# TRANSPORTERS OF MONOCARBOXYLATES: CHARACTERIZAITON AND FUNCTIONAL ROLES

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Abstract—The rapid transport of monocarboxylates, such as lactate, pyruvate and β-hydroxybutyrate, across membranes is essential for maintaining cellular homeostasis. They are mainly transported by three well-characterized protein carrier families: SLC16/monocarboxylate transporters (MCTs), SLC5/sodium-coupled monocarboxylate transporters (SMCTs), and mitochondrial pyruvate carriers (MPCs). There are 14 members in the SLC16 family (MCT1-14), however, only 5 of them (MCT1-4 and MCT7) can transport monocarboxylates. This transport process is proton-linked, electroneutral and driven by a concentration gradient of their substrates. MCT1, MCT2 and MCT4 have a broad expression pattern in various tissues with affinities in the order of MCT2>MCT1>MCT4. They play important roles in local functions and malfunctions of MCTs have been associated with devastating disorders such as cancer, obesity and ischemia. Two members of the SLC5 family, SLC5A8 (SMCT1) and SLC5A12 (SMCT2), transport monocarboxylates in a $Na^+$-dependent, electrogenic manner with a stoichiometry being 2:1 for $Na^+$/substrate. They play particularly important roles in short-chain fatty acids uptake in large intestine and regulation of uric acid reabsorption in kidney. MPCs (MPC1-2) form a large heterocomplex at the inner membrane of mitochondria and are mainly responsible for pyruvate transport into mitochondrial matrix to fuel Krebs cycle. Genetic mutations within these monocarboxylates carrier genes have been identified as causal factors for many diseases. Thus, a better understanding of their functions and regulations will help advance novel therapeutic interventions under certain pathological conditions.

*Keywords—monocarboxylate transporter (MCT); sodium-coupled monocarboxylate transporter (SMCT); mitochondrial pyruvate carrier (MPC; lactate; pyruvate; metabolism; drug transport; cancer; diabetes*

 

## *1. Introduction*

Monocarboxylates, such as lactate, pyruvate and ketone bodies (e.g. acetoacetate and β-hydroxybutyrate), play essential roles in cellular metabolism. Their transport across biological membranes are restricted and can only be mediated by membrane embedded carrier proteins. So far, three known protein families have been identified that can transport monocarboxylates: SLC16 family of solute carriers, SLC5 family of solute carriers and mitochondrial pyruvate carriers (MPCs). Because monocarboxylates are critical intermediate metabolites, their rapid transport across membranes is critical to maintain a balanced carbohydrate, amino acid and fatty acid metabolism (Halestrap 2012). This article will briefly review the key properties of the well-characterized members from the three families as well as their functional roles in a variety of biological processes.

## *2. Slc16 family*

The SLC16 family of monocarboxylate transporters (MCTs) contains a total of 14 members. They typically contain 12 transmembrane domains (TMDs). Both the N- and C-terminal ends are intracellular, along with a large intracellular loop between TMD 6 and 7 (Halestrap 2012). However, only 5 out of the 14 members (MCT1-4 and -7) have been demonstrated as transporters for monocarboxylates, whereas the other MCT isoforms differ greatly in their substrates specificity. The electroneutral transport of monocarboxylates by MCTs are both pH-dependent and gradient-driven, with a cotransport of proton (Halestrap and Price 1999). MCT1, MCT2 and MCT4 are the most widely studied isoforms because of their broader expression patterns as well as critical roles in many biological functions. Each of the three MCTs will be discussed in more details later. MCT3 was first cloned from a chick cDNA retinal pigment epithelium (RPE) library, encoding 542 amino acids (Yoon et al. 1997). It is uniquely expressed on the basolateral side of both RPE and choroid plexus epithelium (Philp, Yoon, and Lombardi 2001). The exact role of MCT7 had remained unknown until it was recently identified as a transporter for ketone bodies (e.g. β-hydroxybutyrate) out of liver in zebrafish (Hugo et al. 2012). Its loss of function causes a failed export of ketone bodies and consequent accumulation of neutral lipids within hepatocytes during fasting.

