Available Online at http://www.journalajst.com

ASIAN JOURNAL OF SCIENCE AND TECHNOLOGY

ISSN: 0976-3376

Asian Journal of Science and Technology
Vol.07, Issue, 05, pp.2864-2868, May, 2016

RESEARCH ARTICLE

ANTICANCER PROPERTIES OF Na^+/K^+-ATPase: A MINI REVIEW

Yiallouris Andreas, Stephanou Anastasis and *Patrikios Ioannis

School of Medicine, European University Cyprus, Nicosia, Cyprus

ARTICLE INFO

Article History:
Received 02nd February, 2016
Received in revised form
16th March, 2016
Accepted 21st April, 2016
Published online 30th May, 2016

Key words:

Cell death,
Apoptosis,
Necrosis, Na^+, K^+-ATPase,
Anti-cancer agents,
Cancer, Tumor,
Neurodegenerative diseases

ABSTRACT

A lot of interest has been recently expressed through scientific literature, concerning the role of Na^+, K^+-ATPase (NKA) especially in relation to various diseases including autoimmune and neurodegenerative such as Alzheimer's and Parkinson's. Moreover, a significant number of reports reveal involvement of NKA in cancer. This mini review focuses on the expression and function, of Na^+, K^+-ATPase but also gives an overview analysis of the recent findings on NKA vs cancer.

INTRODUCTION

P-type ATPases

P-type ATPases are biological pumps existing in all living systems and they have a number of conserved signature motifs associated with their catalytic mechanism (Sarah van Veen *et al.,* 2014). The common region of all P-type ATPases is an acid-stable aspartyl phosphate intermediate firming the catalytic cycle (the reason of the name P-type). The phosphorylated Asp residue is located in a highly conserved DKTG sequence motif found in the cytoplasmic part of the proteins. The procedures of auto-phosphorylation and auto-dephosphorylation are strongly associated to substrate binding, transport and release (Sarah van Veen *et al.,* 2014). Based on phylogenetic analysis and sequence comparison, the P-type transport ATPase family can be categorized into five distinct subfamilies (P1–P5) (figure 1), which can be additionally divided into further subgroups (A, B, etc.) (Axelsen, 1998; Kuhlbrandt, 2004; Palmgren and Nissen, 2011). This phylogenetic division is further separated depending on variances in the preferred transport substrates. The P1-P3 ATPases are well studied ion pumps; specifically, P1A is a member of the K^+ bacteria transport systems, P1B ion pump is a heavy metal transporter, P2A and P2B are Ca^{2+} pumps, P2C Na^+/K^+- and H^+/K^+-pumps are found in animals, P2D are Na^+ pumps found in fungi and mosses, P3A are plasma membrane H^+ pumps present in fungi and plants, whilst the P3B are Mg^{2+} transporters in a small group of bacterial (Sarah van Veen *et al.,* 2014). Contrary to ion transports (P1-P3), P4 ATPases are involved in lipid flipping across membranes, generating membrane curving and baring or removing relevant signaling lipids. The substrate specificity of the P5 ATPase, the last subfamily, has yet to be fully characterized.

Corresponding author: Patrikios Ioannis
School of Medicine, European University Cyprus, Nicosia, Cyprus.

Na^+/K^+-ATPase history

The NKA was one of the first characterized membrane proteins (Glynn, 2002). Overton, around the nineteenth century suggested that Na^+ and K^+ exchange had to be taking place within the cells in order to explain the variations of Na^+ concentration in nerves, leading to their excitability (Overton, 1902). In the 1950s, Hodgkin and Huxley (Hodgkin and Huxley, 1952) proposed the Na^+ pump for the regeneration of dissipating gradients. Later on, in 1957 the NKA as a functioning enzyme was demonstrated by Skou (Skou, 1957) to be a membrane-bound Na^+ and K^+-dependent ATPase. At the same time Post and Jolly (Post *et al.,* 1957) presented that ATPase activity is responsible for the active transport of three Na^+ and two K^+ ions across the plasma membrane of erythrocytes (Glynn *et al.,* 1956).

