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Current Opinion in Microbiology

Post-translational modifications as key regulators of bacterial metabolic fluxes

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In order to survive and compete in natural settings, bacteria must excel at quickly adapting their metabolism to fluctuations in nutrient availability and other environmental variables. This necessitates fast-acting post-translational regulatory mechanisms, that is, allostery or covalent modification, to control metabolic flux. While allosteric regulation has long been a well-established strategy for regulating metabolic enzyme activity in bacteria, covalent post-translational modes of regulation, such as phosphorylation or acetylation, have previously been regarded as regulatory mechanisms employed primarily by eukaryotic organisms. Recent findings, however, have shifted this perception and point to a widespread role for covalent posttranslational modification in the regulation of metabolic enzymes and fluxes in bacteria. This review provides an outline of the exciting recent advances in this area.

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Current Opinion in Microbiology 2015, **24**:29–37

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

Edited by **Carol Gross** and **Angelika Gründling**

For a complete overview see the Issue and the Editorial

Available online 16th January 2015

http://dx.doi.org/10.1016/j.mib.2014.12.006

Introduction

During the last decade we have witnessed a resurgence in metabolic research and a renewal of efforts toward understanding metabolism and the regulation of metabolic fluxes. This renewed interest, propelled by modern mass spectrometry and advances in computational modeling of metabolic networks, is hardly surprising given the central role of metabolism in human health, synthetic biology, and metabolic engineering [1].

The regulation of metabolic enzyme activity, which determines metabolic flux, occurs at different levels: transcriptional, translational, and post-translational. In bacterial systems, a wealth of research has shown that regulation of metabolic fluxes is frequently extremely rapid, on the order of seconds to a few minutes [2–6]. This speedy response, which correlates well with the expected need of bacteria to rapidly respond to environmental perturbations, emphasizes the requirement of fast-acting post-translational regulatory mechanisms of metabolic flux control: that is, allosteric regulation and covalent protein modification [7]. The role of allostery in controlling metabolic fluxes in bacteria is well established and continues to be strengthened by exciting new research [7,8]. However, although the regulation of bacterial metabolic enzymes by post-translational modification (PTM) has long been known via classical examples such as inhibition of glutamine synthetase (GS) by adenylylation [9] or isocitrate dehydrogenase (Icd) by phosphorylation [10], the widespread role that PTMs play in the regulation of metabolic fluxes has only started to come into full light in recent years.

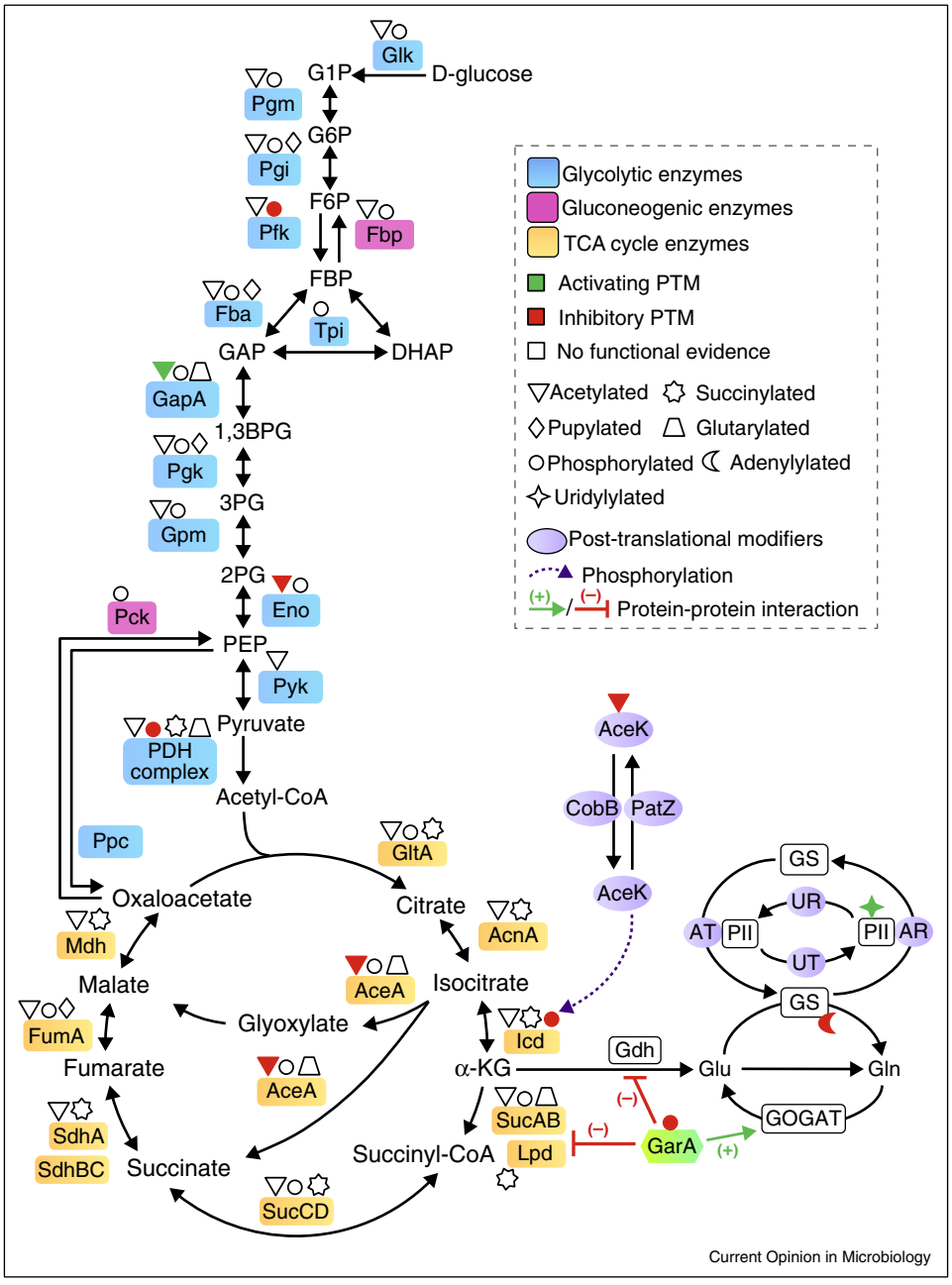
Posttranslational covalent modifications are prevalent in bacteria

