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Roles of Ionic Environments in Growth of Human Cancer Cell and Potentials of Ion Transporter Blockers in Cancer Therapies

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Abstract

Cancer cells produce a large amount of H^+ due to high-rate glycolysis, however cancer cells keep the cytosolic pH (pH_c) slightly higher than that of normal cells even under conditions provided by a large amount of H^+ due to high-rate glycolysis. Further, interestingly cancer cells survive even under starvation conditions utilizing a self-nutrient-recycling autophagy system in lysosome. The intra-lysosomal pH is kept much lower than cytosolic pH, and this lowered intra-lysosomal pH is a key factor for keeping activity of lysosomal enzymes participating in autophagy function. It is notable that Cl^- plays an important role in regulation of pH_c and intra-lysosomal pH. In this article, I discuss roles of H^+ and Cl^- circumstances in cancer cell proliferation, and a possibility of drugs modifying H^+ and Cl^- circumstances used as anti-cancer drugs.

Introduction

Cancer cells live in hypoxic, hypo-nutrient circumstances provided by insufficient angiogenesis due to fast rates of cancer cell proliferation [1,2]. These circumstances lead cancer cells via production of ATP as energy sources mainly via high rate glycolysis, while most normal cells produce ATP via oxidation of pyruvate in mitochondria with relatively low-rate glycolysis compared with cancer cells [3]. The high-rate glycolys is forming lactate produces a large amount of H^+, providing acidic micro environments around cancer cells [4]. Interestingly, cancer cells keep the cytosolic pH (pH_c) slightly higher than that of normal cells even under these environmental conditions provided by a large amount of H^+ due to high-rate glycolysis [5,6]. From a viewpoint of cell cycle arrest, apoptosis and cell growth, pH_c of tumor cells kept at a level slightly higher than that of normal cells is a key factor for prevention from cell cycle arrest and apoptosis even under acidic microenvironments around cancer cells [7,8]. These findings clearly indicate that cancer cells have to maintain their pH_c at a level slightly higher than that of normal cells for survival even under acidic conditions with production of a large amount of H^+. For maintenance of pH_c at a level slightly higher even under acidic environmental conditions than normal one, expression and/or activity of $H^+$and/or HCO_3^-transporting systems in cancer cells would be expected to be higher than normal cells. Further, it is notable that cancer cells utilize a self-nutrient-recycling autophagy system for their survival even under starvation conditions [9-11]. The self-nutrient-recycling autophagy occurs in lysosome, and the intra-lysosomal pH is much lower than the cytosolic one [12,13]. Cl^-also plays a key role in regulation of pH_c and intra-lysosomal pH. In this article, I discuss roles of ionic circumstances in growth and lysosomal function in cancer cells.

Expression of ion transporters regulating pH_c in cancer cells

Cancer cells have been reported to express four major ion transporters participating in keeping pH_c at a normal or slightly higher level even under acidic environmental conditions than normal one [14-16]. These four major ion transporters regulating pH_c are classified into two categories [14-16]; i) H^+ transporters, and ii) HCO_3^-transporters. H^+ transporters, Na^+/H^+ exchanger (NHE) and H^+ pumps (V-type H^+-ATPase, etc.), directly extrude $H^+$from the cytosolic space to the extracellular or into the intra-lysosomal one keeping high pH_c. On the one hand, HCO_3^-transporters, Na^+/HCO_3^- cotransporter (NBC), Na^+-driven Cl^-/HCO_3^- exchanger (NDCBE), and Cl^-/HCO_3^- exchanger (AE), participate in HCO_3^- movement across the plasma membrane regulating pH_c. Unlike H^+ transporters these HCO_3^-transporters do not participate in unidirectional transport of HCO_3^-; *i.e.*, NBC and NDCBE contribute to uptake of HCO_3^- into the cytosolic space using the electrochemical gradient of Na^+ for elevation of pH_c, but AE extrudes HCO_3^- from the cytosolic space to the extracellular one for a decrease in pH_c instead of elevation of the cytosolic Cl^- concentration under general conditions.

