Clinical and Functional Relevance of the Monocarboxylate Transporter Family in Disease Pathophysiology and Drug Therapy

Pascale Fisel1,2, Elke Schaeffeler1,2 and Matthias Schwab1,2,3,4,5,*

The solute carrier (SLC) SLC16 gene family comprises 14 members and encodes for monocarboxylate transporters (MCTs), which mediate the absorption and distribution of monocarboxylic compounds across plasma membranes. As the knowledge about their physiological function, activity, and regulation increases, their involvement and contribution to cancer and other diseases become increasingly evident. Moreover, promising opportunities for therapeutic interventions by directly targeting their endogenous functions or by exploiting their ability to deliver drugs to specific organ sites emerge.

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MONOCARBOXYLATE TRANSPORTER FAMILY

The monocarboxylate transporters (MCTs) belong to the solute carrier (SLC) transporter superfamily and are encoded by the members of the SLC16 gene family. Based on sequence homology, the MCT family comprises 14 members. A phylogenetic tree for the MCT family members is shown in Figure 1. It is important to note that the MCT and SLC16 numbering do not coincide and that, as of 1998 (after publication of Wilson et al.2), several MCT members were renamed after their initial identification. Correct annotation of MCT and corresponding SLC16 nomenclature can be found in Figure 1.

STRUCTURE OF MCT TRANSPORTERS

The topology model for all 14 members is predicted to comprise 12 transmembrane domains and less conserved intracellular C-termini and N-termini as well as a large loop between transmembrane domains 6 and 7 based on hydrophobicity plots.3 Although MCTs are primarily local-
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Figure 1 Predicted phylogenetic tree of the monocarboxylate transporter (MCT) family members and corresponding known endogenous substrates. The phylogenetic tree was generated using MEGA7 (http://www.megasoftware.net/) and sequence alignments were performed using the multiple sequence alignment tool clustal omega (https://www.ebi.ac.uk/Tools/msa/clustalo/). Transporters mediating $\text{H}^+\text{-coupled}$ or $\text{H}^+\text{-independent}$ substrate transport are highlighted in red and yellow, respectively. Next to the transporters, the main known endogenous substrates are depicted and marked in blue. For MCT5–7, MCT13, and MCT14, no substrates have been identified in humans yet.

zebrafish phenotype with hepatic steatosis, indicating a similar function for human MCT7. MCT11 has recently been shown to mediate $\text{H}^+\text{-coupled}$ transport of pyruvate, indicating similar substrate specificities as MCT1–MCT4; however, transport of other monocarboxylates was not tested. Thus, other endogenous or exogenous substrates of MCT11 have not been identified by now. Human MCT5, MCT13, and MCT14 remain orphan transporters with yet unknown functions and substrate specificities. Interestingly, it has been reported that murine MCT14 does not seem to transport the typical substrates of other MCT family members, such as lactate or amino acids. Based on sequence conservation and the presence of key residues required for $\text{H}^+\text{-coupled}$ transport, MCT13 is likely to be an $\text{H}^+\text{-coupled}$ transporter, unlike MCT5 and MCT14, which are predicted to mediate $\text{H}^+\text{-independent}$ transport of substrates (Figure 1). Untargeted metabolomic approaches (e.g., using carriers of genetic variants or knockout mice), represent promising tools to support the identification of endogenous substrates of the remaining orphan transporters in the near future.

TISSUE DISTRIBUTION AND ENDOGENOUS FUNCTION OF MCT TRANSPORTERS

The major differences between the 14 MCT isoforms, despite the distinct substrate affinities and specificities, are their tissue distribution and intracellular localization as well as the regulation of expression. Although the expression profiles partly overlap and some substrates are shared, the tissue distribution and distinct substrate affinities correspond to the particular metabolic need of the respective tissue in which they are expressed (Figure 2). Thus, MCTs enable substrate flux covering the full range of substrate concentrations occurring in these tissues under normal physiological conditions and in response to changing energy and nutrient demands.

The tissue distribution of MCT isoforms is most extensively studied in rodent tissues but species differences have been observed to varying degrees. Although the tissue distribution of the individual human MCT isoforms has been studied extensively on the level of mRNA expression (e.g., by Price et al.), knowledge of functional expression on protein level is of major importance to evaluate their precise physiological role within the tissues they are expressed. Figure 2 summarizes the tissue distribution of MCT isoforms based on published data on human protein expression, according to current knowledge.

Most studies evaluating human MCT protein expression have been performed for MCT1, MCT2, and MCT4. As mediators of $\text{H}^+\text{-coupled}$ translocation of L-lactate, pyruvate, and ketone bodies across cell membranes, MCT1–MCT4 support the maintenance of an energy balance and pH homeostasis and enable metabolic cooperation between different tissues with distinct energetic profiles. In particular, the tissue distribution of MCT1–MCT4 enables a metabolic coupling in which lactate, pyruvate, or ketone bodies produced in one tissue can be taken-up and used by another. MCT1, a transporter with moderate substrate affinities, facilitates either influx or efflux of the substrates depending on substrate and
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Figure 2 Tissue distribution of monocarboxylate transporter (MCT) isoforms. Expression of individual MCT isoforms based on published human protein expression data in different organs according to current knowledge.

