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# ATP-Dependent Protein Kinases in Bacteria

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**Abstract** Protein phosphorylation has been shown to occur in over fifty different bacterial species and, therefore, seems to be a universal device among prokaryotes. Most of the protein kinases responsible for this modification of proteins share the common property of using adenosine triphosphate as phosphoryl donnor. However, they differ from one another in a number of structural and functional aspects. Namely, they exhibit a varying acceptor amino acid specificity and can be classified, on this basis, in three main groups: protein-histidine kinases, protein-serine/threonine kinases and protein-tyrosine kinases. © 1993 Wiley-Liss, Inc

**Key words:** protein kinases, protein phosphorylation, prokaryotes, protein function, nucleotide dependency

## BACTERIAL PROTEIN PHOSPHORYLATION

Protein phosphorylation represents one of the unusual examples in which investigations were initiated in eukaryotic systems and later extended to prokaryotes. Thus, the implication of this chemical modification as a key regulatory mechanism in protein function was first identified in the mid-1950s in the case of rabbit skeletal muscle glycogen phosphorylase, the rate-limiting enzyme in glycogenolysis [Krebs and Fischer, 1956]. Since then, a remarkable number of phosphoproteins has been characterized in a variety of systems ranging from fungi to mammals, and reversible protein phosphorylation has been recognized as a major dynamic process in a wide array of cellular functions [Hunter and Cooper, 1985; Edelman et al., 1987].

For prokaryotes, the interest in protein phosphorylation took much longer to gather momentum, the first experiments being performed only in the late 1960s. In fact, even the existence of this modification in microorganisms was a matter of controversy for several years. However, in the late 1970s, conclusive evidence was presented that it was not confined to eukaryotes, and that bacteria also could harbor specific protein kinases and protein phosphatases [Cozzone, 1988]. Since that time, the number of reports in the field seems to have grown exponentially [Stock et al., 1989; Saier, 1989; Bourret et al., 1991]; and protein phosphorylation has been revealed in a variety of microorganisms that belong to the two bacterial kingdoms, the eubacteria and archaebacteria, as well as to the line of cyanobacteria. All together these organisms comprise over 50 different species which exhibit a great diversity of morphological, physiological, and biochemical features (Table I). It therefore appears that protein phosphorylation is a modification widespread, and probably universal, among bacteria and, more generally, represents an ubiquitous device in biological systems.

## CLASSIFICATION OF PROTEIN KINASES

Protein kinases are classically defined as enzymes that transfer a phosphate group from a nucleoside triphosphate onto an acceptor amino acid in a substrate protein. Several possible classifications of these enzymes have been proposed based on different structural or functional criteria [Hunter, 1991]. A reasonable proposal, recommended by the Nomenclature Committee of the International Union of Biochemists, is to classify protein kinases on the basis of their acceptor amino acid specificity. Five major types of protein kinases can thus be distinguished: 1) enzymes with an alcohol group as acceptor, namely, in serine and threonine residues, that generate phosphate esters; 2) enzymes with a phenolic group as acceptor, in tyrosine residues, that form phosphate esters; 3) enzymes with a basic amino acid as acceptor, such as histidine, arginine, or lysine, that produce phosphoramidates at the 1- or 3- positions of histidine, at the guanido group of arginine, or at the $\epsilon$-$NH_2$ group

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**TABLE I. Bacteria Subject to Protein Phosphorylation**