Roles of NHE and its Inhibitor in Growth of Cancer Cells and Ionic Circumstances in Cancer Cells

Among the pH_c-regulating ion transporters mentioned above, NHE is the major regulator of pH_c ubiquitously expressed in most cells including cancer cells, and 10 isoforms of NHEs have been identified [17-21]. NHE1, an isoform of NHE, is the most ubiquitously expressed one among 10 isoforms [22-28]. Various types of growth factors, integlins, tyrosine phosphatases and cytokines regulate activity of NHE1 [22-28]. NHE, in particular NHE1, in cancer cells plays a crucial role in maintenance of pH_c at a level slightly higher than normal one [29]. Proliferation and migration of many cancer cells require pH_c slightly higher than normal one, which depends on NHE activity [19-21].Therefore, NHE inhibitors should be investigated as anticancer drugs inhibiting proliferation of cancer cells underacidic micro-environmental conditions. Indeed, many researchers have tried to investigate action of NHE inhibitors on proliferation of cancer cells in detail [30]. Recently, we [31] have also reported that 5-(N-ethyl-N-isopropyl) amiloride (EIPA, an NHE inhibitor [32]) inhibits the proliferation of human gastric cancer cells. It is generally thought that inhibition of NHE decreases pH_c. However, our report [31] indicates that inhibition of NHE has no influence on pH_c, but decreases the cytosolic Cl^- concentration ($[Cl^-]_c$).The cytosolic Cl^- has been reported to play important roles in various cell functions including proliferation of cancer cells [33-48]. The role of cytosolic Cl^- in cancer cell proliferation has been also investigated; when $[Cl^-]_c$ is experimentally

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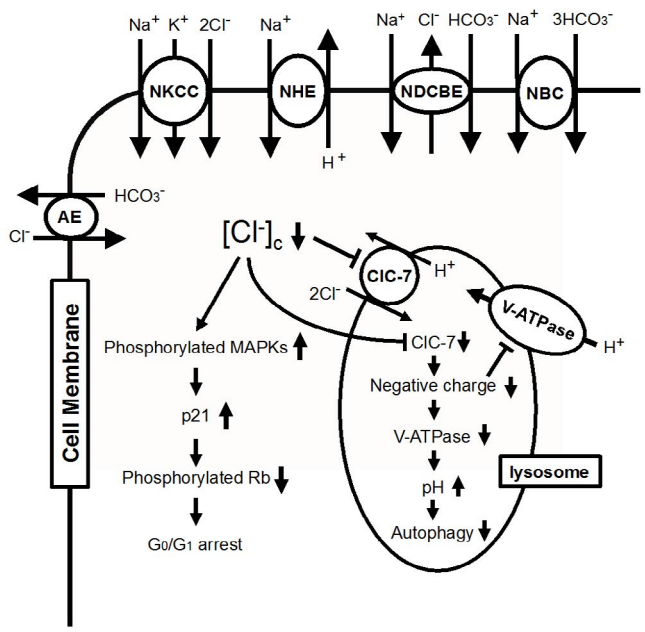

Figure 1: Ion transporters involved in regulation of cytosolic Cl^- environments and roles of cytosolic Cl^- in cell function. Na^+/H^+ exchanger (NHE) has no direct contribution to intracellular Cl^- environments, since NHE directly participates in Na^+ uptake coupling with H^+ extrusion. However, application of an inhibitor of NHE, EIPA, lowers the cytosolic Cl^- concentration ($[Cl^-]_c$) without any effect on cytosolic pH (pH_c) [31]. The EIPA-caused lowered $[Cl^-]_c$ would be due to activation of Na^+-driven Cl^-/HCO_3^- exchanger (NDCBE) compensating the EIPA-caused acute lowered pH_c [31]. For example, in cancer cells mitochondria function is low, leading to low production of CO_2. This means that contents of H^+ and HCO_3^- induced by CO_2 from mitochondria are low in cytosolic space of cancer cells. On the one hand, cancer cells produce a lot of H^+ via glycolysis, being converted to CO_2 and H_2O with HCO_3^- a carbonic anhydrase-mediated process, resulting in lowered HCO_3^- in cytosolic space. Taken together, the amount of HCO_3^- in cytosolic space of cancer cells is much lower than that in normal cells. Thus, activation of ion transporters taking HCO_3^- up into the cytosolic space such as NDCBE, which extrudes cytosolic Cl^- using electrochemical gradient of Na^+, in cancer cells with a low HCO_3^- condition is much effective in lowering $[Cl^-]_c$ than normal cells. Namely, inhibition of NHE and activation of NDCBE would effectively decrease $[Cl^-]_c$, under a condition with low mitochondria function occurring in cancer cells. This leads cancer cells to G_0/G_1 arrest via a MPKs-p21-Rb pathway and autophagy dysfunction via elevation of intra-lysosomal pH. Based on the information described above, some drugs modifying activity of ion transporters involved in regulation of cytosolic Cl^- environments would be useful for anticancer therapies.

