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Review

The Cotransporter NaPi-IIb: Characteristics, Regulation and its Role in Carcinogenesis

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Abstract

Inorganic phosphate (Pi) presents a crucial role in cellular metabolism, with the kidney and intestine as the principal regulating organs of the homeostasis of this nutrient. Maintaining phosphate balance results from the activity of different subtype of transporters of sodium-dependent phosphate that use the electrochemical gradient of sodium ions to carry out cotransport. Several diseases have been related to dysfunctions of phosphate cotransporters, including in the area of oncology. A study using the SAGE technique pointed to a possible role of the type IIb sodium-phosphate cotransporter (NaPi-IIb), encoded by the *SLC34A2* gene, in ovarian carcinogenesis. More recently, such protein was associated with the development of other carcinomas and some of the components that regulate its function were determined. It is believed that in the future, the analysis of SLC34A2 expression in tumor samples will help in the choice of treatment, evaluation of prognosis and be a possible target for new therapeutic strategies.

Keywords: Phosphates. Sodium-Phosphate Cotransporter Proteins, Type IIb. SLC34A2, protein, human. Carcinogens

Abbreviations

Pi: inorganic phosphate; NPT: sodium-dependant phosphate transporter; NaPi-IIb: type IIb sodium-phosphate cotransporter; mRNA: messenger RNA;VDR: vitamin D receptor; FGF23: fibroblast growth factor 23; EGF: epidermal growth factor; SAGE: Serial Analysis of Gene Expression; HOSTs: Human Ovarian Specific Tags; NSCLC: non-small cell lung cancer

Introduction

Inorganic phosphate (Pi) is the principal intracellular anion and is essential for growth, development, cellular metabolism and bone mineralization, in a way that phosphate depletion leads to symptoms of anemia, heart failure, skeletal muscle injury, besides disordered functions of plaques, leucocytes, kidney, liver and brain.[1] The kidney and the intestine are the principal organs responsible for the maintenance of Pi homeostasis in the organism. In this respect, different subtypes of sodium-dependant phosphate transporters (NPTs) have been studied as to their physiologic and pathological aspects.

The NPTs use the electrochemical gradient of sodium ions, resultant of the action of sodium-potassium ATPase, to carry out the above-mentioned cotransport, in which the concomitant influx of phosphate and sodium ions occurs.[2,3] Three types of NPTs (types I - III) are responsible for this function in vertebrates – the

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genes *SLC17*, *SLC20* and *SLC34*, respectively – which act by distinct molecular mechanisms, possess specific physiologic functions, and are expressed in different tissues and organs.[4]

A series of pathologies are involved with phosphate transport deficiencies, among them: pulmonary alveolar microlithiasis[5] and male infertility[6] related to mutations in the *SLC34A2* gene; hereditary hypophosphatemia and nephrolithiasis, related to changes in the *SLC34A3*[7,8] gene, and; mutations in the *SLC34A1* gene that are responsible for bone demineralization, increase of Pi excretion in the urine and hypophosphatemia, but without nephrolithiasis.[9]

In addition to the pathologies related to phosphate homeostasis dysfunctions, the neoplasms appear as a possible malignancy associated with NPT disturbances in, more specifically, the type IIb sodium-phosphate cotransporter (NaPi-IIb), the principal focus of this review.

Gene Organization and Protein Structure of SLC34A2/NaPi-IIb

SLC34A2 is a member of a family of solute carrier genes, located in the chromosome 4p15-p16 and encodes a multiple passage protein membrane composed of 690 amino acids, the NaPi. This gene presents a length of 15.5 kb and is composed of 13 exons. The sequences of messenger RNA (mRNA) deposited in GeneBank [10] were aligned and compared with the sequence NM_0064242.2, chosen as a reference, in the program BioEdit. We observed that there is only one isoform (AK075046.1) highly similar to the *SLC34A2* gene,[11] with the differences observed in exon 12 and in the 3' untranslated region (3' UTR). In exon 12, there is a deletion of 177 nitrogen bases that begins in base 1381, from the first codon of the translation, and goes to base 1557, corresponding to the absence of 59 amino acids in the isoform in relation to the sequence referenced. In 3' UTR, a deletion of 433 bases is observed that encompasses the nitrogen bases 1085 to 3517 counted from the first codon of the translation. The consequences of these deletions in the protein function of isoform AK075046.1 are not yet described in the literature.