| Family/group | Species | References |
|---|---|---|
| Eubacteria | | |
| Bacillaceae | *Bacillus megaterium* | Dadssi and Cozzone, 1990a |
| | *Bacillus sphaericus* | Dadssi and Cozzone, 1990a |
| | *Bacillus stearothermophilus* | Deutscher and Saier, 1988 |
| | *Bacillus subtilis* | Reizer et al., 1988; Kohler and Antranikian, 1989; Tanaka et al., 1991; Dahl et al., 1991; Mitchell et al., 1992 |
| | *Bacillus thuringiensis* | Watson and Mann, 1988 |
| | *Clostridium acetobutylicum* | Balodimos et al., 1990 |
| | *Clostridium histolyticum* | Deutscher and Saier, 1988 |
| | *Clostridium sphenoides* | Antranikian et al., 1985 |
| | *Clostridium thermohydrosulfuricum* | Londesborough, 1986 |
| Bordetellaceae | *Bordetella pertussis* | Miller et al., 1989; Stibitz et al., 1989 |
| Chromatiaceae | *Chromatium vinosum* | Gotto and Yoch, 1985 |
| Corynebacteriaceae | Arthrobacter S1-55 | Dadssi and Cozzone, 1990a |
| Enterobacteriaceae | *Enterobacter aerogenes* | Stewart and Dahlquist, 1987 |
| | *Escherichia coli* B | Dadssi and Cozzone, 1990a |
| | *Escherichia coli* K-12 | Garnak and Reeves, 1978; Manai and Cozzone, 1979b; Enami and Ishihama, 1984; Nimmo, 1984; Wada et al., 1986; Waygood et al., 1987 |
| | *Escherichia coli* K-38 | Amster-Choder and Wright, 1990 |
| | *Escherichia coli* MAR001 | Norris et al., 1991 |
| | *Escherichia coli* ML308 | Borthwick et al., 1984 |
| | *Klebsiella aerogenes* | Magasanik, 1988 |
| | *Klebsiella pneumoniae* | Buikema et al., 1985 |
| | *Salmonella typhimurium* | Wang and Koshland, 1981; Cortay et al., 1986; Waygood et al., 1987 |
| Halobacteriaceae | *Halobacterium halobium* | Spudich and Spudich, 1982 |
| Lactobacillaceae | *Lactobacillus brevis* | Reizer et al., 1988 |
| | *Lactobacillus casei* | Deutscher and Saier, 1988 |
| Legionellaceae | *Legionella micdadei* | Saha et al., 1988 |
| Micrococcaceae | *Staphylococcus aureus* | Reizer et al., 1988; Deutscher and Saier, 1988; Peng et al., 1988 |
| | *Staphylococcus carnosus* | Deutscher and Saier, 1988 |
| Mollicutes | *Spiroplasma melliferum* | Platt et al., 1990 |
| Mycobacteriaceae | *Mycobacterium phlei* | Kimura et al., 1988 |
| Mycoplasmataceae | *Mycoplasma gallisepticum* | Deutscher and Saier, 1988; Platt et al., 1988 |
| Myxococcaceae | *Myxococcus xanthus* | Komano et al., 1982; Lukat et al., 1992; Munoz-Dorado et al., 1991 |
| Neisseriaceae | *Acinetobacter calcoaceticus* | Dadssi and Cozzone, 1990b |
| Pseudomonadaceae | *Pseudomonas aeruginosa* | Kelly-Wintenberg et al., 1990; Deretic et al., 1989 |
| | *Pseudomonas fluorescens* | Dadssi and Cozzone, 1990a |
| Rhizobiaceae | *Agrobacterium tumefaciens* | Jin et al., 1990 |
| | *Rhizobium leguminosarum* | Ronson et al., 1987 |
| | *Rhizobium meliloti* | Gilles-Gonzalez et al., 1991 |
| Rhodospirillaceae | *Rhodobacter sphaeroïdes* | Holmes et al., 1986 |
| | *Rhodocyclus gelatinosus* | Averhoff et al., 1986 |
| | *Rhodomicrobium vannielii* | Turner and Mann, 1986 |
| | *Rhodospirillum rubrum* | Vallejos et al., 1985; Holmes and Allen, 1988 |

*(continued)*

**TABLE I. Bacteria Subject to Protein Phosphorylation**

| Family/group | Species | References |
|---|---|---|
| Streptococcaceae | *Streptococcus faecalis* | Deutscher and Engelmann, 1984 |
| | *Streptococcus lactis* | Deutscher et al., 1984 |
| | *Streptococcus mutans* | Mimura et al., 1987 |
| | *Streptococcus pyogenes* | Deutscher and Engelmann, 1984; Deutscher and Saier, 1988 |
| | *Streptococcus salivarius* | Waygood et al., 1986 |
| Streptomycetaceae | *Streptomyces albus* | Dobrova et al., 1990 |
| | *Streptomyces coelicolor* | Hong et al., 1991 |
| Archaebacteria | | |
| Thiobacillaceae | *Sulfolobus acidocaldarius* | Skorko, 1984 |
| | *Thiobacillus novellus* | Sykora and Charles, 1991 |
| Cyanobacteria | | |
| | *Anabena 7120* | Mann et al., 1991 |
| | *Calothrix 7601* | Schuster et al., 1984 |
| | *Synechococcus 6301* | Sanders et al., 1989 |
| Bacteroids | | |
| | *Bradyrhizobium japonicum* | Karr et al., 1989 |
| | *Bradyrhizobium parasponiae* | Nixon et al., 1986 |

of lysine, 4) enzymes with an acyl group as acceptor, in aspartic and glutamic acid residues, that generate mixed phosphate-carboxylate acid anhydrides; and 5) enzymes with a cysteine residue as acceptor that produce phosphate thioesters [Hunter, 1991; Duclos et al., 1991].