AE, Cl^-/HCO_3^- exchanger; ClC-7, $2Cl^-/1H^+$ exchange; MPKs, mitogen-activated protein kinases; NBC, Na^+-HCO_3^- cotransporter; NDCBE, Na^+-driven Cl^-/HCO_3^- exchanger; NHE, Na^+/H^+ exchanger; NKCC, Na^+-K^+-$2Cl^-$ cotransporter; Rb, retinoblastoma protein; V-ATPase, V-type H^+-ATPase.

decreased by lowering the extracellular Cl^- concentration, gastric cancer cells show diminution of cell proliferation via a p53-independent p21-upregulation pathway [36,43]. Thus, the cytosolic Cl^- is one of the key regulators in cancer cell proliferation [31] (Figure 1).

Autophagy in Cancer Cells

Cells survive even under starvation conditions utilizinga self-nutrient-recycling autophagy system [9-11]. Cells check if they should degrade long-lived or miss-folded proteins, and damaged organelles such as mitochondria utilizing this autophagy system [49-51]. The autophagy system is induced by starvation-caused poverty of nutrients, mainly amino acids, for cells to survive utilizing reproduced nutrients originally contained in cells themselves [9]. Recycled amino acids reproduced by autophagy are utilized for new proteins synthesis [9]. Autophagy is generally activated by starvation, however autophagy process functions even under conditions with rich nutrition [52]. Activity of autophagy is closely correlated with not only cancer [53], but also other diseases such as diabetes mellitus [54], Parkinson disease [51], and inflammatory disease, Crohn disease [55].

Autophagy and Intra-Lysosomal Ionic Circumstances in Cancer Cells

Autophagy ability in cancer cells is much higher than normal cells, since cancer cells have to survive under hypoxic, hypo-nutrient micro environments utilizing recyclable nutrition such as amino acids [53]. It has been reported that Atg5 or Atg7 plays a key role in autophagy function; lack of Atg5 or Atg7 impairs the autophagy system and apoptosis in cancer cells [56-58]. Lysosomal machineries catabolize cell components, indicating that lysosome is a key organelle producing autophagy function in degradation of various compounds [11]. It is well known that the intra-lysosomal pH is lower than pH_c [12,13], and that this lower intra-lysosomal pH is a key factor to maintain the digesting activity of lysosomal enzymes; *i.e.*, lysosomal enzymes require low pH to maintain their enzymatic activities [59]. The V-type H^+-ATPase (proton pump) generates the intra-lysosomal low pH co-operating with ClC-7located on the lysosome membrane [60,61]. ClC-7has stoichiometry of $2Cl^-/1H^+$ exchange, and is assumed to primarily behave as a Cl^- permeation pathway across the lysosomal membrane [60], although there is still some contradictory observations (e.g., [62]). Mutation of ClC-7 impairs lysosomal function, which is detected as abnormal accumulation of proteins into the intra-lysosomal space [63], meaning that the function of ClC-7 as a Cl^- permeation pathway would contribute to lysosomal function (protein degradation) via maintenance of low intra-lysosomal pH. Further, knock down of ClC-7 impairs lysosomal acidification [60], and inhibits cell proliferation associated with abnormal accumulation of proteins in lysosomes [64]. These studies [60,63,64] suggest that ClC-7 would be essential as Cl^- movement/transport for maintenance of low intra-lysosomal pH and autophagy-dependent cell proliferation. Although these studies [60,63,64] suggest the importance of Cl^- movement/transport via ClC-7, the importance of functional presence of $Cl^-$is not confirmed. Our study [65] suggests that the presence of Cl^- itself plays an essential role in autophagy (Figure 1).

Conclusion

Some drugs modifying activity of ion transporters involved in cytosolic Cl^- environments would be useful for anticancer therapies (Figure 1).

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