Available online at www.sciencedirect.com
SCIENCE DIRECT®
ELSEVIER
Biochimica et Biophysica Acta 1754 (2005) 281 – 290
BIOCHIMICA ET BIOPHYSICA ACTA
BBA
http://www.elsevier.com/locate/bba

Review

Mammalian histidine kinases

Paul G. Besant [a,b], Paul V. Attwood [a,*]

[a] School of Biomedical and Chemical Sciences (M310), The University of Western Australia, 35 Stirling Highway, Crawley, WA 6009, Australia
[b] Laboratory for Cancer Medicine, The UWA Centre for Medical Research, West Australian Institute for Medical Research, Level 5, MRF Building, 50 Murray Street, Perth, WA 6000, Australia

Received 6 June 2005; received in revised form 19 July 2005; accepted 19 July 2005
Available online 8 September 2005

Abstract

Protein phosphorylation is one of the most ubiquitous and important types of post-translational modification for the regulation of cell function. The importance of two-component histidine kinases in bacteria, fungi and plants has long been recognised. In mammals, the regulatory roles of serine/threonine and tyrosine kinases have attracted most attention. However, the existence of histidine kinases in mammalian cells has been known for many years, although little is still understood about their biological roles by comparison with the hydroxyamino acid kinases. In addition, with the exception of NDP kinase, other mammalian histidine kinases remain to be identified and characterised. NDP kinase is a multifunctional enzyme that appears to act as a protein histidine kinase and as such, to regulate the activation of some G-proteins. Histone H4 histidine kinase activity has been shown to correlate with cellular proliferation and there is evidence that it is an oncodevelopmental marker in liver. This review mainly concentrates on describing recent research on these two types of histidine kinase. Developments in methods for the detection and assay of histidine kinases, including mass spectrometric methods for the detection of phosphohistidines in proteins and in-gel kinase assays for histone H4 histidine kinases, are described. Little is known about inhibitors of mammalian histidine kinases, although there is much interest in two-component histidine kinase inhibitors as potential antibiotics. The inhibition of a histone H4 histidine kinase by genistein is described and that of two-component histidine kinase inhibitors of structurally-related mammalian protein kinases. In addition, recent findings concerning mammalian protein histidine phosphatases are briefly described.
© 2005 Elsevier B.V. All rights reserved.

Keywords: Histidine kinase; Phosphohistidine; NDP kinase; Histone H4; Protein histidine phosphatase; Kinase inhibitor

1. Introduction

Protein phosphorylation is one of the most common forms of post-translational modification and one of the most important in the regulation of cellular function. Protein kinases are the enzymes that catalyse the transfer of the γ-phosphoryl group from a nucleoside triphosphate, usually ATP, to the side chain of an amino acid residue in the substrate protein. The best-known and most well-characterised protein kinases in mammalian cells are the serine/threonine kinases and the tyrosine kinases, which catalyse the phosphorylation of the hydroxyl oxygen of these amino acids. There is however another type of protein kinase, the histidine kinase, which catalyses the phosphorylation of either the 1-nitrogen or the 3-nitrogen of the imidazole ring of the histidine side chain (Fig. 1). The phosphoramidate bond in phosphohistidine differs from the phosphoester bond in the phosphohydroxyamino acids in that it is unstable under acidic conditions and has a relatively high $\Delta G°$ of hydrolysis [1]. The acid-lability of phosphohistidine has meant that many techniques that are applied to the study of serine/threonine and tyrosine kinases cannot be used or have to be modified for the study of histidine kinases. The high free energy of hydrolysis of phosphohistidine facilitates phosphoryl transfer to other amino acids in intramolecular or intermolecular reactions.

The best known group of this type of protein kinase is the two-component histidine kinases which are found in bacteria,

Abbreviations: NDPK, nucleoside diphosphate kinase; NTP, nucleoside triphosphate; HHK, histone H4 histidine kinase; K_I, inhibitory constant; BCKDHK, branched chain α-ketoacid dehydrogenase kinase; PDHK, pyruvate dehydrogenase kinase; eEF-2, eukaryotic elongation factor-2; eEF-2 kinase, eukaryotic elongation factor-2 kinase; RPTLC, reverse-phase thin layer chromatography; k_{cat}, catalytic rate constant; K_m, Michaelis constant; LHPPase, lysine/histidine protein phosphatase

* Corresponding author. Tel.: +61 8 6488 3329; fax: +61 8 6488 1148.
E-mail address: pattwood@cyllene.uwa.edu.au (P.V. Attwood).

1570-9639/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbapap.2005.07.026

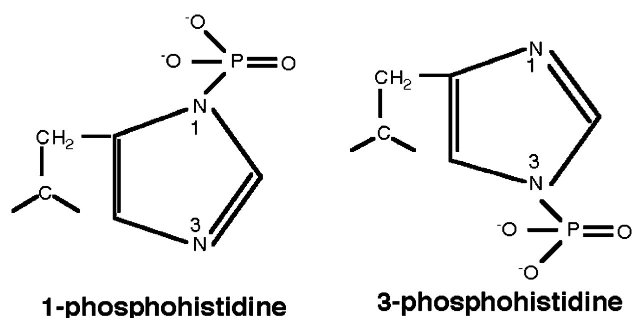

Fig. 1. Phosphorylated imidazole side chain groups of 1- and 3-phosphohistidine.

