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Role of Prokayotic P-Type ATPases

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Abstract

P-type ATPases is a large and varied family of Trans membrane proteins that are responsible for actively pumping ions and small organic molecules, against their concentration gradient, across the cell membrane. They are ubiquitous and reported to be found in bacteria, archaea and eukaryotes. They are responsible for controlling vital functions of the cell like muscle contraction, membrane potential, signaling etc. in eukaryotes. In prokaryotes, relatively few studies have been performed on the biochemical function and *in vivo* importance of these pumps although a plethora of gene sequences have been obtained from bacterial genome sequences. This review puts together the various roles of P-type ATPases in prokaryotes in which their function has been elucidated. The various roles of P-type ATPases in prokaryotes is to confer on them the ability to withstand high concentrations of heavy metals, to overcome high phagosomal metal levels and to aid in the assembly of periplasmic and secreted metalloproteins. These properties are critically required for their survival in extreme conditions (extremophiles), to withstand heavy metal stress and also for bacterial virulence.

Keywords: Prokaryotic P-type ATPases; Biosensors; Virulence; Heavy metal stress; Vaccine targets

Introduction

Active transport across membranes is an essential feature of life. P-type ATPases establish and maintain steep electrochemical gradients of key cations at the expense of ATP as originally proposed by Jardetzky [1]. P-ATPases (also known as E1-E2 ATPases) (EC:3.6.3) are found in bacteria and in a number of eukaryotic plasma membranes and organelles. P-ATPases function to transport a variety of different compounds, including ions and phospholipids, across a membrane using ATP hydrolysis for energy. There are many different classes of P-ATPases, which transport specific types of ion: H^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ag^+ and Ag^{2+}, Zn^{2+}, Co^{2+}, Pb^{2+}, Ni^{2+}, Cd^{2+}, Cu^+ and Cu^{2+}. Trans membrane translocation of cat ions is coupled to intermediate phosphorylation of the enzyme (hence the name 'P-type') and involve specific domain movements [2]. These domains are highly conserved throughout the entire P-type ATPase family [3]. The major advancement in understanding mechanisms of transfer and specificity of substrates have been possible by the increased number of crystal structures deciphered and reviewed [4]. They have been grouped into five subfamilies PI through PV, depending on a wide range of cationic and lipid substrates. PIA, PIB, PIIA, PIII are found both in Archaea and Bacteria while PIIIB is found only in Bacteria. All others are not found in Prokaryotes [2,5].

The cat ionic substrates transported include H^+, Na^+, K^+, Ca^{2+}, Mg^{2+}, Cd^{2+} and Cu^{2+} in species as diverse as bacteria and man [6] and also Zn^+ ,Co^+, Au^+ and Ag^+ which are grouped into the PIB type. Several studies have been made on bacteria such as bacilli [7], pseudomonads [8], *Ralstonia spp* [9] and cyanobacteria [10]. These studies reveal that the PIB-ATPases regulate concentration of metal ions by export of those which are toxic and import of those which are essential. Phylogentic analysis between 16S rRNA and PIB-type ATPase gene trees have revealed in congruencies pointing to instances of lateral gene transfer (LGT) among diverse microbes. This indicates specific functions for the different clades within the PIB-type ATPase phylogeny [11].

Evolution of Metal Homeostasis in P-Type Atpases as Stress Management Strategy

Transition metals are essential micronutrients that participate in biochemical pathways ranging from cellular respiration to gene expression [12] and direct interaction with DNA and proteins through Fenton reactions [13]. Consequently, their presence at high concentrations in the cell can even be toxic [14]. Thus, homeostasis of these metals is crucial to bacterial metabolism where it is found to be ubiquitous. Even relatively

simple bacteria have a number of membrane transporters that maintain the homeostasis of the various transition metals. These include, among others, the P-type ATPases [15-17]. P-type ATPases show existence as a single primitive ATPase, prior to the divergence of eukaryotes from prokaryotes [18]. Thereafter, divergence is seen into heavy metal pumping ATPases and the non-heavy metal ATPases as formation of a distinct evolutionary branch [19]. Genes encoding PIB-type ATPases with conserved motifs are found in the majority of sequenced bacterial and archaeal genomes, suggesting several loss and gain events. This corroborates the fact that these are primitive proteins indispensable for their role in life processes of bacteria [11,19] and archaea [19,20]. Such studies on evolution of metal homeostasis genes have significant contribution for comprehending microbial adaptations in environments stressed and continuously changing. The primary function of P-type ATPases in bacteria has therefore been understood as combat against extreme environmental stress conditions as reviewed and suggested by Chan et al.[21].