The promoter region of *SLC34A2* is of great interest, since its involvement is probable in the control of the gene transcription in homeostasis maintenance of Pi.[12] Studies evaluating the first 500 pb previous to the site of initiation of the transcription of *SLC34A2* demonstrated that in this region there are several transcription factor binding sites, as AP-1, AP-2, AP-4, C/EBP, GATA-1 and Sp1.[13] Various binding sites of GATA-1 were predicted in this region, and this finding is in agreement with previous studies that demonstrated the involvement of CAT transcription factors in the regulation of specific tissue and the cellular type in the gene expression,[14,15] since this gene is expressed only in some tissues, described subsequently.

Bioinformatic analysis suggested that the protein encoded for *SLC34A2*, NaPi-IIb, has at least eight transmembrane domains, five intracellular domains, as well as four extracellular loops , with both N- and C-terminal regions positioned in the cytoplasm, conforming to the illustration in Figure 1. [16]

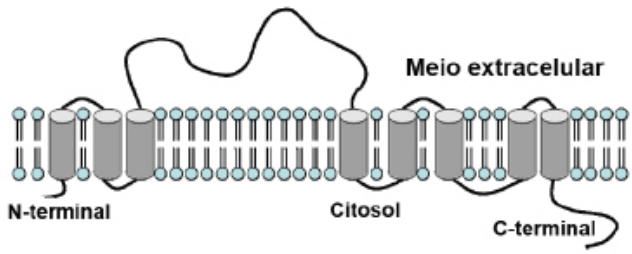

Figure 1 - Scheme of the structural organization of the NaPi-IIb protein.

Sequence analysis of the *SLC34A2* gene product pointed to five potential sites of N-glycosylation in the small region of the peptide, amino acids 295 to 340, located in the extracellular loop. In addition, in silico analysis revealed cysteine-rich regions in the C-terminal cytoplasmatic domain, more specifically,[17] cysteines between the amino acids 613 and 645 that could represent possible sites of palmitoylation. These data show the incident of post-translational modifications of NaPi-IIb through the incorporation of palmitate to the protein, which indicates that the cotransporter is probably palmitoylated in its natural form. Such a protein has shown to be expressed in two principal forms in the plasma membrane, distinguished by its molecular weight in polyacrylamide gel electrophoresis (SDS-PAGE), 90 kDa and 180kDa, which probably represents the monomeric and dimeric forms of the protein, determined by mass spectrometry. [16]

Physiology and Pathophysiology of NaPi-IIb

NaPi-IIb is physiologically expressed in a variety of cellular types, such as the brush borders of enterocytes

of the small intestine, apical pole of alveolar type II cells in the lung, apical membrane of the mammary glands, epididymis cells of the testis, hepatocytes and apical cells of the renal proximal tubule.[17] The expression and regulation of NaPi-IIb in intestinal and renal cells have been extensively studied, since they represent the principal points of entry and exit of Pi in the organism, respectively.

In the small intestine, NaPi-IIb is responsible for the transcellular absorption of alimentary Pi, and in the kidneys the expression of this transporter is related to Pi reabsorption of the luminal compartment from the bloodstream, with dysfunctions involving NaPi-IIb in the kidneys described as responsible for diseases linked to hypophosphatemia.[18] Pulmonary expression of NaPi-IIb is important in the production of surfactant fluids, while liberation of Pi is through the alveolar, [19] such a function is realized because of mutations in the *SLC34A2* gene involved in the origin of pulmonary alveolar microlithiasis, which is characterized by the deposition of calcium phosphate in the lungs.[20] In the liver, NaPi-IIb is involved in Pi reabsorption originating from the primary bile, whereas, in the salivary glands, the function is the secretion of Pi in the saliva, where the high tenor of phosphate is elementary for the remineralization of the dental surface. In the mammary glands, studies in animal models show that NaPi-IIb is expressed, primarily, during lactation, which suggests a possible function of the above-mentioned transporter in the appropriate production and secretion of milk. In the epididymis, the role of *SLC34A2*/NaPi-IIb is not well established, but can be related to a fine adjustment of the Pi luminal concentration, that is required for sperm production, employed in its energetic metabolism; it is known that the altered epididymal expression of NaPi-IIb is a possible causal agent of infertility in mice. [6]

