Published in final edited form as:

Clin Pharmacol Ther. 2016 November ; 100(5): 454–463. doi:10.1002/cpt.418.

Monocarboxylate Transporters: Therapeutic Targets and Prognostic Factors in Disease

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Abstract

Solute carrier (SLC) transporters represent 52 families of membrane transport proteins that function in endogenous compound homeostasis and xenobiotic disposition, and have been exploited in drug delivery and therapeutic targeting strategies. In particular, the *SLC16* family that encodes for the 14 isoforms of the monocarboxylate transporter (MCT) family plays a significant role in the absorption, tissue distribution, and clearance of both endogenous and exogenous compounds. MCTs are required for the transport of essential cell nutrients and for cellular metabolic and pH regulation. Recent publications have indicated their novel roles in disease, and thus their potential as biomarkers and new therapeutic targets in disease are under investigation. More research into MCT isoform function, specificity, expression, and regulation will allow researchers to exploit the potential utility of MCTs in the clinic as therapeutic targets and prognostic factors of disease.

Monocarboxylate transporters (MCTs) are members of the solute carrier (SLC) family (*SLC16*) of proteins and are comprised of 14 isoforms. Previously identified, based on cDNA isolation and homology sequencing, MCTs are present in a wide variety of tissues and are involved in the regulation of fundamental cellular processes, such as glycolysis, fatty acid homeostasis, as well as other key metabolic pathways.^{1,2} Recent research on MCTs has focused on their role in the pathophysiology of disease and as therapeutic targets.

Of the 14 isoforms identified, proton-dependent MCTs 1–4 have been extensively studied due to their importance in transporting L-lactate, pyruvate, and short-chain fatty acids in a wide variety of tissues. Most importantly, many of these MCT isoforms are upregulated in tumor tissues, making them attractive targets and biomarkers for a wide variety of cancers.³ Through the targeted disruption of pH homeostasis and balance of mono-carboxylate compounds, such as lactate, which are essential for oxidative and glycolytic metabolism, MCTs 1–4 are gaining more interest in the field of clinical pharmacology. In addition, MCTs 5–14, many of which have yet to be “de-orphanized” due to their unknown endogenous function and substrate specificity, are of interest due to their differential tissue localization and potential to be manipulated in drug delivery or targeting strategies. Of note, more recently developed high throughput metabolomics analyses and genetically modified

preclinical models have been utilized and allowing researchers to decipher the physiological function of a number of orphan MCTs.^{4–6}

This state of the art topical review will focus on MCTs, highlighting recent publications that have provided insight into their potential roles in clinical pharmacology and therapeutics. Although members of the *SLC5* family of transporters encoding for the sodium-dependent monocarboxylate transporters have also demonstrated a fundamental role in maintaining monocarboxylate homeostasis, for the purpose of this review, the focus will be solely on the *SLC16* family of transporters.

Structure, function, substrate specificity, and regulation

As members of the major facilitator superfamily, the *SLC16* family of MCTs contains shared, conserved structural attributes, and sequence motifs. According to hydropathy plots, all MCT isoforms are predicted to have 12 transmembrane (TM) α -helices with a large intracellular loop between TMs 6 and 7, as well as intracellular C- and N-termini.^{7,8} Specifically, regarding their protein sequences, MCTs share the greatest conservation within the TM regions with more variability in the cytosolic C- and N-termini, as well as the loop between TMs 6 and 7. In addition, two highly conserved motifs include sequences preceding TM1 and TM5, which have been suggested to play a role in the molecular dynamics and conformational changes of MCTs.⁹ Several predicted 3D structures of the MCTs have been proposed from homology-based modeling approaches using the previously characterized *Escherichia coli* glycerol-3-phosphate transporter crystal structure (1PW4).^{10,11} Studies using MCT-transfected *Xenopus laevis* oocytes have been used to characterize the substrate specificity and functionality of specific MCT isoforms in the absence of other MCTs or other anionic transporters with overlapping substrate specificity.

Table 1^{3–5,12–51} summarizes the substrate specificity, tissue localization, and the potential clinical relevance for the MCT isoforms. It is important to note that the discrepancy between MCT isoform number and SLC16A nomenclature evolved from the order in which each cDNA sequence was determined and characterized.² It is apparent that there is a similarity in substrate specificity for lactate for MCTs 1–4 and a high degree of variability among tissue expression levels of all MCT isoforms. In addition, many of the MCT isoforms have demonstrated not just the uptake, but also efflux of their endogenous substrates in order to maintain homeostasis and ion balance. In general, the substrate specificity of MCTs 1–4 has demonstrated affinity for common, endogenous short chain monocarboxylates, including, but not limited to, lactate, pyruvate, butyrate, γ -hydroxybutyrate, and ketone bodies (such as acetoacetate and β -hydroxybutyrate).² Importantly, the specificity for lactate remains restricted to the endogenous stereoisomer L-lactate, in contrast to D-lactate, which is perhaps the single most important substrate in the entire MCT family. L-lactate is not only important for oxidative/glycolytic metabolism and pH regulation, but also acts as a signaling agent to promote angiogenesis and immunosuppression.⁵² Other MCT isoforms, such as MCT6, have demonstrated affinity for a small group of xenobiotics, such as bumetanide, nateglinide, and probenecid,⁵³ whereas MCT7 has been characterized as a transporter of ketone bodies.⁵⁴ MCT8 and MCT10 have been reported to transport thyroid hormones,⁷ and

