Review

Sophisticated Regulation of Transcriptional Factors by the Bacterial Phosphoenolpyruvate: Sugar Phosphotransferase System

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Abstract

The phosphoenolpyruvate:sugar phosphotransferase system (PTS) is a carbohydrate transport and phosphorylation system present in bacteria of all different phyla and in archaea. It is usually composed of three proteins or protein complexes, enzyme I, HPr, and enzyme II, which are phosphorylated at histidine or cysteine residues. However, in many bacteria, HPr can also be phosphorylated at a serine residue. The PTS not only functions as a carbohydrate transporter but also regulates numerous cellular processes either by phosphorylating its target proteins or by interacting with them in a phosphorylation-dependent manner. The target proteins can be catabolic enzymes, transporters, and signal transduction proteins but are most frequently transcriptional regulators. In this review, we will describe how PTS components interact with or phosphorylate proteins to regulate directly or indirectly the activity of transcriptional repressors, activators, or antiterminators. We will briefly summarize the well-studied mechanism of carbon catabolite repression in firmicutes, where the transcriptional regulator catabolite control protein A needs to interact with seryl-phosphorylated HPr in order to be functional. We will present new results related to transcriptional activators and antiterminators containing specific PTS regulation domains, which are the phosphorylation targets for three different types of PTS components. Moreover, we will discuss how the phosphorylation level of the PTS components precisely regulates the activity of target transcriptional regulators or antiterminators, with or without PTS regulation domain, and how the availability of PTS substrates and thus the metabolic status of the cell are connected with various cellular processes, such as biofilm formation or virulence of certain pathogens.

Introduction

Many bacteria and some archaea can incorporate carbohydrates via the phosphoenolpyruvate:sugar phosphotransferase system (PTS). This system, discovered more than 50 years ago [1–3], transports and phosphorylates among others keto- and aldohexoses, di- and trisaccharides, sugar alcohols, amino sugars, gluconic acids, glucosaminate, and the recently reported Maillard reaction products glucoselysine and fructoselysine [4–6]. The PTS is usually composed of four soluble proteins and one membrane-spanning protein. Two of the cytoplasmic PTS components, enzyme I (EI) and HPr, are involved in the uptake of most PTS substrates, whereas the enzyme II (EII) complexes, which consist of EIIA, EIIB, EIIC, and sometimes EIID proteins or protein domains, are usually specific for one PTS substrate or a small group of closely related carbohydrates (Fig. 1). EI and HPr are constitutively expressed or partially inducible and localize at the cell poles, whereas synthesis of the EII complexes, which are localized around the cell periphery [7], is induced by the presence of the corresponding PTS-sugar in the extracellular medium. To indicate EII substrate specificity, a three-letter abbreviation of