H⁺-concentration gradients and is ubiquitously expressed in human tissues. It is expressed in tissues that rely on efflux or uptake of energy metabolites based on the energetic profile but also in the gut to support the absorption of short chain fatty acids, such as acetate, propionate, or butyrate. In contrast, MCT2 is a high affinity transporter with a more restricted protein expression pattern. It is expressed in tissues that depend on substrate uptake as fuel for oxidative phosphorylation or as substrate for gluconeogenesis or lipogenesis and is, therefore, mainly expressed in neurons, testis, liver, kidneys, and adipose tissue. MCT2 protein expression was also found in the pancreas, heart, colon, and stomach. MCT3 expression is confined to the retinal pigment epithelium where it is primarily responsible for the efflux of L-lactate from the retina. MCT4 is a low affinity but high capacity transporter with L-lactate as the main substrate. The transporter is primarily responsible for L-lactate export from highly glycolytic cells and, therefore, shows wider tissue distribution with peak expression levels e.g., in glycolytic white muscle fibers, leukocytes, or astrocytes. Human placenta, kidneys, and small intestine were also demonstrated to express MCT4.

Apart from shuttling metabolites between different tissues with particular energy demands, MCT1–MCT4, with lactate being their quantitatively most important substrate, are attributed a major role in lactate shuttling between different cell types within the same tissue (Figure 3). The concept of metabolic cooperation via lactate shuttling between cell types of the same organ has been described for skeletal muscle, in which highly glycolytic fast-twitch white muscle fibers extrude lactate via MCT4, which is taken up by oxidative slow-twitch red muscle fibers by MCT1 (Figure 3). A rapid exchange of lactate has also been established for different cell types of the brain, known as the astrocyte-neuron lactate shuttle hypothesis. Here, glycolytic astrocytes provide energy via lactate extrusion by MCT1 and MCT4 to oxidative neurons, which express the high affinity uptake transporter MCT2 (Figure 3). Similar cooperation between cell types of the same tissue has been demonstrated to be important for visual function and spermatogenesis (Figure 3).

Only limited systematic studies providing human protein expression data are available for the remaining MCT isoforms. The thyroid hormone transporter MCT8 and the amino acid transporter MCT10 seem to be widely expressed in human tissues. MCT8 expression seems to be of major importance in the brain and placenta for fetal development. Human MCT5 and MCT6 protein were found to be expressed in the human intestine (note: Gill et al. uses former MCT...
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Figure 3 Intracellular lactate shuttling between different cell types of specific organs. Focus on lactate shuttling on cellular level in: (1) the brain, between endothelial cells, glycolytic astrocytes, and oxidative neurons; (2) the eyes, between glycolytic Müller cells and oxidative photoreceptors; (3) the muscles, between lactate producing white muscle cells and lactate consuming red muscle cells; and (4) in testis, between lactate providing Sertoli cells and lactate consuming differentiating germ cells. MCT, monocarboxylate transporter.

numbering). Expression of MCT6 in the human intestine was confirmed by Kohyama et al. Moreover, Jones et al. suggest high MCT6 expression in hepatocytes and intermediate levels in the kidneys and colon (abstracts.aaps.org, AAPS2016, 07M0330). Protein expression of human MCT9 was found in the proximal tubular epithelial cell of the kidneys.

Based on human mRNA expression data, MCT11 is highly expressed in the thyroid, liver, and salivary gland. Peak gene expression levels of MCT12 were observed in the eyes, lungs, kidneys, and testis. Although a first study provides evidence for MCT14 protein expression in the mouse central nervous system (CNS) and kidneys, no human data are available to date. In addition, human MCT7 and MCT13 protein tissue distribution has not yet been elucidated. For selected MCT transporters, human protein expression data can also be found in the Human Protein Atlas (https://www.proteinatlas.org/).

IMPORTANCE AND CLINICAL RELEVANCE OF MCTs IN DISEASES
Owing to their importance in shuttling metabolites used as respiratory fuels or as precursors and intermediates in many metabolic pathways between different cell types and tissues, MCTs are majorly involved in the maintenance of a metabolic homeostasis in response to – possibly rapidly – changing demands. Accordingly, aberrant expression, activity, and function of MCTs confound metabolic homeostasis with detrimental consequences contributing to a number of clinical manifestations ranging from mild disorders to severe diseases.