Pharmacologically, the kinetics of the cotransport of sodium and phosphate pathway NaPi-IIb has been meticulously studied. The basic transport mechanism of phosphate is the same for all the members of the *SLC34* family. NaPi-IIb mediates the divalent Pi transport in an electrogenic manner (HPO42-), independently of external pH, in a +:HPO42 proportion of 3:1. The sodium/phosphate transport cycle pathway NaPi-IIb involves dependent and independent stages of voltage. The voltage dependence in this transport is checked by the direction of the charge when in the absence of ligand, and the binding of one Na+ in the transmembrane electric field. A second electroneutral stage takes place from the binding of a second Na+ that precedes the interaction of Pi. To end, the transporter becomes complete with the binding of a third Na+ which results in a conformational protein alteration, causing the influx of three Na+ ions and one Pi (Figure 2). [2]

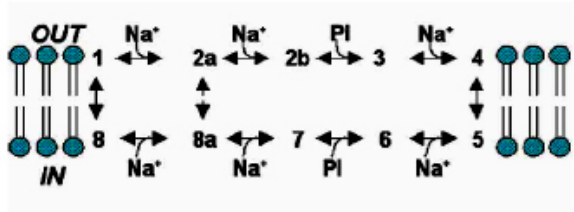

Figure 2 - Kinetic of SLC34A2/NaPi-IIb.

When analyzing Figure 2, we can note that NaPi-IIb acquires electrogenicity from the reorientation of an empty transporter (8-1) and posterior binding of a Na+ ion in the transmembrane electric field (1-2a). A second electroneutral binding stage of a Na+ ion precedes the interaction with Pi (2a-2b). The completely loaded transporter is electroneutral and the reorientation (4-5) has been proposed as rate limiting. The next stages (5-8) show the intracellular liberation of three Na+ ions, as well as Pi.

The intestinal transport of Pi takes place both as an independent mechanism of unsaturable Na+ and as a dependent active process of Na+, principally in the duodenum and jejunum. [21] It is known that the low ingestion of Pi in food regulates gene expression, leading to an increase of NaPi-IIb in the apical cells of the small intestine and also the renal proximal tubule, possibly a physiologic mechanism of compensation that prevents a reduction of Pi concentration, increasing intestinal absorption and renal reabsorption. Katai and collaborators [22] demonstrated that rats treated with a poor diet in Pi showed a two-fold increase of Na+-dependent Pi transport when compared to rats with a diet with normal levels of Pi. [22] It was reported only in 2004 that a decrease ingestion of Pi also causes an increase of NaPi-IIb mRNA abundance. [23]

A central component in the modulation of Pi homeostasis, as well as the uptake of this by the small intestine, is vitamin D3 (vit-D3), which in its active form, 1,25-dihydroxy, ties to a vitamin D receptor (VDR) and induces alterations in gene expression. [24] 1,25-dihydroxy (vit-D3), known to stimulate the abundance of apical NaPi-IIb, of which levels are increased in response to decreased Pi ingestion. Possibly, both described regulation pathways are interconnected, so that the decrease ingestion from Pi results in stimulus of the renal mitochondrial enzyme 25-hydroxyvitamin D3 (1α-hydroxylase), with consequent increase of the synthesis of 1,25-dihydroxy (vit-D3) and subsequent elevation of intestinal and renal

NaPi-IIb expression. [25]

Another determinant in the regulation of *SLC34A2*/NaPi-IIb is fibroblast growth factor 23 (FGF-23). The mechanism for which FGF-23 acts in the control of Pi homeostasis is not completely elucidated, but Miyamoto and collaborators (2005) reported that FGF-23 reduces the reabsorption of Pi and produces hyperphosphaturia; moreover, it also inhibits the synthesis of 1,25-dihydroxy (vit-D3), reducing NaPi-IIb expression in the small intestine. [24] It was therefore suggested that FGF-23 promotes the reduction in the intestinal NaPi-IIb transport activity of a dependent mechanism ofVDR. Thus, when the set of effects mediated for FGF-23 in the organism, hyperphosphaturia associated to reduced Pi absorption, can lead to symptoms of hypophosphatemia. [24,26] Arima and collaborators (2000) have demonstrated that glucocorticoids can also induce a decrease in the cotransport of Na+ and Pi, which is satisfactorily correlated with reductions in the protein levels of NaPi-IIb, as well as mRNA in suckling animals. [27]

Epidermal growth factor (EGF) also constitutes an important physiologic regulator of NaPi-IIb. EGF, a polypeptide of 53 amino acids, is secreted predominantly by the salivary glands and presents inhibitory activity on several intestinal membrane proteins such as alkaline phosphatase, sucrase and maltase. [28,29] It has been demonstrated that EGF is able to reduce the abundance of NaPi-IIb mRNA between 40 - 50% in both rat intestinal cells and human intestinal cells (Caco-2). [13]