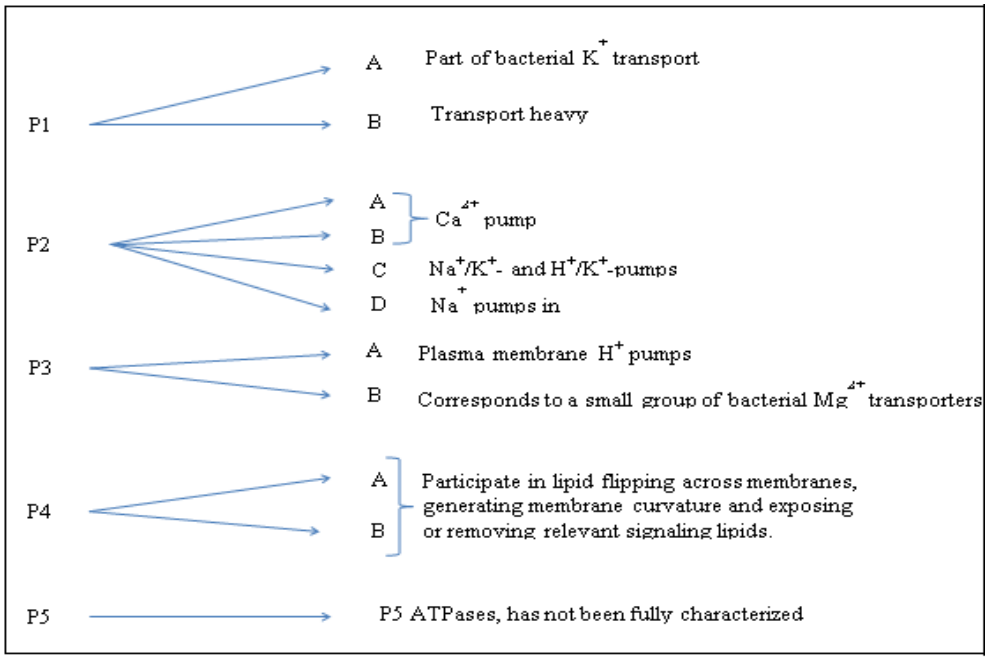

Figure 1. P-type transport ATPase family classification

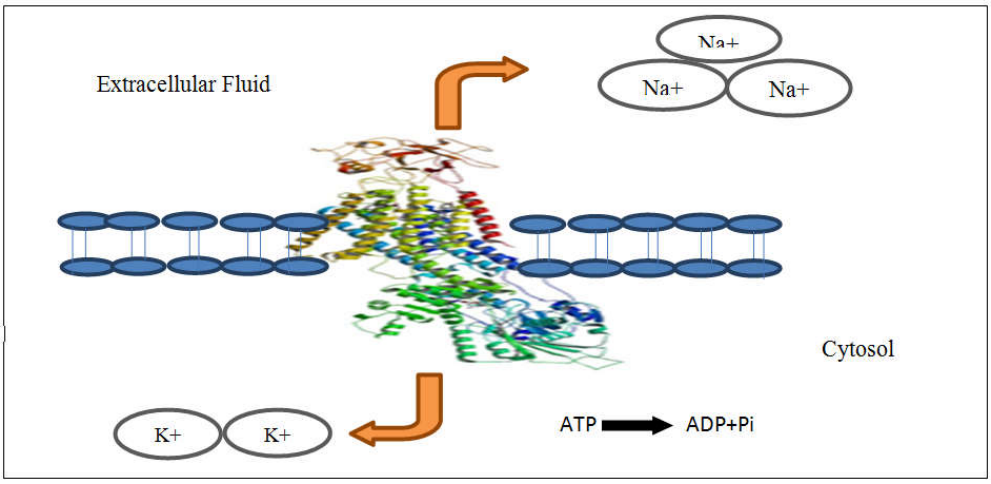

Figure 2. The NKA channel function. The channel scheme is adopted from PDB: 4XE5

Na^+/K^+-ATPase role, function and composition

The NKA, in the plasma membrane of eukaryotes, plays a major role in sodium transport and is therefore important for the cell's homeostasis. The NKA transports three Na^+ ions out of, and two K^+ ions into, the cell for each ATP that is hydrolyzed (figure 2). The action of the pump, together with differential permeability through gated and ion-specific channels, leads to a resting membrane potential that is typically in the range of 30 mV to 70 mV (negative on the inside of the membrane) in most living mammalian cells (Rakowski *et al.,* 1989; Robinson and Flashner, 1979; Geering, 1997; Pavlov and Sokolov, 2000). NKA reported above, belongs to P-type ATPase subclass and it is a transmembrane plasma protein consisting of two subunits, α and β units. The a subunit also known as catalytic subunit consists of 1000 amino acid residues that extents the plasma membrane 10 times, carries the binding sites for ATP and catalyzes the ion-dependent ATPase activity. In humans, four isoforms of the Na^+, K^+-ATPase α-subunit have been identified: α_1 is the predominant and ubiquitously expressed isoform; α_2 is mainly expressed in skeletal, heart and smooth muscle, and in brain, lung and adipose tissue, α_3 is primarily expressed by neurons and heart cells (Sweadner, 1989; Lingrel and Kuntzweiler, 1994; Kaplan, 2002) and isoform α_4 is expressed only in testes (Shamraj and Lingrel, 1994) and has been linked to the mobility of spermatozoa (Woo *et al.,* 2000). The β subunit consists of 300 residues with a single transmembrane spanning section (Jewell and Lingrel, 2000 Malik *et al.,* 1996). The b subunit regulates the conformational activity and stability of the α subunit (Blanco and Mercer, 1998; Eakle *et al.,* 1994). There are three isoforms of the β-subunit; (Sweadner, 1989; Lingrel and Kuntzweiler, 1994; Kaplan, 2002) β_1 is mostly found in tissues and is believed to form a regularly