more recently MCT9 has been characterized as a carnitine efflux transporter⁵⁵ and MCT12 as a creatine transporter.⁶

Studies examining MCT1 molecular dynamics suggest a significant role of a lysine residue (K38) at the extracellular region of the protein in the transport function of MCT1.⁵⁶ The proton-coupled symport activity exhibited by MCT1 is facilitated by sequential proton and lactate binding through electrostatic interactions, altering the conformation of the protein from a “closed” to an “open” state.¹⁰ Amino acid identity to MCT1 is low (~20–40%) for MCTs 5–14, and detailed mechanistic information regarding transporter functionality of other MCT isoforms has yet to be elucidated.

Regulation and trafficking of MCTs 1–4 have been associated with several ancillary proteins, as well as a variety of transcriptional and recently characterized post-transcriptional modulators; information is lacking for the other MCT isoforms. In numerous studies examining MCT trafficking and localization, two proteins, basigin (CD147) and embigin (gp70), have been identified as chaperone proteins important in the trafficking of MCTs 1–4 to the plasma membrane.^{57,58} Depending on the tissue and the MCT isoform, the interactions between these accessory proteins and MCTs have been experimentally confirmed and evaluated through *in vitro* approaches, such as immunoprecipitation and fluorescence resonance energy transfer, as well as *in silico* approaches using homology-based models. More commonly, basigin seems to be the most important protein for trafficking MCTs 1–4, with the exception of MCT2 in which embigin plays the major role in proper trafficking to the membrane.⁵⁷ Although MCTs 5–14 seem to demonstrate independence from these two proteins (or the significance of this interaction has yet to be studied), it is evident that MCTs 1–4 are largely dependent on coexpression of these ancillary proteins for proper localization to the plasma membrane. Besides trafficking to the membrane, the activity of MCTs has also been shown to be modulated by carbonic anhydrases II and IX.^{59,60} The catalytic reaction performed by carbonic anhydrases, involved in the interconversion of carbon dioxide and water to bicarbonate and protons, was hypothesized to provide proton-coupled MCT isoforms 1–4 with enhanced functional activity through a “proton-collecting antenna” and not based on catalytic activity. However, further studies are needed prior to understanding this mechanism in more detail. More recently, the noncovalent interaction between cytosolic carbonic anhydrase II and an intracellular anionic amino acid moiety present in MCTs was investigated, which suggested the importance of the MCT C-terminus in regulatory protein-protein interactions.⁶¹ However, these interactions and their binding kinetics also need to be further evaluated in order to confirm this paradigm.

Regarding the transcriptional regulatory mechanisms of MCT1, nuclear factor of activated T-cells has been implicated in the regulatory binding in the *MCT1* gene promoter region in skeletal muscle.⁵² The upregulation of MCT1 has been evaluated with increased exercise-induced Ca^{2+} -dependent protein phosphatase calcineurin activity, which is responsible for the dephosphorylation and downstream activation of nuclear factor of activated T-cells. This downstream activation is important considering that several consensus sequences for nuclear factor of activated T-cell binding have been identified in the promoter region of *MCT1*, which have been associated with activation of T-lymphocytes and increasing rates of

glycolysis along with the upregulation of *MCT1* gene expression.² In addition, rising levels of AMP in response to exercise have also been associated with stimulation of AMP-activated protein kinase, which may potentially lead to increased gene expression of *MCT1*.¹ Hypoxia-induced transcriptional regulatory mechanisms have also been associated with changes in the gene expression of *MCT4* in a wide variety of tissues in the body. In contrast to *MCT1* and *MCT2*, the *MCT4* promoter region contains two response elements that are responsible for the binding of hypoxia-inducible factor-1 α , leading to the increase in *MCT4* gene expression in response to hypoxic conditions.⁶² Unfortunately, there is very limited information regarding the transcriptional regulation of other members of the MCT family and more research is required in order to elucidate the importance of these regulatory mechanisms. More recently, with the improved abilities to study post-transcriptional modifications and other modes of epigenetic regulation, *MCT1*, *MCT3*, and *MCT4* genes have been shown to be regulated in response to DNA methylation in certain disease states, including breast cancer, atherosclerosis, and renal cancer.^{31,34,63} The miR-29a and miR-29b can contribute to the β -cell silencing of *Mct1* gene in mouse islets, thus demonstrating that miRNA-mediated repression may be primarily involved in regulating the ubiquitous gene expression of *Mct1* in tissues that lack expression, such as the pancreas.⁶⁴ In addition, selective demethylation at the *MCT2* promoter occurs in patients with prostate cancer, such that *MCT2* gene expression may be utilized as a potential biomarker of prostate cancer.²⁵ As more information becomes available regarding the regulation of MCTs 1–4, as well as the other isoforms, a better understanding of their potential significance in the prognosis and treatment of disease may be attained.