MCTs IN CANCER
Role of MCT1, MCT2, and MCT4
The important role of MCT1, MCT2, and MCT4 in cancer is mainly ascribed to the lactate shuttling between cells with distinct energy demands. In cancer, a metabolic cooperation is hypothesized to occur either between hypoxic glycolytic and oxygenated oxidative tumor cells, between hypoxic tumor and endothelial cells, or between oxidative tumor and glycolytic stromal cells. Export of lactate from highly glycolytic tumor (or stromal) cells ensures the progression of glycolysis and prevents intracellular acidification. The extracellular lactate serves not only as a respiratory fuel for oxidative cells, but, together with the H⁺, contributes to an acidic tumor microenvironment and is meanwhile recognized as an important signaling molecule promoting migration, angiogenesis, and immunosuppression. The phenomenon of intratumoral lactate shuttling has been described for several solid tumors and is suggested to occur commonly across cancer types. Accordingly, aberrant expression of MCT1, MCT2, and/or MCT4 has been demonstrated e.g., in colon cancer, glioblastoma, breast cancer, prostate cancer,
pancreatic cancer, or clear cell renal cell carcinoma.\textsuperscript{29,30} A comprehensive overview of aberrant MCT1, MCT2, and MCT4 expression in different cancer entities is provided by Pinheiro et al.\textsuperscript{31} With this important impact on lactate metabolism in tumor cells, MCT1, MCT2, and MCT4 have been proposed as diagnostic biomarkers or prognostic factors for cancer outcome and survival. For instance, increasing MCT1 expression is observed along with tumor aggressiveness especially in cervical cancer or is described as a prognostic marker in invasive breast cancer.\textsuperscript{32,33} In prostate cancer, MCT2 has been proposed as a biomarker for disease diagnosis, because the transporter is not expressed in normal prostate tissue, an increase in expression can be observed in adjacent non-neoplastic tissue and strong MCT2 expression is found in primary prostate tumor tissue samples.\textsuperscript{34} The lactate exporter MCT4, which is overexpressed in glycolytic tumor cells, is a promising candidate for cancer prognosis in various cancer entities, such as ovarian cancer,\textsuperscript{35} clear cell renal cell carcinoma,\textsuperscript{36} or hepatocellular carcinoma.\textsuperscript{37} A recent meta-analysis corroborates that increased MCT4 expression is linked to poor patient outcome across five different cancer entities.\textsuperscript{37}

**Role of other MCT isoforms**

The role of other MCT isoforms in cancer is barely addressed in the literature, which is why their relevance for cancer development or progression is largely elusive so far. However, substantial differences of gene expression levels in various cancer entities can be observed also for the other MCT isoforms. Figure 4 illustrates the gene expression of the individual MCT isoforms in selected cancer entities using data from The Cancer Genome Atlas (TCGA). Strikingly, the gene expression of MCT12 is most frequently downregulated in tumors compared with non-neoplastic tissues in the examined cancer entities. Only few genomewide gene expression profiling studies are available, indicating altered expression of MCT isoforms such as in hepatocellular carcinoma,\textsuperscript{38} thyroid cancer,\textsuperscript{39} adrenal cortical cancer,\textsuperscript{40} or ovarian cancer\textsuperscript{41} but the precise molecular mechanisms behind altered MCT expression are not revealed. Given that tumor growth is a highly energy consuming process and tumors demonstrate metabolic reprogramming and considerable metabolic plasticity, other MCT isoforms presumably play an important role in cancer development and progression as suppliers of nutrients or exporters of metabolic end products. On the other hand, downregulation of MCTs might occur in order to shut down dispensable metabolic pathways in favor of cell growth, proliferation, and metastasis.

**MCTS IN OTHER DISEASES**

**Fatigue**

The first condition associated with a lactate transporter defect that was later proposed to be caused by a mutation in the SLC16A1 gene, was reported as rare cryptic exercise intolerance or fatigue syndrome, manifested through muscle cramping and chest pain, caused by impaired lactate removal after intense exercise in otherwise healthy people.\textsuperscript{42} Whether the mutations or rather impaired interactions with the ancillary protein CD147/basigin are responsible for the MCT1 deficiency was questioned afterward since the in vitro experiments could not prove the reduced transporter activity of the mutated isoform compared with wildtype MCT1.\textsuperscript{15}

**Exercise induced hyperinsulinism**

Sound evidence exists for implications of activating SLC16A1 promoter mutations with hereditary exercise induced hyperinsulinism (EIHI) and hypoglycemia.\textsuperscript{43} This inherited disorder is caused by failed silencing of MCT1 in pancreatic \( \beta \)-cells, leading to pyruvate and lactate uptake, which is normally suppressed in these cells, and subsequent metabolic oxidation. The increased ATP levels generated by the oxidation trigger inappropriate insulin secretion and, hence hypoglycemia during anaerobic exercise in individuals carrying one of the mutations. Very recently, a novel intragenic heterozygous mutation in the SLC16A1 gene was found in an infant with congenital hyperinsulinism and persistent hypoglycemia. Although functional studies have not been performed yet, the missense variant is predicted to be damaging and causes disease.\textsuperscript{44}

**Inflammatory bowel disease**

Because MCT1 is also involved in intestinal absorption of short chain fatty acids, supplying energy substrates for colonic cells, deregulation is also suggested to affect colonic tissue homeostasis and might be involved in inflammatory bowel diseases. For instance, impaired butyrate oxidation has been associated with active mucosal inflammation. Apart from reduced butyrate oxidation itself, impaired butyrate uptake, most likely as a consequence of decreased MCT1 expression, was found in patients with active ulcerative colitis.\textsuperscript{45,46} Moreover, density analyses from an open access genomewide association studies database revealed a dense cluster of associations for SLC16A7 (encoding for MCT2) variants with Crohn disease and high-density lipoprotein (HDL) cholesterol levels, although functional validation is completely missing so far.\textsuperscript{47}

