Possible association between cell membrane *band 3* impairment function and renal tubular acidosis (liver diseases, malignancies and adverse drug reactions)

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Summary. *Renal tubular acidosis (RTA) more frequently develops in case of chronic diseases of inflammatory-immunological origin. RTA is well known to be associated with chronic liver disease (CLD), with nephrolithiasis, common cases of RTA occur among cancer patients. Abnormalities in the expression or function of band 3 in cell membrane may play a role in the pathogenesis of RTA. Cl^-/HCO_3^- anion exchanger (AE2) is an isoform of band 3 protein, which is expressed in cell membranes of organs such as liver cells and kidney endothelium.*

There are reports on downregulated AE2 immunoreactivity in the liver of patients with chronic liver diseases and in the kidney tubular tissue of patients with RTA. The proteolytic damage of cell membrane band 3 in tissues could be related to inflammatory-immunological processes.

Another important factor able to disturb the band 3 function is medicinal products used in the treatment of certain pathologies. The active substance of a drug itself may have a direct effect on this protein or trigger a pathological process. In such cases ADR can take place and may be evaluated as such. Acid-base disturbances, notably metabolic acidosis, are a serious complication of drug treatment.

Reduced AE2 expression or its changed activity (congenital or acquired) could be related with alterations of intracellular pH. This could lead to antigenic changes and autoimmunity. The derangement of band 3 function in organ cell membrane could act as a factor which creates an "acidotic environment" for organ cells. Such circumstances could be the reason for unsuccessful treatment or determine resistance of tumor treatment. The understanding of the mechanisms of RTA development, early diagnostics, and knowledge of the drugs that can cause RTA, are of particular practical significance.

Introduction

Anion transport through the cell membrane is catalyzed by a protein, known as *band 3*, which is the major component of cell membrane. The Cl^-/HCO_3^- anion exchanger 2 (AE2) is an isoform of *band 3* protein, which is expressed in membranes of cells of various tissues (1-3). The AE2 has been reported to have internal sites regulated by internal H^+ concentration in the physiological range (4) and to be able to transport Cl^- or to mediate intracellular pH changes that reflect the Cl^-/HCO_3^- exchanger function (5). AE2 is a candidate for the regulation of intracellular pH and intracellular Cl^- concentration (6), and these processes are strongly dependent on bicarbonate anions (7, 8). Such "cross-talk" between membrane AE2 and Cl^- is recognized as a critical feature to keep a normal intracellular acid-base balance.

Cl^-/HCO_3^- exchanger activity occurs in conjugation with another transport system, Na^+/H^+ antiporter. Reduced Na^+/H^+ antiporter activity would acidify cells. The Cl^-/HCO_3^- exchanger activity is an important regulator of Na^+/H^+ activity, because the activities of these antiporters are coupled (9). Decreased intracellular pH itself will cause an inhibition of AE2 activity (7, 8).

AE2 is involved in the transcellular transport of acid and base through the epithelial cell membrane of kidney or liver, in the regulation of intracellular pH (through Cl^- influx and HCO_3^- efflux), which leads to acidification (8). A substantial portion of the intercalated cells in the cortical collecting duct of kidney are of the β-type, which secrete HCO_3^- by means of an apical Cl^-/HCO_3^- exchanger. A disorder of the Cl^-/HCO_3^- in either α-cells or β-cells might cause RTA. Evidence in

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support of the former possibility has been presented (10). In the kidney it entrains a pathogenic sequence of impaired basolateral Cl^- exit → impaired basolateral Cl^-/HCO_3^- exchanger → impaired HCO_3^- reabsorption.

Reduced anion transport activity in cells of some mutant *band 3* forms was shown (11–13). RTA was shown to be heterozygous for mutations in their red cell Cl^-/HCO_3^- exchanger *band 3* genes. RTA related to a congenitally altered Cl^-/HCO_3^- exchanger may lead to reduced urinary acidification (11). The complete absence of *band 3* appears to result in defective renal acid secretion in cattle (14).

