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Monocarboxylate Transporters (SLC16): Function, Regulation, and Role in Health and Disease

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Abstract—The solute carrier family 16 (SLC16) is comprised of 14 members of the monocarboxylate transporter (MCT) family that play an essential role in the transport of important cell nutrients and for cellular metabolism and pH regulation. MCTs 1–4 have been extensively studied and are involved in the proton-dependent transport of L-lactate, pyruvate, short-chain fatty acids, and monocarboxylate drugs in a wide variety of tissues. MCTs 1 and 4 are overexpressed in a number of cancers, and current investigations have focused on transporter inhibition as a novel therapeutic strategy in cancers. MCT1 has also been used in strategies aimed at enhancing drug absorption due to its high expression in the intestine. Other MCT isoforms are less well characterized, but ongoing studies indicate that MCT6 transports xenobiotics such as bumetanide, nateglinide, and probenecid, whereas MCT7 has been characterized as a transporter of ketone bodies. MCT8 and MCT10 transport thyroid hormones, and recently, MCT9 has been characterized as a carnitine efflux transporter and MCT12 as a creatine transporter. Expressed at the blood brain barrier, MCT8 mutations have been

associated with an X-linked intellectual disability, known as Allan-Herndon-Dudley syndrome. Many MCT isoforms are associated with hormone, lipid, and glucose homeostasis, and recent research has focused on their potential roles in disease, with MCTs representing promising novel therapeutic targets. This review will provide a summary of the current literature focusing on the characterization, function, and regulation of the MCT family isoforms and on their roles in drug disposition and in health and disease.

Significance Statement—The 14-member solute carrier family 16 of monocarboxylate transporters (MCTs) plays a fundamental role in maintaining intracellular concentrations of a broad range of important endogenous molecules in health and disease. MCTs 1, 2, and 4 (L-lactate transporters) are overexpressed in cancers and represent a novel therapeutic target in cancer. Recent studies have highlighted the importance of MCTs in glucose, lipid, and hormone homeostasis, including MCT8 in thyroid hormone brain uptake, MCT12 in carnitine transport, and MCT11 in type 2 diabetes.

I. Introduction

Monocarboxylate transporters (MCTs) are members of the solute carrier 16 (SLC16) family of transporters that are essential for the transport of short-chain monocarboxylates, hormones, nutrients, and amino acids (Price et al., 1998; Halestrap and Price, 1999; Halestrap and Meredith, 2004; Halestrap, 2013b; Jones and Morris, 2016). Due to this broad range in substrate specificity, it is evident that these transporters play a pivotal role in the homeostasis and function of circulating endogenous molecules. In total, there are 14 isoforms within the MCT family (MCTs 1–14, SLC16A1–14), as well as two members of the sodium-dependent MCT family (SMCTs 1/2, SLC5A8/12). MCTs 1–4 are proton-dependent transporters and are well characterized due to their critical role in the transport of products of the glycolysis cycle (i.e., lactate and pyruvate), as well as ketone bodies (such as acetoacetate and β -hydroxybutyrate) across the plasma membrane. The other MCTs 5–14 have been less investigated, although recent studies have provided some information on their substrate specificities. Although not much is known regarding the substrate specificity of MCT5, MCT6 has been shown to transport drugs such as bumetanide, nateglinide, and

probenecid (Murakami et al., 2005; Kohyama et al., 2013). Similar to MCTs 1–4, MCT7 transports ketone bodies (Hugo et al., 2012). MCT8 and MCT10 have been reported to transport thyroid hormones (Halestrap and Meredith, 2004), with MCT10 also being responsible for transporting aromatic amino acids. MCT9 has been characterized as a carnitine efflux transporter (Suhre et al., 2011) and MCT12 as a creatine transporter (Abplanalp et al., 2013). This review will not discuss the SMCTs that are members of the SLC5 family, namely SLC5A8 (SMCT1) and SLC5A12 (SMCT2), which have been the subject of other reviews (Ganapathy et al., 2008).

The first published investigation into this family of transporters was in the 1970s, in which Halestrap and Denton (1974) demonstrated that pyruvate transport was inhibited by α -cyano-4-hydroxycinnamate (CHC) in rat liver mitochondria and human erythrocytes. These data were supplemented with research performed by Mowbray (1974, 1975), which discovered evidence that pyruvate was pumped across the mitochondrial membrane in rat liver, and that this transporter potentially exhibited a broad specificity toward other monocarboxylates and regulated pyruvate oxidation. Subsequently, additional investigation into these MCTs was performed by Halestrap (1976) and coworkers at the

ABBREVIATIONS: AHDS, Allan-Herndon-Dudley syndrome; AICAR, 5-aminoimidazole-4-carboxamide-1- β -D ribofuranoside; AMPK, AMP-activated protein kinase; CARP, carbonic anhydrase-related protein; CHC, α -cyano-4-hydroxycinnamate; CHO, Chinese hamster ovary; HIF-1 α , hypoxia-inducible factor 1 α subunit; MCT, monocarboxylate transporter; miRNA, microRNA; NASH, nonalcoholic steatohepatitis; NF- κ B, nuclear factor κ -light-chain enhancer of activated B cells; PPAR α , peroxisome proliferator-activated receptor α ; RPE, retinal pigment epithelium; SLC, solute carrier; SMCT, sodium-dependent MCT; SNP, single-nucleotide polymorphism; T₃, triiodothyronine; T2D, type II diabetes; TM, transmembrane; UTR, untranslated region.

University of Bristol (Bristol, UK); Halestrap (1976) became an early pioneer in characterizing this family of transporters. Halestrap (1976) investigated the mechanism of transport in human erythrocytes, demonstrating the physiologically relevant monocarboxylate carrier-mediated system. Following protein sequence analysis of the isolated rabbit erythrocyte lactate transporter, cDNA for hamster MCT from Chinese hamster ovary (CHO) cells was used to isolate the gene encoding for human MCT1 (Garcia et al., 1994; Poole and Halestrap, 1994). Following this finding, the first isoform of the MCT family (MCT1) was cloned and expressed in CHO cells from rat skeletal muscle (Jackson et al., 1995), and subsequently in others species. Using expression sequence tags to identify other homologs with similar sequence identity, additional putative MCT isoforms were identified from human cDNA libraries (Price et al., 1998). Eventually, additional MCT isoforms were discovered using similar methods, transfected, and characterized over the next several decades (Halestrap and Wilson, 2012).

II. Structure and Function

Structurally, these MCTs share conserved amino acid identity, predicted topology, as well as homology (Halestrap, 2012). All MCT isoforms are predicted to contain 12 transmembrane (TM) domains, intracellular C and N termini, as well as a large intracellular loop between TMs 6 and 7. The most conserved regions of the MCT isoforms, similar to other solute carriers, are the membrane-spanning regions, in contrast to the TM 6–7 loop and large C-terminal tail residues (Fig. 1). A summary of the percent amino acid identity between the 14 human MCT isoforms is depicted in Table 1. In addition, the sequence similarity among these isoforms in different species tends to depend on

the evolutionary relatedness of their host species. Figure 2 depicts the phylogenetic ancestry of MCTs 1–14 in humans, which shows similar patterns of evolutionary relationships across other mammalian species based on amino acid sequence. Although the MCTs demonstrate conserved sequence motifs, their differential expression, regulation, and variable amino acid residues allow for a dynamic ligand-specific and unique physiologic impact for each isoform. Additionally, MCTs have demonstrated dependencies on a variety of ancillary proteins, in order for proper trafficking and function at the plasma membrane. In particular, basigin, also known as CD-147, has been shown to interact with MCTs 1, 3, 4, 11, and 12 primarily through noncovalent interactions (Kirk et al., 2000; Castorino et al., 2011b; Rusu et al., 2017). In contrast, MCT2 has demonstrated preferentially to form a complex with embigin, otherwise known as gp70, a related member of the Ig superfamily (Wilson et al., 2005).

III. Expression and Localization

Tissue and cellular distribution of MCTs are detailed in Fig. 3 and Table 2 and include the species and type of expression (mRNA/protein) that has been reported. Protein expression data are lacking for MCT5, MCT7, MCT9, and MCT11–14.

IV. Substrates and Inhibitors

Investigation of MCT1 transport initially focused on lactate, but the transporter has more varied substrates than initially thought (Morris and Felmlee, 2008). Inhibitors of MCTs 1–4 include phloretin and quercetin, amphiphilic compounds, and CHC, a bulky monocarboxylate (Morris and Felmlee, 2008). MCT8, 9, 10, and 12 are also known to transport monocarboxylates, including more hydrophobic molecules such as creatinine and carnitine (Fisel et al., 2018). MCT7 has not been extensively studied, but has been shown to transport ketone bodies, specifically β -hydroxybutyrate (Hugo et al., 2012). Transgenic expression of human MCT7 in zebrafish with endogenous MCT7 knocked down has been shown to rescue the phenotype (Hugo et al., 2012). Studies utilizing site-directed mutagenesis and homology modeling were performed to probe the substrate translocation cycle to better understand the dynamics of MCT substrate specificity (Wilson et al., 2009). These studies suggested that conserved amino acid positions (i.e., lysine 38, aspartate 302, and arginine 306) in MCT1 were required for the proposed mechanism, and that these amino acids were also present in MCTs 1, 3, and 4, which is consistent with their similar substrate profile. Seeing as MCT7 is the only other MCT isoform to contain these conserved amino acids (with the exception of glutamate instead of aspartate near the position 302), these findings

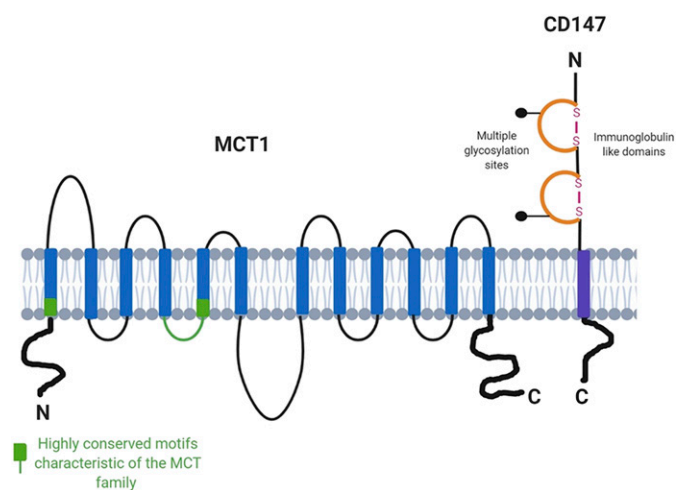


Fig. 1. The proposed topology of the MCT family members. CD147, the ancillary protein that associates with MCT1 and MCT4, is also shown. The N and C termini and the large loop between transmembrane domains 6 and 7 show the greatest variation between family members, whereas the TMDs themselves are highly conserved. Adapted from Halestrap and Meredith (2004) and Halestrap (2013a).