**METABOLIC DISEASES**

**Obesity**

MCTs are not only involved in maintaining energy homeostasis within particular tissues, but also contribute to an energetic balance in the whole body. In this respect, they can act as fuel sensors impacting food intake and body weight. Altered MCT expression levels in key tissues in response to metabolic status, especially in the brain, muscles, liver, intestine, pancreas, and adipose tissue are suggested to be important determinants with respect to whole body energy balance.\textsuperscript{48} As comprehensively reviewed by Carneiro et al.,\textsuperscript{48} considerable alterations in MCT1, MCT2, or MCT4 expression in these tissues are found in accordance to metabolic states (e.g., in obese or fasting subjects). Although, again, most studies refer to rodent or in vitro models, alterations were also confirmed in human tissues. For instance, MCT4 was found to be overexpressed in muscle of obese subjects but decreased after weight loss.\textsuperscript{48} Most striking results were achieved using a heterozygous transgenic MCT1 knockout mouse model (MCT1\(^{-/}\); MCT1\(^{-/-}\) homozygote knockout is lethal), which has been demonstrated to be resistant to diet-induced obesity.\textsuperscript{49} In addition to reduced food intake under high-sugar and high-fat diets, nutrient absorption in
the intestine was shown to be decreased, lipid accumulation in adipose tissue and the liver was decreased or absent, respectively, and glucose intolerance or insulin resistance were not observed in MCT1+/− as compared with MCT1 wild-type mice. Elucidation of the precise mechanisms and the contribution of other MCT isoforms to body weight regulation might reveal interesting novel druggable pathways or targets for prevention of obesity and resultant diseases.

**Gout**

Gout is a metabolic disease caused by elevated serum uric acid (SUA) levels. In a meta-analysis of 14 genomewide association studies as well as in replication studies, a single-nucleotide polymorphism (SNP; rs12356193) within the SLC16A9 gene was identified as a factor contributing to the variability of SUA levels. The variant correlated also to DL-carnitine and propionyl-L-carnitine levels, which, in turn, were strongly associated with SUA. Carnitine was later experimentally validated to be a substrate of MCT9, whereas urate was demonstrated to be not transported by MCT9. Therefore, rs12356193 is suggested to have an indirect effect on urate excretion through aberrant carnitine levels. A contribution of the missense variant rs2242206 (close to the previously identified intronic variant) to the risk of gout could be found only for renal overload gout in Japanese individuals, in contrast to renal underexcretion gout or all gout susceptibility in Europeans, indicating impaired intestinal urate excretion. The functional mechanisms and the clinical relevance of MCT9 and its contribution to the variability of SUA and the susceptibility to resulting diseases, especially gout, are, therefore, not fully clarified and need further investigations. Interestingly, Jansen et al. identified that the SLC16A9 gene variant rs12356193 was associated with lower plasma carnitine levels and led to enhanced...

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**Figure 4** Differential gene expression of monocarboxylate transporter (MCT) isoforms in different cancer entities of The Cancer Genome Atlas (TCGA). The circos plot shows a heat-map of gene expression of the individual members of the solute carrier (SLC) gene family in different cancer entities in tumors and corresponding normal tissues using gene expression data from TCGA (http://cancergenome.nih.gov). Furthermore, fold-changes (log2) of expression levels in tumors compared with normal tissues are represented by grey, orange, or green dots (grey: comparable expression levels in tumors and normal tissues; orange: higher expression in tumors; and green: higher expression in normal tissues). The size of the dots depends on the absolute value of fold-changes (log2). The green and orange lines depict Spearman correlation coefficients (rS > 0.7) between individual SLC16 isoforms in normal (green) and tumor (orange) tissue. BLCA, bladder cancer; BRCA, breast cancer; COAD, colon cancer; GBM, glioblastoma; HNSC, head and neck cancer; KICH, kidney chromophobe; KIRP, kidney papillary carcinoma; LAML, acute myeloid leukemia; LIHC, liver cancer; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; OV, ovarian cancer; PAAD, pancreatic cancer; PRAD, prostate cancer; READ, rectal cancer; STAD, stomach cancer; UCEC, endometrioid cancer.
proliferative capacity of CD8 T-cells and improved response to peginterferon alfa-2a/adevovir treatment in patients with chronic hepatitis B.

Type 2 diabetes mellitus
A genomewide association study in a Latin American population with patients with type 2 diabetes mellitus (T2DM) and nondiabetic controls identified a novel locus reaching genomewide significance spanning the genes SLC16A11 and SLC16A13. The risk haplotype consists of five SNPs, whereby the tag-SNP for the risk haplotype rs17767867 is found most frequently in Native American populations (~50%), at intermediate frequency in Asians (~10%), but occurs rarely in Europe or Africa and might explain, in part, the higher prevalence of T2DM in Mexican Americans.24 The five SNP haplotype comprises a synonymous as well as four missense variants in SLC16A11, of which one was predicted to be damaging, indicating that SLC16A11, encoding for MCT11, is the causal gene for the link with T2DM. Simultaneously, Hara et al.55 identified rs312457, an intronic variant within the SLC16A13 gene, in East Asian populations, which is in linkage disequilibrium with the five SNP haplotypes found in Mexicans. A study investigating Malaysian patients with T2DM revealed overexpression of SLC16A11 gene, which lead to loss of MCT1 function.59 Because ketolytic defects were ruled out, a defect in ketone body utilization during catabolic stress (e.g., induced by infections or fasting) due to reduced uptake of ketone bodies in extrahepatic tissues via MCT1, and, hence, acid-base imbalance, is suggested as the cause of the disorder in these patients. So far, unknown additional triggers accompanying heterozygous MCT1 mutations are expected to contribute to symptom manifestation. The finding was supported by a case report of affected half-siblings with heterozygous MCT1 mutations inherited from their mother, present also in the patients’ half-sister who were both asymptomatic, corroborating that heterozygous mutations can induce recurrent ketoacidosis, but are not necessarily sufficient.60