Proton-coupled MCTs (MCT1–4) and roles in disease

MCT1 has been utilized in drug delivery due to its high protein expression in the intestine: the drug product Horizant (gabapentin enacarbil) targets MCT1 to increase the bioavailability of gabapentin. In addition, MCT1 has been recognized as a useful tool for improving the availability of poorly permeable compounds to the central nervous system due to its protein expression at the blood brain barrier. MCT1-mediated drug delivery has been of particular interest most likely due to the cellular localization of MCT1 protein in the brain and its high protein expression compared with the other MCTs. MCT1 protein has been identified in brain endothelial cells, astrocytes, oligodendrocytes, microglial cells, and there is potential evidence for its neuronal expression in specific areas of the brain.⁵² 4-phenylbutyrate (marketed in the United States as Buphenyl) has been used in the treatment of various conditions, including hyperammonemia, and more recently investigated for its neuroprotective effects. One recent study has demonstrated the likely importance of MCT1 in the facilitation of 4-phenylbutyrate across the blood brain barrier.⁶⁵ For the purpose of this review of MCTs in clinical pharmacology and therapeutics, the primary focus will be on the more recently established roles of MCTs 1, 2, and 4 as targets in a wide variety of cancers. A review written by Pinheiro *et al.*³ in 2012 outlines the role of these transporters in a wide variety of human cancers based on protein expression and their ability to regulate cancer metabolism. Cancer cells have an intrinsic ability to undergo aerobic metabolic processes by which an abundance of lactic acid is produced as a byproduct of glucose metabolism, otherwise known as the “Warburg” effect.⁶⁶ As summarized in Figure 1,⁵²

lactate plays a major role in the symbiotic functioning between glycolytic and oxidative cancer cells. Seeing as lactate is a fundamental metabolic product and signaling agent, controlling its mechanism of transport through the administration of potent MCT inhibitors has been of considerable interest. Also, it has been reported that genes representing major roles in glycolysis are overexpressed in a set of 24 cancers, which encompasses >70% of all human cancer cases in the world.⁶⁷ Several reports have also characterized the protein expression of MCTs 1, 2, and 4 in several types of common cancers.^{3,52,68} In particular, tumor cells are often markedly different than normal cells when comparing their highly glycolytic profile and abnormal hypoxic environments. The majority of the evidence of MCTs 1–4 in treatment of cancer relies heavily on preclinical data suggesting safety and efficacy, as well as from *in vitro* experiments in a wide variety of cancer cell lines. The primary points addressed in this section relate to the interplay of gene expression of MCTs 1–4, their regulation, and association to cancer cell metabolism and other diseased states, which make them attractive targets for the development of novel therapeutics.

MCT1

Out of all the proton-dependent MCT isoforms investigated for their association in disease and therapeutic potential, none are more common than MCT1, which has been investigated for its role in cancer. Most notably, AstraZeneca developed a series of potent MCT1 inhibitors in the search for small molecules for immunosuppression that do not exhibit the same extent of adverse effects as current drugs^{12,13}; one of these inhibitors is currently being evaluated for cancer treatment. A Cancer Research UK Phase I clinical trial of AZD3965 is recruiting patients to examine the safety and evaluate dose tolerance in solid tumors and diffuse large B-cell lymphoma (NCT01791595). The rationale to proceed with this clinical trial arose primarily from AZD3965's efficacy in seven small cell lung cancer cell lines and its ability to reduce tumor growth in an small cell lung cancer tumor xenograft model.^{14,15} The experimental K_i value for this compound was demonstrated to be 1.6 nM for MCT1, exhibiting much less potency for MCT2. One of the primary problems that has been noted from these studies is the ability of MCT4 protein to be upregulated as a compensatory mechanism following MCT1 inhibition. In this regard, other mechanisms of inhibition and different classes of compounds are being evaluated for their clinical utility. Another class of compounds, the carboxycoumarins, has also recently been evaluated for their potential to disrupt the synergistic effect of glycolytic and oxidative metabolism in cancer cells.¹⁶ More specifically, the compound 7ACC2 demonstrated superior inhibition of lactate influx in cancer cells with an IC_{50} of 11 nM. Further investigation of these MCT1 inhibitors in preclinical models and phase I clinical studies is needed. Besides these newly developed compounds, the antitumor agent and mitochondrial hexokinase inhibitor, lonidamine, was found to be a potent inhibitor of the MCTs and mitochondrial pyruvate carrier at the plasma membrane, consistent with the effects of lonidamine on cancer cell pH, and lactate/ATP concentrations.¹⁷ In addition, the cancer chemotherapeutic agent 3-bromopyruvate is dependent on MCT1 for uptake and chemotherapeutic sensitivity.¹⁸