TABLE 1
A summary of the percent amino acid identity of the human MCT isoforms (matrix was generated using Clustal Omega)

	MCT1	MCT2	MCT3	MCT4	MCT5	MCT6	MCT7	MCT8	MCT9	MCT10	MCT11	MCT12	MCT13	MCT14
MCT1	100	59.21	39.43	44.57	24.11	29.07	29.05	22.84	23.03	24.23	28.8	29.37	30.81	24.94
MCT2	59.21	100	42.77	46.74	26.39	32.16	31.61	24.22	26.88	24.38	32.05	29.83	31.83	27.23
MCT3	39.43	42.77	100	56.93	24.71	37.5	28.12	26.34	26.46	26.61	36.05	33.47	34.44	23.98
MCT4	44.57	46.74	56.93	100	25.43	36.81	31.82	26.68	28.68	26.33	32.64	34.85	30.56	27.95
MCT5	24.11	26.39	24.71	25.43	100	24.23	27.48	22.43	25.91	24.16	26.59	29.91	29.8	25.58
MCT6	29.07	32.16	37.5	36.81	24.23	100	28.57	24.19	23.94	23.81	30.32	30.18	28.43	24.71
MCT7	29.05	31.61	28.12	31.82	27.48	28.57	100	21.22	26.62	20.5	25.78	25.48	34.36	22.74
MCT8	22.84	24.22	26.34	26.68	22.43	24.19	21.22	100	25.94	52.17	26.01	22.43	23.13	23.68
MCT9	23.03	26.88	26.46	28.68	25.91	23.94	26.62	25.94	100	27.23	27.47	25.68	29.24	32.16
MCT10	24.23	24.38	26.61	26.33	24.16	23.81	20.5	52.17	27.23	100	25.84	23.64	24.28	26.44
MCT11	28.8	32.05	36.05	32.64	26.59	30.32	25.78	26.01	27.47	25.84	100	30.23	46.93	27.51
MCT12	29.37	29.83	33.47	34.85	29.91	30.18	25.48	22.43	25.68	23.64	30.23	100	33.01	28.57
MCT13	30.81	31.83	34.44	30.56	29.8	28.43	34.36	23.13	29.24	24.28	46.93	33.01	100	26.93
MCT14	24.94	27.23	23.98	27.95	25.58	24.71	22.74	23.68	32.16	26.44	27.51	28.57	26.93	100

support the substrate similarities of MCT7 and MCTs 1–4 and their ability to transport ketone bodies. MCT5, 13, and 14 still have no known substrates and therefore remain orphan transporters. Recently, more substrates and inhibitors have been identified for MCT6, including flavonoids as inhibitors of bumetanide transport (Jones et al., 2017). Substrates and inhibitors of the MCT family members and their respective K_m , K_i , or IC_{50} values, as identified from in vitro systems, are listed in Table 3. It should be noted that K_m values

for MCT1–4 are dependent on the pH gradient of the system, with higher K_m values observed in the absence of a pH gradient (Morse et al., 2012).

V. Regulation and Development

Mechanisms demonstrated to regulate MCTs have only begun to be characterized, including the influence of biologic sex on expression and their developmental regulation. Although most studies have focused on the

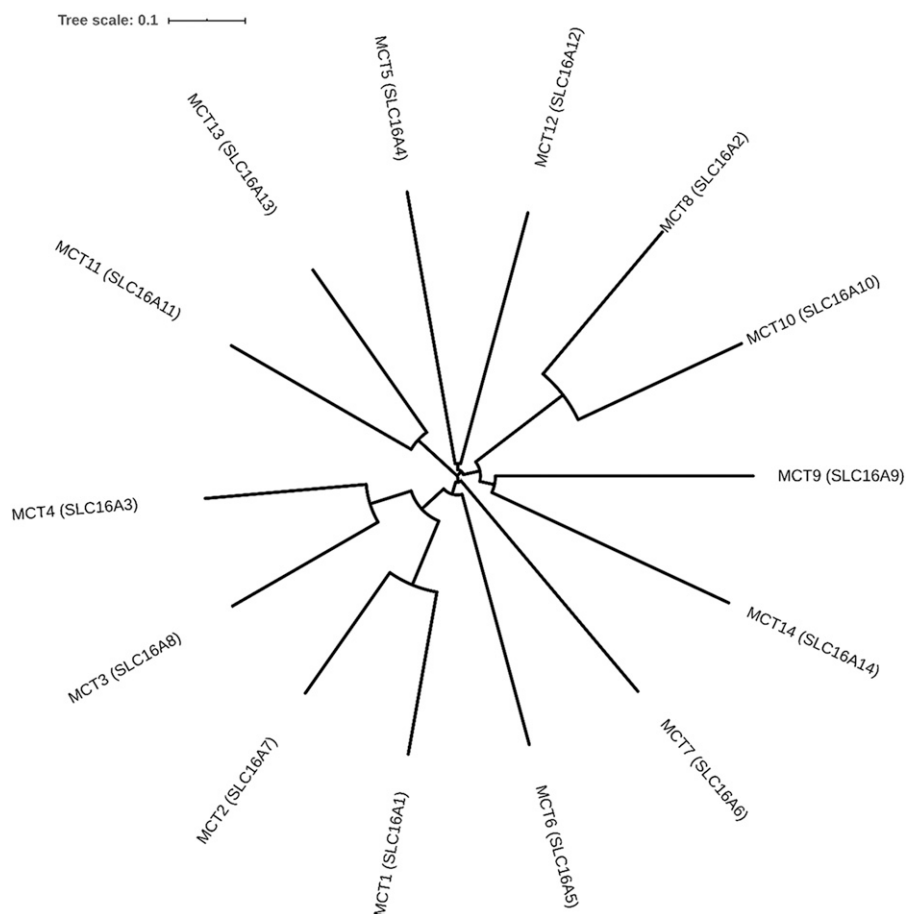


Fig. 2. The phylogenetic tree of human MCT isoforms. Sequence alignments were performed using Clustal Omega, and phylogeny trees were made using interactive Tree Of Life (iTOL). The bar indicates the number of per amino acid residue, with one corresponding to a distance of one substitution per 10 amino acid residues. Adapted from Halestrap (2012).

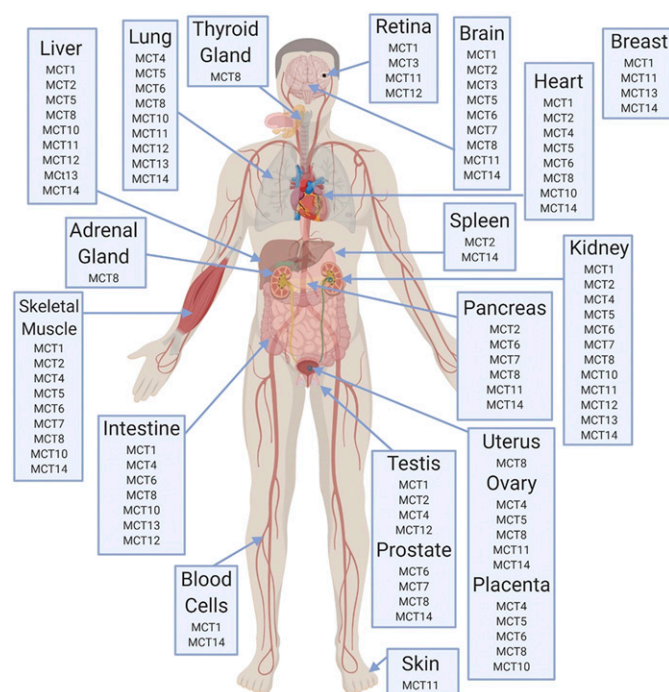


Fig. 3. Tissue protein expression of MCT isoforms in humans, based on data compiled by Morris and Felmlee (2008).

regulation of MCT1 and MCT4, this review includes available data for the other transporters.

A. Regulation

1. Transcriptional Regulation. Numerous studies have demonstrated transcriptional changes in MCTs in a range of tissues and disease states; however, there are limited studies investigating the mechanisms underlying the observed changes in mRNA expression.