Diseases of the central and peripheral nervous system
Some patients with recurrent ketoacidosis caused by MCT1 deficiency also had moderate intellectual disability, epilepsy, or migraine headaches, indicating consequences also for the CNS. Although it remains unknown whether these symptoms were direct effects of MCT1 deficiency in the CNS or were caused by repeated ketoacidosis, an involvement of MCT1 or other MCTs is not unreasonable. The brain is highly dependent on continuous energy supply and disturbed shunting of energy substrates between the different brain cell types may have detrimental consequences for the highly complex and tightly regulated brain physiology and energy homeostasis.61 Most studies investigating diseases of the CNS and/or the peripheral nervous system and the relevance of MCTs were performed in rodent models. However, the findings allow insights and first assumptions of the functional role of MCTs, which are to be validated in appropriate human model systems.

With respect to cognitive functions, it could be demonstrated in rat models that downregulation of MCT1, but also MCT4, in glial cells, and/or MCT2 in neurons prevented learning and long-term memory formation.61 Cognitive impairment due to decreased energy metabolism was also found in the pathophysiology of Alzheimer disease in rats. Indeed, decreased lactate content accompanied by reduced MCT2 expression was demonstrated in the cerebral cortex and hippocampus in a rat model of the disease.61 Changes in rat MCT expression were also observed in response to oxygen deprivation, for instance, due to ischemic stroke.62 In contrast, in a mouse model of Parkinson disease, which is also characterized by compromised energy metabolism, no alterations of MCT expression were found.61

Although functional evidence is missing, there are first indications supporting the assumption that deregulated MCT expression and impaired metabolic interactions contribute to human neurological disorders. Decreased MCT1 protein expressions in human microvessels of the hippocampus as well as a redistribution of MCT2 have been suggested to be involved in the pathophysiology of drug-resistant temporal lobe epilepsy.61 In addition, MCT4 protein expression levels were shown to be significantly decreased in temporal lobe epileptic foci excised from patients with intractable epilepsy.64 Besides altered supply of monocarboxylates, the exact functional relevance of MCTs in epilepsy is unknown to date, just like the question whether the detected altered MCT expression is a cause or a consequence of epileptic seizures.63 Reduced MCT1 expression in oligodendrocytes in the spinal cord is proposed to be involved in neurodegeneration in patients with amyotrophic lateral sclerosis. Here, lactate release from oligodendrocytes via MCT1 has been shown to be critical to metabolically support neuron and axon functions.65 Furthermore, overexpression of MCT1

Ketoacidosis
Apart from the fatigue syndrome, a further manifestation of MCT1 deficiency was found in children who had recurrent ketoacidosis. The affected children were identified to harbor inactivating homozygous, but also heterozygous mutations in the SLC16A1 gene, which lead to loss of MCT1 function.59 Because ketolytic defects were ruled out, a defect in ketone body utilization during catabolic stress (e.g., induced by infections or fasting) due to reduced uptake of ketone bodies in extrahepatic tissues via MCT1, and, hence, acid-base imbalance, is suggested as the cause of the disorder in these patients. So far, unknown additional triggers accompanying heterozygous MCT1 mutations
was found in astrocytes within active white matter lesions of patients with multiple sclerosis, whereas decreased axonal MCT2 expression was found in inactive lesions, presumably leading to insufficient energy supply and progressive neurodegeneration.66

OPHTHALMOLOGICAL DISEASES

Age-related macular degeneration

A meta-analysis of the AMD gene consortium revealed seven new loci associated with age-related macular degeneration reaching genomewide significance levels, including a variant in the SLC16A8 gene, which was independently associated with risk of disease.67 A large genomewide association study including over 16,000 patients with age-related macular degeneration and almost 18,000 controls confirmed the association of the splice variant in SLC16A8 (MCT3) with strongly increased disease risk. A direct involvement in disease pathiology is suggested and seems plausible given the organ confined expression of MCT3 in the human retinal pigment epithelium and the importance of appropriate energy substrate shuttling between the different ocular cell types (Figure 3).68

Juvenile and age-related cataracts

Juvenile cataracts accompanied by microcornea and renal glucosuria were found to be associated with a nonsense mutation in SLC16A12 in a Swiss family, which leads to a truncated form of MCT12 that is retained in the endoplasmic reticulum.69,70 Although physiological functions or the substrate specificity of the transporter was unknown at the time, the speculated involvement in maintenance of homeostasis in the lens was presumed to be of importance also in age-related cataracts. Indeed, in a subsequent study, mutations in the 5’UTR of SLC16A12, leading to altered translational efficiency, were associated with the age-related onset of the disease.69 In the meantime, creatine has been identified as a substrate of MCT12. Although the precise function of MCT12 in creatine metabolism is not yet elucidated, detrimental consequences of MCT12 deficiency are not surprising, because creatine represents a major energy buffer, providing rapid ATP supply during high energy demand, and an antioxidant, protecting cells from oxidative stress. In a study re-evaluating the original family, the cause for renal glucosuria accompanying juvenile cataract in all but three family members, was attributed to a second independent heterozygous mutation in the glucose transporter SGLT2/SLC5A2 rather than the mutation in SLC16A12. Interestingly, this study revealed an indirect link between the SLC16A12 mutation and reduced guanidinoacetate levels, which is a precursor of creatine but not a substrate of MCT12.70 Thus, there are still many open questions regarding the exact role and function of MCT12 in the kidneys.