### *2.1 MCT1/SLC16A1*

#### *2.1.1 Biochemical and molecular characteristics*

The encoding cDNA of MCT1 was first cloned from Chinese Hamster Ovary (CHO) cells. The gene for human MCT1 is located on chromosome 1 between bands p13.2 and p12 (1p13.2-12) (Garcia et al. 1994). It is composed of 5 exons encoding a protein of 500 amino acids. Recent human genetic variation studies have identified single nucleotide polymorphisms (SNPs) within MCT1 gene that can impact its functions. For example, the carriers of A1470T polymorphism possess a worse lactate transport capacity out of muscle cells into venous blood (Cupeiro et al. 2010, Cupeiro et al. 2012).

The successful targeting of MCT1 onto plasma membrane requires its association with a single transmembrane (TM) glycosylated protein. In most reported cases, this protein is CD147 (also known as basigin or emmprin) (Kirk et al. 2000), although a different protein embigin has been identified to serve the same function in rat erythrocytes (Ovens et al. 2010). The transport by MCT1 is pH dependent, saturable and stereospecific (Tamai et al.

 

1995). The Michaelis constant ($K_m$) values for L-lactate, D-lactate and pyruvate are 4.54, 27.5 and 0.72 mM, respectively. The stoichiometry of lactate transport by MCT1 is one proton per substrate being transported (Carpenter and Halestrap 1994).

*2.1.2 Tissue distribution and subcellular localization*

MCT1 is the most widely expressed MCT isoform. Tissues with MCT1 expression include brain (Froberg et al. 2001, Leino, Gerhart, and Drewes 1999, Pierre et al. 2000, Takanaga et al. 1995), gastrointestinal (GI) tract (Englund et al. 2006, Gill et al. 2005, Ritzhaupt et al. 1998), retina (Bergersen, Rafiki, and Ottersen 2002, Gerhart, Leino, and Drewes 1999, Philp, Yoon, and Grollman 1998), kidney (Becker et al. 2010, Yanase et al. 2008), skeletal muscles (Fishbein, Merezhinskaya, and Foellmer 2002, Hashimoto et al. 2005, Wilson et al. 1998), heart (Bonen, Heynen, and Hatta 2006, Bonen et al. 2000, Halestrap et al. 1997), reproductive system (Goddard et al. 2003, Kuchiiwa et al. 2011), placenta (Nagai et al. 2010, Settle et al. 2004), ear (Dai, Yang, and Shi 2011, Shimozono, Scofield, and Wangemann 1997), lung (Johnson et al. 2011), mammary gland (Kirat and Kato 2009, Takebe et al. 2009), adrenal gland (Kirat 2010), fat (Iwanaga, Kuchiiwa, and Saito 2009) and so forth. By transporting monocarboxylates across biological membranes, it plays critical roles in supporting local metabolism as well as maintaining pH homeostasis. Within a cell, MCT1's expression pattern is not evenly distributed, but rather in a polarized manner. For example, in rat RPE, a strong MCT1 signal is found in the apical membrane. No signal is detected in the basolateral side, nor in intracellular compartments (Bergersen et al. 1999, Philp, Yoon, and Grollman 1998). Although MCT1 is mainly expressed on plasma membrane, many studies have detected its expression in mitochondria within tissues like skeletal muscles (Brooks et al. 1999, Yoshida et al. 2007), large intestine (Welter and Claus 2008), brain (Hashimoto et al. 2008) and heart (Martinov et al. 2009).

*2.1.3 Gene regulation*

Given the critical roles of monocarboxylates in cellular metabolism, there have been multiple layers and levels of regulation to this most widely expressed MCT isoform. Ketogenic diet, commonly used for seizure control in epileptic patients, increases MCT1's expression on rat brain endothelial cells by several folds (Leino et al. 2001, Pifferi et al. 2011). During development, a peak expression of brain MCT1 is observed at early postnatal life followed by a rapid decrease to adult level (Leino, Gerhart, and Drewes 1999, Pellerin et al. 1998). As MCT1's substrates, both lactate and butyrate have been shown to regulate its expression. In colonic epithelial cells, butyrate both increases MCT1's transcription and maintains its mRNA stability (Borthakur et al. 2008, Cuff, Lambert, and Shirazi-Beechey 2002). A rapid regulation of MCT1 expression at both mRNA and protein levels by lactate was also observed in L6 skeletal muscle cell line (Hashimoto et al. 2007).