The human MCT1 promoter was identified and characterized in the early 2000s, and potential binding sites have been identified within the promoter region for a range of transcription factors, including USF1, USF2, AP1, AP2, SP1, MZF1, and nuclear factor κ -light-chain enhancer of activated B cells (NF- κ B) (Cuff and Shirazi-Beechey, 2002; Hadjiagapiou et al., 2005). The human MCT1 promoter contains USF1 and 2 binding sites that functionally repress MCT1 transcription in human intestinal Caco-2 cells, whereas the distal SP1 site stimulates promoter activity (Hadjiagapiou et al., 2005). NF- κ B inhibitors reverse the stimulatory effect of butyrate on MCT1 promoter activity in human adenoma-derived (AA/C1) cells, suggesting that the NF- κ B pathway is involved in MCT1 transcriptional regulation (Borthakur et al., 2008). AP2 overexpression in Caco-2 cells increases MCT1 promoter activity, and site-directed mutagenesis of the AP2 binding site results in decreased transcription in response to phorbol 12-myristate 13-acetate, supporting the role of phosphokinase C-dependent AP2 transcriptional regulation of MCT1 (Saksena et al., 2009). The peroxisome proliferator-activated receptor α (PPAR α) agonist WY 14,643 upregulates MCT1 mRNA expression

in the liver, kidney, and small intestine, and this upregulation is absent in PPAR α null mice (König et al., 2008). A putative PPAR α response element was identified in the mouse promoter (König et al., 2008), and expression was induced in the presence of clofibrate and natural PPAR α agonists (König et al., 2010). Skeletal muscle expression of MCT1 mRNA and protein expression are upregulated by exercise and 5-aminoimidazole-4-carboxamide-1- β -D-ribofuranoside (AICAR) treatment, which activate AMP-activated protein kinase (AMPK) in rats (Furugen et al., 2011; Kitaoka et al., 2011b, 2014; Takimoto et al., 2013). This stimulation is muscle-type specific, with MCT1 expression increases in white gastrocnemius, plantaris, and tricep muscle (Furugen et al., 2011; Kitaoka et al., 2011b, 2014; Takimoto et al., 2013). Additionally, upregulation of MCT1, MCT2, and MCT4 mRNA expression was observed in swine containing a gain-of-function mutation in the AMPK gene (England et al., 2017). MCT1 mRNA and protein expression are upregulated by c-Myc in P493-6 B-lymphoma cells through direct binding of c-Myc to the MCT1 promoter region (Doherty et al., 2014). Overexpression of the transcription factor metastasis-associated in colon cancer-1 increases MCT1 protein expression in gastric cancer cell lines, whereas its silencing decreases MCT1 expression (Wang et al., 2017). In human colon cancer NCM460 and HCT15 cells, MCT1 mRNA and protein expression increases with increasing expression of the transcription factor Nrf2 (Diehl et al., 2018). Treatment with small interfering RNA against Nrf2 in NCM460 cells decreases MCT1 expression, confirming the role of Nrf2 in MCT1 regulation in the colon (Diehl et al., 2018); however, whether Nrf2 binds to the MCT1 promoter region was not evaluated.

Studies assessing transcriptional regulation for MCT4 are limited. Nrf2 and c-Myc transcriptionally regulate MCT1, but not MCT4 (Doherty et al., 2014; Diehl et al., 2018). Hypoxia induces MCT4 mRNA expression, and site-directed mutagenesis of the MCT4 promoter demonstrates that hypoxia-inducible factor 1 α subunit (HIF-1 α) binding mediated the observed upregulation (Ullah et al., 2006). Furthermore, this upregulation was not observed in CHO cells lacking HIF-1 α (Ullah et al., 2006). Additionally, HIF-1 α upregulates MCT4 mRNA expression in mouse endothelial cells in response to nitric oxide treatment (Brix et al., 2012). HIF-1 α small interfering RNA treatment of human rhabdomyosarcoma cells decreases MCT4 mRNA and protein expression (Narumi et al., 2012). Functional analysis of the MCT4 promoter showed that hypoxia-response elements within the promoter were critical to the HIF-1 α -mediated activation of MCT4 transcription (Narumi et al., 2012). AMPK activation through AICAR treatment stimulates MCT4 mRNA, and protein expression is white gastrocnemius and planteris muscle, but not in other skeletal muscle types (Furugen et al., 2011; Kitaoka et al., 2011b). AMPK is stimulated during exercise with

TABLE 3
Substrates and inhibitors of monocarboxylate transporters

Km, Ki, and IC₅₀ values were obtained from the listed references and Morris and Felmlee (2008).

Isoform	Species	Expression System	Substrate	Km (mM)	Inhibitor	Ki or IC ₅₀ (μM)	References			
MCT1	Human	Caco-2 <i>Xenopus</i> oocytes	Hesperetin	NA			Shen et al., 2015			
			Lactate	3.5–6	Phloretin	28 ^a	Bröer et al., 1998; Lin et al., 1998; Juel and Halestrap, 1999; Cuff et al., 2002; Cundy et al., 2004; Nancolas et al., 2016; Curtis et al., 2017			
	Pyruvate	1.8–2.5	Quercetin	NA						
	α-Ketoisovalerate	1.3	CHC	425 ^a						
	α-Oxoisohexanoate	0.67	pCMBS	NA						
	α-Oxoisovalerate	1.25	XP13512	0.62 ^b						
	Butyrate	9	Lonidamine	36.8 ^a						
	XP13512	0.22								
	Rat	Jurkat membranes MDA-MB231 <i>Xenopus</i> oocytes	GHB	4.6	AZD3965	0.0016 ^a		Bröer et al., 1998, 1999; Wang et al., 2006a		
			Lactate	3.5	Phloretin	28 ^b				
GHB			4.6	Quercetin	14 ^b					
MCT2	Human	<i>Xenopus</i> oocytes	Pyruvate	0.025	Benzobromaron	22 ^b	Lin et al., 1998; Nancolas et al., 2016			
					CHC	425 ^b				
	Rat	<i>Xenopus</i> oocytes	Lactate	0.74	Lonidamine	36.4 ^a		Broer et al., 1999; Curtis et al., 2017		
			Pyruvate	NA	Phloretin	14 ^b				
					Quercetin	5 ^b				
					Benzobromaron	9 ^b				
					CHC	24 ^b				
					AZD3965	0.020 ^a				
				Recombinant MCT2-expressing yeast membranes						
MCT3	Human	ARPE-19 cells	Lactate	NA		Philp et al., 2003				
MCT4	Human	<i>Xenopus</i> oocytes	L-lactate	28	pCMBS	21 ^a	Manning Fox et al., 2000; Kobayashi et al., 2006; Nancolas et al., 2016			
			D-lactate	519	CHC	991 ^a				
	Pyruvate	153	Phloretin	41 ^a						
	D-β-hydroxybutyrate	130	NPPB	240 ^a						
	Acetoacetate	216	Fluvastatin	32 ^b						
	α-Ketobutyrate	57	Atorvastatin	32 ^b						
	α-Ketoisocaproate	95	Lovastatin	44 ^b						
	α-Ketoisovalerate	113	Simvastatin	79 ^b						
	Rat	<i>Xenopus</i> oocytes	L-lactate	34	Lonidamine	40.4 ^a		Dimmer et al., 2000		
			Pyruvate	36	CHC	350 ^b				
2-Oxoisohexanoate			13	pCMBS	NA					
Acetoacetate			31							
β-Hydroxybutyrate			65							
MCT5	Human	<i>Xenopus</i> oocytes	Unknown							
MCT6	Human	<i>Xenopus</i> oocytes	Bumetanide	0.084	Furosemide	46 ^b	Murakami et al., 2005; Kohyama et al., 2013			
			Nateglinide	0.046	Azosemide	21 ^b				
	Prostaglandin F _{2α}	NA	Piretanide	163 ^b						
	Probenecid	NA	Toraseamide	13 ^b						
			Thiazides	NA						
			Probenecid	NA						
			Glibenclamide	NA						
			Nateglinide	5.4 ^a						
			Quercetin	25 ^b	Jones et al., 2017					
			Luteolin	NA						
		Phloretin	23 ^a , 17 ^b							
		Morin	33 ^b							
MCT7	Human Zebrafish		Ketone bodies (β-hydroxybutyrate)	NA		Hugo et al., 2012				
MCT8	Human	COS1 and JEG3 cells	T ₃	NA			Friesema et al., 2006			
			T ₄	NA						
	Rat	<i>Xenopus</i> oocytes	T ₃	NA	N-bromoacetyl-T ₃	NA	Friesema et al., 2003			
			T ₄	NA	Bromosulfophthalein	NA				
MCT9			Carnitine	NA		Jones and Morris, 2016				
MCT10	Rat	<i>Xenopus</i> oocytes	L-Tryptophan	3.8			Kim et al., 2001			
			L-Tyrosine	2.6						
			L-Phenylalanine	7.0						
			L-DOPA	6.4						
MCT11	Human	<i>Xenopus</i> oocytes	Unknown			Jones and Morris, 2016				
MCT12	Human Rat	<i>Xenopus</i> oocytes	Creatinine	0.57			Abplanalp et al., 2013			
			Creatinine	NA						
MCT13			Unknown			Jones and Morris, 2016				
MCT14			Unknown			Jones and Morris, 2016				

CHC, α-cyano-4-hydroxycinnamate; GHB, gamma-hydroxybutyric acid; NA, not available; NPPB, 5-nitro-2-(3-phenylpropylamino)benzoic acid; pCMBS, p-chloromercuribenzenesulfonate.

^aKi.

^bIC₅₀.

mouse small intestine, and this upregulation was absent in PPAR α null mice (Hirai et al., 2007). Yet, it is unclear whether PPAR α interacts directly with the MCT13 promoter or through an indirect mechanism.

