

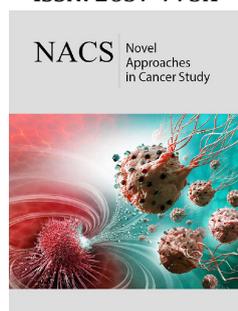
Release of Inorganic Phosphate into the Tumor Environment: Possible Roles of Ecto-Nucleotidases and Ecto-Phosphatases

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Abstract

Inorganic phosphate (Pi) is essential for several biochemical reaction. Serum Pi is maintained at relatively narrow range concentrations, between 0.7 and 1.55mM. Tumor microenvironment presents a high Pi concentration (1.8±0.2mM Pi) and this could be associated with the rapid growth in the "Growth Rate Hypothesis". Several studies have identified high expression of Pi transporters in various tumor tissues. Similarly, ecto-enzymes (like ecto-nucleotidases or ecto-phosphatases) act by dephosphorylating phospho-substrates in the extracellular environment, and its high expression has been observed in various types of cancer. Little is known about the function of these ecto-enzymes on Pi releasing and accumulation in the tumor environment. Therefore, the purpose of this study is to correlate a possible contribution of the Pi release in the tumor microenvironment by ecto-nucleotidases and ecto-phosphatases, concomitant to the regulation of Pi extracellular pool by specific Pi transporters, associating it to the tumorigenesis.

Keywords: Ecto-nucleotidases; Ecto-phosphatases; Pi transporters; Pi release; Cancer

Introduction

Inorganic phosphate is an essential nutrient for the maintenance of cell life, by comprise phospholipids and nucleotides that compose DNA and RNA. Pi plays central role on signaling pathways by protein phosphorylation and dephosphorylation and it participates on energy metabolism in the form of ATP or metabolic intermediates substrates [1,2]. In healthy humans, steady state serum Pi concentrations generally range from 0.70 to 1.55mM [3]. The Pi is absorbed by intestinal cells by Na⁺ dependent Pi transporter (SLC34A2) [4]. About 60-70% of the total Pi in food intake is present as organic phosphate compound, thus, ecto-nucleotidase and ecto-phosphatase enzymes are required to provide it from hydrolysis of phosphorylated compounds such as glucose 1-phosphate, ATP, ADP and 5'AMP [5].

Extracellular nucleosides and nucleotides derived from purine (as adenosine, ADP and ATP) or pyrimidine (as UDP and UTP) moiety, not only act as energy source for living organism, but also performs signaling role, once nucleotide release to extracellular environment, through panexin and connexin junctions, controls various pathological and physiological conditions [6,7]. These signaling molecules modulate a variety of physiological functions such as blood clotting, inflammation and immune reactions and cell proliferation [8]. Those functions are controlled by specific activation of purinergic receptors; those are activated by extracellular nucleotides, like purinergic receptor subtypes: P2 (ATP) and P1 (Adenosine) [6-7]. Activation of purinergic receptors can be controlled by extracellular nucleotide hydrolysis; whereas ecto-nucleotidases are responsible for ATP hydrolysis generating ADP, AMP, adenosine and Pi [6-8]. Another class of enzymes that can hydrolyze phosphorylated compounds are acid ecto phosphatases, like the transmembrane acid prostate phosphatase (TM-PAcP), recently discovered as variant of a secreted phosphatase used in the diagnosis of prostate cancer [9,10].

However, it is currently scarce studies on the role of ecto-nucleotidase and ecto-phosphatases to release Pi towards the extracellular environment. In mouse skin and lung cancer models, a high tumorigenic rate was observed in diets supplemented with Pi, sustaining the Growth Rate Hypothesis (GRH), requiring relatively more phosphate due to their rapid growth rates [2,3,11,12]. In mouse breast tumor cells, a high Pi concentration was identified in

the tumor microenvironment ($1.8 \pm 0.2 \text{ mM Pi}$) compared to normal mammary gland ($0.84 \pm 0.07 \text{ mM Pi}$), suggesting it as a marker for body cancer [12]. Elevated extracellular Pi (3 and 5 mM Pi) also stimulates metastatic capacity in lung (A549) and breast (MDA-MB-231) cancer cells, once it increases FOXC2, OPN and Vegfa mRNA levels, triggering a high migration capacity [13]. Recently, a high affinity Na^+ dependent Pi transporter was characterized in breast cancer cells (MDA-MB-231), and it is related to adhesion and migration capacity [14]. Also, in MDA-MB-231 cells, a low affinity H^+ -dependent Pi transporter is related to cell migration process, especially in high Pi concentrations [15]. Several tumor tissues present high levels of ecto-nucleotidase, ecto-phosphatase and Pi transporters expression [2,16-18]. However, no study has sought to integrate these enzymes by focusing on Pi release towards the tumor environment and its possible functions for tumor progression so far.

