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Monocarboxylate transporters in the brain and in cancer[☆]



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ABSTRACT

Monocarboxylate transporters (MCTs) constitute a family of 14 members among which MCT1–4 facilitate the passive transport of monocarboxylates such as lactate, pyruvate and ketone bodies together with protons across cell membranes. Their anchorage and activity at the plasma membrane requires interaction with chaperon protein such as basigin/CD147 and embigin/gp70. MCT1–4 are expressed in different tissues where they play important roles in physiological and pathological processes. This review focuses on the brain and on cancer. In the brain, MCTs control the delivery of lactate, produced by astrocytes, to neurons, where it is used as an oxidative fuel. Consequently, MCT dysfunctions are associated with pathologies of the central nervous system encompassing neurodegeneration and cognitive defects, epilepsy and metabolic disorders. In tumors, MCTs control the exchange of lactate and other monocarboxylates between glycolytic and oxidative cancer cells, between stromal and cancer cells and between glycolytic cells and endothelial cells. Lactate is not only a metabolic waste for glycolytic cells and a metabolic fuel for oxidative cells, but it also behaves as a signaling agent that promotes angiogenesis and as an immunosuppressive metabolite. Because MCTs gate the activities of lactate, drugs targeting these transporters have been developed that could constitute new anticancer treatments. This article is part of a Special Issue entitled: Mitochondrial Channels edited by Pierre Sonveaux, Pierre Maechler and Jean-Claude Martinou.

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1. Introduction

Monocarboxylate transporters (MCTs) constitute a family of 14 transmembrane proteins encoded by the *SLC16A* family of genes. According to the transporter classification system of Milton Saier (<http://www.tcdb.org>), MCTs belong to the monocarboxylate porter

Abbreviations: AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPK, AMP-activated protein kinase; BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; CA, carbonic anhydrase; CAF, cancer-associated fibroblast; CHC, α -cyano-4-hydroxycinnamate; CN, calcineurin; CTL, cytolytic T lymphocyte; DBDS, 4,4'-dibenzamidostilbene-2,2'-disulphonate; DC, dendritic cell; DIDS, 4,4'-diisothiocyanato-2,2'-stilbenedisulfonic acid; EAAT1, excitatory amino acid transporter 1; glpT, glycerol phosphate transporter; IGF1, insulin-like growth factor 1; I κ B α , inhibitor of NF- κ B kinase β ; LDH, lactate dehydrogenase; MCP, monocarboxylate porter; MCT, monocarboxylate transporter; MDSC, myeloid-derived suppressor cell; MFS, major facilitator superfamily; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NFAT, nuclear factor of activated T cells; NF- κ B, nuclear factor- κ B; NK, natural killer (cell); NMDA, *N*-methyl-D-aspartate; NSCLC, non-small cell lung cancer; OXPHOS, oxidative phosphorylation; pCMBS, *p*-chloromercuribenzenesulphonate; PHD, prolylhydroxylase; ROS, reactive oxygen species; TM, transmembrane (domain); VEGF, vascular endothelial growth factor.

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(MCP) family (2.A.1.13), itself a member of the major facilitator superfamily (MFS). MCTs have been identified in all eukaryotic organisms of which genomes have been sequenced to date. They can transport a wide variety of substrates (Table 1). Four members of the MCT family, MCT1, MCT2, MCT3 and MCT4 are monocarboxylate transporters responsible for the proton-linked transport of several monocarboxylate metabolites, such as pyruvate, *L*-lactate and ketone bodies (acetoacetate and *D*- β -hydroxybutyrate) across the plasma membrane [1,2]. Other best characterized MCTs are MCT8 that has a high affinity for thyroid hormones T3 and T4, and MCT10/TAT1, a transporter of aromatic amino acids [2,3]. MCT6 has been reported to facilitate the proton-linked transport of bumetanide, but its natural substrate is unknown [4]. MCT7 has been implicated in the export of ketone bodies by hepatocytes fueled with circulating fatty acids upon fasting [5]. Accordingly, loss of MCT7 expression resulted in hepatic steatosis in Zebrafishes, which was prevented by the introduction of human MCT7. MCT9 has been clearly identified as a sodium- and pH-independent carnitine efflux transporter when it was expressed in *Xenopus* oocytes injected with [³H]-carnitine [6]. The substrates and functions of the five other MCT family members are currently unknown.

MCTs have numerous physiological functions as they are expressed in a wide range of tissues (such as brain, skeletal muscle, heart, bowel and liver) where they control, among others, the central metabolism of glucose, gluconeogenesis, activation of T-lymphocytes, spermatogenesis,

Table 1
The MCT family of transporters.[§]

Human gene name	Protein name	Sequence accession ID	Main substrates	Tissue distribution
<i>SLC16A1</i>	MCT1	NM_003051	Lactate, pyruvate, ketone bodies	Ubiquitous except β cells of the endocrine pancreas
<i>SLC16A2</i>	MCT8	NM_006517	T2, rT3, T3, T4	Ubiquitous
<i>SLC16A3</i>	MCT4	NM_004207	Lactate, ketone bodies	Skeletal muscle, chondrocytes, leucocytes, testis, lung, brain, ovary, placenta, heart
<i>SLC16A4</i>	MCT5	NM_004696	–	Brain, muscle, liver, kidney, lung, ovary, placenta, heart
<i>SLC16A5</i>	MCT6	NM_004695	Bumetanide probenecid nateglinide	Kidney, muscle, brain, heart, pancreas, prostate, lung, placenta
<i>SLC16A6</i>	MCT7	NM_004694	Ketone bodies	Liver, brain, pancreas, muscle, prostate
<i>SLC16A7</i>	MCT2	NM_004731	Pyruvate, lactate, ketone bodies	High expression in testis, moderate to low in spleen, heart, kidney, pancreas, skeletal muscle, brain and leucocytes
<i>SLC16A8</i>	MCT3	NM_013356	Lactate	Retinal pigment epithelium, choroid plexus
<i>SLC16A9</i>	MCT9	NM_194298	Carnitine	Endometrium, testis, ovary, breast, brain, kidney, spleen, retina
<i>SLC16A10</i>	MCT10/TAT1	NM_018593	Aromatic amino acids, T3,T4	Kidney (basolateral), intestine, muscle, placenta, heart
<i>SLC16A11</i>	MCT11	NM_153357	–	Skin, lung, ovary, breast, lung, pancreas, retinal pigment epithelium, choroid plexus
<i>SLC16A12</i>	MCT12	NM_213606	–	Kidney, retina, lung testis
<i>SLC16A13</i>	MCT13	NM_201566	–	Breast, bone marrow stem cells
<i>SLC16A14</i>	MCT14	NM_152257	–	Brain, heart, muscle, ovary, prostate, breast, lung, pancreas liver, spleen, thymus

[§] Adapted from references [5,6,10].

pancreatic β cell activity, thyroid hormone metabolism and drug transport. In addition to their implication in various physiological processes, they play significant roles in pathological situations as can be exemplified by the case of tumors. This review will summarize the current knowledge pertaining to their functions in the brain, where their physiological roles are starting to emerge in greater details, and in cancer, which represents a pathology in which MCTs are clearly occupying an important position.

2. General description of monocarboxylate transporters

2.1. The MCT family: structural and functional characteristics

2.1.1. Structure

Theoretical predictions and biochemical assays with MCT1 as a model protein indicate that all the members of the MCT family share a common topology. Hydropathy plots predict the presence of 12-transmembrane (TM) helices with intracellular C- and N-termini, a large cytosolic loop between TM helices 6 and 7, and two highly conserved sequences in TM1 and TM5 [7]. A common feature shared with MFS members is a better sequence conservation in TM regions compared to loops and C-termini. To date, no crystallographic characterization of MCTs has been reported, but Halestrap et al. [7–9] have proposed 3D models based on molecular modeling, the structure of the *E. coli* glycerol phosphate transporter GlpT, site-directed mutagenesis and the binding sites for 4,4'-diisothiocyano-2,2'-stilbenedisulfonic acid (DIDS), a MCT1 inhibitor. These models suggest that the structure of MCT1 at the plasma membrane may swing between two states: a closed conformation where the substrate-binding site is cytosolic and an open conformation where this site is extracellular (for a graphical representation, see Fig. 3 in reference [7]).

2.1.2. Mechanism of activity

The predicted open and closed conformations of MCTs and kinetic analyses of proton-linked transport of lactate into erythrocytes are the basis for the proposed translocation mechanism of lactic acid transport by human MCT1 through the plasma membrane. MCT1 preferentially facilitates the uptake of lactic acid and operates in an ordered process that starts when a proton binds to K38 at the extracellular surface of MCT1, providing a positive charge to the lysine [8,9,11]. Proton binding is followed by the binding of one molecule of lactate to form an ionic pair, which promotes a conformational change from closed to open state. It follows that the proton is transferred to D302 and lactate to R306 (both residues are localized at the inner surface of the channel),

thus deprotonating K38, which induces the return to the closed conformation and exposure of the D302/R306 site to the cytosol. The pair H^+ / lac^- is released into the cytoplasm. Another essential residue for MCT1 activity is F360, protruding into the channel of the transporter where it controls substrate selectivity by steric hindrance. According to this mechanism, the transport of lactic acid by MCT1 is passive and bidirectional: import and export depend on the intra- and extracellular concentrations of lactate and protons [2,7]. This molecular model highlights the importance of three residues, which are conserved in the four members of the MCT family that transport monocarboxylates (MCT1, MCT2, MCT3 and MCT4) and in MCT7, where there is a conservative substitution of D302 by E302.