2. Epigenetic Regulation. DNA methylation is a critical epigenetic process, which involves the addition of a methyl group to cytosine adjacent to guanidine (CpG dinucleotides). Alterations in DNA methylation status within a gene can lead to differences in gene transcription and mRNA expression levels without changing the nucleotide sequence. Although hypermethylation is associated with gene silencing, hypomethylation is associated with activation of gene expression. A number of MCTs have been reported to have CpG islands (short DNA sequences with an increased frequency of CpG dinucleotides) within their gene sequence. The majority of studies evaluating DNA methylation as a mechanism of MCT regulation focus on aberrant methylation patterns in disease states; however, DNA methylation may also play a role in tissue differences in MCT expression, such as silencing gene expression in certain tissues.

Methylation of the MCT1 promoter region downregulates MCT1 mRNA expression in MDA-MD-231 cells (human breast cancer), with demethylation (via 5-aza-2'-deoxycytidine treatment) leading to increased mRNA expression (Asada et al., 2003). In contrast, methylation of MCT1 was not involved in gene silencing in the β cells of the pancreas (Pullen et al., 2011). Methylation was evaluated in schizophrenia and bipolar disorder, and MCT2 mRNA expression correlated to DNA methylation status of CpG pairs and differed between healthy and psychotic individuals (Chen et al., 2014). MCT3 mRNA and protein expression inversely correlated with methylation of a CpG island within exon 2 in smooth muscle cells and aorta (Zhu et al., 2005). Furthermore, CpG methylation increased with disease severity, with the highest methylation (80%) observed in aortas with severe atherosclerosis corresponding to decreased MCT3 expression (Zhu et al., 2005). Consistent with the MCT3 data, MCT4 expression (mRNA and protein) was inversely correlated with promoter DNA methylation in clear cell renal carcinoma, with increased MCT4 expression and hypomethylation correlating with decreased survival (Fisel et al., 2013, 2015). MCT6 mRNA expression was altered in response to global hypomethylation in endometrial stromal cells, suggesting that DNA methylation represents a regulatory mechanism for MCT6 expression (Hsiao et al., 2015); however, the methylation status of the MCT6 gene was not directly assessed. Interestingly, MCT11 (an orphan transporter whose function is unknown) demonstrated an inverse relationship between DNA methylation at three CpG sites and mRNA expression in clear-cell ovarian cancer (Cicek et al., 2013). Additional data are needed to identify how specific changes in DNA methylation patterns result in altered regulation of MCTs through transcriptional regulation mechanisms.

3. Post-Transcriptional Regulation. The lack of correlation between tissue mRNA and protein expression patterns of MCTs in a range of tissues strongly suggests the involvement of post-transcriptional regulation mechanisms. These regulation mechanisms likely involve control of protein translation, and may be related to specific sequences in the 5' and 3' untranslated regions (UTRs). Post-transcriptional regulation of MCT1 during the cell cycle may relate to eukaryotic translation initiation factor 4E and its phosphorylation state (Halestrap and Wilson, 2012); however, studies directly assessing the role of eukaryotic translation initiation factor 4E have not been published in the literature.

Evidence for the post-transcriptional regulation of MCTs via microRNA (miRNA) has been increasing in the past decade. miRNAs bind to mRNA in a sequence-specific manner, leading to degradation of the mRNA transcript. Li et al. (2009) demonstrated that miR-124 binds to the 3'UTR of MCT1, leading to a decrease in protein expression; however, they did not observe a direct correlation between miR-124 expression and MCT1 protein expression in medulloblastoma. Furthermore, they identified binding sites for additional miRNAs (miR-9*, -29b, -183, -320, and -377) in the 3'UTR that may explain the lack of correlation that was observed in medulloblastoma (Li et al., 2009). miR-124 binds to the 3'UTR of mouse and human MCT1 and downregulates endogenous MCT1 protein expression in a mouse hepatoma cell line (Pullen et al., 2011). In addition, miR-29a and -29b bind to the 3'UTR of mouse and human MCT1 and downregulate endogenous MCT1 protein expression; however, they decreased protein expression to a lesser extent than miR-124 (Pullen et al., 2011). miR-29a and -29b are expressed in mouse pancreatic islets, which have no miR-124 expression, and are likely responsible for MCT1 silencing in these cells (Pullen et al., 2011). miR-495 binds to the 3'UTR of human MCT1, downregulating both mRNA and protein expression of MCT1 in HeLa cells (Liang et al., 2015). Additionally, MCT1 mRNA expression negatively correlated with miR-146a-5p in healthy human colonic mucosa and patients with ulcerative colitis, with the lowest MCT1 expression observed in inflamed ulcerative colitis biopsy specimens (Erdmann et al., 2019); however, the study did not directly evaluate miR-146a-5p binding to MCT1 mRNA.

Although the majority of studies have evaluated miRNA-mediated regulation of MCT1, a few studies have identified miRNAs that regulate MCT4 and MCT8. Xu et al. (2017) demonstrated that miR-1 mimics and inhibitors altered the mRNA and protein expression of MCT4; however, the MCT4 3'UTR was not a direct target for miR-1, suggesting that this miRNA indirectly regulates MCT4 expression possibly through regulation of HIF-1 α (Xu et al., 2017). mRNA expression of MCT8 was decreased in medullary thyroid carcinoma with a concomitant increase in

miR-375 (Hudson et al., 2013); however, studies assessing whether miR-375 directly binds to the MCT8 3'UTR have not been conducted. Future studies need to focus on tissue-specific regulation of MCTs by miRNA, as this may be one of the underlying mechanisms contributing to tissue differences in MCT expression.

4. Membrane Trafficking Regulation. As previously stated, ancillary proteins are essential for trafficking MCT1–4 to the plasma membrane, and, in their absence, the transporters accumulate within the cell (Kirk et al., 2000; Wilson et al., 2005; Nakai et al., 2006). Two proteins act as chaperones facilitating membrane trafficking of MCT1–4: CD147 (basigin) and embigin (gp70) (Poole and Halestrap, 1997; Wilson et al., 2005). The association of MCTs and the ancillary proteins is necessary for transport activity, and interactions with the ancillary proteins may lead to inhibition of transporter function (Halestrap, 2013a).

MCT1, MCT3, and MCT4 preferentially bind and colocalize with CD147 in tissues (Philp et al., 2003; Halestrap, 2013b). Colocalization of MCT1/MCT4 with CD147 was confirmed by coimmunoprecipitation and fluorescence resonance energy transfer (FRET) analysis (Kirk et al., 2000; Wilson et al., 2002). A strong positive correlation between MCT1/4 and CD147 expression was seen in rat liver; however, this was not a 1:1 correlation as CD147 is involved in the membrane expression of other proteins (Cao et al., 2017). In CD147 knockout mice, MCT1, MCT3, and MCT4 expression was not present in the retinal pigment epithelia, resulting in blindness (Hori et al., 2000; Philp et al., 2003), further supporting the role of CD147 as a chaperone for MCT1, MCT3, and MCT4 membrane expression. In polarized cells in the kidney and retinal epithelia, the interaction between MCT1 and CD147 is involved in the targeting of both proteins to the apical membrane (Deora et al., 2005), whereas MCT3 and MCT4 contain basolateral sorting sequences within their C termini (Castorino et al., 2011a).

Additionally, CD147 regulates membrane trafficking of MCT11 and MCT12. In MCT11-transfected HEK293 cells, plasma membrane expression was regulated by CD147 expression, with knockdown of CD147 leading to significantly reduced plasma membrane MCT11 (Rusu et al., 2017). The direct interaction of MCT11 and CD147 was confirmed with coimmunoprecipitation (Rusu et al., 2017). CD147 colocalized with MCT12 in MCT12-transfected HEK293 cells, and their association was verified utilizing coimmunoprecipitation (Castorino et al., 2011b). Furthermore, a single-nucleotide polymorphism (SNP) in exon 6 (c.643C>T) led to decreased cell surface expression of MCT12, indicating that MCT12 requires CD147 for cell surface expression (Castorino et al., 2011b).

Embigin acts as a chaperone for MCT1 in the absence of CD147 (Wilson et al., 2005). In contrast, embigin has not been demonstrated to function as a chaperone for

MCT3 and MCT4 (Halestrap, 2013b). Embigin is required for MCT2 trafficking to the plasma membrane, and colocalization was confirmed through FRET analysis (Wilson et al., 2005; Ovens et al., 2010).

Neuroplastin functions as an ancillary protein for MCT2; knockdown of neuroplastin in *Xenopus* oocytes leads to decreased cell surface expression of MCT2 (Wilson et al., 2013). Additionally, neuroplastin and MCT2 are colocalized on the plasma membrane in rat cerebellum, suggesting that neuroplastin plays a role in cell surface expression of MCT2 (Wilson et al., 2013).

MCTs 5–10, 13, and 14 have not been demonstrated to require CD147 or embigin to facilitate trafficking to the plasma membrane, and no ancillary proteins have currently been identified that regulate their membrane trafficking.

5. Regulation of Transporter Activity. Although ancillary proteins are involved in MCT membrane trafficking, intra- and extracellular carbonic anhydrases influence MCT activity at the plasma membrane. This interaction was first identified by Becker et al. (2005), who demonstrated that MCT1 transport activity was enhanced by the intracellular interaction with carbonic anhydrase II (Becker et al., 2005). The increase in MCT1 and MCT4 activity was independent of their expression and was observed in the presence of both wild-type carbonic anhydrase II and a catalytically inactive mutant (CAIIV143Y) (Becker et al., 2005, 2010a; Becker and Deitmer, 2008). In contrast, MCT2 activity is not enhanced by intracellular carbonic anhydrase II (Klier et al., 2011; Noor et al., 2015); however, MCT2 activity was augmented by extracellular membrane-bound carbonic anhydrase IV (wild-type and a catalytically inactive mutant C165Y) (Klier et al., 2011). Subsequently, MCT1 and MCT4 transport activity was increased by extracellular catalytically active and inactive carbonic anhydrase IV (Klier et al., 2014). Additionally, carbonic anhydrase IX (active and inactive) augments the activity of MCT1 and MCT4 (Jamali et al., 2015; Mboge et al., 2019). It is hypothesized that the carbonic anhydrases function as a proton-collecting antenna, thereby enhancing the activity of proton-coupled MCTs (Fig. 4).