Since MCT1 is implicated in a variety of pathological conditions, changes of its expression have been associated with and regulated by these diseases. During ischemic stroke, the expression levels of brain MCT1 in various cell types, including neurons, astrocytes and endothelial cells, are all elevated (Zhang et al. 2005). Temporal lobe epilepsy greatly decreases its expression on microvessels in hippocampus, but increases the same transporter on astrocytes (Lauritzen et al. 2011). Tumor cells are hypothesized to exploit a metabolic symbiosis by using MCT1 to uptake lactate as fuels from the glycolytic compartment

 

into oxidative cells (Sonveaux et al. 2008). As a result, increases of MCT1 expression are commonly observed in various tumors, e.g. breast (Pinheiro et al. 2010, Whitaker-Menezes et al. 2011), ovarian (Chen et al. 2010), prostate (Fiaschi et al. 2012), melanoma (Ho et al. 2012, Shimoyama et al. 2007), non-small cell lung carcinoma (Lee et al. 2011) and leukemia (Birsoy et al. 2013).

*2.2 MCT2/SLC16A7*

*2.2.1 Biochemical and molecular characteristics*

MCT2 was first cloned from a hamster liver cDNA library. It shares 60% identity to MCT1 (Garcia et al. 1995). MCT2 is less conserved between species than MCT1 (Jackson et al. 1997). In human, MCT2 is mapped to chromosome 12q13. Human version of MCT2 cDNA is 1,907 bp long and encodes a polypeptide of 478 amino acids (Lin et al. 1998). The targeting of MCT2 onto plasma membrane requires its association with another ancillary protein, embigin (Ovens et al. 2010). Monocarboxylates transport via MCT2 is also driven by an $H^+$ gradient, and is strongly increased with decreasing pH (Broer et al. 1999). The $K_m$ values of MCT2 in transporting its substrates are generally lower than MCT1 and are reported to be 0.74, 1.2, and 2.6 mM for L-lactate, D,L-β-hydroxybutyrate, and acetate respectively, implying that this is a MCT with high affinity.

*2.2.2 Tissue distribution and subcellular localization*

MCT2 expression is detected in most of the tissues where MCT1 is present. This is not unexpected because it has been reported that many tissues can coexpress 4-5 MCTs (Bonen, Heynen, and Hatta 2006). Tissues with detected MCT2 expression include brain (Baud et al. 2003, Chiry et al. 2008, Cortes-Campos et al. 2013, Fayol et al. 2004, Gerhart et al. 1998, Hanu et al. 2000), eye (Chidlow et al. 2005, Gerhart, Leino, and Drewes 1999), inner ear (Okamura, Spicer, and Schulte 2001, Shimozono, Scofield, and Wangemann 1997), GI tract (Iwanaga et al. 2006, Sepponen et al. 2007), kidney (Becker et al. 2010, Wang, Darling, and Morris 2006, Yanase et al. 2008), liver (Jackson et al. 1997), lung (Johnson et al. 2011), testis (Boussouar et al. 2003, Brauchi et al. 2005), osteoblasts (Hinoi et al. 2006), and prostate (Pertega-Gomes et al. 2013, Pertega-Gomes et al. 2011). Like MCT1, the subcellular localization of MCT2 is also polarized in a tissue-specific manner. For example in the brain, MCT2 has been widely reported to be concentrated at postsynaptic membranes such as parallel fiber-Purkinje cell synapses (Baud et al. 2003, Bergersen, Magistretti, and Pellerin 2005, Chiry et al. 2008). This unique localization implies that this transporter is mainly responsible for controlling the influx of energetic substrates in synaptic cleft by neuronal action (Bergersen et al. 2001). Besides, MCT2's expression colocalizes with a peroxisomal marker, rendering it an important redox regulator (Jansen, Pantaleon, and Kaye 2008).