2.1.3. Substrates

MCT1, MCT2, MCT3 and MCT4 are responsible for the bidirectional proton-linked transport of monocarboxylates across the plasma membrane, and will be the focus of this review. These MCT isoforms show preference for short chain monocarboxylates, including those substituted on positions two and three, such as pyruvate, L-lactate, D- β -hydroxybutyrate and acetoacetate. Quantitatively, lactate is one of the most important metabolites for these transporters, with a stereoselectivity for L- over D-lactate [7] consistent with the fundamental role of the L stereoisomer in eukaryotic cell metabolism. With a K_m of 22–28 mM, MCT4 has the lowest affinity for lactic acid [12] (Table 2). However, it has a high turnover rate [13], making it particularly well adapted for the export of lactate by glycolytic cells where it helps to control intracellular pH homeostasis [12,14]. Comparatively, MCT1 has an intermediate affinity for lactate ($K_{m,lactate} = 3.5$ –10 mM) and is widely expressed in healthy and cancer tissues [2,15]. MCT2 ($K_{m,lactate} = 0.5$ –0.75 mM) and MCT3 ($K_{m,lactate} = 5$ –6 mM) show the highest affinity for lactate, but their expression is restricted to very specific tissues (see Section 2.1.5) [16–18]. Differences in the K_m of the transporters for pyruvate are more pronounced, with $K_{m,pyruvate}$ values of 1.0, 0.1 and 153 mM for MCT1, MCT2 and MCT4, respectively [7]. MCT2 has the highest affinity for ketone bodies, with $K_{m,D-\beta\text{-hydroxybutyrate}} = 1.2$ mM and $K_{m,acetoacetate} = 0.8$ mM determined in *Xenopus oocytes* [19]. For MCT1, these values are $K_{m,D-\beta\text{-hydroxybutyrate}} = 12.5$ mM and $K_{m,acetoacetate} = 5.5$ mM [20]. The transport of ketone bodies by MCT3 has not been evaluated, and is not likely to occur through MCT4 due to the very low affinity of the transport for these substrates [7]. Beyond natural substrates, recent evidence also shows that MCT1 is controlling the uptake of 3-bromopyruvate [21] (an alkylating agent developed for cancer therapy) and of dichloroacetate [22] (a pyruvate dehydrogenase kinase inhibitor that restores the mitochondrial metabolism of pyruvate

Table 2
Km values of MCT1, MCT2, MCT3 and MCT4.

Transporter	K _m _{lactate}	K _m _{pyruvate}	K _m _{D-β-hydroxybutyrate}	K _m _{acetoacetate}	References
MCT1	3.5–10 mM	1.0 mM	12.5 mM	5.5 mM	[2,7,15,20]
MCT2	0.5–0.75 mM	0.1 mM	1.2 mM	0.8 mM	[7,16–19]
MCT3	5–6 mM	–	–	–	[16–18]
MCT4	22–28 mM	153 mM	–	–	[7,12]

in glycolytic cancer cells and is currently undergoing clinical trials for several types of cancers).

Lactate is one of the main substrates of MCT1–4. This metabolite is generated from pyruvate (produced from glycolysis and glutaminolysis) during lactic fermentation. In most normal tissues where lactate is produced, MCT1 is responsible for its export across the plasma membrane to the extracellular space [2,23]. However, in glycolytic cancer cells and other specific tissues such as white muscle fibers and astrocytes, MCT4 predominates over MCT1 for lactate export (see details in Sections 3.1 and 4.1) [15,24–26]. The low affinity of MCT4 for pyruvate could prevent the release of pyruvate that is essential for the conversion of NADH into NAD⁺ for the maintenance of a high glycolytic flux [2,23].

In metabolic pathways comprising lipogenesis, gluconeogenesis and oxidative phosphorylation (OXPHOS), lactate can be used as a substrate taken up from the extracellular space. Cells that consume lactate may express MCT1, MCT2 or both depending on tissues and species [2,27]. In many cancer cells with an oxidative metabolic fingerprint, MCT1 is the major MCT isoform to be expressed [2,25,28]. It promotes the import of lactate that then fuels the TCA cycle and OXPHOS [25,29]. Accordingly, there is increasing evidence pointing towards shuttling of this metabolite between cells with different metabolic behaviors in a same tissue. Such phenomenon has been described in the skeletal muscle where glycolytic/white fibers export lactate through MCT4 and oxidative/red fibers express MCT1 to import lactate to be used as a fuel for the TCA cycle [30,31]. A similar mechanism has been proposed to account for a metabolic symbiosis between glycolytic/hypoxic cancer cells and oxidative/oxygenated cancer cells in tumors [25]. In the brain, glycolytic oligodendrocytes and astrocytes export lactate through MCT1 and MCT4 to fuel oxidative neurons expressing MCT2 [32–34]. The roles of MCTs in brain physiology and in tumor pathology are detailed in Sections 3 and 4, respectively.

2.1.4. Inhibitors

Several MCT inhibitors have been identified, but none are specific for a given MCT isoform and most of them present a high affinity for other proteins (Table 3). Oldest described inhibitors are phloretin, flavonoids such as quercetin, stilbene disulphonates (including DIDS and 4,4'-dibenzamidostilbene-2,2'-disulphonate [DBDS]), and α-cyano-4-hydroxycinnamate (CHC) and its analogs [1,7]. All have off-target effects. In particular, CHC has the capacity to inhibit the

mitochondrial pyruvate carrier (MPC, K_i ~ 2 μM), hence the mitochondrial uptake of pyruvate, much more efficiently than MCT1 (K_i 166 μM) [35]. Other inhibitors have been more recently developed that exhibit a high affinity for MCTs [36]. Compound AZD3965 is a dual MCT1 and MCT2 inhibitor currently evaluated as an anticancer agent in Phase I clinical trials for patients with prostate cancer, gastric cancer or diffuse large B cell lymphoma (ClinicalTrials.gov NCT01791595). Importantly, the related compound AR-C155858 is a dual MCT1/2 inhibitor that inhibits MCT2 when it is bound to ancillary protein basigin but not when it is bound to its preferred chaperone protein embigin [36] (see also Section 2.2.3). Draoui et al. [37,38] have recently identified several original compounds belonging to the 7-aminocarboxycoumarine family that potently inhibit MCTs. Measurements of the inhibition of lactate flux revealed that the most active compounds (IC₅₀ = 10–50 nM) are three log orders more active than CHC. Interestingly, 7-(N-benzyl-N-methylamino)-2-oxo-2H-chromene-3-carboxylic acid (7ACC2) was further reported to be an inhibitor of lactate uptake (IC₅₀ = 11 nM on 14C-lactate flux inhibition) that does not inhibit lactate export [38]. Subtle allosteric regulation of MCT conformation was proposed to account for unidirectional flux inhibition. Another possibility that remains to be investigated would be an inhibitory effect on the MPC [35].

2.1.5. Cell-specific distribution

Information exists about the cellular distribution of MCT1–4 (Table 1), although it cannot be considered exhaustive. Expression of MCT1 is viewed as being rather ubiquitous, since it is found in several tissues and organs. It is encountered in all muscle cells, although it is particularly enriched in cells of oxidative (type I) fibers [48–52]. In the heart, it is found in cardiomyocytes [16,53,54]. In the liver, hepatocytes exhibit strong MCT1 expression [16,22,53,55]. Different levels of MCT1 expression are found along the gastrointestinal tract in the stomach, duodenum, jejunum, ileum, cecum, colon and rectum, associated with epithelial cells (including enterocytes) on both basolateral and apical membranes, suggesting that the transporter is involved in both the absorption of monocarboxylates from the lumen and their efflux towards blood [56–62]. In the blood, erythrocytes [53,63–65] and immune cells including lymphocytes and monocytes [66] do express MCT1. The transporter is also present in adipocytes of white adipose tissue [18,67]. In the placenta, MCT1 was found to be expressed in syncytiotrophoblasts in a polarized

Table 3
Comparison of inhibitor selectivity for MCT1, MCT2 and MCT4.

Inhibitor	Inhibition index	MCT1	MCT2	MCT4	Other targets	References
Phloretin	K _i (μM)	5	14	41	GLUT	[14,19,39–41]
Quercetin	% inhibition	89	83	–	Many	[19,42]
DIDS	K _i (μM)	434	–	NI	Aquaporin, Cl [−] /HCO ₃ [−] exchanger	[14,39,43,44]
DBDS	% inhibition at 0.1 mM	0	56	–		[19,39]
NPPB	K _i (μM)	9	–	240		[14,19,39]
CHC	K _i (μM)	166	24	991	Mitochondrial pyruvate carrier	[14,19,35,39]
AR-C155858	K _i (nM)	1.2 (2.3)*	<10* [§]	–		[45,46]
AZD3965	Binding affinity (nM)	1.6	9.6	–		[47]
7ACC2	IC ₅₀ for lactate uptake (nM)	11	–	–		[37,38]

Abbreviations: CHC, α-cyano-4-hydroxycinnamate; DBDS, 4,4'-dibenzamidostilbene-2,2'-disulphonate; DIDS, 4,4'-diisothiocyanostilbene-2,2'-disulphonate; GLUT, glucose transporter; MCT, monocarboxylate transporter; NI, no inhibition; NPPB, 5-nitro-2-(3-phenylpropylamino)-benzoate.

* Determined on rat MCT isoforms.

[§] No significant inhibitory effect when MCT2 is associated with embigin instead of basigin.

manner, but with a different orientation in human *versus* mouse [68, 69]. The transporter is also present in cells of exocrine glands, such as sebaceous glands of the skin and mammary glands [70]. The cellular distribution of MCT1 in the nervous system has been studied and described in more details. MCT1 was found to be expressed in the brain by endothelial cells [71–73], astrocytes [74–77], oligodendrocytes [78,79] and microglial cells [80,81]. In addition, some subsets of neurons express MCT1 [75,82,83], notably in specific brain areas such as the hypothalamus [84,85]. Tanycytes, a glial cell type found in the hypothalamus, do also express MCT1 [86]. In the peripheral nervous system, MCT1 was found in Schwann cells and dorsal root ganglia neurons within the endoneurium [87,88], in addition to the epineurium [89].

MCT2 has a more restricted tissular and cellular distribution than MCT1. It was first described in liver hepatocytes and in the kidney in collecting ducts [16]. MCT2 is also expressed by the spermatid tail in the testis [16,90]. In the central nervous system, it was shown to be the major neuronal MCT isoform [77,83,91]. Some data further suggest that MCT2 could be expressed by endothelial cells delineating cerebral blood vessels [73,92], by some rat astrocytes [76,93] and by tanycytes in the hypothalamus [86].