More recent studies have investigated the mechanisms underlying the augmentation of MCT transport activity by carbonic anhydrases. Carbonic anhydrase II directly binds to the C terminus of MCT1 and MCT4, facilitating the observed increase in transporter activity; however, it does not bind to MCT2 consistent with its inability to augment MCT2 activity (Noor et al., 2015). Interestingly, integration of six histidines into the C terminus of MCT4 enhanced activity, which could be further increased by coexpression with carbonic anhydrase IV, but not carbonic anhydrase II (Noor et al., 2017). Furthermore, the increase in MCT activity due to carbonic anhydrase IV expression requires carbonic anhydrase IV to bind to the ancillary proteins, CD147 and embigin

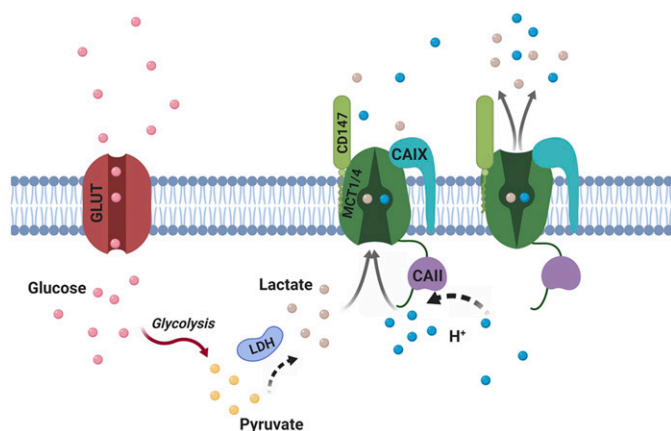


Fig. 4. The proton antenna effect of CAs in the regulation of MCT1/4. CAII/IX, carbonic anhydrase II/IX; GLUT, glucose transporter; H^+ , proton; LDH, lactate dehydrogenase. Adapted from Noor et al., 2018. Created with BioRender.com.

(Forero-Quintero et al., 2019). Augmentation of MCT4 transport activity by carbonic anhydrase IX requires the negatively charged carbonic anhydrase IX proteoglycan-like domain, which can function to transfer protons (Ames et al., 2018).

In addition to carbonic anhydrases, the catalytically inactive carbonic anhydrase-related proteins (CARPs) VIII, X, and XI have recently been demonstrated to enhance the transporter activity of MCT1 when coexpressed in *Xenopus* oocytes (Aspatwar et al., 2019). CARP VIII is an intracellular protein, whereas CARPs X and XI are secreted into the extracellular matrix, suggesting that these proteins function as intra- and extracellular proton antennas (Aspatwar et al., 2019).

B. Sex Differences

Sex differences and sex hormone-mediated regulation of MCTs are tissue-dependent, with studies focused on MCT1, MCT2, and MCT4. In rat hindlimb muscle, MCT1 and MCT4 protein expression increases in response to testosterone treatment in males; however, this induction is muscle-type specific (Enoki et al., 2006). Furthermore, MCT1 induction was not observed in heart muscle, suggesting that sex hormone-mediated regulation is tissue-specific. These results are consistent with sex differences in blood lactate level differences in humans, with males having higher plasma lactate concentrations in response to exercise (Cupeiro et al., 2012); however, a quantitative comparison of MCT1 and MCT4 expression in human muscle is lacking. In contrast to regulation in muscle, testosterone treatment decreases MCT4 mRNA and protein expression in Sertoli cells (involved in spermatogenesis) (Rato et al., 2012; Martins et al., 2013). Removal of endogenous testosterone via castration led to increased testicular MCT2 mRNA expression, which was reversed with the administration of exogenous testosterone (Boussouar et al., 2003).

MCTs are also regulated by female sex hormones in a tissue-specific manner. Hepatic MCT1 and MCT4 mRNA and protein expression varied over the estrus cycle in female rats, with females having lower expression than males (Cao et al., 2017). In ovariectomized females, hepatic MCT1 membrane expression was higher than males, whereas MCT4 expression was lower compared with males, suggesting isoform-specific regulation by female sex hormones (Cao et al., 2017). Few studies have evaluated MCT expression in response to treatment with female sex hormones. The 17β estradiol decreased MCT4 mRNA expression in Sertoli cells, consistent with testosterone-mediated regulation in the same cell line (Rato et al., 2012).

These studies support the involvement of both male and female sex hormones in the regulation of proton-dependent MCTs. Further studies are required to elucidate the role of individual sex hormones in the regulation of MCTs, as well as the underlying regulatory mechanisms.

C. Developmental Expression

MCT expression can be detected as early as oocyte maturation (Vannucci and Simpson, 2003), and MCT1 knockout leads to embryonic lethality, indicating its critical role in development (Lengacher et al., 2013). There is currently minimal information in the literature on developmental expression and regulation of proton-dependent MCTs, with most studies focused on MCT1. The available data suggest that maturation of MCTs occurs in an isoform, tissue-specific, and possibly species-dependent manner.

In humans, hepatic MCT1 membrane protein expression demonstrated a nonlinear maturation pattern with the highest expression seen in infants (Mooij et al., 2016). A subsequent study from the same group demonstrated that MCT1 membrane expression decreased after 15 weeks of age (van Groen et al., 2018); however, high variability in expression was observed in all age groups in this study, and a small sample number was used in the pediatric and adult groups. Renal MCT1 mRNA maturation in rats is consistent with these studies, with higher expression observed at earlier postnatal time points; in contrast, MCT2 mRNA expression was low at birth and increases to adult levels at sexual maturity. In the mouse brain, MCT1 and MCT2 expression peaks at postnatal day 15, with expression levels declining rapidly until postnatal day 30 when expression levels are consistent with adult expression (Pellerin et al., 1998); however, postnatal localization of MCT1 and 2 expression in the brain is not consistent with adult localization (Baud et al., 2003). MCT1 protein expression in the rat brain (cortex, hippocampus, cerebellum, and thalamus) is consistent between 7 and 35 days old, whereas MCT2 protein expression declined with age in the cortex, cerebellum, and thalamus and increased with age in the hippocampus (Vannucci and

Simpson, 2003). At the blood-brain barrier, MCT1 membrane expression was significantly lower in the adult cynomolgus monkey with the higher expression observed in neonates (Ito et al., 2011), which is consistent with MCT1 membrane expression in rat microvessels isolated before and after weaning (Vannucci and Simpson, 2003). In the horse, muscle MCT1 is lower at birth and increases until 2 years of age, but MCT4 expression remained the same during the 24-month study period (Kitaoka et al., 2011a). Development of muscle MCT1 and MCT4 expression is similar in rats, with lower protein expression at birth (Hatta et al., 2001). In contrast, MCT1 and MCT4 expression in the heart was highest at birth and declined over the first year of life (Hatta et al., 2001), supporting the tissue-specific regulation of MCT maturation. Renal MCT4 maturation in rats differs from what has been observed in horse muscle (Kitaoka et al., 2011a), with variable expression prior to weaning, with adult expression reached at 4 weeks old.

There is minimal information on the developmental expression of other MCTs. Expression of MCT8 was detected in the hypothalamus as early as 17 weeks gestation in humans, whereas MCT10 expression was detected at 25 weeks gestation (Friesema et al., 2012). Both MCT8 and MCT10 demonstrated nonlinear maturation patterns: strong expression was observed during early fetal development with expression levels declining at 35 weeks gestation, followed by increased expression after birth (Friesema et al., 2012).

VI. Monocarboxylate Transporters in Health and Disease

A. Monocarboxylate Transporters 1, 2, 4 (*SLC16A1*, *SLC16A7*, *SLC16A3*)

The main physiologic role of MCTs 1–4 is transport of monocarboxylates, including lactate, and this contributes to the maintenance of intracellular pH (Halestrap, 2013b). This implicates these transporters in cancer, as tumor cells are highly glycolytic. Cancer cells with high expression of MCTs are better able to maintain an appropriate pH for tumor growth, therefore contributing to proliferation (Halestrap and Wilson, 2012; Pinheiro et al., 2012). The overexpression of MCT1 and MCT4 has been documented in many cancer types, including breast, bone, colon, and renal cancers (Park et al., 2018). The expression of these transporters has also been linked with worsened prognosis in many cancers, including bladder cancer (MCT1) and prostate cancer (MCT4) (Park et al., 2018). MCT2 has also been implicated as a potential biomarker in prostate cancer, selectively labeling malignant glands and improving the accuracy of diagnosis along with α -methylacyl-CoA racemase (Pertega-Gomes et al., 2013). In addition to diagnostic purposes, the role of these transporters in cancer proliferation also has identified them as a potential target for treatment.