Male infertility

As previously mentioned, lactate shuttling between different cell types is required during spermatogenesis. Whereas lactate is released from Sertoli cells, which express MCT4, it is taken up as fuel by MCT1 and MCT2 expressing germ cells (Figure 3). Indeed, genetic variants in the 3’UTR of the SLC16A7 gene, encoding for MCT2, have been associated with male infertility in Korean men.71 The genetic variant is speculated to cause decreased MCT2 expression during spermatogenesis.71

Rheumatoid arthritis

Although the investigated study cohort was small, synovial fluid of patients with active rheumatoid arthritis (RA) was demonstrated to have lower pH- and increased lactate levels accompanied by increased MCT4 gene and protein expression in synovial fibroblasts compared with patients with osteoarthritis.72 The siRNA-mediated knockdown of MCT4 reduced proliferation of synovial fibroblasts of patients with RA in vitro and reduced severity of disease in mice with collagen-induced arthritis.72 With respect to RA treatment, a missense variant rs3763980 in the SLC16A7 gene, which correlated with gene expression in vitro, was found to be linked to methotrexate response in juvenile idiopathic arthritis (JIA). The association could be validated in an independent cohort of patients with JIA, but was not found in adult patients with RA.73 Because MCT2 has so far not been shown to directly mediate methotrexate transport, the precise mechanism of methotrexate (MTX) response and the relevance of MCT2 remain unclear.73

West Nile virus infection

An important association independent from energy or metabolic homeostasis was identified for SLC16A4, which encodes for MCT5 (formerly referred to as MCT4), with West Nile virus infections.74 In an in vitro RNA interference screen to investigate virus host cell interactions, knockdown of SLC16A4 was demonstrated to enhance West Nile virus infection. In this context, functional MCT5 expression is proposed to be a resistance factor for viral replication by delaying transition of endocytosed West Nile virus particles into the replication phase.74

Allan-Herndon-Dudley syndrome

The Allan-Herndon-Dudley syndrome (AHDS) is a rare hereditary disease, affecting almost exclusively male subjects, that is characterized by severe X-linked psychomotor retardation, severe neurological impairments, including muscle hypotonia and hypoplasia, accompanied by high serum triiodothyronine (T3) levels. In 2004, loss-of-function mutations within the SLC16A2 gene, located on the X chromosome, encoding for the thyroid hormone transporter MCT8, have been identified as the monogenetic cause of AHDS.75,76 Thyroid hormones play essential roles in growth and development of various tissues, especially the brain, and rely on cellular uptake to fulfill their physiological functions.77 Impaired uptake of T3 across the blood-brain barrier (BBB) and into neurons already during embryonic brain development, which is normally mediated via the highly specific thyroid hormone transporter MCT8, leads to the observed neurological defects. Since the initial finding in 2004, over 80 MCT8 mutations across the entire coding region have been described in more than 100 families with AHDS.78 Interestingly, the effect of the mutations on MCT8 activity and function correlates with the severity of the observed variation of AHDS phenotypes.77
Hepatic steatosis
An imbalance of accumulation and removal of triglycerides in hepatocytes characterizes hepatic steatosis, and represents the first pathological stage of fatty liver disease. Although functional investigations have yet only been performed in zebrafish, this study provides first evidence for a contribution of MCT7 in hepatic lipid metabolism by secreting ketone bodies, especially β-hydroxybutyrate. Zebrafish mutants with hepatic steatosis were identified to harbor a loss-of-function mutation in the slc16a6 locus, which causes lipid accumulation in fasted livers. Most interestingly, the steatotic phenotype could be rescued by transgenic expression of the human SLC16A6 orthologue, indicating a similar function for the human MCT7 isoform. However, the significance and contribution of MCT7 to hepatic lipid metabolism in humans needs experimental validation in appropriate model systems. A first indication for an involvement of MCT10 in the pathophysiology of non-alcoholic fatty liver disease (NAFLD) was found in a transcripome analysis by Lake et al., who showed downregulation of SLC16A10 gene expression along with NAFLD progression.

Barely anything is known about the contribution and clinical relevance of the remaining human MCT isoforms in disease pathophysiology. However, as comprehensive characterization of the transporters, including identification of their endogenous substrates and elucidation of their tissue distribution based on functional protein expression levels progress, precise molecular mechanisms will be elucidated and involvement in pathological pathways are expected to become apparent.

