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Review

The proton-coupled folate transporter (PCFT-SLC46A1) and the syndrome of systemic and cerebral folate deficiency of infancy: Hereditary folate malabsorption

Rongbao Zhao [a,b], Srinivas Aluri [a,b], I. David Goldman [a,b,*]

[a] Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, New York, USA
[b] Department of Medicine, Albert Einstein College of Medicine, Bronx, New York, USA

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ABSTRACT

The proton-coupled folate transporter (PCFT) is the mechanism by which folates are absorbed across the apical brush-border membrane of the small intestine. The transporter is also expressed in the choroid plexus and is required for transport of folates into the cerebrospinal fluid. Loss of PCFT function, as occurs in the autosomal recessive disorder "hereditary folate malabsorption" (HFM), results in a syndrome characterized by severe systemic and cerebral folate deficiency. Folate-receptor alpha (FRα) is expressed in the choroid plexus, and loss of function of this protein, as also occurs in an autosomal recessive disorder, results solely in "cerebral folate deficiency" (CFD), the designation for this disorder. This paper reviews the current understanding of the functional and structural properties and regulation of PCFT, an electrogenic proton symporter, and contrasts PCFT properties with those of the reduced folate carrier (RFC), an organic anion antiporter, that is the major route of folate transport to systemic tissues. The clinical characteristics of HFM and its treatment, based upon the thirty-seven known cases with the clinical syndrome, of which thirty have been verified by genotype, are presented. The ways in which PCFT and FRα might interact at the level of the choroid plexus such that each is required for folate transport from blood to cerebrospinal fluid are considered along with a basis for the different clinical presentations of HFM and CFD.

Contents

*Chemical compounds studied in this article:*5-Formyltetrahydrofolate (PubChem CID: 143)Levoleucovorin (PubChem CID: 149436)5-Methyltetrahydrofolate (PubChem CID: 439234)Levomefolic acid (PubChem CID: 444412)Folic acid (PubChem CID: 6037)Methotrexate (PubChem CID: 126941)Pemetrexed (PubChem CID: 446556)

Abbreviations: PCFT, Proton-coupled folate transporter; RFC, reduced folate carrier; 5-formylTHF, 5-formyltetrahydrofolate; 5-methylTHF, 5-methyltetrahydrofolate; HFM, hereditary folate malabsorption; CFD, cerebral folate deficiency; CSF, cerebrospinal fluid; BBB, blood–brain barrier.

* Corresponding author. Department of Molecular Pharmacology, Albert Einstein Cancer Center, Chanin 2, 1300 Morris Park Avenue, Bronx, NY 10461, USA; Department of Medicine, Albert Einstein Cancer Center, Chanin 2, 1300 Morris Park Avenue, Bronx, NY 10461, USA.
E-mail address: i.david.goldman@einstein.yu.edu (I.D. Goldman).

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1. Introduction

The B9 family of folate vitamins plays a central role in mammalian biology by providing the one-carbon moieties required for the synthesis of purines, thymidylate and methionine; the synthesis of glycine from serine; as well as the downstream epigenetic processes for which the synthesis of S-adenosylmethionine is required (Tibbetts and Appling, 2010). Essential to the maintenance of folate sufficiency is its adequacy in the diet, its intestinal absorption, and its transport into systemic tissues and into extrasystemic compartments. These different steps necessary for folate utilization are mediated by three different folate transporters. The identification of these transporters and an understanding of the distinct mechanisms by which folates are transported across cell membranes have emerged from research over the past five decades. This involved investigators that approached folate transport from different biological perspectives. One group focused on the role membrane transport plays as a determinant of the activities of, and resistance to, antifolate chemotherapeutic agents. Another group of researchers was concerned with folate homeostasis, folate deficiency and the critical role of intestinal absorption in folate sufficiency. It was the merging of these interests, that evolved from studies on the mechanism of membrane transport of the new-generation antifolate, pemetrexed, that led to the identification of the proton-coupled folate transporter (PCFT) (Zhao et al., 2004b) (Qiu et al., 2006; Wang et al., 2004).

It is now recognized that there are three folate-specific transporters that account for the transport of folates and antifolates. These are (i) the reduced folate carrier (RFC), ubiquitously expressed and the major and essential route of delivery of folates to systemic tissues (Matherly and Hou, 2008; Zhao and Goldman, 2013); (ii) PCFT, the mechanism by which folates are absorbed across the apical brush-border membrane of the proximal intestine, and essential to the transport of folates across the choroid plexus (Qiu et al., 2006; Zhao and Goldman, 2013); and (iii) the folate receptors, folate receptor alpha (FRα) normally expressed only in epithelia where it plays a role in transepithelial transport processes, and FRβ expressed largely in hematopoietic tissues (Elnakat and Ratnam, 2004; Kamen and Smith, 2004; Ross et al., 1994; Zhao et al., 2011a). This review will focus on PCFT, its functional characteristics, what is known about its structure/function and regulation, and the unique form of systemic and cerebral folate deficiency that occurs when there are inherited mutations in the PCFT gene that cause the loss of expression or function of its protein – hereditary folate malabsorption (HFM). In this review, folates will be used as a generic term for the B9 vitamins. In some cases the folate will be specified: 5-methyltetrahydrofolate (5-methylTHF), the major folate in man; 5-formyltetrahydrofolate (5-formylTHF); and folic acid.

2. Distinguishing PCFT and RFC

RFC and PCFT are both members of the superfamily of solute carriers designated as SLC19A1 and SLC46A1, respectively. Both have secondary structures with twelve transmembrane domains (TMDs) with their N- and C-termini directed to the cytoplasm. The RFC gene is located on chromosome 21q22 while the PCFT gene is located on chromosome 17q11.2. RFC is a larger molecule consisting of 591 (NP_008927) versus PCFT's 459 (NP_542400) amino acid residues. Both human proteins are glycosylated in their first extracellular loop between the first and second TMDs, RFC at Asn66, and PCFT at Asn58 and Asn68, but glycosylation is not essential for their function. The composition of the two proteins is quite different with very low (~13%) sequence homology and, accordingly, there are marked functional differences. RFC is an organic phosphate antiporter that operates most efficiently at pH 7.4. The adenine nucleotide gradient across the cell membrane, in particular, provides the energy source for the RFC-mediated uphill transport of folates into cells. PCFT, on the other hand, is a proton symporter that operates most efficiently at acidic pH; the proton gradient across the cell membrane provides the energy source for the uphill transport of folates into cells. The pH at the microenvironment of the proximal small intestine where folate absorption occurs is 5.8–6.0 generated by sodium–proton exchangers in the apical membrane (Counillon and Pouyssegur, 2000; McEwan et al., 1990; Said et al., 1987). There are important differences in substrate specificity. RFC has a high affinity for the reduced

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