The activity of *SLC34A2*/NaPi-IIb can still be stimulated by mTOR, a serine/threonine –kinase, central in the cellular signaling pathway of phosphatidylinositol 3-kinase/AKT, and basic to the processes of proliferation and cellular growth. In *Xenopus* oocytes expressing *SLC34A2,* Pi induced a current towards the cellular interior that was significantly increased when mTOR was coexpressed, leading, more precisely, to the duplication of this current. It was also observed that the activation of *SLC34A2* by mTOR was interrupted by its inhibitor, rapamycin, which has been evaluated in clinical trials for the treatment of cancer, in part for its capacity of maintaining the cellular cycle in the G1 phase. [30,31]

Studies employing Western blot analysis have demonstrated that treatments with estrogen cause an increase in NaPi-IIb abundance in the intestines of rats. The elevation of Pi uptake in the brush membrane cells detected after treatment is the result of an increase of the apical protein expression of NaPi-IIb. NaPi-IIb gene expression is also stimulated for estrogen, as demonstrated by semi-quantitative RT-PCR in treatments employing Caco-2 cells, which is known to express NaPi-IIb gene endogenously. [13,32] Analyzed together, these data indicate that the intestinal effects of estrogen are due to a gene expression of increased NaPi-IIb.

As a consequence of the above, it is clear that various components and situations already exist that knowingly regulate the expression of SLC34A2/NaPi-IIb, showing the complexity of the control mechanisms of Pi uptake. The exact regulation mechanisms, nevertheless, are still indefinite, which demonstrates a great area for new research that exists around this class of cotransporters. At present, one of the principal aspects of study with NaPi-IIb is a possible relation between the expression of the above-mentioned transporter and the origin of carcinomas in humans.

NaPi-IIb and Carcinogenesis

Even before the sequencing of its gene or the characterization of its protein, SLC34A2/NaPi-IIb was already a target of studies in the area of oncology. In 1987, the immunization of mice with a suspension of ovarian cancer cells derived from solid tumors and ascitic fluid led to the production of five monoclonal antibodies. Such antibodies were specific since they were reacting with the surface of tumor cells of fresh ovarian samples but not with normal mesothelial cells. [33] One of these antibodies, called MX35, proved to be the most specific, while not reacting in tests with carcinomas of colon, bladder, breast and pancreas, evaluated in clinical studies as a possible tool for metastasis detection [34] and in studies with animal models for therapeutic use as radioimmunotherapy. [35] For some time, the antigen responsible for the production of the antibody MX35 was not known, and only in 2008 was it recognized that this antigen was in fact the transporter NaPi-IIb.

The possible involvement of *SLC34A2*/NaPi-IIb in carcinogenesis was initially described in a study using the serial analysis of gene expression (SAGE) technique, which allows the wide-scale analysis of gene expression in entire tumor libraries. In this study, there were five overexpressed genes identified in ovarian carcinoma that were called Human Ovarian Specific Tags (HOSTs), among them is the *SLC34A2* gene, which encodes NaPi-IIb. This gene presented overexpression up to five orders of magnitude in cancerous ovarian cells when compared to normal ovarian superficial epithelial cells, and yet, NaPi-IIb expression occurred in a greater degree in the tumor specimens with well to moderate differentiation. [36]

Most recently, it was demonstrated that in

benign or well-differentiated papillary serous tumors, as well as in well-differentiated endometrioid tumors, an overexpression of NaPi-IIb occurs; however, in malignant or benign mucinous tumors, as well as poorly differentiated endometrioid tumors, there are no signs of altered expression of the protein.[37]

A possible relation was already described between the uptake of phosphate and the induction of cellular apoptosis, which might explain, at least in part, the overexpression of NaPi-IIb in so many carcinomas. Denoyer and collaborators ,[38] in a study carried out with the leukemia cell line U937, identified the expression of the type III cotransporter of dependent potassium of sodium to the detriment of other types of phosphate transporters.[38] In order to evaluate a possible relation between phosphate uptake for this transporter and the induction of apoptosis, tests were carried out with etoposide, a chemotherapeutic that, as expected, increased significantly the apoptosis in this leukemic line. Interestingly, the line treated with etoposide showed a significant reduction in the uptake of phosphate when compared to the control line that had not received the dose of the drug, and yet, the phosphate accumulation was inversely proportional to the percentage of apoptotic cells. [38] Considering that tumor cells direct their metabolic demand for the expression of molecules that favor its proliferative, anti-apoptotic and/or metastatic potential, it is plausible that NaPi-IIb contributes to tumorigenesis exactly while reducing the apoptosis tendency in tumor cells.