Recently, inhibition of MCT1 and MCT4 has been of interest for treatment of cancer due to their importance in regulating energy production in glycolytic and oxidative cancer cell metabolism, otherwise known as the Warburg Effect (shown in Fig. 5). The plasticity of cancer cells and their ability to couple these different metabolic pathways have provided support for targeting these transporters and is extensively described in the literature (Marchiq and Pouyssegur, 2016; Ždravlević et al., 2018). Inhibition of MCT transport has been shown to inhibit growth in cancer cell lines (Guan et al., 2019). The development of highly potent and partially specific MCT inhibitors, such as AZD3965, has resulted in the potential for greater MCT inhibition in cancer treatment. Previously available inhibitors, such as CHC, lack potency and specificity, making them less desirable as a therapeutic agent (Guan et al., 2019). AZD3965 is effective in reducing tumor growth and increasing intratumor lactate in small cell lung cancer cell lines (Polański et al., 2014). AZD3965 is currently in Phase I clinical trials for the treatment of diffuse large B cell lymphoma and Burkitt lymphoma (Noble et al., 2017).

MCT1 exhibits ubiquitous distribution and is involved in a variety of diseases. One disease, exercise-induced hyperinsulinemia, has been associated with mutations in MCT1. Exercise-induced hyperinsulinemia is a hypoglycemic disorder caused by mutations in the promoter region of MCT1, which results in the expression of MCT1 (Otonkoski et al., 2007). Although the activity of MCT1 is not affected in some tissues, the mutation leads to an expression of MCT1 in insulin-secreting β cells, which allows for lactate to be oxidized during exercise and signals insulin secretion leading to hypoglycemia (Halestrap and Wilson, 2012; Halestrap, 2013b).

Recently, a common variant of MCT1 that results in differential lactate transport, and therefore differential physical performance, was reported. The missense mutation (1470T > A) results in an amino acid substitution and less efficient lactate transport (Onali et al., 2018).

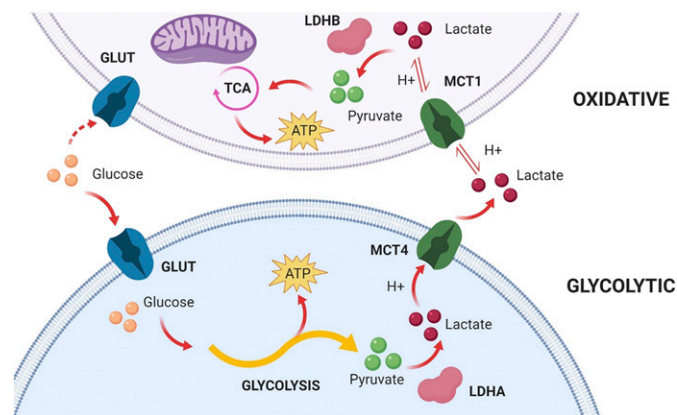


Fig. 5. A representation of the Warburg Effect by which glycolytic and oxidative cancer cells participate in lactate shuttling. GLUT, glucose transporter; H^+ , proton; LDHA/B, lactate dehydrogenase A/B; TCA, tricarboxylic acid cycle. Created with BioRender.com.

The T allele is more common in Sub-Saharan African groups (frequencies 86%–91%) as compared with the remaining world regions (69%–49%) (Onali et al., 2018). The TT genotype is associated with an increased predisposition to sprint/power performances (Onali et al., 2018). A genetic variant of MCT2 has also been associated with male infertility. Two single-nucleotide polymorphisms (rs10506398 and rs10506399) were associated with increased infertility in Korean men (Jones and Morris, 2016).

MCTs may play a significant role in many metabolic diseases. For instance, in obesity, there is evidence for an increased expression of MCT4 in muscle, which decreases after weight loss (Fisel et al., 2018). In addition, it has been shown that in heterozygous knockouts of MCT1 in mice, there was a resistance to diet-induced obesity (Fisel et al., 2018). Further understanding of these mechanisms could lead to a druggable target for obesity related to MCTs. MCT1 deficiency has also been associated with recurrent ketoacidosis in children (Fisel et al., 2018). The MCT1 deficiency results in a reduced uptake of ketone bodies, contributing to acid-base imbalance (Fisel et al., 2018). It is suspected that patients are heterozygous for the MCT1 mutation and that symptoms are brought on by unknown triggers (Fisel et al., 2018).

B. Monocarboxylate Transporter 3 (*SLC16A8*)

MCT3 also regulates lactate transport; it does this specifically in the basolateral membrane of the retinal pigment epithelium (RPE), where it is preferentially expressed (Gallagher-Colombo et al., 2010). The retina is highly metabolically active and produces large amounts of lactate, which are transported through the RPE via MCT1, 3, and 4 (Gallagher-Colombo et al., 2010). It has been demonstrated in chick RPE/choroid explant cultures and human fetal RPE monolayers that wounding of the retina causes alterations in the expression of MCTs in the RPE. After tissue damage, there is a decrease in expression of MCT3 and an increase in the expression of MCT4 (Gallagher-Colombo et al., 2010). The return of expression of MCT3 appeared to be dependent on cell–cell contact as well as the composition of the basement membrane (Gallagher-Colombo et al., 2010). This may indicate that cell–cell contact is crucial in maintaining the differentiation of the RPE.

C. Monocarboxylate Transporter 5 (*SLC16A4*)

Currently, there is no experimental evidence for the substrate specificity of MCT5. Regarding its expression, Gill et al. (2005) demonstrated that MCT5 (which was previously known as MCT4 due to changes in isoform nomenclature) is at the basolateral membrane of human colon, and increases in abundance from the small intestine to the colon. Lin et al. (2019) demonstrated that *MCT5* gene expression was significantly upregulated in colorectal adenocarcinoma, which suggests potential importance of MCT5 in gastrointestinal cancer. Additionally, the National Human Genome Research Institute–

European Bioinformatics Institute Catalog (Buniello et al., 2019) reports a SNP (rs17025736) that results in an intron variant of the human *MCT5* gene that is associated with adolescent idiopathic scoliosis (Liu et al., 2018). However, further validation is required prior to confirming the impact of this variant on MCT5 function and its relation to this disease. In a knockdown study performed in HeLa cells, the strongest enhancement of West Nile virus infection was demonstrated when *MCT5* was silenced, of all the genes silenced in the study (Krishnan et al., 2008; Fisel et al., 2018). Additional experimental data suggested that MCT5 may play a functional role as a viral replication resistance factor, which may provide a protective effect against the disease. Overall, the evidence regarding the potential importance of MCT5 in human health and disease remains limited to gene-related studies, and further investigation is necessary prior to confirming these associations in vivo.

D. Monocarboxylate Transporter 6 (*SLC16A5*)

Similar to MCT5, the studies evaluating MCT6 and its relation to human health and disease are limited. Regarding its substrate selectivity, MCT6 has been shown to transport a small set of xenobiotics: bumetanide, nateglinide, probenecid, and prostaglandin $F_{2\alpha}$; a series of aglycone flavonoids have been identified as inhibitors (Murakami et al., 2005; Kohyama et al., 2013; Jones et al., 2017). Confirming previous reports of MCT6 expression in the intestine (Gill et al., 2005), Kohyama et al. (2013) was able to demonstrate expression of MCT6 in the human small intestine and evaluate the apparent affinity of MCT6 for nateglinide. These findings suggested that MCT6 may play a role in the intestinal absorption of nateglinide; however, other transporters may also be involved. Besides only these two publications, there were no studies specifically studying MCT6 and its potential clinical role. Due to its ability to transport organic anion xenobiotics, others have also suggested that MCT6 may play a role in bumetanide's brain penetration (Römermann et al., 2017); however, further experimental evidence of MCT6 expression in the brain, as well as overall contribution to bumetanide distribution, has not been confirmed.

Regarding its potential utility as a biomarker for human disease, a DNA methylation study performed by Sugito et al. (2013) demonstrated that hypomethylation of *MCT6*, along with hypermethylation of a *ZFN206*, results in significantly prolonged event-free survival in neuroblastomas. Similarly in brain, more recent transcriptomic studies have suggested that MCT6 may play a role as a biomarker in Alzheimer's disease risk (Boada et al., 2014; Wei et al., 2019); however, due to the lack of evidence demonstrating the expression of MCT6 in brain tissue, these associations remain to be evaluated experimentally.

More recently, a clinically significant variant (rs4788863) was identified for human *SLC16A5* (Drögemöller et al.,

2017). This retrospective study reported that rs4788863 resulted in a significant decrease in cisplatin-induced ototoxicity severity in testicular cancer patients. In addition, cisplatin dose-dependently induced *SLC16A5* expression in HeLa cells; this may be indirectly related to the ototoxicity. Although this study was limited, it represented the first clinical evidence of MCT6 in relation to the pharmacological/toxicological effects of a drug. Although the mechanism underlying *SLC16A5*-related ototoxicity of cisplatin is largely unknown, there is evidence to suggest that MCT6 may play a role in prevention of chemotherapy-induced hearing loss.

E. Monocarboxylate Transporter 7 (*SLC16A6*)

Although MCT7 has been studied with respect to the transport of ketone bodies, such as β -hydroxybutyrate, MCT7 has also been suggested to play a role in liver disease primarily from evidence gathered in preclinical models. In a zebrafish model of hepatic steatosis that results in a loss-of-function mutation for *slc16a6a*, the gene encoding for the orthologous equivalent of human MCT7, the introduction of the human *MCT7* gene results in a phenotypic rescue from this metabolic disorder (Hugo et al., 2012). This suggests an important role of MCT7 in maintaining intracellular ketone body homeostasis, which protects the cell from excess synthesis of triglycerides. Subsequently, Karanth and Schlegel (2019) demonstrated that homozygous *slc16a6a* mutants resulted in increased growth, and variants present in human *MCT7* gene are strongly associated with human height. Although these variants still need to be validated experimentally, these in vitro experiments and associations provide initial evidence as to the potential functional role of MCT7 in humans. Not surprising due to its ability to transport ketone bodies, other in vivo evidence suggests that MCT7 is regulated by fasting and caloric restriction (Kim et al., 2016), which could impact its ability to maintain monocarboxylate homeostasis.