Perturbations in *MCT1* gene expression levels have also been associated with a range of debilitating diseases. Exercise-induced hypoglycemia, caused by the failed silencing of the *MCT1* gene in pancreatic β -cells, was found to be an inherited genetic disease mapped to

chromosome 1.^{19,20} In normal pancreatic β -cells, most gene expression of *MCT1* and other MCT isoforms is negligible⁹; however, in this genetic disorder, *MCT1* gene expression is activated in response to mutations within the binding sites of several transcription factors in the promoter region. This inappropriate *MCT1* expression results in a signaling cascade promoting ATP synthesis and secretion of insulin leading to hypoglycemia. Additionally, several missense mutations in the *MCT1* gene can result in lactate transport deficiency.²¹ However, further studies evaluating the clinical relevance are needed in order to confirm the importance of these genetic mutations. One of the most commonly studied polymorphic variants of *MCT1* is the *MCT1*-T1470A polymorphism (rs1049434), which has been previously suggested to influence changes in blood lactate concentrations during weight training and muscle injury in football players.^{22,23} This single nucleotide polymorphism results in the conversion of aspartic acid to glutamic acid at the 490 position, and patients carrying the T-allele exhibited a reduction of 35–40% in erythrocyte lactate transport rate.²¹ Although this reduction is large, more extensive studies are required to determine the clinical utility of this variant. The role of MCT1 in diet-induced obesity was also investigated recently in a preclinical haploinsufficient mouse model, which resulted in findings suggesting a role of MCT1 in dietary regulatory processes.²⁴ Further studies into the clinical significance of MCT1 in diet and obesity are needed.

MCT2

In addition to MCT1, MCT2 has been investigated regarding its clinical relevance and potential as a drug target and biomarker in cancer, as well as other diseases. MCT2 generally has a higher affinity than MCT1 for monocarboxylates, such as lactate and pyruvate, which make it an ideal candidate in targeting cancer cell metabolism. Interestingly, findings from studies evaluating MCT2 protein expression in various cancer cells indicate that it is expressed primarily in the cytosol, suggesting its potential localization within intracellular organelles, such as mitochondria.³ More recently, MCT2 protein expression was demonstrated to be localized to the peroxisomes of human prostate cancer cells, and associated with malignant transformation processes.²⁶ Of the cancerous tumors investigated for MCT2 protein expression, MCT2 was found to be expressed in colon, brain, breast, lung, and prostate cancers.

MCT2 protein expression has been recently evaluated as a potential candidate as a biomarker for prostate cancer.^{25,27} In one study, MCT2 was demonstrated to be comparable to α -methylacyl-CoA racemase, a previously established biomarker for prostate cancer.²⁷ According to the American Cancer Society, prostate cancer is one of the most common cancers in men, making the investigation into new biomarkers an even more significant area of research. In neurodegenerative diseases, MCT2 protein expression was markedly downregulated with decreased lactate content in the cerebral cortex and hippocampus of an $A\beta_{25-35}$ -treated rat model of Alzheimer's disease.²⁸ However, in the MPTP mouse model of Parkinson's disease, MCT2 protein expression levels were found to be unaltered and the metabolic impairments associated with Parkinson disease were not related to abnormalities of MCT2 protein expression.²⁹ Considering MCT2 protein expression remains relatively high in neurons in comparison to other cell types in the brain, further investigation into MCT2's role in neurodegeneration could prove fruitful as a future drug targeting modality.⁵²

Although the clinical relevance of MCT2 in neurodegenerative diseases needs to be further investigated, it is apparent that there may also be variability in different preclinical models of neurodegenerative diseases that adds uncertainty in determining the association of MCT2 with neurodegeneration.

Additionally, investigation into genetic variants of *MCT2* has also suggested the potential functional and clinical relevance of MCT2 in male spermatology and infertility.³⁰ In this study, two single nucleotide polymorphisms (rs10506398 and rs10506399) were associated with male infertility in Korean men, resulting in a 2.4-fold decrease in sperm count with men exhibiting the homozygous rs10506399 variant. The findings of this study suggest that *MCT2* single nucleotide polymorphisms may help us to understand its regulatory role in reproductive diseases, as well as aid in genetic risk assessments.

