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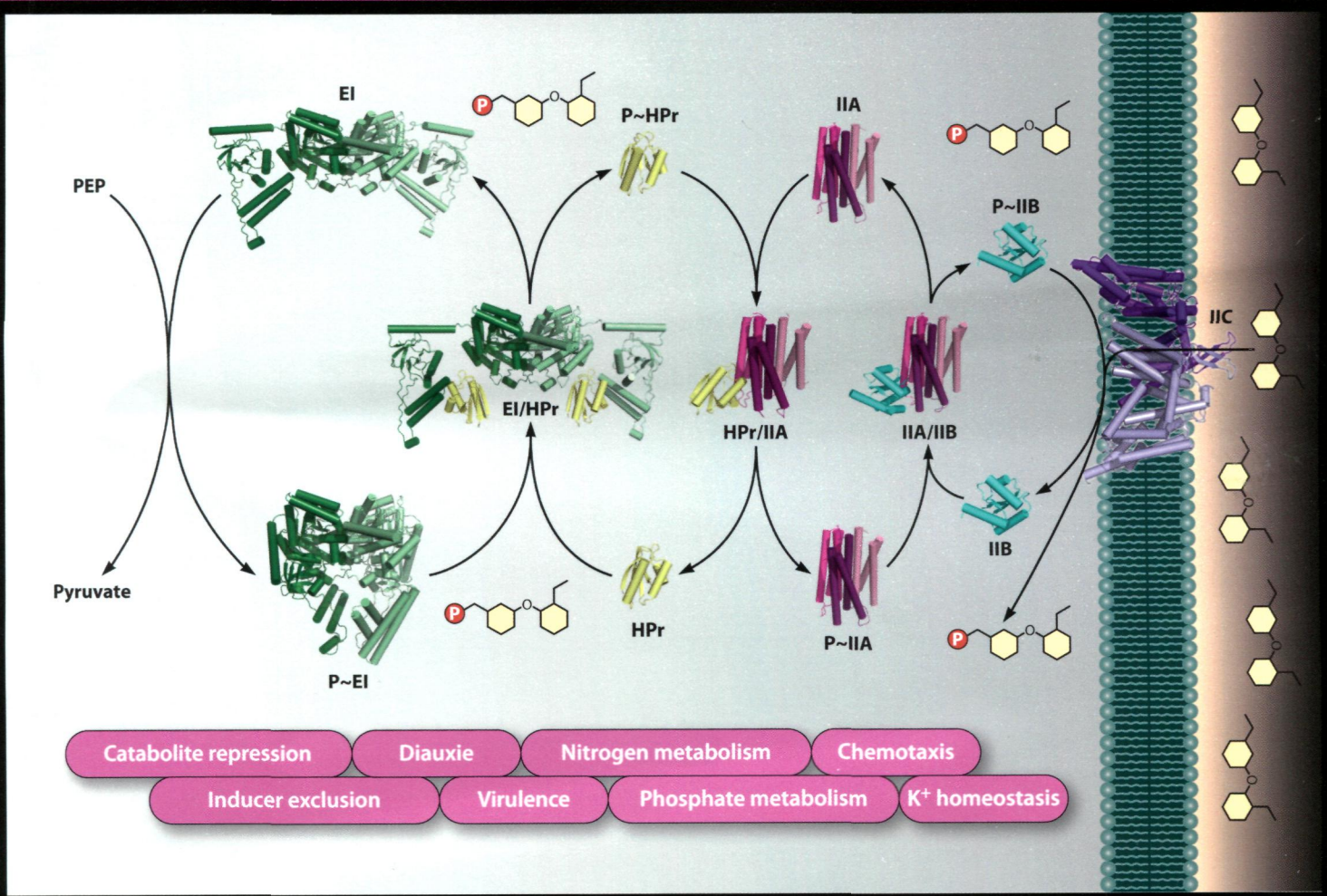