MCT3 is expressed by only two cell populations in the entire organism. It is found on retinal pigmented epithelial cells [94,95] as well as on the choroid plexus epithelium [17].

MCT4 was shown to be expressed by a subset of muscle cells composing glycolytic (type II) fibers [49,50,96]. It is also present in some types of white blood cells, including macrophages [66,97,98]. In the central nervous system, the transporter is found exclusively in astrocytes [83,99], with the exception of tanycytes in the hypothalamus [86]. In the peripheral nervous system, Schwann cells have been recently found to express MCT4 [87].

2.1.6. Subcellular distribution

Since MCTs play an essential role in the exchange of metabolites between the cytoplasm and the extracellular environment, a great majority of reports have described them to be localized at the subcellular level on the plasma membrane of every cell type in which they were described. There are, however, a few examples for which further details about the subcellular distribution have been reported. In muscle cells, both MCT1 and MCT4 were found to be associated with intracellular structures such as triads, T tubules, sarcoplasmic reticulum and intracellular membranes, but to a different degree for each transporter [52,96]. Similarly in neurons, which are highly polarized cells, a specific subcellular distribution of MCT2 was evidenced and described: MCT2 expression is particularly enriched in dendritic spines, associated with the postsynaptic density [91,100]. MCT2 was found not only to colocalize with several postsynaptic density proteins (e.g. PSD95), but also to be associated with a subset of proteins specifically enriched in the postsynaptic density including PICK1 and GluR2/3, a subunit of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [101, 102]. Moreover, MCT2 was detected within spines in a vesicular-like compartment [101,102], suggesting that it could undergo some trafficking between this intracellular compartment and the plasma membrane. Indeed, it was shown that neuronal stimulation with neuroactive substances such as glutamate (in the presence of glycine) or brain-derived neurotrophic factor (BDNF) can induce the translocation of the intracellular MCT2 pool to the plasma membrane and, thereby, enhance lactate uptake [102]. Likewise, in several types of cancers, MCT2, MCT3 and MCT4 have been found to be expressed at the membrane of intracellular substructures [103,104], which could indicate intracellular trafficking also in tumors.

In addition to its association with vesicle-like structures in neuronal spines, MCT2 can also be found on the intracellular membrane of mitochondria in neurons [105,106]. Such an expression in mitochondria, in association with the presence of the lactate dehydrogenase B (LDHB) isoform, was proposed as an evidence for direct lactate oxidation within mitochondria [105,107]. A similar observation was reported for MCT1

in neurons [105] and in cardiac and skeletal muscle cells [108,109]. These observations, however, remain highly controversial, notably due to the non-specific binding of antibodies and contamination of mitochondrial membrane preparations, as extensively reviewed and discussed previously [35].

2.2. Regulation

Most of the studies pertaining to MCT regulation focused on MCT1, so most available information is related to this protein. Known regulatory processes can be divided in 3 categories: transcriptional, expressional and regulation through interactions with proteins.

2.2.1. Transcriptional and epigenetic regulations

SLC16A1/MCT1 gene expression can be regulated in different ways depending on cell and tissue types and on metabolic needs. In the skeletal muscle, increases in Ca^{2+} and AMP levels due to chronic stimulation or exercise increase *MCT1* transcription and promote the activity of the Ca^{2+} -dependent protein phosphatase calcineurin (CN) and of AMP-activated protein kinase (AMPK) [110,111]. CN is responsible for the dephosphorylation and activation of nuclear factor of activated T cells (NFAT), a transcription factor that recognizes several NFAT-binding consensus sequences on the *MCT1* promoter [111]. In the skeletal muscle, inhibition of CN by cyclosporine A and FK506 induced a phenotypic reshaping of red oxidative fibers rich in MCT1 into white slow oxidative fibers with low MCT1 and higher MCT4 expression [111,112]. In myocytes, cyclosporine A can further prevent hypertrophy [112], a process related to upregulation of MCT1 [111]. Thus, although it was not yet formally demonstrated, the control of the expression of MCT1 in the exercising muscle probably depends on the binding of NFAT to the gene promoter. When AMP levels rise, AMPK stimulates PGC1 α , a transcriptional coactivator that upregulates MCT1 expression and promotes the formation of highly oxidative muscle fibers [113]. Accordingly, exercise stimulation of rats resulted in a transient increase in both *MCT1* and *MCT4* mRNA levels, with evidence for AMPK involvement as an upstream intermediate [114,115]. In another report, however, direct AMPK activation by 5-aminoimidazole-4-carboxamide-1- β -D-ribofuranoside (AICAR) has been shown to stimulate MCT1 promoter activity in both L6 myoblasts and HepG2 hepatoma cells, but it significantly reduced the activity of the MCT4 promoter by more than 50% [23]. AICAR has also been reported to decrease the activity of the MCT1 promoter in Sertoli cells [116]. It has further been reported that thyroid hormone T3 is able to increase the levels of *MCT1* and *MCT4* mRNAs, although in the skeletal muscle only MCT4 protein expression increased [117]. In cancer, MCT1 expression has been found to be repressed in human breast cancer cells through hypermethylation of CpG islands in the promoter region of the gene [118]. Still in cancer, MCT1 protein expression has also been reported to be regulated by hypoxia in a p53-dependent manner [119]. A direct interaction between p53 and the *MCT1* gene promoter was proposed to decrease *MCT1* mRNA stability.

MCT2 expression is mainly controlled posttranscriptionally, although some authors have described that food deprivation can induce the *SLC16A7/MCT2* mRNA expression in rat brain stem cells for the use of ketone bodies as respiratory fuels [120]. In the brain, stimulation of the PI3K-Akt-mTOR pathway by insulin, insulin-like growth factor 1 (IGF1) or noradrenaline induces a translational activation of MCT2 in a way similar to the increment seen in cultured cortical murine neurons treated with BDNF [121–123]. An epigenetic regulation of *SLC16A7/MCT2* was also evidenced in prostate cancer cells [124]. A selective demethylation of an internal promoter and a reciprocal hypermethylation of an upstream promoter region led to a switch in MCT2 isoform expression and a distinct regulation of MCT2 translation.

The promoter activity of *SLC16A3/MCT4* is stimulated by hypoxia following the binding of transcription factor hypoxia-inducible factor-1

(HIF-1) to two hypoxia-responsive elements (HRE) located upstream to the transcription start [23,24]. Consequently, hypoxia increases MCT4 expression in several cell types, including cancer cells. An epigenetic regulation of *SLC16A3/MCT4* was also evidenced in clear cell renal cell carcinoma [125]. Indeed, lower DNA methylation at specific CpG sites resulted in higher *MCT4* mRNA expression and correlated with worst outcome for patients.

Information regarding other MCT isoforms is very limited, though there is a study connecting MCT8 expression changes with development and disease [3].

2.2.2. Expressional regulation

Mechanisms implicated in the regulation of MCTs have not been deeply investigated, but some authors have pointed at the importance of some specific sequences and secondary structures in the 5' and 3' untranslated region (UTR) of MCTs mRNAs. In particular, the 3' UTR of *MCT1* is much longer than the ones of *MCT2* and *MCT4*, and it contains a potential cytosolic polyadenylation element and hexanucleotide repeats [23]. These elements might be critical for polyadenylation at the exit of the mitotic phase during cell cycle and for the regulation of initiation factor eIF4E, which could be linked with the increase in *MCT1* expression observed at protein but not mRNA level [23,111]. In addition, *MCT1* bears in its C-terminus a LL motif and two acidic clusters of amino acids that could be involved in protein targeting [111], for example in the translocation of the protein to the sarcolemma in cisternae close to the t-tubules in cardiomyocytes [126]. Sequence analysis suggests that MCTs are not targets for posttranslational modifications such as glycosylation, and to date no evidence of other posttranslational modifications has been reported.

2.2.3. Regulatory proteins

The correct expression, localization and activity of MCTs depend on interactions with ancillary proteins, primarily basigin/CD147 and embigin/gp70 [8,127,128]. These proteins are anchored to the plasma membrane through a single transmembrane domain containing a conserved glutamate residue. They also possess a short intracellular C-terminus and a large glycosylated extracellular domain with two or three immunoglobulin domains depending on the splice variant [129]. In addition to its chaperone role, basigin presents a huge variety of ligands, such as cyclophilins and integrins, taking part in several functions including the induction of metalloproteinases, spermatogenesis and responsiveness to lymphocytes [130].

Several groups have demonstrated with different techniques (e.g. immunofluorescence, co-immunoprecipitation, cross-linking and fluorescence resonance energy transfer) the crucial role of ancillary proteins for MCTs to be localized and active at the plasma membrane [36,128,131–133]. In their absence, MCTs are not able to reach their final position and accumulate in the Golgi apparatus [128,132]. Basigin is more widely expressed in tissues than embigin, and appears more frequently as the preferential partner for *MCT1*, *MCT3* and *MCT4*, whereas *MCT2* preferentially interacts with embigin [36,128]. Experiments of site-directed mutagenesis have further revealed that the transmembrane domain of the ancillary protein lies adjacent to TM3 and TM6 of MCTs [8,36] and that disruption of the interaction between *MCT1* and basigin by organomercurial p-chloromercuribenzenesulphonate (pCMBS) induces inhibition of *MCT1* activity [128]. Besides *MCT1–4*, the necessity of the other members of the MCT family to interact with ancillary proteins remains unclear. *MCT8* does not require such interaction for its correct plasma membrane localization and activity [134].