EPIGENETIC REGULATION OF MCT FAMILY MEMBERS

The expression and function of transport proteins is not only affected by genetic variation, but also by nongenetic factors, such as age, gender, or disease state, regulatory factors, like transcription factors, or by epigenetic mechanisms. Regarding regulation of MCT expression, again, mainly MCT1, MCT2, and MCT4 were examined. The regulation of MCT gene expression has to be tissue-specific and, if necessary, very rapid in order to enable adaption to changes in activity or different metabolic states. Transcriptional or post-transcriptional mechanisms of MCT regulation have been identified and summarized in a comprehensive review. In line with its expression in highly glycolytic and hypoxic tissues, MCT4 possesses hypoxia response elements within its promoter region and the transcription is upregulated by the hypoxia-inducible factor (HIF) [1, 31]. In contrast, MCT1 is regulated by transcription factors, such as MYC, PGC-1α, or p53 or post-transcriptionally by miRNA-29, which is involved in the cell-type specific inhibition of MCT1 expression in pancreatic β-cells. 15, 82

Epigenetic regulation is based on DNA modifications, which do not change the DNA sequence and include histone modifications and DNA methylation. Regulation of MCT expression by promoter DNA methylation has been described for MCT2 in prostate cancer. It was suggested that hypomethylation of an internal promoter region and hypermethylation of an upstream promoter leads to the expression of an alternative MCT2 isoform, differing only in the 5’UTR, which leads to MCT2 overexpression compared with benign tissue. MCT4 expression has been shown to be regulated by DNA methylation in clear cell renal cell carcinoma, whereby a single CpG site within the SLC16A3 promoter was identified to be a prognostic marker for patient survival. Of note, promoter DNA methylation of the ancillary protein CD147 did not have an influence on protein expression. Furthermore, in patients with temporal lobe epilepsy, cortical MCT4 expression levels were significantly lower at least partially due to SLC16A3 promoter methylation.

THERAPEUTIC APPROACHES

Importance of MCTs for drug delivery
Besides endogenous substrates, some MCTs have been identified to contribute to the disposition of xenobiotic compounds, including drugs. Because MCTs are localized in the gastrointestinal tract, liver, and kidneys, as well as the BBB, their expression is suggested to have an impact on drug pharmacokinetics by influencing intestinal absorption, tissue distribution, or renal reabsorption of substrate drugs. Whereas for MCT1, MCT2, MCT4, and MCT6, several xenobiotic substrates have been identified, the implication of other MCT isoforms in drug transport is not well understood. Mainly in vivo and in vitro studies with rodent MCTs and some in vitro studies with human MCTs demonstrated the transport of, for example, γ-hydroxybutyrate, 4-phenylbutyrate, valproic acid, nicotinic acid, salicylic acid, some β-lactam antibiotics, or selected statins. The expression of MCT1 at the BBB is, therefore, of specific clinical relevance, as it is suggested to contribute to the delivery of drugs for treatment of neurological diseases, such as 4-phenylbutyrate, nicotinic acid, or valproic acid, to the brain. The expression of MCT1 in the intestine can be exploited to improve the bioavailability of substrate drugs. For instance, XP13512, a prodrug of gabapentin, was specifically designed as MCT1 substrate to improve the bioavailability of the pharmacologically active metabolite. Similarly, the prodrug arbaclofen placarbil (XP19986) has improved the bioavailability of the active metabolite. Because MCT isoforms are overexpressed on tumor cells, the transporters represent attractive targets to specifically deliver chemotherapeutics to cancer tissue. The efficacy of the anticancer drug 3-bromopyruvate has been demonstrated to depend on MCT1-mediated uptake into the tumor cells. A genomewide genetic screen identified MCT1 to be the main determinant of 3-bromopyruvate sensitivity in human cancer cell lines and tumor xenografts. A recent study from Lopes-Coelho et al. confirms that MCT1 expression mediates 3-bromopyruvate transport in vitro using AML cell lines and suggests MCT1 expression as a predictive biomarker for response to 3-bromopyruvate treatment.

MCT-mediated adverse drug reactions
On the downside of drug delivery to target organ sites, MCT-mediated distribution of substrate drugs can induce unintended adverse drug reactions. Thus, penetration of the
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Figure 5 Therapeutic approaches involving isoforms monocarboxylate transporter (MCT)1 and MCT4. (a) MCT1 expression can be exploited for targeted drug delivery (e.g., of 3-bromopyruvate), into MCT1 expressing tumor cells. (b) MCT4 represents an attractive target for inhibition in tumor cells. Compounds, such as bindarit or modified derivatives, represent promising candidates. (c) Targeted DNA methylation of the hypomethylated SLC16A3 promoter, mediated, for example, by a CRISPR-dCas9-DNMT construct, might represent an alternative approach to restore normal MCT4 expression levels in tumor cells.

BBB by statins can induce sleep disturbances as unwanted side effects. In addition, depending on the substrate concentrations, the statins can act as competitive MCT inhibitors. In this way, inhibition of MCT4, especially by lipophilic statins, is proposed to be involved in statin-induced cytotoxicity and muscle pain. A very recent study demonstrates a novel association between a genetic variant in the SLC16A5 gene, encoding for MCT6, and cisplatin-induced hearing loss. The common genetic synonymous variant, rs4788863, in the coding region of SLC16A5, which is predicted to alter the rate of codon usage, exerted a protective effect on cisplatin-induced ototoxicity in patients with testicular cancer. Although the endogenous function of MCT6 is unknown so far, this study indicates a role of MCT6 for hearing. In addition, the protective effect of impaired MCT6 function can be exploited by combinatorial treatment of cisplatin with cimetidine as inhibitor, which did not compromise the anticancer effect of cisplatin in vivo in a mouse model but prevented ototoxicity.