Ecto-Nucleotidases

Ecto-nucleotidases are a set of enzymes that hydrolyze extracellular phosphorylated nucleotides derived from purine or pyrimidine. The four main classes of ecto-nucleotidase are:

- Ecto-nucleoside triphosphate diphosphohydrolase (E-NTPDase): generating ADP and AMP from ATP hydrolysis [19-21];
- Ecto-nucleotide pyrophosphatase/phosphodiesterases (E-NPPs): hydrolysis of ATP to AMP;
- Ecto-5-nucleotidase (e5NT): generating adenosine from 5'AMP hydrolysis [8]. The E-NTPDase family comprises eight enzymes, which differ in cell location and substrate specificity, whereas four presents extracellular catalytic site: NTPDase1 (CD39), NTPDase2 (CD39L1), NTPDase3 (CD39L3) and NTPDase8(CD39L4) [6-7]. High ATP hydrolysis or NTPDases overexpression has been observed in several cancers such as: melanomas [18], Walker 256[22], bladder cancer [23] and breast cancer [24].

Regarding the family of E-NPPs, has been reported seven class of enzymes (E-NPP1 - E-NPP7), however, four are able to hydrolyze a variety of nucleotides: E-NPP1 (PC-1), NPP2 (autotaxin), NPP3 (CD203c) and NPP4 [8,17]. Regarding the expression of these enzymes in tumor tissues, NPP1 is widely identified in neural brain tumors [25], rat C6 glioma cell membranes [26], human astrocytic brain tumors [27], and human glioblastoma stem cells [17,28]. NPP2 has been closely associated with the migration phenotype in melanomas [29] and various tumors such as hepatocellular carcinoma [30], neuroblastoma [31], prostate carcinoma [32] and non-small cell lung cancer [33,34]. Moreover, NPP3 has been related to tumor development and transformation, showing that its expression in fibroblast and glioma cells induced enhanced invasive properties [34,35].

Ecto-5'-nucleotidase (Ecto-5'-NT; CD73) is a transmembrane enzyme found in vertebrates, plants and even bacteria. Ecto-5'-nucleotidase hydrolyzes AMP into adenosine, which is a major source of adenosine for adenosine (P1) receptors [7]. Ecto-5'-NT

is anchored to the plasma membrane by a GPI anchor. Ecto-5'-NT catalyses the hydrolysis of 5' carbon esterified phosphate from ribose or deoxyribose [6]. CD73 overexpression is well established in the literature for various cancers including walker 256 tumor bladder Buffon [20], [23], leukemia [36], glioma [37], glioblastoma [38], melanoma[39], ovarian cancer [40], thyroid cancer [41], esophageal cancer [42], gastric cancer [43], colon cancer [44], prostate cancer [45], breast cancer [18,22,24,46], pancreatic cancer [47], hepatocarcinoma [48] and salivary gland tumors [49].

Another type of enzymes able to hydrolyze nucleotides are the Alkaline phosphatases. Alkaline phosphatases (ALP) are ubiquitous metalloenzymes and represent a protein family of phosphomonoesterases. These enzymes can be divided into two groups, tissue nonspecific alkaline phosphatase (TNALP) and tissue specific ALPs including placental ALP (PALP), intestinal ALP (IALP) and ALP germ cells (GCALP) [8]. All these isoforms present high levels of expression in cancer cells: TNALP was identified in osteoblastic bone metastases [50]; PALP was identified in ovarian, testicular, lung, breast, gastrointestinal tract and choriocarcinoma cancer [51-53]; IALP was identified in hepatocellular carcinoma [54] and GCALP was identified in carcinoma testis [55-57].

Acid Ecto Phosphatases

Acid phosphatases are enzymes that hydrolyze phosphorylated substrates in acidic environments; five class of enzymes have been reported in human tissues [58]. In human prostate, a prostatic acid phosphatase (PACp) is reported intracellularly. However, in patients with advanced prostate cancer, an elevation of serum acid phosphatase (sPACp) was identified, accompanied by a decrease in expression of (PACp). Both forms of PACp are transcribed from the same gene but follow different post-transcriptional modifications [9]. Recently, a new spliced variant PACp mRNA encoding a transmembrane type I protein with extracellular phosphatase activity (TM-PACp) was identified in various tissues such as brain, kidney, liver, lung, muscle, placenta, salivary gland, spleen, thyroid, thymus. TM-PACp expression was also observed in human prostate cancer tissue samples [10].