MCT3

MCT3 is distinct from other MCT isoforms because it is expressed predominantly in retinal pigmented epithelial cells and the choroid plexus epithelium.^{69–71} Although MCT3 remains less studied than MCTs 1, 2, and 4, preliminary evidence suggests that MCT3 may play a role in maintaining pH balance, ion homeostasis, and modulating wound healing in the retinal pigment epithelium.^{32,33} In 2008, Daniele *et al.*³³ generated *Mct3*^{−/−} knockout mice in order to examine the physiological role of MCT3 in the retina. The authors concluded that the disruption of pH homeostasis and lactate transport in this animal model resulted in increased lactate levels in the retina, suggesting an influence on the light responses of photoreceptors. Following this study, researchers evaluated the protein expression of MCT3 in chick and human fetal retinal pigmented epithelium (RPE) cell cultures in response to wounding and cell differentiation.³² It was noted that the mechanical disruption of the RPE resulted in decreased protein expression of MCT3 and positive MCT4 protein expression at the leading edge of the wound, followed by the re-expression of MCT3 protein in RPE cells dependent on the re-establishment of cell-cell contacts and the composition of the basement membrane.³² The changes in levels of expression of MCT3 protein suggest its utility as a biomarker for differentiated RPE cells. It is important to note that, with regards to the clinical relevance of this study, the authors concluded that by better understanding the changes in MCT expression within different RPE cell populations, we may be able to better understand retinal pathophysiology in cases, such as vitreoretinopathy, in which cell therapies could be utilized to treat damaged RPEs.

MCT4

With respect to MCT4 gene and protein expression in different cell types, MCT4 tends to have a much more abundant expression profile than MCT1 in cells where rates of glycolysis are high, such as lymphocytes, astrocytes, white muscle fibers, and tumor cells.² The high affinity of MCT4 for pyruvate supports the theory that MCT4 promotes the uptake and subsequent metabolism of pyruvate to L-lactate. In addition, the protein expression of MCT4 in multiple cancer types shed light on its potential as a useful prognostic factor and potential cancer treatment strategy.³ Considerable data regarding MCT4 and its association with cancer have been generated in numerous experiments over the past decade, using a wide

variety of *in vitro* and preclinical *in vivo* xenograft models. One of the major findings has been the association between breast cancer and MCT4 protein expression. In one experiment, it was shown that upregulation of MCT4 protein expression occurs in cancer-associated fibroblasts co-cultured with the MCF7 breast cancer cell line, in which oxidative stress activates hypoxia-inducible factor-1 α inducing *MCT4* gene transcription.^{35,62} In addition, the differential protein expression of MCT1 was also found to be upregulated; however, it was mainly localized to epithelial cancer cells, whereas MCT4 remained in stromal cells. This makes MCT4 a potential candidate target in blocking cancer metabolite homeostasis between glycolytic cancer fibroblasts and metabolic coupling to adjacent cancer cells using lactate as a fuel for energy production. This phenomenon, known as the “reverse Warburg effect,” has been evaluated more recently in the literature as a cancer cell targeting modality and for prognosis.^{36,37} By testing 181 patients with triple-negative breast cancer for MCT4 protein expression using immunostained tissue microarrays, stromal MCT4 was concluded to be a predictor of high-risk patients.³⁷ The authors concluded that MCT4 inhibitors should be further developed in order to treat aggressive human breast cancer, while indicating the potential for MCT4 targeting in other cancers. In a comprehensive study investigating 17 breast cancer cell lines, MCT4 was found to play a major role in breast cancer cell survival, despite the large genetic diversity of the disease.³⁶ Indeed, cancer cell metabolic adaptations are necessary for their growth and survival, suggesting that MCT4 represents a novel cancer treatment opportunity.

Besides the interest in MCT4 as a novel therapeutic target, its utility as a potential clinical biomarker for a wide variety of cancers has been investigated by several groups. As mentioned previously, *MCT4* gene expression has been shown to be upregulated in clear cell renal cell carcinoma mediated by DNA methylation in the promoter region, also associated with cancer-related death.³⁴ Data from this study showed that *MCT4* gene expression and DNA methylation were predictive in assessing outcomes of patients with clear cell renal cell carcinomas, as well as predicting cancer-related death. More detailed and larger studies, however, are necessary in order to clinically determine the DNA methylation of the *MCT4* gene as a predictive biomarker. *MCT4* gene expression has also been shown to be highly upregulated in a glycolytic subset of pancreatic cancer, and the data demonstrated that elevated gene expression of *MCT4* was associated with poor survival.³⁸ Similarly, experimental evidence also suggests metabolic differences between adeno- and squamous cell non-small cell lung cancers, in which high *MCT4* gene expression was indicated in more aerobic and glycolytic adenocarcinomas.³⁹ In all these cases, it has been suggested that MCT4 and its association with glycolytic, metabolically active cancer cells can be used as not only a prognostic tool, but also a novel targeting strategy to inhibit the growth and function of these diseases.