*2.2.3 Gene regulation*

Similar to MCT1, the expression of MCT2 in rodent brain also shows a regulatory pattern by development. Specifically, *in situ* hybridization shows that its expression peaks around early postnatal days (day 15) but rapidly declines to its adult level by postnatal day 30 (Pellerin et al. 1998). Hormones regulate cellular metabolism and neuronal plasticity. Acute injection of brain-derived neurotrophic factor (BDNF) into mouse hippocampal area causes an isoform specific upregulation of MCT2 (Robinet and Pellerin 2011). Under various pathological conditions, MCT2 expression can also be

 

changed. In spontaneous hypertensive rats, five days after a permanent occlusion of the left middle cerebral artery (MCAO), a well-established ischemic model, brain MCT2 mRNA level increases in cells within the infarct and bordering the scar, suggesting a possible role of hypoxia dependent regulation (Zhang et al. 2005). In the development of obesity, as shown by mice fed on a high fat diet and genetically obese animals, the expression of MCT2 is increased throughout the brain but prominently in cortex and hippocampus (Pierre et al. 2007). Analysis of human gastrointestinal stromal tumor samples reveals a high expression of MCT2 (de Oliveira et al. 2012), supporting the critical role of MCTs in transporting lactate generated by the aerobic glycolysis in tumors.

*2.3 MCT4/SLC16A4*

*2.3.1 Biochemical and molecular characteristics*

MCT4 (formerly designated as MCT3) is identified as the major MCT isoform in fast-twitching fibers and responsible for the efflux of glycolytic lactate out of white skeletal muscles (Wilson et al. 1998). Human MCT4 gene is localized on chromosome 1p13.3. The $K_m$ values of MCT4 for L-lactate, D-lactate and pyruvate are 28, 519 and 153 mM, respectively. Genetic variations of MCT4 gene in Chinese and Indian groups of Singaporean population identify multiple polymorphisms spreading over all the parts of its genomic sequences, including promoter region, 5'-UTR, coding exons, introns and 3'UTR (Lean and Lee 2012). Out of all the variants, only 44C>T (Ala15Val) missense mutation is predicted to have a potentially damaging effect on MCT4 protein function. The successful targeting of MCT4 onto plasma membrane also requires its association with the same ancillary protein as that of MCT1, namely CD147 (Kirk et al. 2000).

*2.3.2 Tissue distribution and subcellular localization*

Expression of MCT4 has been demonstrated in tissues including brain (Bergersen et al. 2001, Pellerin et al. 2005, Rafiki et al. 2003), skeletal muscles (Bonen, Heynen, and Hatta 2006, Dubouchaud et al. 2000, Pilegaard et al. 1999), adipocytes (Perez de Heredia, Wood, and Trayhurn 2010), blood cells (Merezhinskaya, Ogunwuyi, and Fishbein 2006, Moreau et al. 2011), eye (Chidlow et al. 2005, Philp et al. 2003, Vellonen et al. 2010), reproductive system (Brauchi et al. 2005, Galardo et al. 2008, Herubel et al. 2002, Rato et al. 2012), GI tract (Kirat et al. 2007, Sepponen et al. 2007), placenta (Nagai et al. 2010, Settle et al. 2004) and lung (Johnson et al. 2011). At subcellular level, MCT4 has been detected in sarcolemma-enriched fraction and this subcellular localization is correlated positively to a net lactate release, consistent with its role of transporting lactate across plasma membrane out of glycolytic muscle cells (Dubouchaud et al. 2000, Hashimoto et al. 2005). Although MCT4 is well known positioned on plasma membrane, expression of this transporter has been detected in mitochondria (Benton et al. 2004). Species difference of MCT4 polarity has been reported since it is found on apical surface of corneal endothelial cells in bovine, but on the lateral membrane of the same cells in rabbit (Nguyen and Bonanno 2011, 2012).

*2.3.3 Gene regulation*

The expression of MCT4 can be regulated by a variety of factors, such as development/aging, differentiation, diet, exercise, hormones, hypoxia and pathologies. For example, both mRNA and protein expression of MCT4 in rat heart is only detectable by postnatal day 10 and

 

disappears afterwards (Hatta et al. 2001). In the rat brain, MCT4 expression is very low at birth but reaches adult level by postnatal day 14 (Rafiki et al. 2003). Hormones can regulate a wide range of cellular metabolism; as a result, evidences of their modulation on MCT4 have been reported. In rat skeletal muscles, testosterone increases MCT4 protein levels without altering its mRNA (Enoki et al. 2006). MCT4 expression has been associated with and regulated by the progression of various cancer types. For example, compared with control tissues, the cytosolic expression of MCT4 in prostate tumor samples is dramatically increased (Pertega-Gomes et al. 2011). Besides, MCT4 is strongly implicated in metastasis and a significantly higher expression of MCT4 has been reported in metastatic renal carcinomas (Keshari et al. 2013). Regulation of MCT4 by other forms of pathologies include mitochondrial myopathy (MM), pulmonary diseases, ischemia and obesity. Specifically, expression of MCT4 in the skeletal muscles of a patient with MM is increased in order to extrude excessive lactate out of cells to avoid lactic acidosis (Baker, Tarnopolsky, and Bonen 2001). During ischemic insult, MCT4 expression increases in cells within the infarct and bordering the scar, similar to the findings of MCT1 and MCT2 (Zhang et al. 2005).