Pi Transporters

Pi enters the cells via Pi cotransporters. These cotransporters constitute two large families of inorganic phosphate transporters that have been characterized in mammals, namely, SLC20 :expressed almost exclusively in the kidney and SLC34 (consists of three members, NaPi-IIa (SLC34A1): expressed in kidney, osteoclasts, neurons; NaPi-IIb (SLC34A2): expressed in small intestine, lung, testis, liver, secreting mammary gland; and NaPi-IIc (SLC34A3), expressed in kidney [2,4]. Specifically, in relation to cancer, several studies have identified increased expression of Pi transporters in tumor tissues compared to normal tissues such as ovarian [59], thyroid [60], breast [61], lung [62] and kidney [2,63]. Regarding Pi another class of transporter has been recently studied, an H^+ -dependent Pi transporter in Caco2BBE human intestinal cells [64], osteoclasts-like cells [65] and recently in MDA-MB-231, breast cancer cells [15].

Co-Relation of Ecto-Nucleotidases, Ecto-Phosphatases and Pi Transport

Decades ago, many studies sought to relate the importance of ecto-nucleotidases and ecto-phosphatases for the absorption of their generated products. Knowing that there was a high expression of non-specific alkaline phosphatase in rat small intestine epithelial cells, Rothstein et al. [5] identify the importance of ALPs for 1-phosphate glucose hydrolysis generating glucose to be transported into the cells. Regarding the absorption of Pi, in microorganisms like *Escherichia coli*, extracellular low Pi concentration induces an increased expression of ecto-phosphatases, strongly suggesting a function for these enzymes in Pi pool availability [66]. Years later, it has been demonstrated an increase in intracellular Pi in cell intestines of chickens and rats when is added a phosphorylated compound (β -glycerophosphate), suggesting a relation between alkaline phosphatase activity and Pi absorption [67,68]. However, once inhibiting alkaline phosphatase, no regulation of intracellular Pi levels was observed; but the presence of other ecto-phosphatase activities cannot be excluded Valinietse et al. [68]; Shirazi, 1981 and Moog F [67]. In the last twenty years, studies relating ecto-nucleotidases and/or ecto-phosphatases and Pi transporters have become scarce. After the elucidation of the homeostatic system of Pi in humans, new studies focused to solve the structure of the carrier and relationship to pathophysiology [4].

Increasing expression of ecto-nucleotidases and ecto-phosphatases in tumor tissues have mostly been associated with the release of extracellular adenosine, as an adenosine receptor agonist (P1 receptor) triggering signaling involved with proliferation and metastasis processes [18]. Little is discussed about the contribution of Pi released from hydrolysis to these tumor tissues. Bobko et al. [12] showed that the concentration of interstitial Pi in the tumor to approximately 2mM may be a direct consequence of the high hydrolysis of ATP by tumor cells. We recently suggested that the high level of Pi in the tumor environment would be inducing a downregulation expression of a high affinity Pi Na⁺ dependent transporter and consequently increasing the activity level of a low affinity Pi H⁺ dependent transporter, acting as a compensatory mechanism to obtain more inorganic phosphate [15]. Further studies need to be done to relate the importance of ecto-nucleotidases and ecto-phosphatases for Pi release in the tumor environment and the possible regulation of these enzymes according to extracellular Pi concentration.

Conclusion

In general, high levels of expression of ecto-enzymes were observed in tumor tissues. In this review, we suggest a possible contribution of these overexpressed enzymes to a high amount of Pi been released in the tumor environment. Due to the Growth Rate Hypothesis (GRH), tumor cells require more Pi to fuel high energy rate tumor processes such as proliferation and metastasis. At high Pi levels, tumor cells would increase the activity of the low affinity H⁺ dependent Pi transporter and may represent a biological advantage for tumors in providing the cells with the incorporation

of extra Pi even under those conditions where Na⁺ dependent Pi transport is saturated by a high extracellular Pi (approx. 2mM). The importance of accumulating and transporting more Pi would be to promote cell transformation and tumorigenesis via specific molecular mechanisms and increase ATP production through oxidative phosphorylation.

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Conflict of Interest

None declared.

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