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Review

Transport of haloacids across biological membranes

Xianbin Su [a,*], Ruihong Li [b], Ka-Fai Kong [c], Jimmy S.H. Tsang [c,*]

[a] Key Laboratory of Systems Biomedicine (Ministry of Education), Shanghai Center for Systems Biomedicine, Shanghai Jiao Tong University, Shanghai 200240, PR China
[b] Shanghai Quality Safety Centre of Agricultural Products, Shanghai 200335, PR China
[c] Molecular Microbiology Laboratory, School of Biological Sciences, The University of Hong Kong, Pokfulam Road, Hong Kong

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ABSTRACT

Haloacids are considered to be environmental pollutants, but some of them have also been tested in clinical research. The way that haloacids are transported across biological membranes is important for both biodegradation and drug delivery purposes. In this review, we will first summarize putative haloacids transporters and the information about haloacids transport when studying carboxylates transporters. We will then introduce MCT1 and SLC5A8, which are respective transporter for antitumor agent 3-bromopyruvic acid and dichloroacetic acid, and monochloroacetic acid transporters Deh4p and Dehp2 from a haloacids-degrading bacterium. Phylogenetic analysis of these haloacids transporters and other monocarboxylate transporters reveals their evolutionary relationships. Haloacids transporters are not studied to the extent that they deserve compared with their great application potentials, thus future inter-discipline research are desired to better characterize their transport mechanisms for potential applications in both environmental and clinical fields.

Contents

1. Haloacids: environmental pollutants or potent antitumor drugs?

Haloacids are halogenated derivatives of carboxylic acids with hydrogen atom(s) replaced by halogen atom(s) like fluorine, chlorine, bromine, or iodine. Halogenated derivatives of acetic acid are called haloacetic acids (HAAs), and commonly found HAAs include monochloroacetic acid (MCA), dichloroacetic acid (DCA), trichloroacetic acid (TCA), monobromoacetic acid (MBA), and dibromoacetic acid (DBA) (structural formulas shown in Fig. 1). Haloacids are considered to be environmental pollutants widely distributed in the biosphere [1,2]. They are produced by both natural processes [3] and human activities, and photo-degradation of herbicides in the soil [4] and water disinfection via chlorination [5] are two important anthropogenic sources. There have been widespread

Abbreviations: 2,2DCPA, 2,2-dichloropropionate; 2MCPA, 2-monochloropropionic acid; 3-BrPA, 3-bromopyruvic acid; 5-FU, 5-fluorouracil; *Bcc*, *Burkholderia cepacia complex*; CCCP, carbonyl cyanide *m*-chlorophenyl hydrazine; DBA, dibromoacetic acid; DCA, dichloroacetic acid; FA, fluoroacetate; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GBM, glioblastomas; HAAs, haloacetic acids; HDAC, histone deacetylase; HKII, hexokinase isoform II; MBA, monobromoacetic acid; MCA, monochloroacetic acid; MCT, monocarboxylate transporter; MHS, metabolites:H^+ symporter; MPC, mitochondrial pyruvate carrier; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PET, positron emission tomography; PGK, 3-phosphoglycerate kinase; SDH, succinate dehydrogenase; TCA, trichloroacetic acid; TCA cycle, tricarboxylic acid cycle; TCDB, Transporter Classification Database.

* Corresponding authors.
E-mail addresses: xbsu@sjtu.edu.cn (X. Su), onlylonely1022@163.com (R. Li), kongkf@hku.hk (K.-F. Kong), jshtsang@hku.hk (J.S.H. Tsang).

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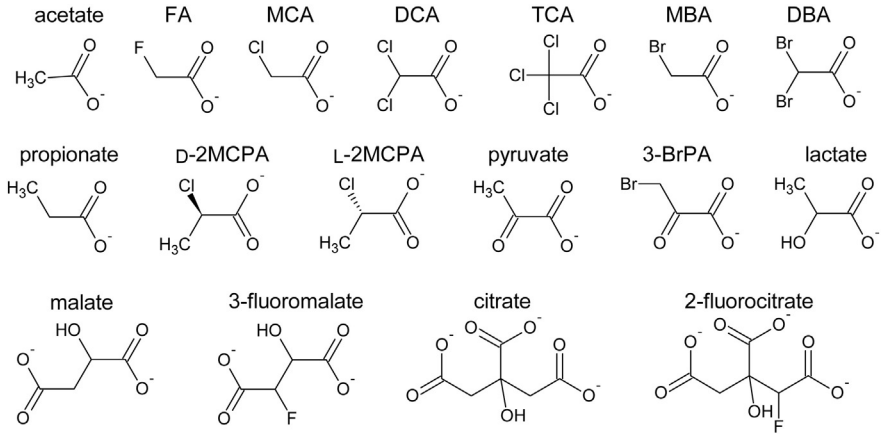

Fig. 1. Structural formulas of some haloacids and related carboxylic acids. They will be transported in ionic forms at physiological pH, so their anions are shown here. Abbreviations: FA, fluoroacetate; MCA, monochloroacetate; DCA, dichloroacetate; TCA, trichloroacetate; MBA, monobromoacetate; DBA, dibromoacetate; 2MCPA, 2-monochloropropionate; 3-BrPA, 3-bromopyruvate.

concerns about their potential toxicity, mutagenicity and carcinogenicity towards living organisms [6–8], and total concentration of five HAAs (MCA, DCA, TCA, MBA, and DBA) in drinking water is restricted to be below 60 μg L^{-1} [9].