*2.4 Functional roles of MCTs*

*2.4.1 Skeletal muscles*

The expression patterns of MCTs in the metabolically heterogeneous skeletal muscles reflect different roles of these isoforms. MCT1 is highly expressed in oxidative fibers but is almost absent in glycolytic fast-twitch fibers where MCT4 is predominantly expressed (Fishbein, Merezhinskaya, and Foellmer 2002, Wilson et al. 1998). Consistent with MCT1 being the isoform of higher affinity whereas MCT4 has a lower affinity but a higher transport capacity, their divergent locations indicate that MCT4 is mainly responsible for efflux of excessive lactate out of glycolytic muscles, whereas MCT1 takes up lactate as fuels into oxidative muscles for mitochondrial consumption (Bonen, Baker, and Hatta 1997, McCullagh et al. 1996). Because muscle fatigue can be partially contributed to an increased accumulation of lactate within muscle cells, an enhanced lactate transport across sarcolemmal membranes via MCT1 and MCT4 could constitute an advantage during intense muscle activities (Messonnier et al. 2006).

*2.4.2. Brain functions*

Like in skeletal muscles, MCTs show a heterogeneous expression pattern across the brain on different cell types, with MCT1 being mostly expressed on brain endothelial cells, astroglia, oligodendrocytes and a subset of neurons, MCT2 being mainly on neurons and MCT4 on astrocytes (Canis et al. 2009, Debernardi et al. 2003, Gerhart et al. 1997, Leino, Gerhart, and Drewes 1999, Mac and Nalecz 2003). The neuronal expression of MCT2, the MCT isoform with highest affinity, ensures a successful delivery of lactate and other energetic monocarboxylates into neurons for consumption, even at their low concentrations. Consistent with their localizations, an astrocyte-neuron lactate shuttle hypothesis has been proposed that lactate is generated and mobilized from astrocytes through MCT1/4 and transported into neurons via MCT2 for oxidative metabolism (Pellerin et al. 1998). Although this hypothesis is still controversial, lactate transport through MCTs between different brain compartments has been shown to be critical for various brain functions. For example, during long term memory (LTM) formation in hippocampus, astrocytic lactate generated through glycogenolysis is first extruded out via MCT1/4 and then taken up

 

via MCT2 into neighboring neurons. This lactate transport between the two compartments is essential for strengthening synaptic plasticity that is required for LTM formation, because blocking MCTs on either side compromises this process (Suzuki et al. 2011). These findings all poise proper MCTs expression in the brain an essential role in maintaining important functions.

*2.4.3 Drug transport*

Many pharmaceutical agents containing monocarboxylate group(s) can be recognized and thus transported by MCTs. The broad expression patterns of MCTs in a lot of tissues, including GI tract, blood-brain barrier, retina and kidney, make them suited for an efficient absorption or extrusion of monocarboxylic drugs. For example, the transport of benzoic acid, a drug that has been used for treating fungal skin diseases, is mediated via MCT1 in both porcine brain capillary endothelial cells and corneal epithelium (Kido et al. 2002, Vellonen et al. 2010). Valproic acid is widely used as an antiepileptic drug; its transport across intestinal epithelium and brain endothelium in order to reach brain parenchyma is mediated by an unknown $H^+$-dependent MCT and MCT1 at the two sites, respectively (Fischer et al. 2008). The transport of γ-hydroxybutyrate (GHB), an approved therapeutic agent for treating cataplexy with narcolepsy, into an intestinal cell line Caco-2 is mediated by an $H^+$-dependent MCT. More interestingly, concomitant administration of GHB with flavonoids decreases the former's reabsorption at kidney, thus leading to an increased rate of clearance (Wang and Morris 2007a, b). These findings may have important clinical implications because GHB is a widely abused euphoriant.