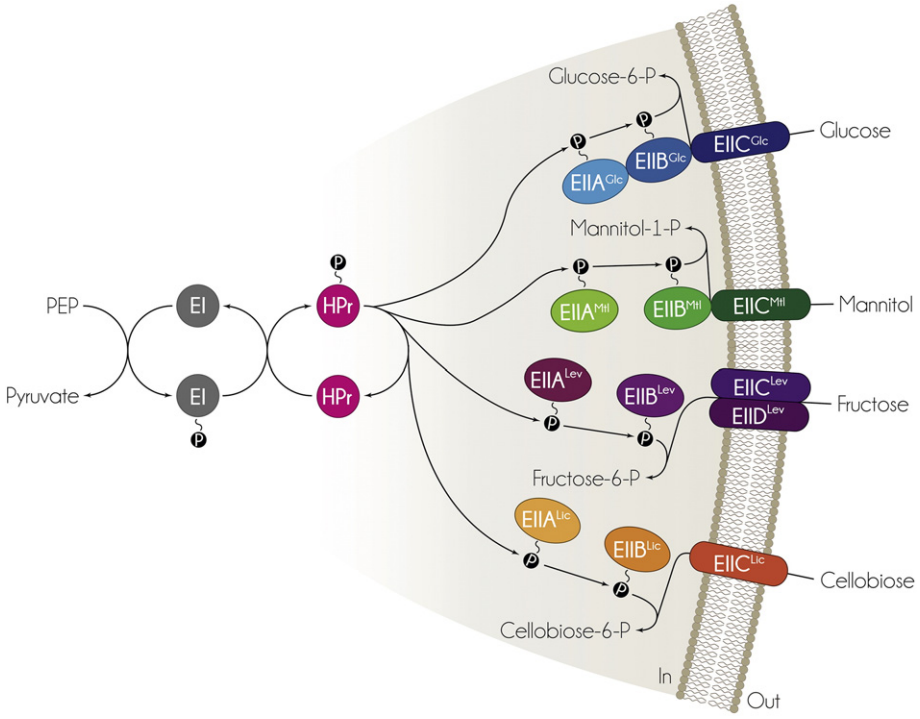

Fig. 1. PTS-mediated uptake of glucose, mannitol, fructose, and cellobiose in *B. subtilis*. The first step of the phosphorylation cascade catalyzed by the PTS is the autophosphorylation of EI with PEP. EI subsequently transfers its phosphate group to HPr that usually phosphorylates all EIIAs present in an organism. The P ~ EIIAs transfer their phosphoryl group to their cognate EIIBs. Each EIIB irreversibly phosphorylates the carbohydrate bound to the corresponding membrane-integral EIIC or EIIC and EIID in the case of the fructose-transporting PTS^{Lev}. Then, the phosphorylated carbohydrate is liberated into the cytoplasm. The organization of the EII domains with the same substrate specificity can be different in other organisms.

the carbohydrate transported or of the associated regulatory function is added as superscript to the corresponding EII domain; for example, $EIIA^{Glc}$ corresponds to the glucose-specific EIIA component and $EIIA^{Ntr}$ to the EIIA of the nitrogen regulatory PTS. Not all carbohydrates are taken up by the PTS, and a distinction is made between PTS-sugars and non-PTS-sugars. Non-PTS substrates, such as glycerol, glucuronate, D-arabinose, etc., are transported by permeases, ABC transporters, or carbohydrate facilitators [8,9]. However, a substantial variation exists, and what is true for one bacterial species is not necessarily true for another [10]. Detailed information about the various PTS families and their substrates in various organisms can be found in Refs. [11,12].

The first step of the concomitant transport and phosphorylation of a carbohydrate by the PTS is the autophosphorylation of EI [13], which requires phosphoenolpyruvate (PEP), an unusually high-energy phosphoryl donor [4]. EI has recently been proposed to catalyze under certain growth conditions also the reverse flux from pyruvate to PEP [14]. For carbohydrate transport, phosphorylated EI (P ~ EI) transfers its phosphoryl group to HPr. These two proteins are known as the general energy-coupling cytoplasmic proteins because with a few exceptions (for example, in the PTS^{Fru} of enterobacteria, an HPr-like domain is fused to the $EIIA^{Fru}$), they are used by all EII complexes of the PTS. P ~ HPr transfers its phosphoryl group to EIIA, which phosphorylates EIIB. All these high-energy phosphoryl group transfers are reversible and occur at histidyl residues, except for EIIB proteins in which usually a cysteine residue is phosphorylated. The PTS substrates bind to the outward directed configuration of their EIIC. Based on the solved crystal structures of two EIICs, an elevator-type mechanism was proposed for the transfer of the substrate from the surface to the inner side of the membrane [15]. In the last step, P ~ EIIB transfers its phosphoryl group to a carbohydrate molecule bound to the cognate inward directed EIIC. Under physiological conditions, this reaction is practically irreversible. Phosphorylation of the carbohydrate probably lowers its affinity for the EIIC and it is released into the cytoplasm (Fig. 1).

Numerous proteobacteria possess an incomplete PTS lacking EIIB and EIIC components, which are required for carbohydrate transport and phosphorylation, thus suggesting that the PTS carries out additional functions [16]. Indeed, in many bacteria, the PTS does not only transport and phosphorylate