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REVIEWS

Summary: The ability to produce water-soluble proteins with the capacity to oligomerize and form pores within cellular lipid bilayers is a trait conserved among nearly all forms of life, including humans, single-celled eukaryotes, and numerous bacterial species. In bacteria, some of the most notable pore-forming molecules are protein toxins that interact with mammalian cell membranes to promote lysis, deliver effectors, and modulate cellular homeostasis. Of the bacterial species capable of producing pore-forming toxic molecules, the Gram-positive pathogen *Staphylococcus aureus* is one of the most notorious. *S. aureus* can produce seven different pore-forming protein toxins, all of which are believed to play a unique role in promoting the ability of the organism to cause disease in humans and other mammals. The most diverse of these pore-forming toxins, in terms of both functional activity and global representation within *S. aureus* clinical isolates, are the bicomponent leucocidins. From the first description of their activity on host immune cells over 100 years ago to the detailed investigations of their biochemical function today, the leucocidins remain at the forefront of *S. aureus* pathogenesis research initiatives. Study of their mode of action is of immediate interest in the realm of therapeutic agent design as well as for studies of bacterial pathogenesis. This review provides an updated perspective on our understanding of the *S. aureus* leucocidins and their function, specificity, and potential as therapeutic targets.

Summary: The bacterial phosphoenolpyruvate (PEP):carbohydrate phosphotransferase system (PTS) carries out both catalytic and regulatory functions. It catalyzes the transport and phosphorylation of a variety of sugars and sugar derivatives but also carries out numerous regulatory functions related to carbon, nitrogen, and phosphate metabolism, to chemotaxis, to potassium transport, and to the virulence of certain pathogens. For these different regulatory processes, the signal is provided by the phosphorylation state of the PTS components, which varies according to the availability of PTS substrates and the metabolic state of the cell. PEP acts as phosphoryl donor for enzyme I (EI), which, together with HPr and one of several EIIA and EIIB pairs, forms a phosphorylation cascade which allows phosphorylation of the cognate carbohydrate bound to the membrane-spanning EIIC. HPr of firmicutes and numerous proteobacteria is also phosphorylated in an ATP-dependent reaction catalyzed by the bifunctional HPr kinase/phosphorylase. PTS-mediated regulatory mechanisms are based either on direct phosphorylation of the target protein or on phosphorylation-dependent interactions. For regulation by PTS-mediated phosphorylation, the target proteins either acquired a PTS domain by fusing it to their N or C termini or integrated a specific, conserved PTS regulation domain (PRD) or, alternatively, developed their own specific sites for PTS-mediated phosphorylation. Protein-protein interactions can occur with either phosphorylated or unphosphorylated PTS components and can either stimulate or inhibit the function of the target proteins. This large variety of signal transduction mechanisms allows the PTS to regulate numerous proteins and to form a vast regulatory network responding to the phosphorylation state of various PTS components.

Summary: Integrons are versatile gene acquisition systems commonly found in bacterial genomes. They are ancient elements that are a hot spot for genomic complexity, generating phenotypic diversity and shaping adaptive responses. In recent times, they have had a major role in the acquisition, expression, and dissemination of antibiotic resistance genes. Assessing the ongoing threats posed by integrons requires an understanding of their origins and evolutionary history. This review examines the functions and activities of integrons before the antibiotic era. It shows how antibiotic use selected particular integrons from among the environmental pool of these elements, such that integrons carrying resistance genes are now present in the majority of Gram-negative pathogens. Finally, it examines the potential consequences of widespread pollution with the novel integrons that have been assembled via the agency of human antibiotic use and speculates on the potential uses of integrons as platforms for biotechnology.