expressed $\alpha_1\beta_1$ complex of the NKA, (Woo *et al.,* 2000; Shyjan *et al.,* 1990) β_2 is mainly expressed by neurons and in lower levels, by heart cells in rats (Chow and Forte, 1995); β_3 is expressed in testes (Jewell *et al.,* 1991) and has also been detected in neurons during early brain development in *Xenopus laevi's* (Good *et al.,* 1990).

Table 1. Scientific findings of previously published work on Na^+, K^+-ATPase and cancer

Trial type	Findings	References
In vitro	Na+, K+-ATPase in regulating carcinoma cell motility	Barwe SP1, Anilkumar G, Moon SY, Zheng Y, Whitelegge JP, Rajasekaran SA, Rajasekaran AK. (2005)
In Vitro & In Vivo	Cardiac glycoside inhibitor of the Na^+/K^+ ATPase pump promotes cell death	Emilie Denicolaï, Nathalie Baeza Kallee, Aurélie Tchoghandjian, Manon Carré, Carole Colin, Carine Jiguet Jiglaire, Sandy Mercurio, Christophe Beclin, and Dominique Figarella-Branger. (2014)
In vitro	Na+, K+-ATPase α1 Subunit as a Potential Target to Combat Apoptosis Resistant Glioblastomas	Lefranc F, Kiss R. (2008)
In vitro	Na, K-ATPase subunits expression is significantly reduced in canine PCa.	Ali Mobasheri, Richard Fox, Iain Evans, Fay Cullingham, Pablo Martín Vasallo, and Christopher S Foster. (2003)
In vitro	K1-isoform expression and an increase in the K3-isoform expression maybe associated with human colorectal cancer.	Hideki Sakaia, Tomoyuki Suzukia, Mizuki Maedaa, Yuji Takahashia, Naoki Horikawab, Tetsuji Minamimurab, Kazuhiro Tsukadab, Noriaki Takeguchia. (2004)
In vitro	NKA inhibition promotes hybrid cell death	Dongdong Chen, Mingke Song, Osama Mohamad and Shan Ping Yu. (2014), Shan Ping Yu (2003)
In vivo	Na+/K+ ATPase inhibition on distant tumor formation in mouse models	Simpson CD, Mawji IA, Anyiwe K, Williams MA, Wang X, Venugopal AL, GrondaM, Hurren R, Cheng S, Serra S, Beheshti Zavareh R, Datti A, Wrana JL, Ezzat S, Schimmer AD (2009) [54]
In vitro	Isoforms such as α1, α3, and β1 found that were highly expressed in metastases and tumor cells	Marc Baker Bechmann1, Deborah Rotoli, Manuel Morales, María del Carmen Maeso, María del Pino García, Julio Ávila, Ali Mobasheri, and Pablo Martín-Vasallo. (2016)