F. Monocarboxylate Transporter 8 (*SLC16A2*)

Besides MCTs 1–4, MCT8 is the most studied MCT isoform, due to its ability to influence thyroid hormone transport. A rare X-linked neurologic disorder, known as Allan-Herndon-Dudley syndrome (AHDS), is the consequence of various mutations in the *MCT8* gene. These mutations lead to increased serum thyroid hormone: triiodothyronine (T_3), due to the decrease in its cellular uptake (Friesema et al., 2003; Dumitrescu et al., 2004, 2006; Schwartz et al., 2005; Trajkovic et al., 2007; Wirth et al., 2009). Due to these pronounced changes, those suffering from this disorder experience symptoms of intellectual disability and impaired muscular activity due to both lack of intracellular T_3 and high plasma T_3 (Schwartz et al., 2005; Novara et al., 2017). Currently, there is a Phase II clinical trial, which has not yet begun recruitment, aimed at evaluating treatment of AHDS-afflicted patients with Triac, a thyroid

hormone analog that is not dependent on MCT8 for cellular uptake (NCT02396459).

G. Monocarboxylate Transporter 10 (*SLC16A10*)

MCT10, otherwise known as T-type amino acid transporter 1, is an aromatic amino acid transporter. Due to its relatively high amino acid identity to MCT8 (58%), it is not surprising that MCT10 also shares some overlapping substrate selectivity with MCT8 for thyroid hormones (Johannes et al., 2016). A SNP in the *MCT10* gene was associated with lower free plasma T_3 concentrations (van der Deure et al., 2007), which supports the role of MCT10 in the homeostasis of thyroid hormone levels. Besides contributing to the regulation of thyroid hormone concentrations, there is some preclinical evidence for the importance of MCT10 in maintaining circulating and liver aromatic amino acid concentrations in vivo (Mariotta et al., 2012). Although the contribution of MCT10 to aromatic amino acid homeostasis in humans has yet to be evaluated, this study provided preliminary evidence that it may play an important role. More recently, Lake et al. (2015) provided some of the first evidence for the functional role of MCT10 in aromatic amino acid transport and its potential relation to nonalcoholic steatohepatitis (NASH) due to the significant downregulation of gene expression. The authors concluded that this downregulation may be the potential cause for the increase in aromatic amino acid concentrations (specifically tyrosine and phenylalanine) in NASH liver samples. Whereas the specific mechanism of MCT10 in NASH and clinical utility of this finding have yet to be elucidated, it is apparent that this transporter is associated with NASH disease progression to some extent.

H. Monocarboxylate Transporter 11 (*SLC16A11*)

Recently, mutations in the gene encoding for MCT11 have been implicated in the risk of type II diabetes (T2D). A genome-wide association study conducted by the Slim Initiative in Genomic Medicine for the Americas T2D Consortium in a Mexican and other Latin American populations revealed a haplotype with four missense SNPs resulting in decreased functional activity of MCT11 (Williams et al., 2014; Rusu et al., 2017; Kimura et al., 2018). Another SNP (rs13342232) coding sequence mutation resulting in a synonymous variant (Leu > Leu) was found to be significantly associated with the occurrence of T2D in adults and children (Miranda-Lora et al., 2017). This variant also provided the first evidence of the role of MCT11 in determining the risk of early-onset T2D. The trafficking of MCT11 to the plasma membrane was shown to be mediated by basigin (CD147), an ancillary protein that plays a role in other MCT isoform membrane localization (Rusu et al., 2017). A study published by Rusu et al. (2017) described the disruption of this membrane trafficking in T2D as a consequence of *MCT11* variants. Subsequently,

additional research by Zhao et al. (2019) using a Mct11 knockout mouse model suggested that the mutant murine Mct11 protein gained abnormal function, resulting in altered lipid metabolism that contributes to the development of T2D. Although the specific mechanisms by which MCT11 plays a role in T2D risk and progression have yet to be clarified, the evidence for a clinical impact of this transporter in T2D warrants further experimental investigation.

I. Monocarboxylate Transporter 12 (*SLC16A12*)

In 2008, a nonsense mutation in the gene encoding for MCT12 was identified in a Swiss family with autosomal dominant juvenile cataracts, microcornea, as well as renal glucosuria (Kloeckener-Gruissem et al., 2008). In addition, this study demonstrated positive gene expression of *MCT12* in kidney tissue as well as multiple sites in the eye, including the retina, retinal pigmented epithelium, and lens in a human donor eye. The study was the first to conclude a potential importance in the pathogenesis of MCT12 in eye-related diseases. Following this study, a SNP was identified in the 5'UTR of *MCT12*, which provided evidence for its role in regulation of translational efficiency that could potentially be associated with age-related cataracts (Zuercher et al., 2010). Further investigation into the reported heterozygous nonsense mutation in the coding region of *MCT12* of exon 6 yielded evidence that suggested that the variant most likely impacts correct protein folding and trafficking with basigin, which was supported using a humanized rat model (Castorino et al., 2011b). In the same laboratory, Abplanalp et al. (2013) provided in vitro and in vivo evidence for the role of MCT12 in creatine transporter, which supported a plausible mechanism by which *MCT12* mutations lead to perturbations in the eye. After further research performed on MCT12 activity, substrate selectivity, and analysis of a separate mutation in the sodium/glucose cotransporter 2 gene (*SGLT2*; *SLC5A2*), it was determined that MCT12 most likely affects the renal handling of creatine transport and systemic concentrations of its precursor, guanidinoacetate (Dhayat et al., 2016). However, the mechanism by which the mutation in *MCT12* alters guanidinoacetate remains unclear. Additionally, the phenotype of renal glucosuria, present in the Swiss family, was attributed primarily to the mutation in *SGLT2*. Later studies investigating exogenous supplementation of basigin and its ability to partially rescue the decreased activity of *MCT12* mutations supported the importance of MCT12–basigin interactions in the development of age-related cataracts (Stäubli et al., 2017).

J. Monocarboxylate Transporter 13/14 (*SLC16A13/16A14*)

There is sparse information on MCT13 and MCT14 in the literature regarding their substrate selectivity and functional role in human health and disease. Evidence

demonstrates that T2D-associated variants span the adjacent *MCT11* and *MCT13* gene loci, and suggests that MCT13 may play a functional role in T2D risk; however, there is no experimental evidence to support this association (Rusu et al., 2017). Regarding MCT14, initial studies investigating the gene and protein expression of murine Mct14 revealed positive histologic staining of the protein in excitatory, inhibitory neurons, and epithelial cells (Roshanbin et al., 2016). Additionally, *MCT14* gene expression increased 2.1-fold following treatment with ethanol for 48 hours versus no treatment in immortalized lymphoblastoid cells originally isolated from subjects enrolled in the Collaborative Study on the Genetics of Alcoholism (McClintick et al., 2019). The relevance of MCT14 and alcohol consumption remains uncertain, but this study provides some transcriptional evidence for this association. A summary of the potential role of MCTs in health and disease is present in Table 4.

VII. Findings from the Use of Genetically-Modified Mct Rodent Models

To gain a better understanding of each MCT isoform in vivo, genetically modified rodent mouse models have been developed for experimental characterization.

A. Monocarboxylate Transporter 1

Because the Mct1 homozygous mouse model results in embryonic lethality, a haploinsufficient (Mct1^{+/-}) mouse model was developed to understand MCT1 in diet-induced obesity and cellular energy homeostasis (Lengacher et al., 2013; Chatel et al., 2017). Because of the ubiquitous expression and importance of Mct1 in transporting protons, short chain fatty acids, and energy utilization, it was understandable that this mouse model suggested that Mct1 played a role in resistance to weight gain from a high-fat diet, as well as pH homeostasis in skeletal muscle. Using the same model, it was also shown that downregulation of Mct1 resulted in impairment of long-term memory development (Tadi et al., 2015). This is supported by the dominant role of MCT1 in the brain and its responsibility in the neuron–astrocyte lactate shuttle (Vijay and Morris, 2014; Pérez-Escuredo et al., 2016).

B. Monocarboxylate Transporter 2

Currently, there has been no known Mct2 genetic knockout mouse model developed. However, humanized MCT2 transgenic mice were developed to evaluate its contribution to the effects of sleep apnea (Wang et al., 2011). Interestingly, decreases in human MCT2 expression and function in these mice were related, in part, to increased central nervous system vulnerability to the effects of sleep apnea.