Most bacterial protein kinases utilize the $\gamma$ phosphate of ATP as the phosphate donor in the phosphorylation reaction and are called "ATP-dependent" enzymes for that reason. They will be analyzed in the next sections of this article. However some bacterial phosphorylating enzymes make use of other phosphate donors in the form of either phosphoenzyme intermediates or low molecular weight metabolites, such as phosphoenol pyruvate, acetyl phosphate, or carbamoyl phosphate [Saier et al., 1990; Lukat et al., 1992]. These enzymes may be considered as phosphotransferases rather than protein kinases stricto sensu. Similarly, enzymes that undergo autophosphorylation reactions may not correspond strictly to the definition of classical protein kinases.

## PROTEIN-HISTIDINE KINASES

A variety of signal transducing systems, referred to as "two-component regulatory systems," allow bacteria to respond to environmental stimuli and to control gene transcription and cellular behavior [Stock et al., 1989; Bourret et al., 1991]. These systems have been found in over 20 different functional contexts including chemotaxis, nitrogen and phosphate regulation, porin gene expression, sporulation, competence, virulence, alginate production, and exoprotein synthesis, among others. The molecular mechanism responsible for the stimulus-response coupling involves the following components in a chronological order: 1) a sensory protein kinase that detects environmental changes and autophosphorylates, 2) a phosphorylated response regulator protein, 3) a target of regulator action, and 4) a protein phosphatase that restores the regulator protein to its unphosphorylated state. Signal transduction occurs through the transfer of phosphoryl groups from ATP to histidine residues in the sensor protein kinases, and then from the phosphohistidine residues of the kinases to aspartic acid residues in the response regulators. In some instances, however, the term "two-component system" is inadequate since a single polypeptide chain is bearing both the protein-histidine kinase and the response-regulator functions. Protein FrzE, which controls motility and development in myxobacteria, is an example of such a one-component system [McLeary and Zusman, 1990]. In other cases, the sensor function is separated from the protein-histidine kinase thus generating a three-component system, such as the Uhp proteins involved in the uptake of hexose phosphates [Weston and Kadner, 1988].

Members of the sensor class of protein-histidine kinases share sequence similarities at their C-terminal ends, namely, six amino acids (including one asparagine) that are especially con-

served in this region [Stock et al., 1989]. In addition, all of the kinases except CheA and FrzE possess a conserved histidine that precedes the conserved asparagine by about 100 amino acids. This histidine is presumably the site of autophosphorylation in these kinases. By contrast, the remaining portions of the molecules tend to be quite variable.

Many protein-histidine kinases are associated with membranes, with two hydrophobic transmembrane sequences bordering a domain that seems to be localized to the outer surface of the cytoplasmic membrane. These kinases appear to function as membrane receptors: their N-terminal extracytoplasmic regions would interact with stimulatory molecules in the periplasm, and transmembrane signals would control the kinase/or phosphatase activities of their C-terminal regions in the cytoplasm [Forst and Inouye, 1988]. Exceptionally, kinases CheA and NtrB are cytoplasmic proteins that receive signals within the cytoplasm [Stock et al., 1989; Magasanik, 1989].

Of interest is the fact that, although a specific kinase is essentially implicated in the regulation of a given response regulator, considerable cross specificity has been observed [Ninfa et al., 1988; Olmedo et al., 1990]. For instance the first component of the chemotaxis system, phospho-CheA, can transfer its phosphate to the second component of the nitrogen system, NtrC, and conversely. Such regulatory interactions may be especially important as a way of directly linking different systems in a network to coordinate cell growth and metabolism [Wanner, 1992].