To date, four genes (a1–a4) encoding the α subunit, three genes (b1–b3) encoding the β subunit, and one gene for the γ subunit have been identified in mammals (Malik *et al.,* 1996). The nervous system contains all the isoforms but particularly the α1 is abundant in kidneys, α2 abundant in brain, skeletal muscle and heart and α3 mainly expressed in brain, but it is also present in heart (McGrail *et al.,* 1991; Watts *et al.,* 1991). A third small polypeptide the γ subunit, is associated with the αβ dimmer in a tissue-specific manner; this subunit does not seem to be required for functional Na, Na^+, K^+-ATPase and may play a regulatory role (Watts *et al.,* 1991). Failure of the NKA, results in reduction of intracellular K^+, increasing intracellular Na^+, and therefore, leads to membrane depolarization and increases in intracellular free Ca^{2+} due to activation of voltage-gated Ca^{2+}channels (Therien and Blostein, 2000; Archibald and White, 1974).

NKA and diseases

It has already been showed that deficiency of NKA may be a common pathogenesis of systemic lupus erythematosus, Alzheimer's, Multiple Sclerosis, Parkinson's disease, Down syndrome, as well as other autoimmune and neurodegenerative disorders (Xiao *et al.,* 2002). More specific, the neurological disorders: alternating hemiplegia of childhood (AHC), familial hemiplegic migraine type2 (FHM2) and rapid-onset dystonia Parkinsonism (RDP) are autosomal dominant disorders caused by mutations of the NKA gene (Kumar and Kurup, 2002). For Example, red blood cell NKA is involved in intra and extracellular cation regulation (homeostasis). Dysfunctional NKA has also been reported as a complication of diabetes mellitus (Koc *et al.,* 2003). Chronically demyelinated axons that lack NKA are unable to exchange axoplasmic Na^+ for K^+ and so unable to transmit the nerve impulse. Loss of axonal NKA is possible as a major contributor to nonstop neurological degeneration in chronic stages of MS. Quantitative magnetization transfer ratios and T1 contrast ratios may provide a non-invasive surrogate marker for monitoring this loss in MS patients (Young *et al.,* 2008).

NKA and cancer: Altered NKA activity in regulating carcinoma cell motility has been previously reported (Barwe *et al.,* 2005).

Cardiac glycoside inhibitor of the Na^+/K^+ ATPase pump displayed cytotoxic properties, triggered cell death, induced G_2/M phase blockade in all the glioblastoma cell lines and impaired Glioblastoma (GBM) stem self-renewal capacity even at low concentrations. Heterotopic and orthotopic xeno-transplantations were used to confirm *in vivo* anticancer effects of proscillaridin A, in both controls xenograft growth with improved mice survival. Altogether, these results suggested that proscillaridin A is a promising candidate against glioblastoma. Further reports showed cardiac glycosides to be associated with anticancer activity in other cancers (Emilie Denicolaï *et al.,* 2014). NKA has also been reported as directly involved in the migration of cancer cells in general and of glioma cells in particular. The NKA α1 subunit is highly expressed in glioma cells versus normal brain tissue and has been proposed as a new and novel target for malignant glioma treatment (Lefranc and Kiss, 2008). Glioblastomas as tumors that over-express NKA α1 subunit are highly resistant to chemotherapy but they could benefit from a treatment using ligands with higher binding affinity for the enzyme α subunit (Lefranc and Kiss, 2008).