Association between RTA and cell membrane *band 3* expression in chronically ill patients

There are increasing evidences to point to the autoimmune mechanism of RTA. The commonest form of RTA is associated with multiple systemic autoimmune diseases (15). It has been shown that anti-renal-tubular cell autoantibodies may have a causal relation to the defective distal tubular acidosis (16). It was suggested that neutrophil-induced IgG binding to the cell membrane due to the combined action of proteinases and oxidants might explain the accelerated destruction of cell *band 3* in inflammatory and autoimmune diseases (17). Cohen et al. reported a renal biopsy of 3 patients with RTA (caused by hypergammaglobulinemia) to show that in 2 patients distal nephron intercalated cells did not stain for *band 3* (18).

More than 30% of patients with chronic liver disease (CLD) have a concomitant renal tubular acidosis (19, 20). RTA in CLD is mainly distal RTA and presents either as an overt or an incomplete (latent) variety, although a combination of distal and proximal varieties has been described (21). Incomplete RTA and overt RTA may be different stages of the same underlying pathophysiology. Distal RTA was suggested to be a proximal tubular cell disorder (22).

The molecular basis of RTA is not well known. The association between CLD and RTA could be multifactorial. CLD as well as chronic active hepatitis have more than one site of renal tubular involvement and can lead to a hybrid of proximal and distal defect (23). The possibility of such association, which has received little attention, is a defect in the Cl^-/HCO_3^- anion exchanger on the basolateral membrane of kidney tubule (10, 24). Abnormalities of H^+ and bicarbonate transport are related with the dysfunction of proximal tubular cells (25).

Cl^-/HCO_3^- exchanger activity is believed to be essential for the function of endothelial cells of the liver (26). A decreased AE2 immunoreactivity in the liver cell membrane of patients with liver cirrhosis was reported (1, 2). Reduction of AE2 expression in liver cells could result from inflammatory changes as well as could be predetermined genetically. An impaired expression of AE2 was reported in other cells and tissues from CLD patients (in peripheral blood mononuclear cells) (1). On the other hand, a disturbed lymphocyte expression of AE2 could play a role in the complex immune dysfunction characteristic of CLD patients (27). Reduced AE2 expression (congenital or caused by proteolysis) could be related to changes in intracellular pH. This could lead to protein mistargeting in liver cells (28) and in kidney tubules (29), antigenic changes and autoimmunity.

Band 3 damage could be related with a decreased antiproteolytic activity in blood serum or in tissues related to α-1-PI deficiency (congenital or acquired). The α-1-PI is present in the renal proximal tubular epithelium in humans (30, 31). Patients with a deficient α-1-PI phenotype showed a weak, if any, positive staining for α-1-PI in proximal tubules (32). It is recognized that the normal staining of α-1-PI of proximal tubules is related to their normal function. Among patients with severe α-1-PI deficiency, 15% had a damage of kidney tubular tissue (33). *Band 3* protein was found to be susceptible to degradation by neutrophil elastase (34) and by other proteinases (35). A significant antiproteinase response was observed in the proximal tubules in a group of patients with tubulo-interstitial lesions, indicating a direct damage of cell membrane by proteinases (36). These data show that α-1-PI could be an important factor working against renal tubular damage. There are experimental data supporting the idea that α-1-PI deficiency could be involved in RTA pathogenesis. Pontaglio et al. showed the inactivation of hepatocyte nuclear factor 1 (HNF1) to be related to pathogenesis of RTA in mice lacking the HNF1 model. The HNF1 is a transcriptional activator of the hepatic α-1-PI gene. The RTA pathogenesis in this model is caused by renal proximal tubular dysfunction (37).

The relationship between chronic liver disease and α-1-PI deficiency is well known. The frequency of deficient phenotypes of α-1-PI in European populations (38, 39) also shows that this problem is obvious. There are no studies on the relationship between α-1-PI deficiency and RTA or on the involvement of α-1-PI deficiency in RTA pathogenesis.

RTA is one of the causes of nephrolithiasis (40). In connection with this and with above data, it is important to stress one more peculiar fact: 30% of the subjects in whom a lethal sequence of hepatitis B infection developed had a history of nephrolithiasis (41).

RTA in cancer patients

Acid-base regulation and chemotherapy in oncology. Measurements of extracellular pH (pHe) *in vivo* have shown that the microenvironment in tumors is more acidic than in normal tissues. This gives rise to a reversed pH gradient between tumors and surrounding tissue, which implies that cells within solid tumors are capable of maintaining their intracellular pH (pHi) at physiological levels, despite lower than normal levels of pHe (42). The incubation of tumor cells at low pH has been shown to induce more expressed invasive behavior *in vitro* (43).