*3. SLC5 FAMILY*

*3.1 Biochemical and molecular characteristics*

SLC5 family of solute carriers are also known as sodium-coupled monocarboxylate transporters (SMCTs). SMCT1 (SLC5A8) was originally cloned from a human kidney cDNA library in the attempt to identify new iodide transporters in thyrocytes (Rodriguez et al. 2002). Human SMCT1 gene is localized on chromosome 12q23.1, composed of 15 exons and encoding a protein of 610 amino acids. SMCT1 is a sodium-coupled and electrogenic transporter for monocarboxylates (Ganapathy et al. 2005, Gopal, Umapathy, et al. 2007, Martin et al. 2006). The stoichiometry for SMCT1 is shown to be an invariant 2:1 for Na+/substrate (Coady et al. 2007). The $K_m$ of SMCT1 is 0.18 mM for L-lactate, 1.4 mM for β-D-hydroxybutyrate, 0.39 mM for pyruvate and 0.21 mM for acetoacetate (Martin et al. 2006). SMCT2 (SLC5A12) was first isolated from a mouse kidney cDNA library and identified as the twelfth member of the SLC5 family (Srinivas et al. 2005). Its human orthologue is localized on chromosome 11p14.2, encoding a protein of 618 amino acids (Gopal, Umapathy, et al. 2007). It shares a similar substrate specificity to that of SMCT1, however, the substrate affinities of SMCT2 are much lower than those of SMCT1.

*3.2 Tissue distribution and subcellular localization*

Reported tissues expressing SMCT1 include brain, kidney, large intestine, retina and thyroid gland (Cui and Morris 2009, Gopal, Umapathy, et al. 2007, Martin et al. 2007, Martin et al. 2006, Srinivas et al. 2005), whereas the documented expression patterns of SMCT2 are limited to tissues like intestine, kidney and retina. On subcellular level, polarized expression of SMCTs has

 

been reported, as in the case of MCTs. In intestine, SMCT1 mainly localizes on the luminal membrane of intestinal epithelial cells and, together with SMCT2, on the brush border of enterocytes in the intestinal villi (Gopal, Miyauchi, et al. 2007, Teramae et al. 2010). In kidney, both SMCTs are mostly expressed on cortex and localized on the apical membrane of the tubular cells (Gopal, Umapathy, et al. 2007).

*3.3 Gene regulation*

Multiple regulatory mechanisms for SMCTs have been documented, mainly in tissues of colon and kidney. In colonic epithelium, transcription factors CDX1 and CDX2 bind the promoter region and upregulate expression of SMCT1 (Kakizaki et al. 2010). In the same cell type, probiotic *Lactobacillus* species induce the promoter activity and mRNA expression of SMCT1 (Borthakur et al. 2010). Sex hormones have differential roles in regulating SMCT1, since testosterone enhances both mRNA and protein expression in kidney, whereas progesterone suppresses SMCT1 protein levels in the same tissue (Hosoyamada et al. 2010, Takiue et al. 2011).

*3.4 Functional roles*

*3.4.1 Cancer*

One of the major mechanisms of SMCT1 as a tumor suppressor gene is its function to transport butyrate across intestinal epithelium. Butyrate is a byproduct of bacterial fermentation of dietary fibers in large intestine and serves as a major fuel for colonocytes. It not only maintains a balanced homeostasis by ameliorating mucosal inflammation, but also protects against colorectal cancer by inhibiting histone deacetylases (HDACs) (Gupta et al. 2006, Treem et al. 1994). In fact, many pathological changes leading to the development of colorectal cancer have been shown to work through SMCT1. For example, oxidative stress has proinflammatory and procarcinogenic effects by inhibiting SMCT1 mediated uptake of butyrate into intestinal epithelium, although the expression levels of SMCT1 is not altered here (Goncalves et al. 2013).

*3.4.2 Drug transport*

SMCT1 exhibits substrates specificity similar to that of the SLC16/MCTs family. So, SMCT1 can also transport a lot monocarboxylate drugs in intestinal tract for their absorption, such as benzoate, salicylate, and 5- aminosalicylate (Gopal, Miyauchi, et al. 2007). Moreover, nicotinic acid, a precursor for nicotinamide adenine dinucleotide (NAD), is an efficient substrate of SMCT1 with $K_m$=0.23 mM. In RPE, transport of 2-oxothiazolidine-4-carboxylate (OTC) via SMCT1 is saturable with Kt=104 µM (Babu et al. 2011). OTC can increase intracellular glutathione levels and protect RPE cells from oxidative stress induced cell death.