Furthermore, NKA inhibitor demonstrates the induction of hybrid cell death in glioblastoma cells and enhanced cell death of a temozolomide (TMZ)-resistant cancer cell line. Based on its high expression level in TMZ-resistance cells, NKA may be a therapeutic target for the treatment of glioblastoma; sensitizing glioblastoma cells to conventional chemotherapy (Hideki Sakaia *et al.,* 2004). In this study, instead of giving a detailed description of the structure and regulation of Na^+, K^+-ATPase, the authors are focused on the most recent evidence indicating the unique role of Na^+, K^+-ATPase in cell death, including apoptosis and the newly recognized and defined ''hybrid death'' of concurrent apoptosis and necrosis within the same cell population (Shan Ping Yu, 2003). Loss of epithelial structure, function and transformation of normal epithelial cells to malignant cells in the canine prostate NKA have also been reported. Specifically, the α2, α3 and γ subunits of NKA are not expressed in this tissue. Immunohistochemical and image analyses suggested that NKA expression is significantly reduced in canine PCa (Ali Mobasheri *et al.,* 2000). Other studies reported the association of NKA with apoptosis. Apoptosis or programed cell death is characterized

by DNA fragmentation, nuclear condensation, chromatin margination, cell body shrinkage, and formation of apoptotic bodies (Raff *et al.,* 1993; Thompson, 1995; Kerr *et al.,* 1972; Majno, 1995). Apoptosis is also mediated by cascade activation, formation of the apoptosome, release of cytochrome c from mitochondria and activation of endonucleases (Mark *et al.,* 1997; Bratton and Cohen, 2001; Chen and Wang, 2002; Hengartner *et al.,* 2002; Li and Yuan, 1999; Adams and Cory, 2002). Studies have demonstrated that α3-isoform protein increased in 13 of 17 carcinomas (76%) compared with the accompanying normal mucosae, with the α2- or α4-isoform remained to the same levels in colorectal carcinoma.

In addition, a significant level of α3-isoform protein was consistently detected in human colonic adenocarcinoma cell lines such as KM12-L4, T-84 and HT-29. These results strongly suggested that decrease in the K1-isoform expression and an increase in the K3-isoform expression maybe associated with human colorectal cancer (Hideki Sakaia *et al.,* 2004). *In Vivo* studies have also demonstrated the effects of Na^+/K^+ ATPase inhibition on secondary tumor formation in mouse models. In these mouse models, quabain inhibited tumor metastases but did not alter the growth of subcutaneous tumors. After all, these results show a novel mechanism to sensitize resistant cells to anoikis (cells' apoptotic response to the absence of cell–matrix interactions) and decrease tumor metastasis. Furthermore, they are suggesting a potential mechanism for the observed clinical reduction in metastasis and relapse in breast cancer patients who have undergone treatments with cardiac glycosides (Simpson *et al.,* 2009). Finally, NKA α and β subunit isoforms expression was determined in colorectal cancer cells and liver metastasis (Simpson *et al.,* 2009). In general, isoforms such as the α1, α3, and β1 found to be highly expressed in metastases and tumor cells. More specific, α1β1 and α3β1 isozymes found in cancerous cells resulted to be associated with highest and lowest Na^+ affinity respectively and with the highest K^+ affinity. These findings demonstrated that α3β1 isozyme could serve as a new experimental biomarker of colorectal metastatic cells in liver (Marc Baker Bechmann *et al.,* 2016).