Multidrug resistance (MDR) is a significant obstacle to providing effective chemotherapy to many patients. Most chemotherapeutic drugs in use today are hydrophobic small molecules, which are also typically either weakly basic, weakly acidic or charged. Thus, changes in the pHi or pHe of tumor cell have important effects on their transmembranous diffusion and cellular retention. It is logical to propose that many of the characteristics of MDR tumor cells could be due to perturbations in cellular ions transport, related to pHi/or pHe change (44).

Cellular uptake of chemotherapeutic drugs may be dependent on the pH gradient between pHi and pHe compartments, in murine tumor models where the extracellular environment is acidic relative to the intracellular environment, this gradient favors the preferential accumulation of drugs that are weak acids into cells (45).

Ion-trapping theory predicts that alkalinization of tumor extracellular pH will enhance the anti-tumor activity of weak–base chemotherapeutics. Chronic and acute treatment of tumor-bearing mice with sodium bicarbonate results in tumor-specific alkalinization of pHe (46).

Hypericin, an antineoplastic agent, is a pigment found in plants (St. John's Wort – *Hypericum perforatum*) and its toxicity is absolutely light dependent. The biological activity of hypericin is linked to its ability to produce a photogenerated pH drop in target cells (47).

Understanding the pH-related tumor acidity molecular mechanisms could open new opportunities for tumor therapy. Theoretical considerations of causes of tumor pHi, hypotheses to explain extracellular acidity and the possibility that low pHe might be an intrinsic feature of the tumor phenotype may appear very important for concepts of treatment based on extracellular and intracellular pH.

pHi or pHe changes and the efficacy of chemotherapy. The effects of pHi on the cytotoxicity of anthracyclines, taxanes, anti-metabolites and alkylating agents were determined, and ion trapping was confirmed by monitoring the effect agents of pH on the cellular uptake of radiolabeled agents (48). Uptake of weak acid and weak base chemotherapeutic drugs by tumors is greatly influenced by the tumor extracellular/interstitial pH, the pHi maintained by the tumor cells, and by the ionization properties of the drug itself. The acid-outside plasmalemmal pH gradient in tumors acts to exclude weak base drugs like anthracyclines, anthraquinones, and vinca alkaloids from the cells, leading to a substantial degree of "physiological drug resistance" in tumors (49). Results suggest that acidification of organelles is causally related to drug resistance and is consistent with the hypothesis that sequestration of drugs in acidic organelles (weak base chemotherapeutic drugs, e.g., anthracyclines and vinca alkaloids) and subsequent extrusion from the cell through the secretory pathways contribute to chemotherapeutic resistance (50).

The difference in doxorubicin accumulation and cytotoxicity at the same extracellular pH was found to be dependent on the difference in the transmembrane pH gradient of the two cell types (51). DNA analysis of cell cycle distribution revealed that intracellular acidification, as observed during incubation at low pHe and/or using pHi modifiers, resulted in accumulation of cells in G1 phase, where they may be more resistant to these drugs. Reduced uptake of weak bases (mitoxantrone) at low pHe and altered cell cycle kinetics upon acidification are the postulated causes of reduced cytotoxicity of the agents investigated (52). In order to effectively overcome multidrug resistance it will be necessary to design new strategies that combine modulating agents and approaches (53).

The inhibitor of Cl^-/HCO_3^- exchange that regulates pHi, 4-acetamido-4'-isothiocyanostilbene-2,2'-disulfonic acid (SITS) interferes with chloride transport and chloride (Cl^- anions) acidify pHi. This implies that Cl^- is involved in cisplatin activation. Cisplatin toxicity in EMT6 cells was evaluated in a chloride-deficient medium. EMT6 cells cultured in a chloride-deficient medium were less sensitive to cisplatin than cells cultured in a chloride-containing medium (54).

