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A GLANCE ON P-TYPE ATPASE

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ABSTRACT

ATPases, the ion channels bound to the membrane which help in the ion movement across the cell either by generating or hydrolyzing a nucleotide. Among the various ATPases, Na^+/K^+-ATPase has an important role. This enzyme, found in all mammalian cell membranes, is an important ion transporter which pumps three sodium out of cells in exchange for two potassium ions, thereby generating large ionic gradient, membrane potential and osmotic equilibrium of the cell. It consists of two protein subunits: a catalytic subunit (α) and a glycoprotein subunit (β). The isoforms α (α1, α2, α3 and α4) and β (β1, β2 and β3) combine to form a number of Na^+/K^+-ATPase isozymes. So in present study, a brief description regarding the ATPase family and their function, role of the sodium pump as an ion regulator.

Keywords: ATPase, disease, protein expression, Na^+/K^+-ATPase, Sodium Pump.

I. INTRODUCTION

The ATPase family: ATPases are the ion channels bound to the membrane which aid in the ion movement across the cell either by generating or by hydrolyzing a nucleotide. These enzyme utilizes the energy produced from the breakage of the ATP phosphodiester bond and hence creates an ion gradient. Na^+/K^+-ATPase belongs to P type ATPases along with Ca^{+2} ATPase of sarcoplasmic reticulum and plasma membrane, plasma membrane H^+-ATPase and proton potassium ATPase of stomach and colon [1]. The widely distributed class of P-type ATPases is responsible for the active transport of a variety of cations across cell membranes. They are found in both prokaryotic and eukaryotic cells, and are used for transporting H^+, Na^+, $Mg^{2+,}$ K^+, Ca^{2+}, $Cu^{2+,}$ and $Cd^{2+,}$. All of these enzymes use the hydrolysis of ATP to drive the transport of cations against an electrochemical potential.

The characteristic feature of P type ATPase is the formation of the phosphorylated intermediate state during the reaction cycle [2]. Hence this features differentiates it from other types of ATPases i.e. F-ATPases (present in mitochondria, chloroplasts and bacterial plasma membranes) and V-ATPases (present in eukaryotic vacuoles). The presence of conserved sequence motifs in the cytoplasmic domains defines the primary structure of P-type ATPases. Nucleotide-binding (N), phosphorylation (P) and an actuator (A) domain are the three domains present in the cytoplasmic domain [3]. A common feature of all known P-type ATPases is the presence of the transmembrane (M) domain having a central core of six alpha helices [1]. These comprise of one polypeptide i.e. α chain which is responsible for ion transport and ATP hydrolysis and a large protein family which pump ions like 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+} and lipids across

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cellular membranes [4,5]. P-ATPases bind and transport the ions by cycling between the two different cation-dependent conformations called as E1 and E2 states [4]. The two P-type ATPases that have been studied most are the Na^+/K^+ [6]. and the Ca^{+2} [3,7] which are involved in electrolyte and fluid balance and in muscle relaxation respectively [8].

II. NA^+/K^+-ATPASE

The Na^+/K^+ ATPase, an integral membrane protein present in all animal cells, is responsible for maintaining Na' and K' gradients across the plasma membrane by translocation of three sodium ions out of the cell and two potassium ions into the cell for every molecule of ATP that is hydrolyzed [9, 10]. The ion gradients produced by the enzyme has been associated with the cellular uptake of nutrients, such as sugars and amino acids and movement of such ions as Ca^{2+} and H^+ across the membrane. Moreover, pumping of Na^+ and K^+ across the cell membrane is also essential for maintaining the resting membrane potential of the cell, cell volume regulation, osmotic balance, and for the electrical activity of muscles and nerves [4,9,11].