Conclusion

Overall, this review shows that further studies are necessary to determine the feature of the channel regulation in relation to cancer. NKA is not only a worth to study enzyme that has a number of functions and a manifold association but also could pave the way to prevent, treat and cure cancer. The regulation of the NKA channel could act as a cell death initiator. Several i*n vitro* as well as *in vivo* tests have been performed with positive effects but further studies with properly designed protocol clinical trials need to be performed, for more conclusive results and/or any possible anticancer efficacy as a result of NKA channel up/down regulation.

REFERENCES

Adams JM, Cory S. 2002. Apoptosomes: engines for caspase activation. *Curr. Opin. Cell Biol*. 14:715–20.

Ali Mobasheri, Richard Fox, Iain Evans, Fay Cullingham, Pablo Martín-Vasallo, and Christopher S Foster. 2003. Epithelial Na, K-ATPase expression is down-regulated in canine prostate cancer; a possible consequence of metabolic transformation in the process of prostate malignancy. *Cancer Cell Int*. 3: 8.

Archibald JT, White TD. 1974. Rapid reversal of internal Na^+ and K^+ contents of synaptosomes by ouabain. Nature. 252:595–6.

Axelsen K. B., Palmgren M. G. 1998. Evolution of substrate specificities in the P-type ATPase superfamily. *J. Mol. Evol.* 46, 84–101.

Barwe SP, Anilkumar G, Moon SY, Zheng Y, Whitelegge JP, Rajasekaran SA, Rajasekaran AK.. 2005. Novel role for Na, K-ATPase in phosphatidylinositol 3-kinase signaling and suppression of cell motility. *Mol. Biol. Cell*. 16:1082–1094.

Blanco G, Mercer RW. 1998. Isozymes of the Na-K-ATPase: heterogeneity in structure, div ersity in function. *Am J Physiol.* 275:F633–50.

Brashear, A., Ozelius, L. J., and Sweadner, K.J. 2014. ATP1A3mutations: what is the phenotype? *Neurology* 82, 468–469

Bratton SB, Cohen GM. 2001.. Apoptotic death sensor: an organelle's alter ego? *Trends Pharmacol. Sci*. 22:306–15.

Chen M, Wang J. 2002. Initiator caspases in apoptosis signaling pathways. Apoptosis. 7:313–9.

Chow DC, Forte JG. 1995. Functional significance of the beta-subunit for heterodimeric P-type ATPases. *J. Exp. Biol.* 198:1–17.

DiPolo R, Beauge L. 1991. Regulation of Na-Ca exchange. An overview. *Ann NY Acad. Sci*. 639:100–11.

Dongdong Chen, Mingke Song, Osama Mohamad and Shan Ping Yu1. 2014. Inhibition of Na^+/K^+-ATPase induces hybrid cell death and enhanced sensitivity to chemotherapy in human glioblastoma cellsChen et al. BMC Cancer. 14:716.

Eakle KA, Kabalin MA, Wang SG, Farley RA. 1994. The influence of beta subunit structure on the stability of Na^+/K^+-ATPase complexes and interaction with Kþ. *J. Biol. Chem.* 269:6550–7.

Emilie Denicolaï, Nathalie Baeza-Kallee, Aurélie Tchoghandjian, Manon Carré, Carole Colin, Carine Jiguet Jiglaire, Sandy Mercurio, Christophe Beclin, and Dominique Figarella-Branger. 2014. Proscillaridin A is cytotoxic for glioblastoma cell lines and controls tumor xenograft growth in vivo. Oncotarget. 5(21): 10934–10948.

Geering K. 1997. Na, K-ATPase. Curr. Opin. Nephrol. Hypertens. 6:434–9.

Glynn, I. M. 1956. Sodium and potassium movements in human red cells. *J. Physiol*. 278–310.

Glynn, I. M. 2002. A hundred years of sodium pumping. *Annu. Rev. Physiol*. 1–18.

Good, P. J., Richter, K. and Dawid, I. B. 1990. A nervous system specific isotype of the beta subunit of Na^+, K^+-ATPase expressed during early development of Xenopus laevis. *Proc. Natl Acad. Sci. USA*. 9088–9092.