Adriamycin accumulation in Ehrlich ascites tumor cells decreased with an increasing concentration of DIDS (4,4-diisothiocyanstilbene 2,2-disulphonic acid – an inhibitor of Cl^-/HCO_3^- antiport). These findings demonstrate that the influx of adriamycin is closely related to the activities of Cl^-/HCO_3^- exchanger. Therefore, raising the extracellular pH and enhancing the activities of Cl^-/HCO_3^- exchanger may result in the

potentiation of the cytotoxic effect of adriamycin through an increase of its influx (55).

A correlation was seen between relative resistance/ daunorubicin accumulation and acid extrusion rate in wild-type Ehrlich ascites tumor cells (EHR2), which is likely to be due to aspects of development of drug resistance other than P-glycoprotein (P-gp) (56).

Also, it was found that the efficiency of Cl^- dependent reacidification of pHi after an intracellular alkaline shock was found to reduce in the MDR cells. This effect appears to correlate with the relative expression of MDR protein, but not with the relative expression of Cl^-/HCO_3^- exchanger (AE), which was also found altered in the series of cells. There are data to show a relationship between increased Cl^- conductance and the expression of MDR protein (57).

Possible association between band 3 function and tumor treatment effectiveness. Bicarbonate pretreatment enhances the anti-tumor activity of doxorubicin and mitoxantrone in different mouse tumor models. Alkalinization with HCO_3^- selectively enhances the tumor uptake of radiolabeled mitoxantrone. These results suggest that inducing HCO_3^- anion in patients would have a positive effect on response to mitoxantrone therapy (46). Treatment of C3H tumor–bearing mice with 12 mg/kg mitoxantrone resulted in a tumor growth delay of 9 days, whereas combined $NaHCO_3^-$ – mitoxantrone therapy resulted in a tumor grow delay of up to 16 days (49). MCF-7 human breast cancer cells *in vitro* are more susceptible to doxorubicin toxicity at pH 7.4 than at pH 6.8. 31P-magnetic resonance spectroscopy has shown that the pHe of MCF-7 human breast cancer xenografts could be effectively and significantly raised with bicarbonate in drinking water. The bicarbonate-induced extracellular alkalinization leads to significant improvements in the therapeutic effectiveness of doxorubicin against MCF-7 xenografts *in vivo* (58).

To evaluate the importance of pHi in determining drug toxicity, survival of EMT6 mouse mammary tumor cells was determined for cells treated with cisplatin in the presence of SITS. Cells cultured with SITS were less sensitive to cisplatin. The cisplatin resistance obtained could be attributed to the presence of SITS (59).

Of the drug-resistant lines, one contained Pgp (MCF-7/DOX, also referred to as MCF-7/D40), and the others (MCF-7/MITOX) showed no expressed anion exchanger (AE) activity (60). The cytotoxicity of mitoxantrone, paclitaxel and topotecan was assessed at low pHe and after manipulation of pHi in murine EMT6 and in human MGH-U1 cells. The cytotoxic efficacy of all three agents was reduced at pHe 6.5 as compared to pHe 7.4. The DIDS – an inhibitor of Cl^-/HCO_3^- antiport – was used to cause intracellular acidification. The combined use of cytostatic drugs with pHi modifiers reduced their cytotoxicity under both physiological and low-pHe conditions (52).

Reduction in intracellular accumulation of cisplatin is believed to be dependent on the concentration of intracellular chloride (Cl^-) ions and intracellular pH. It was shown that cell (cisplatin-sensitive (COS31) and cisplatin-resistant (COS31/rCDDP) canine osteosarcoma cells) survival can be influenced by inhibition of the Cl^-/ HCO_3^- exchanger with SITS. Addition of SITS increases the intracellular Cl^- concentration in canine osteosarcoma cells cultured in a bicarbonate-containing medium. In a bicarbonate-free medium, addition of SITS results in downregulation of cytotoxic action of cisplatin (61). The pH regulation in HT29 colon carcinoma cells has been found related to the Cl^-/HCO_3^- exchanger (62).

DIDS slightly inhibited proliferation of the murine tumor L929 cell line and did not influence proliferation of tumor P815 cells. These results demonstrate the importance of Cl^-/HCO_3^- exchange in tumor cell proliferation and indicate the possibility that ion exchange inhibitors could act as antitumor reagents (63).