## PROTEIN-SERINE/THREONINE KINASES

A large proportion of bacterial protein kinases belongs to the family of protein-serine/threonine kinases. Within this family, phosphorylation occurs much more frequently at serine than at threonine residues in proteins, as judged from the proportions of phosphoserine and phosphothreonine in total or individual phosphoproteins [Cortay et al., 1986b]. In both Gram-negative and Gram-positive species, two main classes of kinases with a different intracellular location are present: one is in the cytoplasmic fraction and the other is attached to the ribosome/membrane fraction [Manaï et al., 1982; Mimura et al., 1987]. Both classes correspond strictly to the definition of classical protein kinases in the sense that 1) they use only nucleoside triphosphates, mostly ATP, as phosphate donors to yield acid-resistant phosphoamino acids in substrate proteins, and 2) they do not autophosphorylate. Several protein-serine/threonine kinases have been partially purified from a series of bacterial species [Cozzone, 1988]. A few of them have been purified to homogeneity which has made possible their analysis at a molecular level. Among these the ATP-dependent protein kinases that phosphorylate protein HPr at a serine residue in the phosphoenolpyruvate: sugar phosphotransferase system (PTS system) have been isolated from *Streptococcus faecalis* [Deutscher and Engelmann, 1984], *S. pyogenes,* and *Bacillus subtilis* [Reizer et al., 1988]. All three enzymes are associated to membranes. They can phosphorylate HPr proteins different from their specific substrate, such as HPr of *S. lactis, Staphylococcus aureus,* and *B. stearothermophilus,* but not HPr of *Escherichia coli.* Their activities are dependent on divalent cations, are strongly inhibited by EDTA and diethylpyrocarbonate, but are insensitive to sulfhydryl reagents. Phosphorylation catalyzed by these enzymes is strongly impaired by inorganic phosphate but stimulated by a number of metabolites, namely, fructose-1,6-diphosphate [Reizer et al., 1988]. Other protein kinases have been purified to homogeneity from *E. coli* cells: one is able to phosphorylate specifically a 90 kDa-protein from the cytoplasm and another can modify two periplasmic transport proteins [Urban and Celis, 1990].

The enzyme which has been studied so far with the most thoroughness, from both biochemical and genetic aspects, is isocitrate dehydrogenase kinase/phosphatase from *E. coli.* This bifunctional enzyme plays a key role in the control of the partition of carbon molecules between the tricarboxylic acid cycle and the glyoxylate bypass [LaPorte and Koshland, 1982]. It has been totally purified by different groups [LaPorte and Koshland, 1982; Malloy et al., 1985; Varela and Nimmo, 1988]. The complete nucleotide sequence of the corresponding gene, *aceK,* was first determined by our group [Cortay et al., 1988]. It consists of 1,731 nucleotides coding for a 66 528 Da-protein. Similar results were presented afterwards in another report [Klumpp et al., 1988]. The *aceK* gene is part of the acetate operon whose transcriptional regulation by a specific repressor, termed protein IclR, has been investigated in detail [Cortay et al., 1991; Nègre et al., in press]. The amino acid sequence of the *E. coli* isocitrate dehydrogenase kinase/phosphatase deduced from the nucleotide sequence of the *aceK* gene is largely unrelated to that of the eukaryotic protein kinase family. This obser-

vation, together with the amino acid sequence analysis of various bacterial protein-histidine kinases [Stock et al., 1989], support the concept that bacterial kinases strikingly differ in their structure, and hence in their function, from the kinases of higher organisms.

However, recent data indicate that, in the Gram-negative bacterium *Myxococcus xanthus,* a gene called *pkn1* encodes a protein-serine/threonine kinase showing significant sequence similarity with the catalytic domain of eukaryotic kinases [Munos-Dorado, 1991]. The corresponding gene product, Pkn1, which autophosphorylates at both serine and threonine residues, plays an important role in the onset of proper differentiation. In addition another gene, *pkn2,* also encoding a protein kinase with high similarity to eukaryotic enzymes, has lately been identified in the same bacterium [M. Inouye, personal communication]. The corresponding gene product, Pkn2, autophosphorylates predominantly at a threonine residue. It is required to maintain the viability of cells during the stationary phase and the proper timing for aggregation during the developmental cycle. These two genes, *pkn1* and *pkn2,* are probably not unique in *M. xanthus* since a total of 26 putative kinase genes has been detected in this bacterium [M. Inouye, personal communication].

Interestingly, a protein kinase C-like activity has been described recently in the pathogenic strain MAR001 of *E. coli* [Norris et al., 1991]. This enzyme is calcium- and phospholipid-dependent and is stimulated by diacylglycerol and phorbol esters, like eukaryotic protein kinases C. Similarly, there is good evidence for the presence of a protein kinase C-like activity in *B. subtilis,* based on cross reaction with different monoclonal antibodies and phosphatidylserine fixation [S. Seror, personal communication]. These findings suggest that at least some classes of protein kinases are similar, if not identical, in prokaryotic and eukaryotic organisms, which would partially reverse the concept of dissimilarity mentioned above. From this point of view, it is worth noting that a number of effectors of eukaryotic protein kinases, such as calmodulin, appear to have counterparts in bacteria [Fry et al., 1991].