Hengartner MO, Ellis RE, Horvitz HR. 1992. Caenorhabditis elegans gene ced-9 protects cells from programmed cell death. Nature. 356:494 9.

Hideki Sakaia, Tomoyuki Suzukia, Mizuki Maedaa, Yuji Takahashia, Naoki Horikawab, Tetsuji Minamimurab, Kazuhiro Tsukadab, Noriaki Takeguchia. 2004. Up-regulation of Na^+, K^+-ATPase α3-isoform and down-regulation of the α1-isoform in human colorectal cancer. FEBS Letters. 151-154.

Hodgkin, A. L. and Huxley, A. F. 1952. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol*. 500–544.

Jewell, E. A. and Lingrel, J. B. 1991. Comparison of the substrate dependence properties of the rat Na^+, K^+-ATPase alpha 1, alpha 2, and alpha 3 isoforms expressed in HeLa cells. *J. Biol. Chem.* 16925–16930.

Kaplan, J. H. 2002. Biochemistry of Na^+, K^+-ATPase. Annu. *Rev. Biochem*. 71, 511–535.

Kerr JF, Wyllie AH, Currie AR. 1972. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *Br. J. Cancer*. 26:239–57.

Koc B, Erten V, Yilmaz MI, Sonmez A, Kocar IH. 2003. The relationship between red blood cell Na^+/K^+-ATPase activities and diabetic complications in patients with type 2 diabetes mellitus. *Endocrine*. 21(3):273-8.

Kuhlbrandt W. 2004. Biology, structure and mechanism of P-type ATPases. *Nat. Rev. Mol. Cell Biol*. 282–295.

Kumar AR, Kurup PA. 2002. Inhibition of membrane Na^+-K^+ ATPase activity: a common pathway in central nervous system disorders. *J Assoc. Physicians India* 50:400–6.

Lefranc F, Kiss R. 2008. The sodium pump alpha1 subunit as a potential target to combat apoptosis-resistant gliobastomas. Neoplasia. 10:198–206.

Li H, Yuan J. 1999. Deciphering the pathways of life and death. *Curr. Opin. Cell Biol*.11:261–6.

Lingrel, J. B. and Kuntzweiler, T. 1994. Na^+, K^+-ATPase. *J. Biol. Chem.* 269, 19659–19662.

Majno G, Joris I. 1995. Apoptosis, oncosis, and necrosis. An overview of cell death. *Am J Pathol*. 146:3–15.

Malik N, Canfield VA, Beckers MC, Gros P, Levenson R. 1996. Identification of the mammalian Na, K-ATPase 3 subunit. *J. Biol. Chem*. 271:22754–8.

Marc Baker Bechmann, Deborah Rotoli, Manuel Morales, María del Carmen Maeso, María del Pino García, Julio Ávila, Ali Mobasheri and Pablo Martín-Vasallo. 2016. Na,K-ATPase Isozymes in Colorectal Cancer and Liver Metastase. *Front Physiol*. 7: 9.

Mark, R.J., Pang, Z., Geddes, J.W., Uchida, K., Mattson, M.P. 1997. Amyloid beta peptide mimpairs glucose transport in hippocampal and cortical neurons: involvement of membrane lipid peroxidation. *J Neurosci*. 17:1046–54.

McGrail, K.M., Phillips, J.M., Sweadner, K.J. 1991. Immunofluorescent localization of three NaK-ATPase isozymes in the rat central nervous system: both neurons and glia can express more than one Na^+, K^+-ATPase. *J. Neurosci*.; 11:381–91.

Overton, E. 1902. Articles on the general muscle- and nerve physiology - Second Notice - The indispensability of natrium (or lithium. ions for muscle contraction. Archiv Für Die Gesamte Physiologie Des Menschen Und Der Tiere 346–386.

Palmgren M. G., Nissen P. 2011. P-type ATPases. Annu. Rev. Biophys. 243–266.