Other proteins have been suggested to bind to MCTs. The receptor for hyaluronic acid CD44 can interact with *MCT1* and *MCT4* in lung and prostate cancer cells [103]. Carbonic anhydrase II (CAII, a cytosolic CA isoform) and CAIV (an extracellular CA isoform) can also establish interactions with MCT/basigin complexes via MCTs on the cytosolic side and basigin on the extracellular side, enhancing the activity of the transporters [135,136]. Increased MCT activity by CAs could be due to

a process whereby CAs supply MCTs with protons, or to faster transport. Nonetheless, improved MCT activity was also seen with catalytically inactive CAs [135,136], a phenomenon that is still incompletely understood. *MCT1* has also been reported to colocalize with LDH in the mitochondria of L6 rat skeletal muscle cells and to co-immunoprecipitate in the mitochondrial fraction of the protein extract in absence of detergent, suggesting a weak interaction between both proteins at least at the mitochondrial level in these cells [137]. The authors proposed a model of “intracellular lactate shuttle/lactate mitochondrial oxidation complex” in which lactate would be reduced in pyruvate by LDH and further imported into the mitochondrial stroma by *MCT1* for further oxidation. Because LDHB and LDHA have different affinities for lactate and pyruvate and as MCT isoforms have different K_m and V_{max} values depending on their substrate, potential interactions of LDHs with MCTs could represent a mechanism to fine-tune monocarboxylate transport orientation across membranes. As mentioned earlier, however, the concept of intracellular lactate shuttle and lactate mitochondrial oxidation is highly disputed for several reasons [35]. Finally, in neurons, *MCT2* binds to the AMPA receptor subunit GluR2, of which it controls the plasma membrane localization [102,138]. Moreover, it was shown that two adhesion molecules, the neuroplastins, can also serve as accessory proteins for *MCT2* in the central nervous system and regulate its exposure at the cell surface [139].

3. MCTs in the central nervous system

3.1. MCTs and the astrocyte-neuron lactate shuttle

The cellular distribution of MCTs in the central nervous system associated with the distribution of other essential metabolic components (such as the LDH isoenzymes [140,141]) has suggested a key role of these carriers in the shuttling of energy metabolites between brain cells. Indeed, the expression of *MCT4* on astrocytes that produce large amounts of lactate and the expression of *MCT2* on neurons using lactate as an efficient oxidative energy substrate have contributed to the emergence and establishment of the “astrocyte-neuron lactate shuttle” concept [32,141–143] (Fig. 1).

Glutamate uptake by astrocytes via the high affinity, Na^+ -dependent glutamate transporters GLAST and GLT1 was initially reported to cause a rise in intracellular Na^+ that would activate the Na^+/K^+ ATPase [144–147]. As a consequence, glucose uptake would be enhanced and would result in a greater lactate production and release [148,149]. Both *MCT1* and *MCT4* can convey lactate release by astrocytes: *MCT1* appears to be involved in basal lactate release, whereas *MCT4* would be required for enhanced lactate export [150,151]. In addition to glutamate, K^+ can also enhance glycolysis in neurons [152–154]. Moreover, it was recently demonstrated that NH_4^+ constitutes a signal released by neurons that favors lactate release by astrocytes, most likely via MCTs [155]. Lactate constitutes not only a suitable oxidative energy substrate for neurons, but it can even be preferred over glucose both *in vitro* and *in vivo* [156–161]. The expression of *MCT2* by neurons, together with LDHB, provides an ideal condition for lactate uptake and utilization as an energy substrate by these cells. It has further been shown that the level of *MCT2* expression at the plasma membrane of these cells can be modulated by specific neuroactive substances, including BDNF, via a translocation mechanism allowing for a rapid regulation and control of energy substrate supply [162]. In addition, *MCT2* expression can also be regulated at the translational level in cultured cortical neurons by various neuroactive substances including BDNF, insulin, IGF-1 and noradrenaline [121–123,162]. Such a relatively rapid mechanism to enhance *MCT2* expression occurs at the level of neuronal processes and does not require the cell body, suggesting a synapse-specific regulation [123]. A similar enhancement of *MCT2* expression, together with the synaptic proteins PSD95 and the AMPA receptor subunit GluR2, was demonstrated in mice *in vivo* after injection of BDNF into the hippocampus [163].

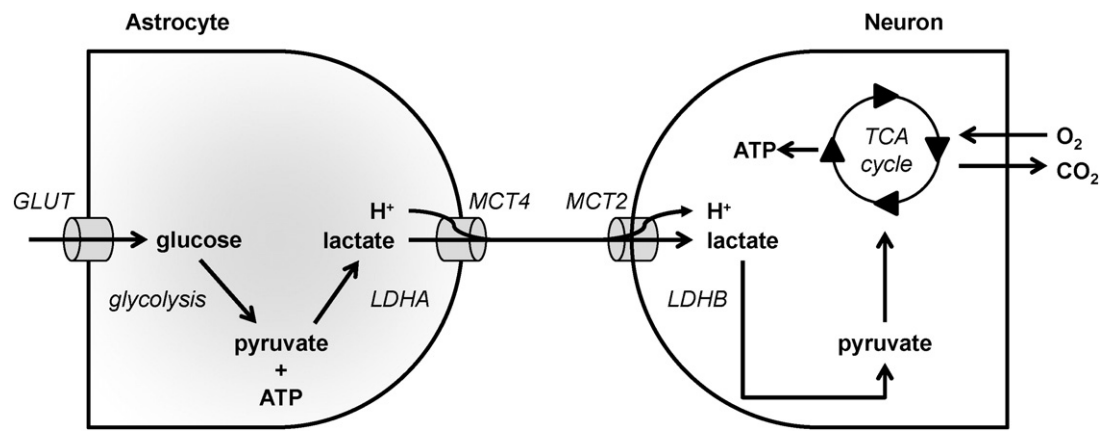


Fig. 1. Model depicting MCT-mediated lactate exchanges between astrocytes and neurons in the brain. In the model, astrocytes, depicted on the left, have a high glycolytic metabolism. They import glucose *via* glucose transporters (GLUT) and then sequentially convert glucose to pyruvate and ATP using glycolysis, and pyruvate to lactate using lactate dehydrogenase A (LDHA). Lactate is exported together with protons *via* MCT4. Neurons, depicted on the right, import lactate and protons *via* MCT2. Lactate is oxidized to pyruvate by lactate dehydrogenase B (LDHB) and pyruvate fuels the TCA cycle to support ATP production through oxidative phosphorylation.

3.2. MCTs, learning and memory

As mentioned in Section 3.1, the neuronal expression of MCT2 is regulated in parallel with other proteins that are also regulated in a synapse-specific manner (such as PSD95), whereas MCT2 is even associated physically with GluR2, a specific subunit of AMPA receptors with which it undergoes trafficking either by being inserted together into the plasma membrane or being internalized from the plasma membrane into the endosomal system [102,138]. Moreover, MCT2 expression *in vivo* is regulated by the same mechanism that activates some immediate early genes, *i.e.*, *Arc* and *Zif268*, known to be involved in synaptic plasticity [163]. These observations strongly suggest that MCT2 plays a key role in the supply of energy substrates to neurons in order to sustain changes involved in synaptic plasticity. Indeed, Alberini et al. [164] have shown that downregulating the expression of not only MCT2 (the neuronal transporter) but also of the two glial transporters MCT1 and MCT4 in the rat hippocampus prevented learning and memory. Remarkably, while exogenously supplied lactate could overcome the deficit when either of the glial transporters, MCT1 or MCT4, were downregulated, it was not the case for MCT2, further demonstrating the importance of lactate release from astrocytes and its use by neurons *via* MCT-mediated transfer. These results were confirmed in a different learning task involving spatial memory [165]. Interestingly, exposure of neurons to lactate can lead to the modification of *N*-methyl-*D*-aspartate (NMDA) receptor-mediated currents and to enhancement of plasticity gene expression [166]. These effects require the presence of neuronal MCTs. Lactate indeed acts by modifying the level of intracellular NADH (which requires lactate to be metabolized intracellularly) and, thus, the redox state of the cell.

3.3. MCTs in brain diseases

3.3.1. Neurodegenerative diseases

Considering the important emerging roles of MCTs in metabolic interactions between the different brain cell types, it is not surprising to discover that alterations of MCT expression are implicated in a variety of diseases involving the central or the peripheral nervous systems. It is specifically the case for neurodegenerative diseases. Thus, together with the discovery that oligodendrocytes express MCT1 and are involved in a lactate shuttle to provide energetic support to axons [33, 167], it was also shown that a reduction of MCT1 expression in a transgenic mouse model leads to axonal degeneration, notably in the spinal cord [79]. A similar reduction of MCT1 expression was evidenced in the spinal cord of amyotrophic lateral sclerosis patients [79]. Similarly,

in parallel with the finding that MCT1 and MCT4 are expressed by Schwann cells, a reduction of the expression of MCT1 in cultured cells was reported to alter myelination [87], which was associated with a delay of regeneration following nerve crush in a transgenic mouse model [88]. Accordingly, in brain tissues of multiple sclerosis patients, astrocytes exhibit enhanced MCT1 expression, whereas demyelinated axons have lower MCT2 expression in inactive lesions [81].

In a rat model of Alzheimer's disease where rat received bilateral intrahippocampal injections of the A β 25–35 fragment, MCT2 expression was reduced in parallel with decreased lactate content and cognitive deficits in spatial learning and memory, as assessed by the Morris Water Maze test [168]. In contrast, no alteration of the expression and localization of MCT1 and MCT2 was found in the substantia nigra and striatum of a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease [169].

3.3.2. Epilepsy

Epilepsy represents a condition for which several studies have reported changes in the expression and/or localization of the different MCTs in the brain. In the human epileptogenic hippocampus, MCT1 expression is decreased in microvessels [170], whereas MCT2 is redistributed from astrocytic end-feet to plasma membranes facing synapses [171]. In an immature and an adult lithium-pilocarpine rat model of epilepsy, MCT1 mRNA was found to be commonly enhanced, but more in the adult during the acute phase of status epilepticus [172]. MCT2 mRNA increased mainly in adults within the circuit of seizures. In three other rat models of epilepsy, one using the drug methionine sulfoximine and two using episodes of perforant path stimulation, MCT1 expression was reduced in microvessels, whereas it was enhanced in astrocytes of the hippocampus [173]. The expression of MCT4 was also investigated in patients with temporal lobe epilepsy and in a pilocarpine rat model of temporal lobe epilepsy. A decrease in MCT4 expression was detected in the cortex of temporal lobe epilepsy patients, and a similar decrease was observed in the pilocarpine rat model 12 to 14 h after drug administration [174]. The reduction of the abundance of MCT4 (which is essentially an astrocytic transporter) was linked to a parallel reduction of the glial glutamate transporter excitatory amino acid transporter 1 (EAAT1), an observation that could explain neuronal hyperexcitability and epileptogenesis.