fungi and plants (for a review, see [2]). These histidine kinases are usually membrane receptor proteins, which either exist as dimers or dimerise in response to external stimuli. In response to the stimulus (e.g., change in osmolarity; ethylene concentration), a *trans*-phosphorylation reaction occurs in which one kinase of the dimer phosphorylates the other kinase on a specific, conserved histidine residue. The phosphoryl group is then transferred directly to a conserved aspartate residue on a response-regulator protein (often a transcription factor), thus activating it and initiating the cellular response. Alternatively, there are multi-component phosphorelay systems in which the phosphoryl group from phosphohistidine is firstly transferred to an aspartate residue, either in another domain of the histidine kinase or in a separate protein. The phosphoryl group is then transferred from the phosphoaspartate to a histidine residue that is again, either in another domain of the histidine kinase or in a separate protein. The phosphoryl group is then transferred to the aspartate of the response regulator protein (examples of such phosphorelay systems are given in [3]). As suggested by Besant et al. [3], this type of phosphotransfer system, which does not occur in phosphohydroxyamino acid-containing phosphoproteins, may be a reason for the occurrence of histidine kinases in mammalian cells.

The existence of histidine kinases in mammalian cells has been recognised for more than 30 years, with the early work of Smith and co-workers providing an initial impetus for further research in this area [4–7]. Although Matthews mainly worked on yeast histone H4 histidine kinase and protein histidine phosphatases, his development of assays and other methods for the investigation of protein histidine phosphorylation reinvigorated the field in the 1990s [8–16]. At the same time, Wieland and co-workers [17–22] and Kowluru and co-workers [23] were working on the histidyl phosphorylation of the β subunit of heterotrimeric G-proteins and the subsequent transfer of this phosphoryl group to GDP bound on the α subunit. Interest was also growing in the ability of NDP kinases (human Nm23s) to act as protein kinases, in particular as protein histidine kinases [24–26]. Our interest in mammalian histone H4 histidine kinases also started in the late 1990s [27].

The aim of this review is to cover recent advances in our understanding of mammalian histidine kinases and the role of histidine phosphorylation in mammalian cells. We mainly concentrate on NDP kinases and histone H4 histidine kinases, as there has been the most progress in these areas. We shall also refer to advances in methodologies in the investigation of protein histidine phosphorylation and the assay and detection of histidine kinases. In addition, we shall consider what is known about histidine kinase inhibitors with reference to particular mammalian enzymes.

2. Nucleoside diphosphate kinases (NDPKs)

In the 1990s there were a number of reports which suggested that some forms of NDPK could act as histidine kinases [24–26]. NDPK autophosphorylates on an active site histidine (using NTP as a substrate) and it was proposed that this phosphoryl group could then be transferred to histidine residues on other proteins. Wagner and Vu [25] found that rat liver NDPK could phosphorylate a histidine residue on ATP-citrate lyase. Later, Wagner et al. [26] showed that Nm23-H1, a human NDPK involved in the suppression of tumour metastasis, could also phosphorylate ATP-citrate lyase on a histidine residue. In addition, it was shown that Nm23-H1 could also phosphorylate a histidine residue on succinate thiokinase [28]. Lu et al. [24] showed that NDPK was capable of phosphorylating histidine residues in the two-component histidine kinases EnvZ and CheA in *Escherichia coli*.

More recently, doubt has been cast on the ability of NDPK to directly phosphorylate the above-mentioned proteins on histidine residues. Levit et al. [29] were able to demonstrate that CheA and EnvZ, which undergo histidyl autophosphorylation in the presence of ATP, would not autophosphorylate when incubated with GTP but could be phosphorylated using this nucleotide in the presence of NDPK. However, this phosphorylation only occurred when ADP was present in the reaction mixture and even concentrations of ADP as low as 1 nM were sufficient to promote phosphorylation of CheA and EnvZ. To explain these results, Levit et al. [29] proposed that NDPK autophosphorylated using [γ-^{32}P]GTP as a substrate, this phosphorylated NDPK then transferred its [^{32}P]phosphoryl group to ADP to form [γ-^{32}P]ATP. The [γ-^{32}P]ATP was then used as a substrate by CheA or EnvZ for their autophosphorylation and resulted in the re-formation of ADP, which was then re-phosphorylated by NDPK. The apparent phosphorylation of both succinate thiokinase and ATP-citrate lyase by NDPK may thus be explained as autophosphorylation events in these enzymes. Both ATP-citrate lyase and succinate thiokinase have a reactive histidine residue in their active sites which undergoes autophosphorylation in the course of their normal catalytic cycles [25,30].

Whilst autophosphorylation may explain the phosphorylation of succinate thiokinase and ATP-citrate lyase, this does not explain the phosphorylation of aldolase C by Nm23-H1 and rat liver NDPK [31]. Aldolase C was found to be phosphorylated on D319 by purified, autophosphorylated NDPK and Nm23-H1 [31]. With respect to the phosphorylation of a target protein on aspartate by enzymes that autophosphorylate on histidine, NDPK and Nm23-H1 behave in a similar way to two-component histidine kinases. Mutant forms of Nm23-H1 which lack the ability to suppress cell motility also showed much

Download English Version:

https://daneshyari.com/en/article/9745096

Download Persian Version:

https://daneshyari.com/article/9745096

Daneshyari.com