MCTs as drug targets
Understanding of molecular mechanisms in which MCTs are involved and how altered transport may lead to disease pathology helps to develop therapeutic interventions restoring normal physiological metabolism or interfering with pathophysiological metabolic pathways. The use of MCT inhibitors represents an attractive opportunity to elucidate precise mechanisms and to eventually therapeutically target altered MCT function. A number of MCT inhibitors, such as p-chloromercuribenzenesulfonate (pCMBS), stilbene disulfonates, cyanocinnamates, quercetin, phloretin, or statins, have been described. However, these compounds are unspecific and cannot be used to determine the individual role of MCT isoforms or to particularly inhibit one specific altered MCT in a pathophysiological pathway. Still, unspecific MCT inhibitors have been demonstrated to exert therapeutic effects. Especially in cancer, MCT1, MCT2, and MCT4 are considered attractive targets to inhibit lactate shuttling and thereby interfering with tumor energy metabolism. For instance, the anticancer drug lonidamine is especially effective in sensitizing tumor cells to other chemotherapeutic agents and this activity can be attributed, in part, to impaired lactate transport by unspecific inhibition of MCT1, MCT2, and MCT4.

In the meantime, several specific inhibitors, targeting only MCT1 and MCT2, have been developed and their efficacy has been investigated in the preclinical setting. The MCT1/2-inhibitor AR-C155858 has been found to inhibit T-lymphocyte activation by blocking lactate efflux and, therefore, has an immunosuppressive effect. A second class of more potent MCT1/2 inhibitors has been designed, and one of these, AZD3965, is currently tested in phase I/II clinical trials for treatment of patients with advanced prostate cancer, gastric cancer, or diffuse large B-cell lymphoma (NCT01791595). Preclinical studies in patients with small cell lung cancer indicate that this compound might also be effective in this cancer entity. Due to the overexpression of MCT4, especially in hypoxic tumor regions, it has long been searched for an MCT4-specific inhibitor. AstraZeneca developed a specific and effective MCT4 inhibitor (AZ93), but no preclinical data were published so far. Just recently, first data of an MCT4-specific inhibitor, namely bindarit, were...
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published by Futagi et al. 97 Bindarit, already known as an anti-inflammatory agent inhibiting the production of selected cytokines, such as CCL2, as discussed in Futagi et al., 97 is a potent and highly selective noncompetitive MCT4 inhibitor, because it is ~15 times more selective for MCT4 than for MCT1. Therefore, bindarit is suggested to be a good pharmacological tool to decipher particularly the physiological role of MCT4. Further improvement is being refined to increase the inhibitory function, which might help to use the compound as an anticancer agent (Figure 5b) 97 and may also reduce the effect of suppressing the transcription of selected cytokines. An alternative approach to revert MCT4 overexpression to normal physiological levels, apart from isoform-specific inhibition, is to interfere with promoter DNA methylation. 98 The observed hypomethylated SLC16A3 promoter region in clear cell renal cell carcinoma might be specifically targeted by, for example, CRISPR/dCas9-mediated remethylation using DNA methyltransferases, thereby decreasing MCT4 overexpression (Figure 5c) 97,98.

Despite all the efforts, knockdown or inhibition studies have demonstrated that, due to the functional redundancy of MCT1 and MCT4, selective inhibition of either one of the isoforms may induce tumor growth arrest or may increase chemosensitivity and radiosensitivity but is not sufficient to induce tumor cell death. 27 Even simultaneous inhibition of MCT1 and MCT4 can ultimately induce a metabolic shift toward oxidative phosphorylation and survival of tumor cells. In order to tackle this metabolic plasticity, rational drug combinations, including MCT1 and MCT4 inhibitors, as well as inhibitors of oxidative phosphorylation, such as metformin or phenformin, are considered the most promising approach to run the tumor cells into a "metabolic catastrophe," leading to tumor cell death. 27,99

With respect to other MCT isoforms, data regarding their usefulness, not to mention their clinical relevance as therapeutic targets, are limited. The recently identified and characterized function of MCT11 and its contribution to T2DM, suggests MCT11 as a new drug target for the treatment of T2DM. 100 In addition, first evidence from in vitro studies shows that the impaired MCT12 function caused by selected genetic variants, leading to juvenile and age-related cataracts, can be rescued by exogenous expression of the chaperone CD147. 101 Although clinical relevance remains to be elucidated, the study highlights the importance of CD147 for functional MCT expression.

CONCLUSION

The involvement of MCTs in key metabolic pathways, such as glycolysis, fatty acid, or lipid metabolism, and not least their importance for lactate shutting, implies detrimental consequences of altered expression or function to the pathophysiology of mild disorders or severe diseases. Better understanding of the precise molecular mechanisms involving MCTs is expected to uncover novel targets and approaches for therapeutic intervention. Research into most MCT isoforms is just starting out as their importance emerges from (combined) genomewide, transcriptome-wide, proteome-wide, or metabolome-wide association studies. Moreover, due to overlapping substrate specificities, it can be expected that there is cooperation between members of the MCT (SLC16) transporter family and ABC or other SLC transporters to enable coordinate vectorial transport of substrates across plasma membranes. Altered expression or function of either one of the involved transporters can be assumed to hamper substrate flux and contribute to accumulation of substances and, hence, the pathophysiology of diseases. Thus, systematic characterization of the so far insufficiently investigated MCT transporters, further validation of preliminary findings, and elucidation of involved molecular mechanisms are absolutely necessary in the near future and are expected to provide promising new insights into disease pathophysiology.

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