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Summary: Viruses were defined as one of the two principal types of organisms in the biosphere, namely, as capsid-encoding organisms in contrast to ribosome-encoding organisms, i.e., all cellular life forms. Structurally similar, apparently homologous capsids are present in a huge variety of icosahedral viruses that infect bacteria, archaea, and eukaryotes. These findings prompted the concept of the capsid as the virus "self" that defines the identity of deep, ancient viral lineages. However, several other widespread viral "hallmark genes" encode key components of the viral replication apparatus (such as polymerases and helicases) and combine with different capsid proteins, given the inherently modular character of viral evolution. Furthermore, diverse, widespread, capsidless selfish genetic elements, such as plasmids and various types of transposons, share hallmark genes with viruses. Viruses appear to have evolved from capsidless selfish elements, and vice versa, on multiple occasions during evolution. At the earliest, precellular stage of life's evolution, capsidless genetic parasites most likely emerged first and subsequently gave rise to different classes of viruses. In this review, we develop the concept of a greater virus world which forms an evolutionary network that is held together by shared conserved genes and includes both *bona fide* capsid-encoding viruses and different classes of capsidless replicons. Theoretical studies indicate that selfish replicons (genetic parasites) inevitably emerge in any sufficiently complex evolving ensemble of replicators. Therefore, the key signature of the greater virus world is not the presence of a capsid but rather genetic, informational parasitism itself, i.e., various degrees of reliance on the information processing systems of the host.

Summary: N-glycosylation of proteins is one of the most prevalent posttranslational modifications in nature. Accordingly, a pathway with shared commonalities is found in all three domains of life. While excellent model systems have been developed for studying N-glycosylation in both *Eukarya* and *Bacteria*, an understanding of this process in *Archaea* was hampered until recently by a lack of effective molecular tools. However, within the last decade, impressive advances in the study of the archaeal version of this important pathway have been made for halophiles, methanogens, and thermoacidophiles, combining glycan structural information obtained by mass spectrometry with bioinformatic, genetic, biochemical, and enzymatic data. These studies reveal both features shared with the eukaryal and bacterial domains and novel archaeon-specific aspects. Unique features of N-glycosylation in *Archaea* include the presence of unusual dolichol lipid carriers, the use of a variety of linking sugars that connect the glycan to proteins, the presence of novel sugars as glycan constituents, the presence of two very different N-linked glycans attached to the same protein, and the ability to vary the N-glycan composition under different growth conditions. These advances are the focus of this review, with an emphasis on N-glycosylation pathways in *Haloferax*, *Methanococcus*, and *Sulfolobus*.

Cover photograph (Copyright © 2014, American Society for Microbiology. All Rights Reserved): The phosphoenolpyruvate (PEP):glycose phosphotransferase system (PTS) celebrates the 50 years since its discovery. The phosphorylation cascade of the *N,N′*-diacetylchitobiose-specific *Escherichia coli* PTS (PTS^{Chb}) has been built with the crystal or solution structures of the four soluble unphosphorylated components, of phosphorylated enzyme I (P~EI), P~HPr, and P~IIB, of the three transition-state complexes intermediately formed during phosphoryl-group transfer, and of the membrane-integrated IIC. For clarity, only one HPr and one IIB molecule are bound to the trimeric IIA in the HPr/IIA and IIA/IIB complexes, respectively. The structures are in the Protein Data Bank (PDB), with the following accession numbers: 2KX9 (EI), 2HWG (P~EI), 1POH (HPr), 2XDF (EI/HPr), 1PFH (P~HPr), 1WCR (IIA), 2LRL (HPr/IIA), 1IIB (IIB), 2WY2 (IIA/IIB), 1H9C (P~IIB), and 3QNQ (IIC). The structure of phosphorylated IIA was not available, and the structure of the unphosphorylated protein was used instead. *N,N′*-Diacetylchitobiose molecules are symbolized by two hexagons connected via an oxygen atom (O); they bind to IIC and become phosphorylated by P~IIB before they enter into the cytoplasm. Some of the major regulatory functions of the PTS are listed in the lower part of the image. (Protein structure images were created by Sylvie Nessler based on data from the Protein Data Bank.) *(See related article on page 231.)*