Today, it is known that the altered expression of NaPi-IIb is not exclusive of ovarian carcinomas. As previously described, *SLC34A2* has a known function in the lung and is expressed in a gradually increasing manner during pulmonary development. Surgical samples of non-small cell lung cancer (NSCLC) demonstrated a pattern of gene expression with an opposite tendency to that observed during fetal pulmonary development, so that SLC34A2, one of the genes overexpressed during this process, has expression reduced up to ten times in lung cancer samples when compared to normal lung. [39]

Another malignancy in which the involvement of SLC34A2/NaPi-IIb has been evaluated is papillary thyroid cancer. A study with the technique of DNA microarray published in 2008 compared the gene expression pattern of neoplastic cells derived of surgical samples of papillary thyroid cancer with cells that had been derived from non-cancerous thyroid. A group of genes was proposed relevantly overexpressed in the tissues of papillary thyroid cancer in relation to the normal thyroid, and among these genes is *SLC34A2,* data confirmed by RT Real-Time PCR. [40]

NaPi-IIb as Tumor Marker and Therapeutic Target

Due to high specificity and high gene expression levels in cancer, it has been suggested that *SLC34A2* can represent a clinically useful tumor marker. The large number of ovarian cancer studies can make the use of this gene as a marker for this cancer a more tangible possibility. Normal ovarian tissue does not express NaPi-IIb in a way that detection by mRNA, or the protein by molecular and/or immunologic techniques, is clinically feasible to be used. In spite that ovarian cancer has been more extensively studied as to NaPi-IIb expression, we still lack the data that connects the gene expression of this protein with clinical data in samples of ovarian cancer. It is possible that, in the future, the analysis of *SLC34A2* expression in biopsy samples or in tumors after surgical excision will help doctors in the diagnosis, the determination of staging, choice of treatment, evaluation of the prognosis or evaluation of tumor progression. What exists is the fact that ovarian cancer is directly related between the gene expression of the transporter, the differentiation of the tumor and the histological type. [36,37]

The same facts that make NaPi-IIb a good marker for use in the diagnosis and prognosis in ovarian cancer, also makes it possible to suppose that this protein would make a good target for new therapeutic strategies. Some studies in mice using NaPi-IIb as a target for radioimmunotherapy have already been carried out and have obtained some promising results. These studies propose the use of the antibody MX35F(ab')$_2$ labeled with the α-particle emitter ^{211}At for ovarian cancer therapy and its metastasis in the peritoneal cavity. Such a therapy would dedicate the radionuclide directly to the cancerous cells so that its action would be practically limited to the malignant cells. Other immunotherapeutic strategies, such as those that use the cytotoxicity mediated by antibodies and direct immunotoxicity, are also promising approaches for ovarian cancer.

Few articles have been published with respect to the analysis of *SLC34A2* expression in thyroid cancer. In 2005, data referring to the construction of a gene expression profile using the DNA microarray technique were published, being that *SLC34A2* was significantly more expressed in malignant cells than in normal cells. [40] Following, an algorithm called recursive feature replacement was proposed for a group of genes which expression analysis could have diagnostic implications; among these genes is *SLC34A2*. [40] These data, however, do not allow us to evaluate what would be the usefulness

of *SLC34A2* as a tumor marker, or even as a therapeutic target. In 2006, a Polish group published an article that revealed that there is a high degree of overexpression of *SLC34A2* in samples of papillary thyroid cancer and defended the use of *SLC34A2* as a molecular marker for the disease.

Lastly, for lung cancer, the data referring to SLC34A2 expression are still very insipient. For some time, the expression of this gene has been studied during the pulmonary development in the embryonic period in animal models; however, only in a publication in 2008 that these data could be extrapolated for humans. [37] It was exactly in this study for the first time that pulmonary carcinogenesis was associated to the low expression of *SLC34A2*. The fact that non-neoplastic pulmonary cells physiologically express NaPi-IIb make its use as a therapeutic target for pulmonary cancer therapy difficult; however, the difference in the expression of the transporter between normal and cancerous cells, evaluated by more detailed new studies, could figure as a possible prognostic factor and help in the staging of lung cancer.

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