C. Monocarboxylate Transporter 3

Due to its expression and localization in the retinal pigment epithelium (Yoon et al., 1997; Philp et al.,

TABLE 4
MCT variants and MCT up/downregulation in disease

	Health/Disease Relation	Reference
MCT1, 2, 4	High expression in many cancer types, including breast, bone, colon, bladder, prostate, and renal cancers	Park et al., 2018
MCT1	Mutations in promoter region lead to exercise-induced hyperinsulinemia The missense mutation (1470T > A) results in an amino acid substitution leading to less efficient lactate transport Deficiency has also been associated with recurrent ketoacidosis in children	Otonkoski et al., 2007 Onali et al., 2018 Fisel et al., 2018
MCT2	Acute exercise-induced upregulation in skeletal muscle SNPs (rs10506398 and rs10506399) were associated with increased infertility in Korean men	Bickham et al., 2006 Jones and Morris, 2016
MCT4	Implicated as a potential biomarker and treatment of prostate cancer Increased expression in obesity, followed by a decreased expression with weight loss	Pertega-Gomes et al., 2013 Fisel et al., 2018
MCT3 and 4	Upregulation via hypoxia through a HIF-1 α -dependent pathway Wounded RPE results in a decrease in expression of MCT3, and an increase in the expression of MCT4	Ullah et al., 2006 Gallagher-Colombo et al., 2010
MCT5	Gene expression was significantly upregulated in colorectal adenocarcinoma SNP (rs17025736) results in an intron variant of the human <i>MCT5</i> gene, which is associated with adolescent idiopathic scoliosis Enhancement of West Nile virus infection was demonstrated when <i>MCT5</i> was silenced	Liu et al., 2018 Buniello et al., 2019 Krishnan et al., 2008; Fisel et al., 2018
MCT6	Plays a role in the intestinal absorption of nateglinide, bumetanide's brain penetration Hypomethylation of <i>MCT6</i> , along with hypermethylation of a <i>ZFN206</i> , results in significantly prolonged event-free survival in neuroblastomas May play a role as a biomarker in Alzheimer's disease risk Significant variant (rs4788863) resulted in a significant decrease in cisplatin-induced ototoxicity severity in testicular cancer patients	Kohyama et al., 2013; Romermann et al., 2017 Sugito et al., 2013 Boada et al., 2014; Wei et al., 2019 Drögemöller et al., 2017
MCT7	Suggested to play a role in liver disease primarily from evidence gathered in preclinical models	Hugo et al., 2012; Kim et al., 2016; Karanth and Schlegel, 2019
MCT8	Various mutations results in AHDS, which results in increased serum thyroid hormone: T ₃ , due to the decrease in the cellular uptake	Friesema et al., 2003; Dumitrescu et al., 2004, 2006; Schwartz et al., 2005; Trajkovic et al., 2007; Wirth et al., 2009
MCT10	A SNP in the gene was found to result in lower free plasma T ₃ concentrations Importance in maintaining circulating and liver aromatic amino acid concentrations in vivo Functional role in aromatic amino acid transport and its relation to NASH due to the significant downregulation of gene expression	van der Deure et al., 2007 Mariotta et al., 2012 Lake et al., 2015
MCT11	Mutations in the gene encoding for <i>MCT11</i> have been implicated in the risk of T2D SNP (rs13342232) was found to be significantly associated with the occurrence of T2D in adults and children	Williams et al., 2014; Rusu et al., 2017; Kimura et al., 2018 Miranda-Lora et al., 2017
MCT12	Mutation in the gene encoding for <i>MCT12</i> was identified in a Swiss family with autosomal dominant juvenile cataracts, microcornea, as well as renal glucosuria A SNP was identified in the 5'UTR of <i>MCT12</i> , which provided evidence for its role in regulation of translational efficiency that could potentially be associated with age-related cataracts Mutation in <i>MCT12</i> 's coding region of exon 6 yielded evidence that suggested that the variant most likely impacts correct protein folding and trafficking with basigin In vitro and in vivo evidence for <i>MCT12</i> 's role in creatinine transporter, which supported a plausible mechanism by which <i>MCT12</i> mutations lead to perturbations in the eye Impacts the renal handling of creatinine transport and systemic concentrations of its precursor, guanidinoacetate	KloECKener-Gruissem et al., 2008 Zuercher et al., 2010 Castorino et al., 2011b Abplanalp et al., 2013 Dhayat et al., 2016
MCT13	May also play a functional role in T2D risk	Rusu et al., 2017
MCT14	Gene expression was shown to increase 2.1-fold following treatment with ethanol for 48 hours vs. no treatment in immortalized lymphoblastoid cells originally isolated from subjects enrolled in the Collaborative Study on the Genetics of Alcoholism	McClintick et al., 2019

2001; Gallagher-Colombo et al., 2010), researchers suggested that MCT3 may be involved in similar functions of MCTs 1–4, such as pH and monocarboxylate homeostasis in the eye. Mct3 knockout mice were generated to investigate this hypothesis, and it was found that Mct3^{-/-} mice demonstrated significant differences in lactate concentration and pH in the

retina (Daniele et al., 2008). Because of these findings, the authors concluded that inhibition of Mct3 can have an overall impact on pH-sensitive regulation of vision.

D. Monocarboxylate Transporter 4

MCT4 has been shown to be upregulated in a wide variety of cancers (Pinheiro et al., 2010; Gotanda et al.,

2013; Yan et al., 2014; Baenke et al., 2015), and, because of this, researchers have become increasingly interested in understanding its role in these diseases. In particular, high MCT4 expression in head and neck squamous cell carcinoma has been associated with poor prognosis. Because of this finding, researchers investigated whether MCT4 played a major role in oral cancer. *Mct4*^{-/-} mice demonstrated that *Mct4* was a potential driver of oral squamous cell cancer disease progression (Bisetto et al., 2018). In addition, unlike *Mct1*^{-/-} mice resulting in lethality, *Mct4*^{-/-} mice were almost indistinguishable from wild-type control mice.

E. Monocarboxylate Transporter 8

MCT8 is an important thyroid hormone transporter in the brain, as well as the major contributor to the X-linked mutation causing AHDS (Schwartz et al., 2005). To study MCT8 and its importance in thyroid hormone homeostasis, numerous studies have been performed using a *Mct8*^{-/-} mouse model (Dumitrescu et al., 2006; Di Cosmo et al., 2010; Mayerl et al., 2014; Stohn et al., 2016). These studies indicated that *Mct8* significantly contributed to the intracellular thyroid hormone concentrations. In addition, the role of *Mct8* in thyroid hormone secretion from the thyroid gland was also demonstrated in this mouse model, suggesting its potential impact on thyroid hormone regulation in MCT8-deficient patients. As well as the thyroid gland and the brain, *Mct8* was found to be a significant contributor to bone maintenance, suggesting that this transporter has multitissue roles in thyroid hormone homeostasis. Of all the MCT isoforms currently being studied outside of MCTs 1–4, it is apparent that MCT8 is a significant determinant of thyroid hormone homeostasis.

F. Monocarboxylate Transporter 10

Similarly, due to its ability to transport thyroid hormone and similarity in phylogeny to MCT8, *Mct10*^{-/-} mice were generated to understand its contribution in the thyroid hormone homeostasis pathway (Müller et al., 2014). Interestingly, the role of *Mct8* and *Mct10* was shown to be shared when perturbations were seen in the serum thyroid hormone profile of *Mct10*^{-/-} mice. In addition, when the double-knockout mice were generated (*Mct8*^{-/-}/*Mct10*^{-/-}), these mice exhibited loss of cochlear hair cells, resulting in deafness, suggesting an importance of thyroid hormone transport in ear development (Sharlin et al., 2018).

G. Monocarboxylate Transporter 12

Considering MCT12 mutations have been associated with cataracts (Abplanalp et al., 2013; Stäubli et al., 2017), researchers developed a transgenic *Slc16a12* rat model to verify the contribution of MCT12 and a mutant allele to cataract formation (Castorino et al., 2011b). Further research, however, is needed to confirm the mechanism by which MCT12 contributes to this pathway.

H. Other Monocarboxylate Transporter Isoforms

No other genetically modified animal models have been developed for the study of other *Mct* isoforms.

VIII. Conclusions and Future Studies

The SLC16 family of transporters represents a significant group of 14 membrane proteins important for the disposition of both xenobiotics and endogenous compounds. Given their extensive tissue distribution and broad range of substrates, MCTs have the potential to influence the pharmacokinetics of many endogenous compounds and pharmaceutical compounds. Of particular note, protein expression of MCTs is present in critical tissues for elimination and absorption, including the liver, kidney, intestines, and the blood brain barrier. The importance of members of the SLC16 family, including MCT1–4 and MCT8, is now well recognized. Of note, MCTs 1 and 4 are overexpressed in cancers, and inhibition of transport represents a current area of investigation as a chemotherapeutic strategy in cancers. A mutation in the MCT8 (SLC16A2) gene (located on the X chromosome) causes an X-linked psychomotor intellectual disability, due to limited thyroid hormone uptake at the blood brain barrier, leading to lack of normal brain development.

Research in elucidating the role of other MCT isoforms will add significantly to the current knowledge of this 14-member transporter family. Several MCT isoforms remain classified as orphan transporters, meaning that they have no known endogenous substrates or physiologic role. These transporters were outlined in a publication by Halestrap (2013b) in which MCTs 5–7, 9, and 11–14 were defined as being orphan transporters. Since then, the functions of some of these orphan transporters have been partially characterized. In 2017, mutations in *SLC16A12* (MCT12) were identified in patients with age-related cataracts (Stäubli et al., 2017). These mutations, resulting in abnormal creatine transport, suggested that MCT12 plays a major role in the prevention of cataract formation. Additionally, a haplotype consisting of five variants for human *SLC16A11* (MCT11) resulted in decreased MCT11 gene expression and cell surface localization (Rusu et al., 2017). This haplotype resulted in changes in fatty acid and lipid metabolism and was significantly associated with the increased T2D risk in a Mexican population. The authors concluded that this association with T2D risk suggested that MCT11 induction could be therapeutically beneficial. In the same year, a synonymous mutation in the coding region of *SLC16A5* (MCT6) (rs4788863, p.Leu41Leu), which was predicted to decrease the rate of codon usage (potentially decreasing protein translation), resulted in a protective effect from cisplatin-induced ototoxicity in patients with testicular cancer (Drögemöller et al., 2017). However, the mechanism behind this protective effect has yet to be

evaluated. Although there has been an increase in research on MCTs within the last few years, further research elucidating the functions of the 14 MCTs is needed to understand the role of these transporters in both drug disposition and endogenous compound homeostasis, as well as their roles as potential targets in disease.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Jones, Felmlee, Rodriguez-Cruz, Follman, Morris.

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