## PROTEIN-TYROSINE KINASES

The first indication of a protein-tyrosine kinase activity in bacteria was reported in the case of *E. coli* by showing that phosphotyrosine is present in partial acid hydrolysates of proteins [Manaï et al., 1983]. In addition it was found that one *E. coli* protein resolved by gel electrophoresis is detectable after treatment of the gel with alkali, this treatment being used to enrich for phosphotyrosine [Cortay et al., 1986a]. These observations have been confirmed in the case of *Rhodospirillum rubrum* [Vallejos et al., 1985], *Rhodomicrobium vannielii* [Turner and Mann, 1986], *Clostridium thermosulfuricum* [Londesborough, 1986], *S. pyogenes* [Chiang et al., 1989], *Pseudomonas aeruginosa* [Kelly-Wintenberg et al., 1990], and a variety of other bacterial species [Dadssi and Cozzone, 1990a]. However the question has been raised of whether or not the source of phosphotyrosine in bacteria could be the nucleotidylation of proteins rather than their phosphorylation [Foster et al., 1989]. Phosphotyrosine would then be generated by partial hydolysis of proteins to which a nucleotide or nucleic acid would be linked via a phosphodiester bond to the phenolic hydroxyl of a tyrosine residue. Recently this possible ambiguity has been ruled out by clearly demonstrating, through a series of assays, the occurrence of a protein-tyrosine kinase activity in the bacterium *Acinetobacter calcoaceticus* [Dadssi and Cozzone, 1990b]. Interestingly, this kinase does not exhibit much functional similarity with the homologous eukaryotic enzymes since, in particular, it does not respond to the same inhibitors or activators. An additional firm evidence for a bacterial protein-tyrosine kinase has been obtained by showing that one of the two kinases of *S. pyogenes* can phosphorylate in vitro a 4:1 glutamate: tyrosine copolymer which is a tyrosine kinase-specific substrate.

Obviously, the purification and/or molecular cloning of bacterial protein-tyrosine kinases are now required for a better understanding of their structure and function. Considering the crucial role played by phosphorylation of proteins at tyrosine in several cellular processes in eukaryotes [Hunter and Cooper, 1985], the challenge is to determine its physiological significance in bacteria.

## ENZYME CHARACTERISTICS

The ATP-dependent protein kinases of bacteria utilize ATP selectively as phosphate donor. An exception to this rule, however, concerns the phosphorylation of protein AlgR2 in *P. aeruginosa.* Protein AlgR2 is a kinase involved in the two-component system that participates in the synthesis of the exopolysaccharide alginate. Recent results have shown that it can autophos-

phorylate in the presence of GTP as well as ATP [Roychoudury et al., 1992].

The activity of bacterial ATP-dependent protein kinases is generally cyclic nucleotide independent. The pattern of protein phosphorylation in vitro is identical whether or not cyclic AMP or cyclic GMP is present during incubation of cellular extracts from *E. coli* [Manaï and Cozzone, 1982; Dadssi and Cozzone, 1985], *R. rubrum* [Vallejos et al., 1985], *Sulfolobus acidocaldarius* [Skorko, 1984], and several other species [Dadssi and Cozzone, 1990a]. When protein phosphorylation in vivo in wild-type cells is compared to that in adenylate cyclase deletion mutants of *E. coli* [ Malloy and Reeves, 1983; Dadssi and Cozzone, 1985] or *S. typhimurium* [Wang and Koshland, 1981], similar results are obtained. One can thus envisage that in bacteria cyclic nucleotides, namely, cAMP, are specialized for the regulation of gene expression and protein synthesis, while protein phosphorylation regulates specific metabolic processes and is itself controlled by metabolites. As an exception, *Legionella micdadei* contains two different protein kinases: PK1 is cyclic nucleotide-independent, but PK2 is cAMP- and cGMP-dependent [Saha et al., 1988].

Another general characteristic of bacterial kinases is their incapacity to phosphorylate exogenous proteins such as casein, histones, protamines, or phosvitin, which are, on the other hand, readily targeted by eukaryotic kinases [Manaï and Cozzone, 1979a; Cozzone, 1988]. Considering such high selectivity of the bacterial enzymes, it is understandable that early searches employing these exogenous proteins as substrates failed to demonstrate the presence of kinases in prokaryotes. Only in the case of *S. pyogenes* two bacterial kinases are capable of phosphorylating histones and protamines in vitro in addition to endogenous proteins [Chiang et al., 1989]. For the other kinases, several attempts have been made to identify phosphorylatable substrates. In particular, a synthetic hexapeptide containing one serine residue has been found to be a quite suitable substrate for *E. coli* protein kinases [Dadssi et al., 1989].

In terms of substrate specificity, further analysis of the cross talk process [Ninfa et al., 1988; Wanner, 1992] in two-component systems should bring useful information on the mechanism of substrate/kinase recognition. Also it should throw some light on the question of whether or not protein kinases have a pleiotropic action and therefore are less numerous than phosphoproteins.

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