2.1 Structure of Na^+/K^+-ATPase

Na^+/K^+-ATPase is a heterodimer composed of three subunits α, β, and a FXYD2 (γ subunit) protein [10]. The α subunit consists of 1020 amino acids and the presence of the conserved sequence motifs in this subunit define the P-type family. The β subunit of the Na^+/K^+-ATPase is glycosylated and composed of about 370 amino acids. The molecular weight of α subunit is 100 kDa and of β subunit is 55 kDa [10]. The α subunit contains the catalytic site for ATP hydrolysis while β subunit is a glycosylated polypeptide. γ subunit (FXYD proteins) belong to a family of small-membrane proteins. Na^+/K^+ -ATPase α and β subunits are each encoded by multigene families. Molecular cloning has identified four α and three β subunit genes in humans and rodents [12]. These isoforms exhibit specific pattern of tissue expression which is important in the maintenance and regulation of Na^+/K^+-ATPase activity. The isoforms combine to form a number of Na^+/K^+-ATPase isozymes that are expressed in a tissue and cell specific manner [13]. Cardiotonic steroids such as ouabain binds to the alpha subunit of Na^+/K^+-ATPase. ATPase inhibitors such as ouabain and cardiotonic steroids, including endogenous forms of digitalis-like substances, are thought to be important in regulating cardiac and vascular tone.

2.2.1 Alpha Subunit

The α subunit is the catalytic unit with a molecular mass of 100–113 kDa, which consists of ten transmembrane helices [4], three cytoplasmic conserved domains, actuator (A), nucleotide binding (N), and phosphorylation (P). ATP binds to the N domain and phosphrylates P domain. It is the site for both ATP binding and ion occlusion [3, 4]. Analysis of cDNA sequences of the alpha subunit has revealed that there are 10 transmembrane domains (M1–M10) which enclose cation binding sites [14]. Helices M4 and M5 and M2 and M3 contain two cytoplasmic loops i.e. major and minor loops respectively [15]. It has four isoforms; αl, α2**,** α3 and α4 encoded by *ATP1A1*, *ATP1A2*, *ATP1A3* and *ATP1A4* genes respectively.

2.2.2 BETA SUBUNIT

The β subunit is highly glycosylated and has a relative molecular mass of about 60 kDa [10]. It is important for ATP hydrolysis, ion transport and for binding of inhibitors such as ouabain [10] and has three isoforms, β1, β2 and β3. β subunit makes direct contact with the alpha subunit [16] and so helps in the stabilization of the α

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subunit and also aid in the transportation of alpha subunit from the endoplasmic reticulum to the plasma membrane [17]. It is also required for maturation of the Na^+/K^+-ATPase and alters the activity of the Na^+/K^+-ATPase [9].

2.2.3 FXDY2 (Gamma subunit)

γ subunit is a strech of 30 amino acids of α helical structure having molecular mass 7–11 kDa [2]. It is a single-span membrane protein with the carboxyl terminus exposed to the cytosol [18,19] and associates with various isoforms of Na^+/K^+-ATPase [20]. FXYD2 is found to be associated with renal Na^+/K^+-ATPase. The FXYD proteins (FXYD1–7) effects the function of Na^+/K^+-ATPase.

III. DISEASE RELATED TO ISOFORMS

Deficient function of the a2- or a3-isoform of the Na^+/K^+-ATPase, caused by mutations in the genes *ATP1A2* or *ATP1A3*, is associated with the neurological diseases hemiplegic migraine (HM) and rapid-onset dystonia parkinsonism (RDP), respectively [21, 22]. RDP, first described in 1993 [23], is a movement disorder characterized by sudden onset of dystonia often with signs of parkinsonism. Recently, mutations in the *ATP1A3* gene were found associated with another neurological disease, alternating hemiplegia of childhood (AHC), as well [24, 25]. The pathophysiological mechanisms underlying these disorders are poorly understood.

IV. CONCLUSION

The Nobel Prize in Chemistry 1997 was given to Jens C. Skou "for the first discovery of an ion-transporting enzyme, Na^+/K^+-ATPase". Na^+/K^+-ATPase carries out coupled hydrolysis of ATP and hence actively transport the ions across membrane. Na^+/K^+-ATPase performs diverse cellular functions as the regulation of cell volume and pH, nutrient uptake, and membrane excitability. Isoforms of Na^+/K^+-ATPase exhibit tissue specific expression. Any alterations in the regulation of sodium pump may lead to disorder and hence understanding the mechanism of regulation of sodium pump is essential.

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