3.3.3. Brain ischemia

Changes in MCT expression have been reported following brain ischemia. In a transient global rat ischemia model, intense MCT1 labeling was found in CA1 pyramidal neurons, astrocytes, endothelial cells and ependymocytes [175]. An increase in the expression of MCT1 and

MCT2 associated with microglial cells was found 48 h after focal ischemia induced by compression in rats [80]. In addition, modulation of MCT4 expression by hypoxia, as demonstrated in cultured astrocytes [151], could provide a mechanism by which neuronal death can be preserved under ischemic conditions [176] and could be exploited as a neuroprotective strategy in intermittent hypoxia preconditioning-induced epileptic tolerance [177].

3.3.4. Metabolic diseases

A distinct class of pathologies in which modulation of brain MCT expression could play a role is represented by certain metabolic diseases. Indeed, repeated hypoglycemia was reported to have an impact on MCT expression in various brain regions. This is the case in the hypothalamus, an important region for nutrient sensing and metabolic homeostasis. Thus, an injection of insulin to induce an hypoglycemic episode altered MCT2 expression of the vagal complex in opposite direction between male rats and estrogen-treated ovariectomized female rats [178]. Recurrent insulin-induced hypoglycemia enhanced MCT2 expression in the dorsal vagus complex, whereas acute hypoglycemia suppressed MCT2 expression in the ventromedial hypothalamus [179]. Conversely, catecholaminergic A2 neurons in the dorsal vagal complex exhibited reduced MCT2 expression following insulin-induced hypoglycemia [180].

In contrast to hypoglycemia, hyperglycemia was found to enhance MCT1 expression globally in the brain, most likely in endothelial cells and astrocytes [181], while having no effect on MCT1, MCT2 and MCT4 expression in the medio-basal hypothalamus [182]. Exposure of mice to a high fat, high sugar diet for several weeks induced the cortical expression of MCT1, MCT2 and MCT4 that occurred preferentially in neurons throughout the cortex [183].

While these data suggest the possible involvement of MCTs in metabolic homeostasis and its possible dysregulations, clear evidence was provided by the phenotypical characterization of haploinsufficient MCT1 transgenic mice [184]. These mice were shown to resist to the development of diet-induced obesity and its associated metabolic dysfunctions, including insulin resistance and hepatic steatosis. Interestingly, under a high fat, high sugar diet, haploinsufficient MCT1 mice had reduced food intake, suggesting that MCTs could be key factors implicated in nutrient sensing and subsequent food intake regulation and, eventually, dysregulation. This would certainly constitute an interesting topic for future investigation.

4. MCTs in cancer

4.1. Expression of MCTs in different cancer types

MCT1 and MCT4 are the most widely MCT isoforms expressed in cancer cells. MCT1 expression has been reported in a variety of human cancers including head and neck, breast, lung, stomach, colon, bladder, prostate and cervix cancers, as well as gliomas [25,26,185–188]. MCT1 has also been proposed to be the most important isoform responsible for lactate transport across the plasma membrane in breast cancer, bladder cancer, non-small cell lung carcinomas (NSCLC) and ovarian carcinomas [103,188]. MCT4 is also widely distributed in different cancer types. Its expression has indeed been reported in breast, colon, bladder, and prostate cancers, as well as in cancers of the gynecologic tract and gliomas [103,186–188]. Despite a low expression at the plasma membrane, MCT4 is further present intracellularly in NSCLC [104]. Comparatively to MCT1 and MCT4, MCT2 and MCT3 have been less studied in cancer. MCT2 has been found in the cytoplasm of breast carcinoma, NSCLC, colon adenocarcinoma and ovarian adenocarcinoma cancer cells [103,104], and MCT3 has also been reported to be expressed intracellularly in cancer and stromal cells of NSCLC [104]. With respect to MCT2 and MCT4, some authors have postulated that a high intracellular expression could reflect the localization of these transporters on the

membranes of intracellular vesicles or organelles where they could potentially transport lactate and/or pyruvate [26,188].

The expression of the chaperon proteins of MCTs in cancer cells is an important factor to take into account because they behave as key mediators in oncogenesis. CD147 and CD44 have been associated to MCT1 and MCT4 in different tumor types. MCT1 and CD147 expression have been significantly correlated in bladder [188] and ovarian cancers [103], and CD44 was reported to be associated with MCT1 expression in lung cancer [103]. CD147-MCT1 double-positive bladder tumors showed poor prognosis and unfavorable clinical pathological parameters [188]. In addition, experimentally induced CD147 downregulation increased the chemosensitivity of bladder cancer cell lines to cisplatin chemotherapy [188]. MCT4 expression has also been correlated to CD147 expression in prostate, breast and lung cancers [103,188]. Recently, Pertega-Gomes and Baltazar [189] further reported a correlation between the expression of MCT1, MCT2 and MCT4 and the different stages of prostate cancer progression. MCT1 was present in both normal epithelium and malignant glands, MCT2 was expressed from benign to prostate intraepithelial neoplasia lesions and in malignant glands, and MCT4 was expressed only in malignant glands associated to poor prognosis. Therefore, the authors proposed that MCT1 and MCT2 would play a role in tumor maintenance, whereas MCT4 would increase tumor aggressiveness. MCT2 was also proposed as an interesting biomarker for prostate cancer [189]. In another study in NSCLC [104], Eilertsen et al. proposed MCT1 as a biomarker for prognostic and survival. The co-expression of GLUT1 and MCT1 and of GLUT1 and MCT4 was found as a negative prognostic factor associated with poor disease-specific survival.

4.2. MCTs in the metabolic relationships between glycolytic and oxidative cancer cells

From a metabolic standpoint, established tumors contain different types of cancer cells. Oxidative cancer cells can use different metabolic substrates to fuel OXPHOS, including glucose, glutamine, lipids and lactate [15]. Glycolytic cancer cells result from environmental selection (e.g. by hypoxia) or from metabolic adaptation in order to sustain biosynthesis for proliferation (the ‘Warburg effect’) [190–194]. The switch from an oxidative to a glycolytic metabolism formally corresponds to unframing glycolysis from the TCA cycle and OXPHOS in order for glycolysis to preferentially fuel lactic fermentation. The conversion of glycolytic end-products pyruvate, NADH and H⁺ into lactate and NAD⁺ indeed serves to regenerate the NAD⁺ pool necessary to maintain glycolysis at a high rate [195]. In the glycolytic compartment of tumors, metabolism accounts for elevated lactate production and for an extracellular lactate accumulation up to concentrations that can reach 10 to 40 mM [196]. These high levels of lactate have been shown to correlate with tumor aggressiveness and poor prognosis in several types of human cancers [15,196–202]. MCTs play an essential role in the metabolic homeostasis of the tumor microenvironment: they ensure the maintenance of glycolytic and acid-resistant phenotypes [15,203], thus contributing to the malignant behavior of cancer cells. MCTs allow glycolysis to operate at high speed by facilitating lactate export, and they are also involved in pH regulation by the co-transport of protons.

Lactate is not a metabolic dead-end product of glycolysis but is rather a tumor growth-promoting factor. In a striking similarity with brain metabolism, lactate can be used as a metabolic substrate by a variety of oxidative cancer cells. Lactate can indeed generally fuel the oxidative metabolism of oxygenated cancer cells [25,29]. According to the ‘metabolic symbiosis’ hypothesis initially proposed by Sonveaux et al. in cancer [25], lactate produced by glycolytic cancer cells that rely on glucose as a main fuel is imported by oxidative cancer cells that use lactate in mitochondrial metabolism as a main fuel compared to glucose, thus sparing glucose for glycolytic cancer cells [204,205] (Fig. 2). Indeed, this concept seems to also apply for brain tumors (gliomas) in which the occurrence of an intercellular lactate shuttle akin to the one normally

operating to fuel neurons would take place, subverting the normal cellular metabolic interactions to sustain the survival and growth of the tumor [206]. MCT4, which has a low affinity for lactate but a high turnover rate, is particularly well adapted to facilitate lactate export by glycolytic cancer cells [12,13]. Its expression is up-regulated by hypoxia: when the O_2 supply is compromised, cancer cells activate transcription factor HIF-1, of which MCT4 is a target gene [24]. MCT4 also shows a higher K_m for pyruvate compared to lactate, which prevents the efflux of pyruvate that would be detrimental for the maintenance of a high glycolytic flux. Conversely, MCT1 has a high affinity for lactate and is preferentially expressed in oxidative cancer cells that take up lactate [25,207]. The use of pharmacological inhibitors and RNA interference experiments have revealed that MCT1 is the main transporter responsible for lactate uptake by these cells [25,119,207,208]. Inside oxidative cancer cells, lactate reacts with NAD^+ to yield pyruvate, $NADH$ and H^+ (the LDHB reaction), and both pyruvate and $NADH$ can fuel the TCA cycle and OXPHOS in mitochondria, which depends on the malate–aspartate shuttle for the mitochondrial import of $NADH$ [29].

In addition to its function as a metabolic substrate, lactate can also act as a signaling agent in oxidative cancer cells. In two seminal papers [209,210], Lu et al. initially showed that lactate can behave as a hypoxia mimetic factor capable of activating transcription factor HIF-1 in normoxic cancer cells. In the process, lactate must be taken up by cancer cells through a MCT1-facilitated process, oxidized to pyruvate by LDHB, and pyruvate competes with 2-oxoglutarate to inhibit the prolylhydroxylases (PHDs) of HIF-1 [207,209,210] (Fig. 3), *i.e.*, oxygen- and 2-oxoglutarate-dependent enzymes that catalyze the hydroxylation of HIF-1 subunit α on two proline residues to initiate the proteasome-dependent degradation pathway of HIF-1 α [211]. Thus, by interfering with the normal degradation pathway of HIF-1 α , lactate can trigger HIF-1 activity independently of hypoxia in oxidative cancer cells. An established consequence of such signaling is an increased transcription and release of vascular endothelial growth factor (VEGF) by oxidative cancer cells, which can stimulate endothelial cells to initiate and angiogenic response [194,207] (Fig. 3, see also Section 4.3). Because MCTs are equilibrative lactate/ H^+ transporters and glycolytic cancer cells produce large amounts of lactate and protons, these cells cannot abundantly take up exogenous lactate and, therefore, do not activate HIF-1 upon exposure to lower levels of exogenous lactate [195,207].