Heavy metal stress

Several studies on the function of PIB type ATPases in efflux of toxic metals like Fe^{2+} in *B. subtilis* [22] and Pb^{2+} in *Staphylococcus aureus* [23] have been made. An extensive exploration into the mechanisms of buffering optimum metal concentrations for cell viability in metal stressed bacteria has revealed the indispensable role of P-type ATPases in efflux mechanisms with a range of substrates (Cu^{+}, Zn^{2+}, Co^{2+}). They can also transport non-physiological substrates (Cu^{2+}, Cd^{2+}, Pb^{2+}, Au^{+}, Ag^{+} due to the structural similarities among transition metals [24]. PIB-ATPases not only maintain cytoplasmic metal levels but also provide metals for the periplasmic assembly of metalloproteins [25]. Since PIB-ATPases appear key players in overcoming high phagosomal metal levels and are also required for the assembly of periplasmic and secreted metalloproteins that enable survival in extreme oxidant environments. Copper transporting P-IB type ATPases are the most studied .Genome database analyses have demonstrated that copper translocating PIB-type ATPases are highly conserved in *Staphylococcus aureus* [26].

Pathogenecity stress

Stress is also experienced by pathogenic bacteria during establishment of infection in the host cells where they come across change of temperature, pH, cation concentration. Infection not only triggers adaptive responses within bacteria to these specific stress conditions but also directs them to express virulence-associated genes in a spatiotemporally appropriate manner .It has been shown that P-type ATPase in in *Streptococcus pneumoniae* for Ca^{2+}- transporting PIIB ATPase [27], *Listeria monocytogenes* [28] and enteric pathogen *Salmonella* [29], is vital for survival of the pathogen in the infected host, where Ca^{2+} concentration is very high and must be actively removed from bacterial cell . Transition metal PIB type ATPases have been reviewed and found to play similar role [30]. The role of metal intoxication in host–pathogen interactions was first noted owing to the virulence defects of bacteria that are defective in Zn(II) and Cu(I) efflux [31-34]. Similar studies have been performed for Fe^{2+} and Mn^{2+} intoxication [35- 38]. Efflux systems have thus been established to function as virulence factors as also reported in several bacterial pathogens [27-40]. The role of bacterial P-type ATPases has been summarized in Table 1. This shows the great versatility of tasks performed by them.

Table 1: Biochemically characterized functions of various P-type ATPases in Prokaryotes.

S.N.	P-Type Atpase	Function	Organism	Reference
1	P-type Ca^{2+} ATPase	Virulence	Streptococcus pneumonia	26
2	P-type H^{+}-ATPase,	generation of the primary electrochemical potential across thermophilic archaeal membrane.	Methanococcus jannaschii	19
3	soft-metal-transporting P-type ATPases, CadA and ZntA.	Resisitance to cadmium and Zinc	Ralstonia metallidurans	41
4	PIB-ATPase	cobalt, zinc, and cadmium resistance	Cupriavidus metallidurans	6, 42
5	P-type Cd(2+)-ATPase	$Cd(2^{+})$ extrusion for cadmium resistance	Staphylococcus aureus 17810R	43
6	P-type Na(+)-ATPase	electrogenic transport of Na(+) in anaerobic alkaliphile	Exiguobacterium aurantiacum	44
7	P1B-4-ATPase	Co^{+} transport	Sulfitobacter sp. NAS-14.1	45
8	P(1B)-type ATPases	Cu^{2+} Transport	Archaeoglobus fulgidus	30
9	CtpA, a copper-translocating P-type ATPase	assembly of membrane and periplasmic copper enzymes	Rubrivivax gelatinosus,	25
10	$Ca2^{+}$ P-type ATPase	Ca^{2+} extrusion	Streptococcus lactis	46
11	Na^{+}-P-type ATPase	Na^{2+} extrusion	halotolerant cyanobacterium, Aphanothece halophytica	46
12	copper-transporting P-type-ATPase	Cu^{2+} transport in Anaerobic sulphur-metabolizing hyperthermophilic archaea.	Archaeoglobus fulgidus	47,48 ,49
13	copper-transporting P-type-ATPase	Cu^{2+} transport	Aquifex aeolicus.	50

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14	P-type Cd+ ATPAse	Cadmium extrusion to ensure detoxification of the bacteria	Listeria monocytogenes	51
15	P1B-type transport ATPase	Iron binding for possible iron transport or oxygen sensing by conformational changes induced by iron binding	Acidothermus cellulolyticus	52

Potential Applications of P- Type Atpases

Heavy metal efflux systems enable growth of such heavy metal resistant bacteria in high concentrations of these metals. This property can be potentially harnessed in bioremediation of poorly cultivable soil high in heavy metal content, by precipitation of these heavy metals. Since the regulation of metal resistant gene expression is specific for each heavy metal and is dependent upon metal species concentration, the promoters and regulatory genes from the bacterial operons responsible for resistance can be used to create metal-specific biosensors (promoter-reporter gene fusions) [53]. The recent insights into the role of P-type ATPases in virulence new vaccine strategies that target metal transport systems have been developed. Components of the Zn^{2+} (ZnuD in *Neisseria meningitidis*) [54] and M^{2+} (MntC in S. aureus and PsaA in *S. pneumoniae*) uptake systems have been identified as potential vaccine targets [55]. Potential drug targets for intervention for the prevention or treatment of infectious diseases in the light of a deeper understanding of host microenvironment, infection and stress resistance, have been reviewed by Fang et al. [26]. The Prokaryotic P-type ATPases are thus, a yet untapped storehouse of solutions to environmental problems and novel drug development.

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