes, including host environments and resistance to host defences.

Lamarche et al. (2008b) reviewed the relationship between the Pho regulon, metabolism and pathogenicity. Here, we present a review specifically focusing on the effects on virulence of *Escherichia coli* by the induction of the Pho regulon. First, we briefly overview the induction of the Pho regulon, then discuss the different virulence attributes affected by the induction of the Pho regulon of pathogenic *E. coli*, including resistance to oxidative stress, membrane perturbation, production of adhesins and adaptation to environmental stimuli.

2. Induction of the Pho regulon

As mentioned above, phosphate starvation is sensed by the TCRS PhoBR. PhoBR is activated when the extracellular phosphate concentration falls below 4 μM, inducing transcription of genes belonging to the Pho regulon. This

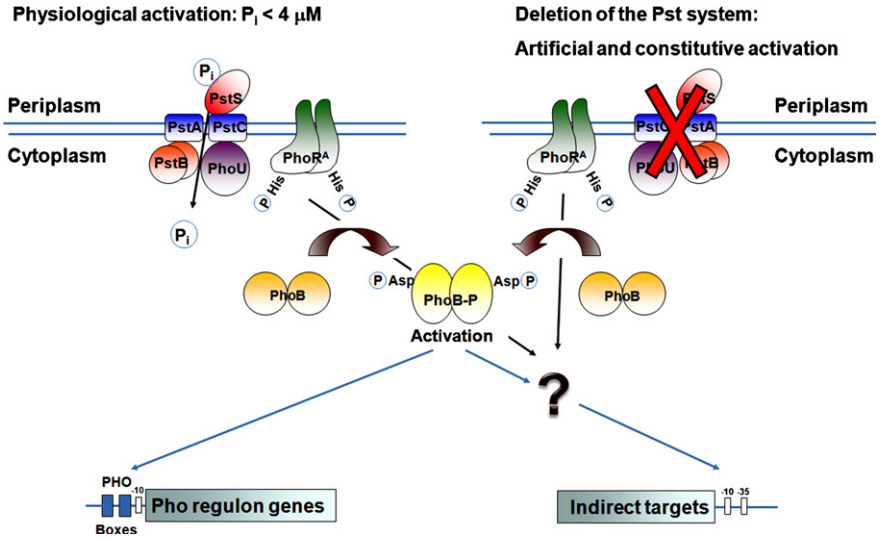

Fig. 1. *Induction of the Pho regulon by phosphate starvation and inactivation of the Pst system*. Adapted from Lamarche et al. (2008b), with kind permission of John Wiley and Sons. Under phosphate starvation, PhoR autophosphorylates a histidine residue. The phosphoryl group is then transferred onto an aspartate residue of PhoB. This phosphotransfer activates PhoB, which can then bind to Pho boxes and activate transcription of Pho-regulated genes. PhoB or PhoR can also act indirectly on gene expression by regulating other regulators. Furthermore, mutations in any of the genes of the *pst* operon result in constitutive expression of the Pho regulon, regardless of environmental phosphate availability. *Abbreviations:* P_i, inorganic phosphate; PstS, periplasmic P_i-binding protein; PstA et PstC, integral membrane channel proteins; PstB, ATP-binding protein; PhoU, regulatory protein; PhoB, RR; PhoR, sensor protein (A, autophosphorylated; P, phosphorylated).