MCTs also promote migration and invasion processes in cancer. Izumi et al. [212] first showed that MCT1 and MCT4 expression

correlates with invasion in human lung cancer cells. In agreement with their findings, others further showed that the MCT inhibitor CHC decreases the migration and invasion of glioma cells [187]. Moreover, in conditions of glucose deprivation, MCT1-CD147 complexes were found to be stabilized and MCT1 actively promoted the migration of oxidative SiHa and HeLa human cervix cancer cells towards glucose through a mechanism that was blocked using specific shRNAs targeting MCT1, or CHC to inhibit MCT1 activity [208]. However, whether and how MCT1 could function as a glucose sensor is still unknown.

4.3. MCTs in the crosstalk between cancer and endothelial cells

Endothelial cells are responsive to lactate stimulation in a way that promotes tumor progression. Indeed, similar to oxidative cancer cells, endothelial cells can take up lactate in a MCT1-facilitated process, although, contrary to oxidative cancer cells, they do not efficiently use lactate as a fuel [213]. In normoxic endothelial cells, lactate was found to stimulate HIF-1 activity in a manner similar to what was described for oxidative cancer cells, *i.e.*, by sequentially serving as a precursor of pyruvate, inhibiting HIF PHDs, stabilizing HIF-1 α and activating HIF-1 [213] (Fig. 3). However, the final proangiogenic effectors identified are different. Indeed, in endothelial cells, lactate did not stimulate VEGF production but rather increased the production of basic fibroblast growth factor (bFGF) and the expression of the prototypical VEGF receptor VEGFR2. Taking into account the fact that lactate can stimulate VEGF production independently of hypoxia in cancer cells [207,209,210], both paracrine VEGF signaling and autocrine bFGF signaling on endothelial cells could thus account for the proangiogenic effects of lactate in tumors.

Independently of HIF-1, lactate has also been shown to sequentially activate NF- κ B, trigger proangiogenic IL-8 production and activate the IL-8 pathway in an autocrine manner in endothelial cells [214,215] (Fig. 3). This pathway shares with the lactate-HIF-1 pathway MCT1-facilitated lactate uptake, lactate oxidation to pyruvate (the LDHB reaction) and pyruvate-mediated PHD inhibition. PHD inhibition then rescues inhibitor of NF- κ B kinase β (I κ B β) from degradation, resulting in inhibition of inhibitor of NF- κ B α (I κ B α). NF- κ B activation was found to further mandatorily require $NADH$, the byproduct of the LDHB reaction, to be available to sequentially fuel $NAD(P)H$ oxidases, trigger the production of reactive oxygen species (ROS), and fully inactivate I κ B α [214]. Accordingly, the mitochondrial use of $NADH$ by oxidative cancer cells but not by endothelial cells that are more glycolytic explains why

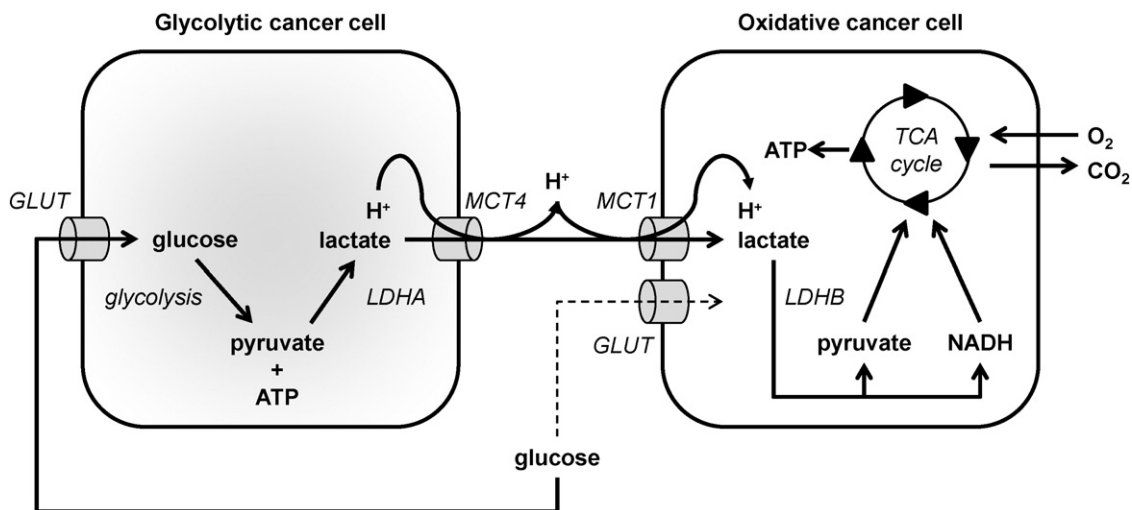


Fig. 2. Model depicting a metabolic symbiosis based on the exchange of lactate between glycolytic and oxidative cancer cells. In the model, glycolytic cancer cells, depicted on the left, import glucose *via* glucose transporters (GLUT) and then sequentially convert glucose to pyruvate and ATP using glycolysis, and pyruvate to lactate using lactate dehydrogenase A (LDHA). Lactate is exported together with protons *via* MCT4. Oxidative cancer cells, depicted on the right, import lactate and protons *via* MCT1. Lactate is oxidized to pyruvate by lactate dehydrogenase B (LDHB) generating $NADH$ as a byproduct, and both pyruvate and $NADH$ fuel the TCA cycle to support ATP production through oxidative phosphorylation.