More recently, a group at the British Columbia Cancer Research Centre investigated the utility of targeting the *MCT4* gene using antisense oligonucleotides in castration-resistant prostate cancer.⁴⁰ This study investigated the protein expression of MCT4, as well as the safety and efficacy of these antisense oligonucleotides in human castration-resistant prostate cancer cells and a PC-3 tumor xenograft mouse model. Results suggested that along with the elevated MCT4 protein expression in higher grade castration-resistant prostate cancer biopsies, there was increased immune cell penetration and activation following antisense

oligonucleotide treatment.⁴⁰ The results indicated by the study are exciting because there has been little *in vivo* evidence thus far suggesting the utility of MCT4 as a drug target in cancer. Considering there has been little success at generating small molecules as specific inhibitors of the MCT4 isoform, the generation of highly specific forms of treatment, such as oligonucleotides, represents an exciting advancement in the therapeutic targeting of MCT4.

MCT isoforms 6, 8–10, and 12 and roles in disease

MCT isoforms 5–14 have been substantially less addressed throughout the literature with regard to their clinical relevance and functional roles, compared with MCTs 1–4. More specifically, there is no information in the literature regarding MCTs 5, 11, and 13–14 other than data regarding the relative mRNA expression in human tissues, and little information on MCT7. Limited information is available regarding substrate specificity, functional characterization, and potential roles *in vivo* for the other MCT isoforms. This section will focus on the effect of MCTs 6, 8–10, and 12 in pathophysiology and disease and their potential clinical relevance as novel drug targets.

MCT6

With its endogenous function unknown and the lack of clarity surrounding MCT6 substrate specificity and functionality, MCT6 still remains an orphan transporter. Two major studies performed by the Yamamoto laboratory have attempted to classify MCT6 substrates, inhibitors, as well as its functional characterization using MCT6-transfected *X. laevis* oocytes.^{53,72} The results suggested that MCT6 is neither proton-, sodium-, nor bicarbonate-dependent, and primarily relies on pH and membrane potential as regulators and major driving forces for transport. Only a handful of drug substrates were identified (e.g. bumetanide, nateglinide, and probenecid), which suggests that MCT6 is a xenobiotic transporter.

Transcriptomic analyses performed in mouse liver homogenates in two separate studies indicate a role of MCT6 in regulating hepatic diet-induced changes in lipid and glucose homeostasis.^{41,42} Protein expression data available from the Human Protein Atlas suggests a high expression of MCT6 in human hepatocytes, which does not correlate to human mRNA expression data. These data suggest that MCT6 may have a fundamental role in the regulation of dietary fatty acids in the liver. It is important to note that further studies are required *in vivo*, potentially using a genetically deficient Mct6 knockout mouse model, prior to confirming the role of MCT6 and its potential importance in a clinical setting.

MCT8 and MCT10

MCT8 and MCT10 have both demonstrated affinity for thyroid hormones; however, mutations associated with the *MCT8* gene have been associated with an X-linked mental retardation syndrome, known as Allan-Herndon-Dudley syndrome.^{4,5,43–46} Localized primarily to the neurons, as determined in mouse studies, MCT8 seems to be responsible for the specific neuronal uptake of a variety of thyroid hormones, such as diiodothyronine, triiodothyronine, and thyroxine. Although there is some evidence suggesting MCT8 mRNA

and protein expression in human cerebral microvessels, more studies are required prior to confirming its significance in facilitating thyroid hormone transport across the blood brain barrier, compared with other transporters.⁷³ These mutations in the *MCT8* gene locus result in abnormal levels of thyroid hormones in the blood at an early age, which result in phenotypes, such as hypotonia, muscle hypoplasia, weakness, and developmental delays.⁴⁵ Studies performed in *Mct8*-deficient mice have also demonstrated similar abnormalities to humans suffering from this disease.^{4,46} Due to the difficulty of studying this disease in humans, models such as these represent useful tools in studying the abnormalities associated with MCT8-deficiency and thyroid hormone disease. Although there is currently no defined treatment of this syndrome, a phase II clinical trial is ongoing using a triiodothyronine analog, Triac, to assist in normalizing serum thyroid hormone levels in patients with Allan-Herndon-Dudley syndrome (NCT02060474). Although Allan-Herndon-Dudley syndrome is a rare disorder with a low frequency of occurrence, the findings from these studies suggest that MCT8 plays a major role in regulating tissue-specific thyroid hormone levels and physiological development.