In vitro treatment of drug-sensitive HL60 cells with DIDS resulted in a concentration-dependent decreased accumulation and increased resistance to daunorubicin and decreased pHi. These data show that altered Cl^- permeability is associated with MDR and suggest that Cl^- channels may play a role in MDR. Similarly camp-activated Cl^- currents were minimal in multidrug-resistant subline HL60/AR cells (0.2 pA/pF) as compared to HL60 cells (8 pA/pF) (64).

Anticancer drug-inducing RTA. Metabolic acidosis due to RTA is a serious complication of several anticancer drug chemotherapies. Several mechanisms of RTA have been described, including: 1) direct, dose-dependent, proximal tubular toxicity leading to bicarbonate loss; 2) proximal tubular defect consistent with the acquired Fanconi syndrome; 3) distal tubular damage, including type 1 RTA; 4) a combination of the above defects (65–67).

RTA was described in patients suffering from acute lymphoblastic leukemia (68), in multiple myeloma (69, 70), pancreatic cancer (71), breast cancer and colon carcinomas (72, 73), osteosarcoma, etc. (74).

Patients with cancer are frequently at risk of RTA secondary to disease-related and iatrogenic causes. In literature there are data on anticancer drugs suspected of RTA as an adverse drug reaction. Among such medicinal products are ifosfamide (73–76), chloro-

ethylnitrosourea compounds (carmustine, semustine, streptozocin (76), cisplatin, carboplatin (74, 75), azacitidine (76), irofulven (71), glufosfamide (72), thiotepa (73) combination thiotepa plus melphalan/busulfan (77), filgrastim (73, 78), paclitaxel (73, 78) and methotrexate (74).

Concluding remarks

The defect of Cl^-/HCO_3^- exchanger in cell membrane can arise in the following ways: 1) genetically determined Cl^-/HCO_3^- exchanger activity; 2) *band 3* pathological damage of renal tubular cells along the immunological and inflammatory disease course; 3) drug-induced RTA (RTA manifestation in the presence of a concomitant decreased expression of *band 3* of congenital or inflammatory origin or activity changed by drug effect).

The elucidation of drugs able of inducing RTA as well as investigations of the drug-related pathogenic mechanisms of this pathology are very urgent. Studies to test our hypothesis might elucidate how RTA could be related to alterations in the *band 3* functional activity in kidney tissues. A further study of *band 3* mutations, morphological and functional changes after autoimmune-inflammatory or malignant processes as well as in the effect of drugs, is likely to shed a light on the novel aspects of the molecular and cellular biology of *band 3* and its role in RTA pathogenesis. Such understanding could appear very valuable for treatment strategies of these disorders, especially for the treatment of resistant tumor forms. Investigation of pathogenetic mechanisms of RTA and determination of a possible role of drugs in these processes is an important area of pharmacovigilance.

Galima sąsaja tarp ląstelės membranos *band-3* baltymo funkcinio aktyvumo sutrikimo ir inkstų tubulinės acidozės raidos

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Raktažodžiai: inkstų tubulinė acidozė, membranos baltymas, šalutiniai reiškiniai, vėžys, hepatitas.

Santrauka. Inkstų tubulinė acidozė neretai atsiranda sergant imuninės-uždegiminės kilmės lėtinėmis ligomis. Gerai žinoma, kad inkstų tubulinė acidozė neretai pasitaiko sergant lėtiniu hepatitu, inkstų akmenlige, neretai ji būna metabolinės acidozės priežastis sergant onkologinėmis ligomis. Inkstų tubulinė acidozė gali būti susijusi su vienu pagrindinių ląstelių membranos baltymų – *band-3* funkcijos sutrikimu. Šis baltymas lemia Cl^-/HCO_3^- apsikeitimą per ląstelės membraną, kartu yra vienas pagrindinių veiksnių, reguliuojančių ląstelės pH. Imuniniai kompleksai, uždegimo mediatoriai, taip pat ir vaistai (ypač vartojami onkologinėms ligoms gydyti) gali sutrikdyti šio baltymo funkcinį aktyvumą, kartu gali sukelti inkstų tubulinę acidozę. Straipsnyje pateikiama minėtais klausimais literatūros duomenų apžvalga, aptariamas galimas nepalankus vaistų poveikis, ląstelės pH reguliacijos sutrikimai, galintys lemti net atsparumą priešnavikiniams preparatams.

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