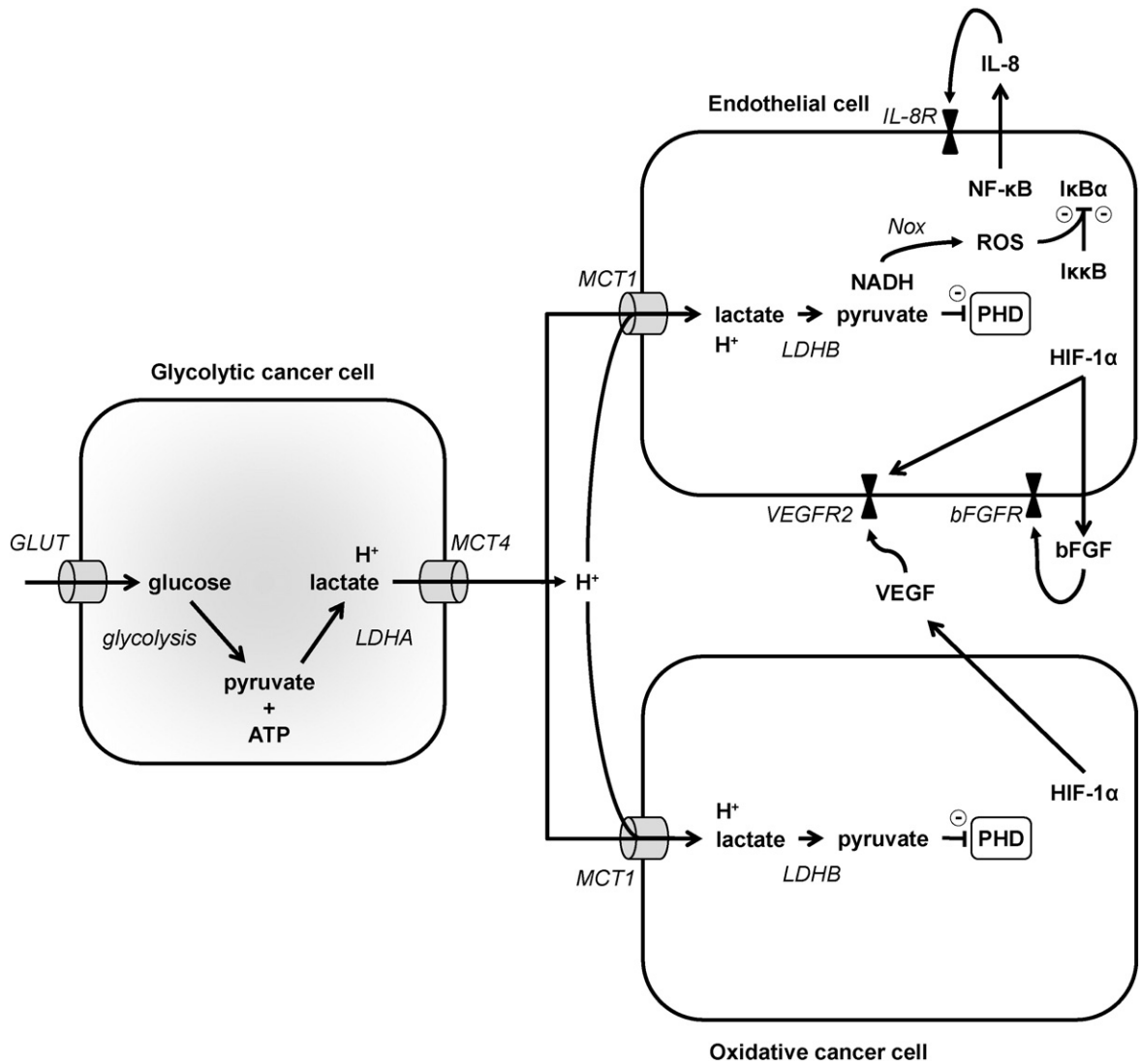


Fig. 3. Model depicting proangiogenic lactate signaling in cancer. In the model, glycolytic cancer cells, depicted on the left, import glucose *via* glucose transporters (GLUT) and then sequentially convert glucose to pyruvate and ATP using glycolysis, and pyruvate to lactate using lactate dehydrogenase A (LDHA). Lactate is exported together with protons *via* MCT4. MCT1 is expressed in endothelial cells and in oxidative cancer cells, depicted on the left, and catalyzes the uptake of lactate together with protons. In these cells, lactate is oxidized to pyruvate by LDHB, producing NADH as a byproduct. Pyruvate inhibits prolylhydroxylases (PHDs). In endothelial cells, PHD inhibition stabilizes hypoxia-inducible factor (HIF-1) subunit α , triggering HIF-1 activation and the transcriptional upregulation of vascular endothelial growth factor receptor 2 (VEGFR2). HIF-1 also indirectly increases bFGF, which is secreted and activates the proangiogenic bFGF receptor (bFGFR). PHD inhibition further stabilizes inhibitor of NF- κ B kinase β (I κ NB β), an inhibitor of inhibitor of NF- κ B α (I κ B α). NADH alimments NAD(P)H oxidases (Nox) that produce reactive oxygen species (ROS) to further inhibit I κ B α . Consequently, transcription factor NF- κ B is activated and upregulates IL-8, which is secreted and activates the proangiogenic IL-8 receptor (IL-8R). Oxidative cancer cells share with endothelial cells the lactate-HIF-1 pathway, but not the lactate-NF- κ B pathway. HIF-1 activation by lactate in these cells transcriptionally upregulates VEGF, which upon secretion can activate proangiogenic VEGFR2 in endothelial cells. Lactate signaling as a whole can thus trigger angiogenesis independently of hypoxia.

the oxidative pathway of lactate can activate NF- κ B in endothelial cells but not in oxidative cancer cells [29].

The proangiogenic properties of lactate and MCT1 are also supported by observations in ischemic wound healing. Indeed, chronic lactate delivery to the wound site from a poly-*D,L*-lactide-co-glycolide polymer was shown to accelerate revascularization, hence wound healing [216]. Conversely, pharmacological inhibition of MCT1 by CHC blocked reparative angiogenesis and the healing activity of lactate.

4.4. MCTs in the crosstalk between cancer and stromal cells

Over the past decades, studies on cancer metabolism highlighted the importance of the interaction between cancer cells and their microenvironment, and particular attention has been paid to interactions between cancer cells and fibroblasts. Lisanti et al. [217] proposed the existence of a metabolic relationship between stromal fibroblasts and oxidative

epithelial cancer cells involving MCTs, which they coined ‘Reverse Warburg Effect’. In this process, oxidative cancer cells induce an oxidative stress in fibroblasts that triggers a glycolytic switch, MCT4 expression and the secretion of lactate, pyruvate and ketone bodies (Fig. 4). These metabolites are then imported in a MCT1-dependent manner and used oxidatively by the cancer cells. Experimentally, co-culturing breast cancer cells with normal fibroblasts upregulated MCT4 expression in the fibroblasts, which was prevented by the use of anti-oxidants such as *N*-acetyl-*L*-cysteine [218]. The co-culture also stimulated MCT1 expression in the cancer cells. In another experiment, HaCaT human epithelial keratinocytes were co-cultured with fibroblasts, resulting in MCT4 induction in the fibroblasts [219]. Mechanistically, ROS production following activation of the RAS oncogene and transcription factor NF- κ B in cancer cells was reported to be responsible for metabolic reprogramming and enhanced MCT4 expression in fibroblasts [219].

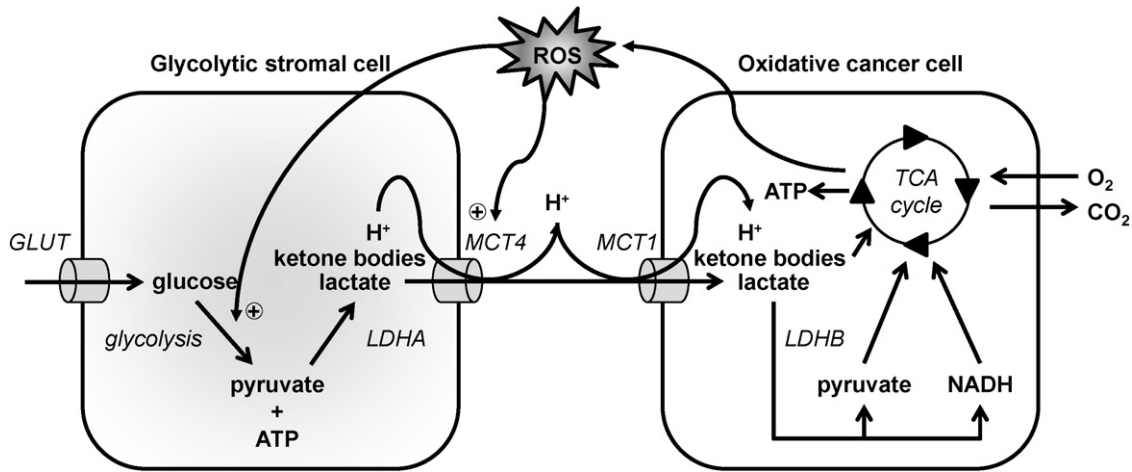


Fig. 4. Model depicting metabolic commensalism of oxidative cancer cells for stromal cells. In the model, oxidative cancer cells, depicted on the right, produce reactive oxygen species (ROS) that promote glycolysis and MCT4 expression in stromal cells. Glycolytic stromal cells, depicted on the left, import glucose via glucose transporters (GLUT) and then sequentially convert glucose to pyruvate and ATP using glycolysis, and pyruvate to lactate using lactate dehydrogenase A (LDHA). They also produce ketone bodies. Lactate and ketone bodies are exported together with protons via MCT4. Oxidative cancer cells import lactate, ketone bodies and protons via MCT1. Lactate is oxidized to pyruvate by lactate dehydrogenase B (LDHB) generating NADH as a byproduct, and both pyruvate and NADH fuel the TCA cycle to support ATP production through oxidative phosphorylation. Ketone bodies can also be catabolized.

In vivo observations support, to some extent, the existence of a metabolic commensalism whereby oxidative cancer cells exploit the metabolic activities of stromal cells. In biopsies of human breast cancer, MCT1 expression was found to predominate in epithelial cancer cells, whereas stromal cells preferentially expressed MCT4 [218]. Tissue analysis of positive lymph nodes revealed amplified mitochondrial mass and metabolism in metastatic breast cancer cells and a lack of detectable mitochondria together with high MCT4 expression in stromal cells, including cancer-associated fibroblasts (CAFs), adipocytes and inflammatory cells [220]. Frozen sections of primary tumors were further screened for functional mitochondria. Analyses showed higher expression and activity of succinate dehydrogenase and cytochrome C oxidase, as well as higher levels of NADH, in epithelial cancer cells compared to adjacent stromal cells, thus convincingly indicating strong OXPHOS activity in the cancer cells [221]. High MCT4 expression in the stromal tissue has been proposed to have an important prognostic role in breast cancer, which could improve the prognostic value of other biomarkers: stromal MCT4 expression is normally inversely correlated to the expression of caveolin-1, and the combination of the two markers could be helpful to identify intermediate risk groups [222,223].

In human head and neck cancer, MCT1 expression was reported to be associated to cancer cells [224]. Cancer-associated fibroblasts (CAFs) had high MCT4 expression.

In human prostate cancer, MCT1 was present in cancer cells and MCT4 in CAFs [189]. CAFs also had high CAIX expression, suggesting a glycolytic metabolism. Interestingly, the concomitant presence of elevated levels of MCT4 in CAFs and MCT1 in cancer cells was related to a poor clinical outcome [189]. An independent study confirmed MCT1 expression in prostate cancer cells [225], but it was associated to a strong cytoplasmic reactivity for LDHA, which would indicate a glycolytic rather than an oxidative metabolism of the cancer cells. In the same study, MCT1 was found in CAFs and tumor-associated myoblasts, with LDHB upregulation (compared to cancer cells) indicative of an oxidative metabolism of the stroma in 40% of cases. Similar findings have been made in lung cancer, with, comparatively, MCT1 and LDHA overexpression in cancer cells and no MCT but LDHB expression in CAFs [226].

Collectively, these data support the general existence of MCT-dependent relationships between cancer cells and stromal cells that could encompass metabolic commensalism of cancer cells for stromal cells but also the opposite situation where stromal cells would metabolically use lactate and other monocarboxylates exported by cancer cells.

4.5. MCTs in the crosstalk between cancer and immune cells

Cancer cells and immune cells interact in a broad range of manners. As recently reviewed by Hirt et al. [227], the *in vitro* study of those interactions in 3D models replicates better *in vivo* observations than standard 2D co-cultures. Among protumoral immune influences on cancer cells, a well-known observation is that chronic inflammation can promote oncogenesis, as illustrated for example by the higher incidence of colorectal cancer in inflammatory bowel disease patients. With respect to metabolism, various studies point the high intratumoral lactic acid concentration as a unifying mechanism of the immunosuppressive effects of cancer cells [228].

Using monocyte-derived dendritic cells (DC), Puig-Kroger et al. [229] first observed that lactate can decrease the DNA binding activity of NF- κ B in a dose-dependent manner, thus impairing DC maturation. They also showed that TNF α release was decreased, although this occurred only at higher lactate concentrations (40 mM), *i.e.*, the highest dose of lactate that can be found in human tumors. Nasi et al. [230] analyzed the defect of DC differentiation in dense cell cultures, and identified lactic acid as being responsible for this. In their experiments, DC induced to differentiate in high density cultures developed an anti-inflammatory phenotype (with IL-10 production) and displayed a preserved osteoclast differentiation potential, whereas low density cultures resulted in IL-12- and TNF α -producing cells capable to migrate towards lymphoid tissue chemokine. While acidic pH alone had no effect and lactate alone had only a weak effect, lactic acid reproduced the effects of high density culture, underlying the potential role of MCTs in DC differentiation [230].