MCT10 (also referred to as TAT1) shows overlapping substrate specificity with MCT8 for transporting thyroid hormones; however, unlike MCT8, MCT10 demonstrates low affinity aromatic amino acid transport with compounds, such as tryptophan, tyrosine, and phenylalanine.^{74,75} Investigation into the contribution of MCT10 to thyroid hormone transport was performed in *Mct10* knockout mice, and interestingly, no effects were seen in thyroid hormone levels in blood and tissue.⁴⁸ However, the compensatory effects of *Mct8* protein expression could potentially be playing a role in this model. In addition, the authors demonstrated that thyroid hormone concentrations within the livers and kidneys of double *Mct8/Mct10* knockout mice were elevated compared to the *Mct8* knockout mice, suggesting that both transporters contribute to the efflux of thyroid hormones. The clinical relevance of MCT10 has yet to be established, considering that it does not seem to be a major thyroid hormone transporter. However, further research into MCT10 substrate specificity and tissue-specific regulatory mechanisms may reveal its role in certain disease states.

MCT9

To date, very little evidence is available to suggest MCT9's potential clinical relevance. However, one study suggested that a frequently occurring missense variant (rs2242206) of the *MCT9* gene, resulting in a lysine change to a threonine at the 258 amino acid position, was significantly associated with an increase in risk of renal overload gout.⁴⁷ Although studies have characterized MCT9 as a carnitine transporter,⁵⁵ no evidence has suggested that it is responsible for the transport of urate, which would suggest its physiological association to gout. The importance of MCT9 *in vivo* has yet to be evaluated using a preclinical genetic knockout mouse model, which would assist in characterizing the clinical contribution to maintaining urate homeostasis.

MCT12

Recent evidence has suggested the potential physiological role and importance of MCT12 in humans; however, there still remains some debate surrounding its association with

glucosuria and cataract formation.^{49–51} A nonsense mutation in the *MCT12* gene that results in a Q215X amino acid mutation was found in a group of 12 subjects suffering from cataracts and elevated glucose levels in the urine.⁵⁰ The premature termination of the *MCT12* protein sequence is suggested to yield a highly or fully dysfunctional protein, which could lead to tissue-specific defects. Further studies were performed assessing the functional mechanism of this mutation in the development of cataracts.⁴⁹ *In vitro* evidence and *in vivo* studies performed using genetically-modified *Mct12* in rats in this study suggested that the human Q215X mutation in *MCT12* resulted in cataract formation most likely due to protein misfolding and the inability to traffic to the plasma membrane. Interestingly, transposon-modified *Mct12* rats resulting in the complete loss of *Mct12* did not result in any detectable abnormal ocular phenotype, which suggests that there could be interspecies differences. More recently, *MCT12* was characterized as a creatine transporter using *MCT12*-transfected *X. laevis* oocytes and the utilization of a high-resolution metabolomics approach.⁶ In order to further clarify the association of the *MCT12* mutation and its relation to glucosuria, detailed *in vitro* studies and analysis of patients with the *MCT12* mutation were performed.⁵¹ Although individuals with an *MCT12* mutation displayed unaltered creatine levels from the wild-type patients, there was increased renal secretion of creatine's precursor, guanidinoacetate. The glucosuria observed in the *MCT12* mutation was also evaluated and demonstrated to be more directly correlated to a heterozygous *SLGT2* mutation, and not *MCT12*.⁵¹ Further studies and more detailed data collection *in vivo* are still necessary, however, prior to characterizing the mechanistic effect of the *MCT12* mutation on guanidinoacetate homeostasis.

Conclusions and future directions: Where are we headed?

Research targeting SLC transporters as therapeutic strategies in disease⁷⁶ support the need for further investigations of SLC transport proteins as promising therapeutic targets in disease and drug therapy. This review highlights the emerging roles of the SLC16A family of transporters in drug targeting and as prognostic factors in disease, roles that will impact the field of clinical pharmacology. Currently, although MCTs 1–4 have been well-characterized, there still remain many undefined orphan MCTs, having no known endogenous substrates. MCTs 1–4 are lactate transporters, with MCT 1, 2, and 4 proteins being overexpressed in a variety of cancers and representing potential therapeutic targets for cancer treatment. MCT1, quantitatively the most important MCT, is a target for drug delivery both at the intestine and at the blood brain barrier. Investigations have suggested an important role of MCT3 in retinal pathophysiology, MCT6 in glucose and lipid homeostasis, MCT8/10 in thyroid hormone regulation, MCT9 in renal pathophysiology, and MCT12 as a creatine transporter that is potentially important in cataract development. Further research is needed for the characterization of these MCT enzymes, defining their roles in both xenobiotic disposition and in endogenous compound homeostasis, and for the determination of specific inhibitors of the MCT isoforms. The identification of specific substrates and inhibitors of the MCT isoforms has been limited, partly due to the lack of experimentally characterized 3D protein crystal structure resulting in the inability to reliably perform *in silico* ligand docking simulations. In addition, there remains very limited information available regarding genetic variability of these transporters, their roles in physiology and

pathophysiology, as well as the clinical significance of the MCT family members in disease and their potential as disease biomarkers, prognostic factors, or therapeutic targets for the treatment of disease. With the exception of MCT1, the majority of the potential clinical relevance of MCTs as therapeutic targets is based primarily on preclinical and *in vitro* evidence. Therefore, more research is needed in order to fully understand the role of MCTs in disease and as drug targets.