For effective removal of haloacids, there are two approaches, abiotic methods such as UV irradiation [10], and bacterial biodegradation [11,12]. The key step in haloacids biodegradation is the cleavage of halogen-carbon bond by a group of enzymes called dehalogenases, whose classification and working mechanisms have been extensively studied during the past several decades [13–17]. As polar molecules containing hydrophilic carboxyl groups, haloacids are not able to freely pass the lipid bilayers of biological membranes, and specific haloacids transporters are needed to facilitate this process. In contrast to well characterized dehalogenases, haloacids transporters are not studied extensively.

Fluorinated carboxylic acids form another important group of haloacids. Fluoroacetate (FA) is produced by many poisonous plants in Africa, Australia, South America and India for self-defense purpose, and it is the main constituent of compound 1080 which has been used as vertebrate pesticide to control invading animals in Australia and New Zealand for decades [18,19]. FA is not toxic to enzymes, but due to structural similarity with acetate, it will react with coenzyme A to form fluoroacetyl-CoA, enter tricarboxylic acid (TCA) cycle and form fluorocitrate, which could tightly bind aconitase, causing TCA cycle halt and citrate accumulation [18,20]. Sir Peters defined this phenomenon as "lethal synthesis" [18]. 5-Fluorouracil (5-FU) and 5-fluoro-orotic acid have been shown to exert antitumor activity against various transplanted tumors, with 5-FU being more effective [21]. Since then, 5-FU has been used as an antimetabolite drug to treat various tumors for several decades, and its working mechanisms have been extensively studied [22]. However, some tumors will develop drug resistance to 5-FU after initial treatments and limit its clinical applications [22]. Cardiotoxicity and neurotoxicity are also observed after 5-FU administration, probably related to the metabolites of 5-FU, such as FA, α-fluoro-β-hydroxypropionic acid and α-fluoro-β-alanine [23–25]. The interference of α-fluoro-β-alanine with GABA reuptake is one possible reason for the neurotoxicity [26]. Chemicals that are able to circumvent the formation of these metabolites have been exploited to attenuate the toxic side-effects of 5-FU [27]. Although most studies focused on the toxicity of FA, there has also been research to test the antitumor activity of FA. Sodium fluoroacetate was previously shown to inhibit the growth of Ehrlich cancer, but later results showed that mono-therapy showed no significant antitumor activity, but it could enhance the effects of cyclophosphamide and increase the duration of the effects [28]. Fluorinated compounds are playing increasingly important roles in medical chemistry, and another application is ^{18}F labeled tracers for positron emission tomography (PET) [29–31]. The half-life of ^{18}F is 110 min, relatively longer than that of ^{11}C, ^{15}O or ^{13}N, making it more suitable for clinical applications. Besides the application of [^{18}F]-FA in PET imaging [32], various ^{18}F labeled fluorinated amino acids have also been tested to image specific tumors [33–37]. The transport of fluorinated amino acids is thus important to make sure tumors rather than normal tissues could be imaged. Various types of amino acid transport systems are involved in the uptake of fluorinated amino acids, and they have been reviewed elsewhere [29,38,39].

Cancers have been shown to have different metabolism patterns compared with normal cells, and Warburg effect is an important feature which describes the reliability of cancer cells on glycolysis rather than oxidative phosphorylation inside mitochondrion for energy production even in the presence of oxygen [40]. In contrast to the efforts by environmental scientists to figure out ways to degrade haloacids, some of them have been investigated as potential antitumor drugs [41,42], with 3-bromopyruvic acid (3-BrPA) and DCA as two examples.

3-BrPA caused cell deaths in cultured hepatoma cells and completely eradiated advanced glycolytic cancers, confirming its role as antitumor agent both in vitro and in vivo [43,44]. Intra-arterial delivered 3-BrPA significantly reduced cancer cells in liver-implanted rabbit tumors, and systematically delivered 3-BrPA suppressed metastatic tumors arise in the lungs [45]. Ko et al. reported a translational study using 3-BrPA to treat a patient with fibrolamellar hepatocellular carcinoma, and the results gave the promise of using 3-BrPA as potent antitumor drug without obvious cytotoxicity when formulated properly [46]. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) [47], 3-phosphoglycerate kinase [48], succinate dehydrogenase [48], histone deacetylase (HDAC1 and HDAC3) [49], and hexokinase [50] are the possible inhibition targets of 3-BrPA (Fig. 2A).

DCA has been studied for several decades to treat lactic acidosis [51–53], and recently to prevent restenosis in vessel injury [54] and treat various types of cancer [55–60]. Like pyruvate, DCA is able to inhibit pyruvate dehydrogenase kinase (PDK), resulting activation of pyruvate dehydrogenase (PDH) and shift of glycolysis to mitochondrial oxidation of pyruvate (Fig. 2A). By inhibiting PDK and increasing the expression of K^+ channel Kv1.5 in cancer cells but not normal cells, DCA induced apoptosis and inhibited proliferation and tumor growth without apparent toxicity [61]. In a translational study, DCA was shown to reverse mitochondrial hyperpolarization in freshly isolated glioblastomas (GBM) from 49 patients, and apoptosis was induced in patient-derived GBM cells and putative GBM stem cells both in vitro and in vivo for five patients treated with DCA [62]. At doses that didn't cause peripheral neuropathy, DCA was sufficient to inhibit the PDK II that was highly expressed in glioblastoma [62]. Cancer patients are thus eager to take un-approved DCA, despite possible health risk [63].