Activated T cells depend on glycolysis for energy production and therefore need to release lactate, which depends on MCT1 in these cells [231–233] (Fig. 5). In tumors, they are in competition with cancer cells for nutrients, which, in addition to low pH, promotes T cell anergy [227]. In this context, Fischer et al. [234] observed that lactic acid inhibits the proliferation of human cytolytic T lymphocytes (CTLs) in a dose-dependent manner. Neither sodium lactate, lactic acid in a solution buffered at pH 7.4 nor acidification alone had antiproliferative effects, indicating a specific activity of lactic acid. Upon lactic acid treatment, CTLs showed decreased IL-12 and IFN- γ production and a lower cytotoxic activity linked to a decrease in granzyme and perforin B content [234]. Because lactic acid blocked the release of lactate by CTLs and pharmacological MCT1 inhibition had a similar antiproliferative

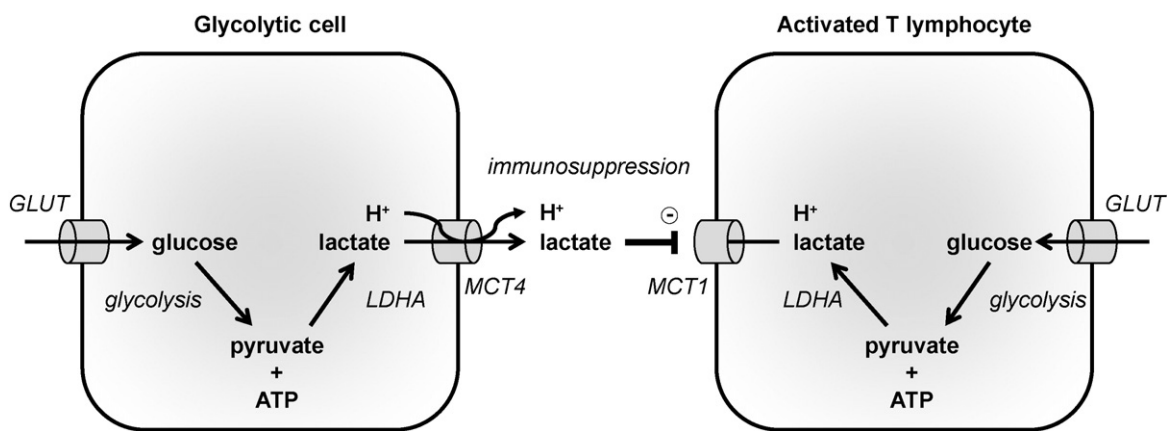


Fig. 5. Model showing the immunosuppressive activity of lactic acid on T cells. In the model, glycolytic cells, depicted on the left, import glucose *via* glucose transporters (GLUT) and then sequentially convert glucose to pyruvate and ATP using glycolysis, and pyruvate to lactate using lactate dehydrogenase A (LDHA). Lactate is exported together with protons *via* MCT4. Activated T lymphocytes, depicted on the right, also depend on a glycolytic metabolism and must release lactate and protons, which in these cells is facilitated by MCT1. MCT1, however, is a passive transporter that is antagonized by the high microenvironmental levels of lactic acid that can be found in glycolytic tissues.

effect than lactic acid, immunosuppression of T cells by lactic acid most likely depends on lactate efflux inhibition [234] (Fig. 5). Consistently, others independently showed that CTL stimulation in a lactic acidosis medium, without prior exposure to lactic acid, decreased IFN- γ , TNF α and IL-12 production, a response that was concentration-dependent [235]. While cytokine production was completely inhibited at 20 mM of lactic acid, exocytosis of lytic granules was reduced by only 50% at this concentration, and CTL viability was not affected. This rapid effect of lactic acid is concordant with the fast uptake of lactate. The differential manifestation of the two types of responses was explained by a rapid inhibition of the MAPK-p38-JNK pathway by lactic acid, whereas ERK and Akt pathways were preserved [235]. In these assays, similar to what had been observed by Fischer et al., lactate alone or acidic pH alone did not recapitulate the effects of lactic acid.

Lactate is also involved in tumor immune escape. *In vivo*, knocking-down LDHA in cancer cells (and thus decreasing their glycolytic rate and lactate secretion) resulted in natural killer (NK) cell activation, reduced accumulation of myeloid-derived suppressor cells (MDSCs), reduced immunosuppressive activity and smaller tumor sizes [236]. Direct effects of lactate were demonstrated by the same authors *in vitro*, by showing that lactate, *per se*, decreases NK cell activity and increases the differentiation of peripheral blood mononuclear cells to MDSCs and their immunosuppressive activity. *In vivo*, a ketogenic diet, used as a surrogate of LDHA knock-down, improved antitumor immunity, although to a lesser extent [236]. Regulatory T cells and MDSCs were less present than with a normal diet, and the number of immune effector cells was increased.

In tumors, myeloid cells may polarize into M1 tumor-suppressive macrophages or into M2 tumor-associated macrophages that secrete proliferation- and survival-stimulating cytokines and proangiogenic factors. Lactate can influence this process. Colegio et al. [237] indeed showed that lactate can activate HIF-1 in macrophages, driving their polarization to the M2 phenotype with a high VEGF secretion that would promote tumor angiogenesis. Importantly, lactate needed the presence of free protons to exert its effect, but an acidic pH alone was not sufficient to stabilize HIF-1 α and activate HIF-1. When HIF-1 α was silenced, the effects of lactate were absent.

5. Conclusions

MCTs represent the major path for inward and outward monocarboxylate fluxes from cells and are key regulators of intracellular and extracellular pH.

The description of the cell-specific distribution of MCT1–4 has contributed to the emergence of the physiological concept of intercellular

lactate shuttle [238,239]. First described in muscles by George Brooks [240], this concept has seen its scope enlarged by its description in other organs and tissues like the testis [90,241]. In the brain, the debated but now largely supported establishment of the 'astrocyte-neuron lactate shuttle' concept is also expanding by the description of similar lactate exchanges taking place between oligodendrocytes and axons [34,167], as well as between Schwann cells and peripheral nerves [87]. Considering the importance of such a mechanism of metabolic cooperation between cells under physiological activity, it may come as no surprise that under pathological conditions such as cancer, a similar mechanism operates or is used for the benefit of cancer cells. Cancer cells being opportunistic, they have developed strategies to survive in their environment, and the expression of appropriate MCTs contribute to their adaptation to many situations, as described in Section 4 by many examples.

In the brain, the type of metabolic cooperation between cells is less opportunistic but more homeostatic. It is for the functional benefit of the organ that these metabolic exchanges have developed, and they rely on subtle equilibria. Any imbalances may lead on the long run to deleterious consequences. Indeed, there is more and more evidence that metabolic dysfunctions underlie neurodegenerative diseases rather than being mere consequences [242]. Thus, it has been proposed in many instances that bolstering neuroenergetics (including the capacity of brain cells to produce and/or utilize monocarboxylates, which also include ketone bodies) might be a good neuroprotective strategy [243, 244]. This possibility remains to be fully tested, but we lack for the moment a proper strategy to be able to enhance these aspects of energy metabolism. This is why we need to gather more information about the mechanisms regulating the expression of MCTs in the various brain cell types. A better characterization of these mechanisms might provide the necessary insights to develop an appropriate therapeutic approach based on this knowledge.

Due to their important activities and their general overexpression in cancers compared to healthy tissues, MCTs are interesting targets for cancer therapy. In tumors, MCT1 gates lactate uptake by oxidative cancer cells and by endothelial cells, thus simultaneously controlling the cataplerotic (Figs. 2 and 3), proangiogenic (Fig. 4) and pro-migratory activities of lactate. Consequently, MCT1 inhibition can have antimetabolic, anti-angiogenic and anti-migratory effects that repress tumor growth [25,119,207,213,214] and, potentially, progression to the metastatic state [208]. In fact, *in vitro* MCT1 inhibition has been found to decrease intracellular pH [25], elicit cell death [25,245] and decrease cancer cell migration [208]. MCT4 also represents an interesting anticancer target, as can notably be illustrated by the fact that MCT4 inhibition by siRNAs reduced the migration of breast cancer cells [246].

Developing MCT inhibitors for anticancer therapy is currently an ongoing task. While historical inhibitors are poorly selective for MCTs, CHC in particular has been the focus of a vast number of *in vitro* and *in vivo* studies showing its therapeutic effects [26]. However, this compound has several drawbacks. It is poorly specific for a given MCT isoform and can also inhibit the mitochondrial pyruvate carrier and anion exchanger 1 [26]. Moreover, it is usually described to be active in the upper micromolar range. More recently, AR-C155858, a highly potent MCT1/2 inhibitor, and AZD3965, a second-generation MCT1/2 inhibitor, have been disclosed by AstraZeneca [46,233]. AZD3695 is currently in Phase I/II clinical trials for advanced solid tumors and diffused B cell lymphomas [247]. However, these molecules present a limited therapeutic action due to the compensatory effect of MCT4, which they do not inhibit [248]. A new family of inhibitors, of which 7ACC2 is the leading compound, has been recently disclosed and described to selectively inhibit lactate uptake (*versus* export) by cancer cells expressing both MCT1 and MCT4 [37,38]. The future *in vivo* evaluation of these compounds will provide key information about their therapeutic activity and suitability for clinical evaluation.

Important issues still remain to be addressed for the clinical exploitation of MCT inhibitors. First, the physiological role of these transporters is still poorly characterized in many tissues. Systematic characterization could benefit from the generation of tissue-specific MCT-deficient mice that would further potentially reveal so far unsuspected toxicities linked to MCT inhibition. Second, little is currently known about the regulation of MCT expression and activity. A better characterization of endogenous and exogenous factors, including conventional therapies, capable of influencing MCTs could eventually allow to identify efficient treatment combinations. Interestingly, MCTs can transport anticancer agents 3-bromopyruvate, dichloroacetate and iodoacetate across cancer cell membranes [26]. The study of MCT substrates that can act as anticancer compounds is an interesting new field that should be further explored. Finally, the preclinical and clinical development of MCT inhibitors would benefit from the identification and validation of biomarkers of MCT activity that would allow to predict and to document a therapeutic response.

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