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Figure 1.

A scheme illustrating the lactate shuttling pathway in glycolytic and oxidative cancer cells. Glycolytic cancer cells (Left), dependent on glucose uptake via glucose transporters (GLUTs), undergo glycolysis to produce pyruvate and ATP, in which pyruvate undergoes further metabolism into lactate via lactate dehydrogenase A (LDHA). Proton symport-mediated lactate efflux occurs by MCT4. In oxidative cancer cells (Right), proton symport-mediated lactate influx and efflux occurs by MCT1. In these cells, lactate is transformed into pyruvate via lactate dehydrogenase B (LDHB) with the generation of NADH as a byproduct. These two metabolic products are then incorporated into the TCA cycle in mitochondria, to supplement the production of ATP via the oxidative phosphorylation pathway. This figure and caption was adapted from Perez-Escuredo *et al.*⁵²

Table 1

The SLC16A family: substrates, tissue expression, and potential clinical relevance

Protein	Gene	Key substrates	Human mRNA tissue/cellular expression	Potential clinical relevance (ref.)
MCT1	<i>SLC16A1</i>	Lactate, pyruvate, ketone bodies	Ubiquitous (except β -cells of the endocrine pancreas)	Cancer ^a , immunosuppression ^a , lactate transporter defect ^b , glucose regulation ^a (12–24)
MCT2	<i>SLC16A7</i>	Pyruvate, lactate, ketone bodies	High expression in testis, moderate to low in spleen, heart, kidney, pancreas, skeletal muscle, brain, leucocytes	Cancer ^a , prostate cancer biomarker ^a , neurodegenerative disease ^b , male infertility ^b (25–30)
MCT3	<i>SLC16A8</i>	Lactate	Retinal pigment epithelium, choroid plexus	Atherosclerosis ^c , altered visual function ^b , wound healing ^c (31–33)
MCT4	<i>SLC16A3</i>	Lactate, ketone bodies	Skeletal muscle, chondrocytes, leucocytes, testis, lung, ovary, placenta, heart	Cancer ^a and prognosis ^a (3,34–40)
MCT5	<i>SLC16A4</i>	Unknown	Brain, muscle, liver, kidney, lung, ovary, placenta, heart	Unknown
MCT6	<i>SLC16A5</i>	Bumetanide, nateglinide, probenecid	Kidney, muscle, brain, heart, pancreas, prostate, lung, placenta	Diet-induced lipid/glucose homeostasis ^b (41–42)
MCT7	<i>SLC16A6</i>	Ketone bodies	Liver, brain, pancreas, muscle, prostate	Unknown
MCT8	<i>SLC16A2</i>	Thyroid hormones (T2, rT3, T3, T4)	Most tissues including liver, heart, brain, thymus, intestine, ovary, prostate, pancreas, placenta, lung, kidney, skeletal muscle	Allan-Herndon-Dudley syndrome ^a (4,5,43–46)
MCT9	<i>SLC16A9</i>	Carnitine	Endometrium, testis, ovary, breast, brain, kidney, spleen, retina	Uric acid homeostasis ^b , renal overload gout ^b (47)
MCT10	<i>SLC16A10</i>	Aromatic amino acids, T3, T4	Kidney, intestine, muscle, placenta, heart	Similar to that of MCT8 ^a (48)
MCT11	<i>SLC16A11</i>	Unknown	Skin, lung, ovary, breast, lung, pancreas, retinal pigment epithelium, choroid plexus	Unknown
MCT12	<i>SLC16A12</i>	Creatine	Kidney, retina, lung, testis	Cataracts ^b , glucosuria ^b (49–51)
MCT13	<i>SLC16A13</i>	Unknown	Breast, bone marrow stem cells	Unknown
MCT14	<i>SLC16A14</i>	Unknown	Brain, heart, muscle, ovary, prostate, breast, lung, pancreas liver, spleen, thymus	Unknown

MCT, monocarboxylate transporter; SLC, solute carrier.

Table adapted from ref. 2.

^aSupported by *in vitro* and *in vivo* data.

^bSupported by *in vivo* data.

^cSupported by *in vitro* data.

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