Through the application of mass-spectrometry-based proteomics methods, it is now clear that PTMs, particularly acetylation and phosphorylation, are highly prevalent in bacteria [3,11]. Phosphoproteome and acetylome studies in an increasing number of bacteria, including *Escherichia coli* [12–15], *Bacillus subtilis* [16], *Streptococcus pneumoniae* [17], *Mycobacterium tuberculosis* [18], *Salmonella enterica* [19], *Staphylococcus aureus* [20], *Thermus thermophilus* [21,22], *Mycoplasma pneumoniae* [23], *Rhodopseudomonas palustris* [24], and *Corynebacterium glutamicum* [25•], have shown that a significant fraction of their proteomes is subject to PTM. Although proteins with many types of functions are subject to PTM, a unifying trend in these studies has been the high prevalence of PTMs among metabolic enzymes (Figure 1 and Table 1).

N-Lysine acetylation and the regulation of acyl-CoA synthetases

N-Lysine acetylation (KAc) is a reversible PTM best known for its role in controlling eukaryotic gene regulation through histone modification [26]. KAc is catalyzed by acetyltransferases and reversed by deacetylases, although it may also occur non-enzymatically [27]. The acyl group transferred onto lysine residues comes most frequently from acetyl-CoA [28]. KAc is prevalent in bacterial proteomes, and the acetylation of metabolic

Figure 1



Post-translational modifications (PTMs) are ubiquitous in bacterial central metabolic enzymes. The PTMs shown here were identified in *E. coli*, *S. enterica*, *R. palustris*, *M. smegmatis*, *M. tuberculosis*, *B. subtilis*, *T. thermophilus*, and/or *S. cerevisiae* as referenced in the main text and in Table 1. The *in vivo* functionality of most PTMs remains to be elucidated (non-colored symbols); if known, it is indicated by green (activating effect) or red (inhibitory effect). For example: isocitrate dehydrogenase phosphatase/kinase (AceK) phosphorylates isocitrate dehydrogenase (Icd) to inhibit its function; in turn, AceK is negatively controlled by PatZ-mediated acetylation. As a second example: adenylyltransferase and adenylyl-removing enzyme (AT/AR) regulates glutamine synthetase (GS) activity; PII, which is controlled by uridylyltransferase/uridylyl-removing enzyme (UT/UR), in turn determines the activity (adenylylation versus de-adenylylation) of AT/AR. See text for additional details. Metabolite abbreviations: 1,3BPG, 1,3-bisphosphoglycerate; α-KG, α-ketoglutarate; DHAP, dihydroxyacetone phosphate; F6P, fructose-6-phosphate; FBP, fructose-1,6-bisphosphate; G1P, glucose-1-phosphate; G2P, 2-phosphoglycerate; G3P, 3-phosphoglycerate; G6P, glucose-6-phosphate; GAP, glyceraldehyde-3-phosphate; Gln, glutamine; Glu, glutamate; PEP, phosphoenolpyruvate. Enzyme abbreviations: AceA, isocitrate lyase; AcnA, aconitate hydratase; Eno, enolase; Fba, FBP aldolase; Fbp, FBP phosphatase; FumA, fumarase; GapA, GAP dehydrogenase; Gdh, glutamate dehydrogenase; Glk, glucokinase; GltA, citrate synthase; Gpm, phosphoglycerate mutase; Lpd, α-KG dehydrogenase complex; Mdh, malate dehydrogenase; Pck, PEP carboxykinase; Pdh, pyruvate dehydrogenase; Pfk, 6-phosphofructokinase; Pgi, phosphoglucose isomerase; Pgk, phosphoglycerate kinase; Pgm, phosphoglucomutase; Ppc, PEP carboxylase; Pyk, pyruvate kinase; SdhABC, succinate dehydrogenase; SucAB, SucCD, succinyl-CoA synthetase; Tpi, triose phosphate isomerase.