*3.4.3 Urate homeostasis*

Urate, the end product of purine degradation in human, not only maintains *in vivo* homeostasis but also is capable of removing 60% free radicals from the serum (Waring, Webb, and Maxwell 2001). Abnormal levels of urate are associated with multiple diseases, such as Hodgkin's disease, Alzheimer's disease, gout, hypertension, cardiovascular diseases and type 2 diabetes (Choi et al. 2005, Ioachimescu et al. 2008, Kutzing and Firestein 2008, Lu, Nakanishi, and Tamai 2013, So and Thorens 2010, Tykarski 1988). Urate is mainly excreted into urine and cleared through kidney. There is a urate transporter 1 (URAT1) located on the apical side of the renal proximal tube to reabsorb and thus regulate the blood level of urate (Enomoto et al. 2002). SMCTs at the same site are proposed to enhance URAT1-mediated urate reabsorption by providing

 

exchanging monocarboxylates (e.g. lactate and nicotinate), indicating that SMCTs could be potential targets for indirectly modulating urate serum levels (Lu, Nakanishi, and Tamai 2013). Pyruvate is at the diverging

*4. MPCs*

*4.1 Discovery, structure and molecular characteristics*

point for fermentative and oxidative metabolism. The presence of a pyruvate transporter at mitochondria had been hypothesized based on kinetics and inhibitor studies (Halestrap 1975); however, only recently was it identified and characterized (Bricker et al. 2012, Herzig et al. 2012). Two evolutionally conserved proteins, MPC1 and MPC2 (formerly known as BRP44L and BRP44, respectively), form a large heterocomplex that is responsible for taking up pyruvate across the inner mitochondrial membrane. Human MPC1 gene is located on chromosome 6q27, encoding two variants of 109 or 66 amino acids. MPC2, the paralog of MPC1, is located on chromosome 1q24, coding for a protein of 127 amino acids.

*4.2. Functional roles in metabolism and diseases*

Altered MPCs activity can impact numerous diseases and biological functions, such as cancer, insulin secretion from β cells as well as insulin sensitization in peripheral tissues. Specifically, the relative usage of pyruvate for oxidative phosphorylation in cancerous mitochondria is usually decreased. However, the metabolic flux through Krebs cycle is maintained by deriving compensatory acetyl-CoA molecules from glutaminolysis, a process that is highly favored by cancer cells (Vander Heiden, Cantley, and Thompson 2009). Concomitant administration of inhibitors to MPCs and glutaminolysis depletes both sources of acetyl-CoA and significantly impairs tumor growth (Yang et al. 2014). In pancreatic β cells, pyruvate transport into mitochondria plays an important role in stimulating insulin release. Mice with genetically disturbed Mpc2 gene show a reduced pyruvate oxidation ability and an impaired glucose tolerance due to a decreased secretion of insulin from β cells (Vigueira et al. 2014). Recent findings have linked MPCs with the action of thiazolidinediones (TZDs), the widely used insulin sensitizing drugs in type 2 diabetes. Evidences show that TZDs target and inhibit MPC complex. This acute inhibition significantly enhances glucose uptake in human skeletal muscle myocytes (Colca et al. 2013, Divakaruni et al. 2013). As a result, MPCs may reveal a valuable therapeutic target for improving peripheral insulin sensitivity.

*5. Conclusions*

Given the central role of monocarboxylates, such as lactate, pyruvate and β-hydoxybutyrate, in cellular energy metabolism, it is not surprising that their transporters are involved in so many biological functions and pathological states. Further studies to decipher more regulatory mechanisms will be necessary in order to manipulate the transport activities of MCTs/SMCTs/MPCs as needed. In addition, future characterization of the so far unknown MCTs will provide new routes for drug delivery options. Together, a better understanding of all the monocarboxylates transporters, under both physiological and pathological conditions, is beneficial for novel therapeutic design to diseases such as cancer, diabetes and ischemia.

 

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