Pavlov KV, Sokolov VS. 2000. Electrogenic ion transport by Na^+/K^+-ATPase. Membr Cell Biol 13:745–88.

Post, R. L. and Jolly, P. C. 1957. The linkage of sodium, potassium, and ammonium active transport across the human erythrocyte membrane. Biochim. Biophys. Acta. 118–128.

Raff, M.C., Barres, B.A., Burne, J.F., Coles, H.S., Ishizaki, Y., Jacobson, M.D. 1993. Programmed cell death and the control of cell survival: lessons from the nervous system. Science. 262:695–700.

Rakowski RF, Gadsby DC, De Weer P. 1989. Stoichiometry and voltage dependence of the sodium pump in voltage-clamped internally dialyzed squid giant axon. *J Gen Physiol*. 93:903–41.

Robinson JD, Flashner MS. 1979. The Na^+, K^+-activated ATPase. Enzymatic and transport properties. *Biochim. Biophys.* Acta. 549:145–76.

Sarah van Veen, Danny M. Sørensen, Tine Holemans, Henrik W. Holen, Michael G. Palmgren and Peter Vangheluwe. 2014. Cellular function and pathological role of ATP13A2 and related P type transport ATPases in Parkinson's disease and other neurological disorders Frontiers in Molecular Neuroscience. 7:48

Shamraj, O. I. and Lingrel, J. B. 1994. A putative fourth Na^+,K^+- ATPase α-subunit gene is expressed in testis. *Proc. Natl Acad. Sc*i. USA 91, 12952–12956.

Shan Ping Yu. 2003. Na^+, K^+-ATPase: The new face of an old player in pathogenesis and apoptotic/hybrid cell death S.P. Yu / Biochemical Pharmacology. 1601–1609.

Shyjan, A. W., Gottardi, C. and Levenson, R. 1990. The Na, K-ATPase β2 subunit is expressed in rat brain and copurifies with Na^+,K^+-ATPase activity. *J. Biol. Chem*. 5166–5169.

Simpson CD, Mawji IA, Anyiwe K, Williams MA, Wang X, Venugopal AL, GrondaM, Hurren R, Cheng S, Serra S, Beheshti Zavareh R, Datti A, Wrana JL, Ezzat S, Schimmer AD. 2009. Inhibition of the sodium potassium adenosine triphosphatase pump sensitizes cancer cells to anoikis and prevents distant tumor formation. Cancer Res. (7):2739-47.

Skou, J. C. 1957. The influence of some cations on an adenosine triphosphatase from peripheral nerves. Biochim. *Biophys. Acta*. 394–401.

Sweadner, K. J. 1989. Isozymes of the Na^+/K^+-ATPase. *Biochim. Biophys. Acta* 988, 185–220.

Therien AG, Blostein R. 2000. Mechanisms of sodium pump regulation. *Am. J. Physiol. Cell Physiol*. 279:C541–66.

Thompson CB. 1995. Apoptosis in the pathogenesis and treatment of disease. Science. 267:1456–62.

Watts, A.G., Sanchez-Watts, G., Emanuel, J.R, Levenson. R, 1991. Cell-specific expression of mRNAs encoding Na^+,K^+-ATPase a- and b-subunit isoforms within the rat central nervous system. *Proc Natl Acad Sci. USA* 88:7425–9.

Woo, A. L., James, P. F. and Lingrel, J. B. 2000. Sperm motility is dependent on a unique isoform of the Na, K-*ATPase. J. Biol. Chem.* 275, 20693–20699.

Xiao AY, Wei L, Xia S, Rothman S, Yu SP. 2002. Ionic mechanism of ouabain-induced concurrent apoptosis and necrosis in individual cultured cortical neurons. *J. Neurosci.* 22:1350–62.

Young EA, Fowler CD, Kidd GJ, Chang A, Rudick R, Fisher E, Trapp BD. 2008. Imaging correlates of decreased axonal Na^+/K^+ ATPase in chronic multiple sclerosis lesions. *Ann Neurol*. 63(4):428-35.

****