Lactate transporters as therapeutic targets in cancer and inflammatory disease

Pucino, Valentina; Cucchi, Danilo; Mauro, Claudio

DOI:
10.1080/14728222.2018.1511706

Expert Opinion on Therapeutic Targets

ISSN: 1472-8222 (Print) 1744-7631 (Online) Journal homepage: http://www.tandfonline.com/loi/iett20

Lactate transporters as therapeutic targets in cancer and inflammatory disease

Valentina Pucino, Danilo Cucchi & Claudio Mauro

To cite this article: Valentina Pucino, Danilo Cucchi & Claudio Mauro (2018): Lactate transporters as therapeutic targets in cancer and inflammatory disease, Expert Opinion on Therapeutic Targets, DOI: 10.1080/14728222.2018.1511706

To link to this article: https://doi.org/10.1080/14728222.2018.1511706

Accepted author version posted online: 14 Aug 2018.

Publisher: Taylor & Francis

Journal: *Expert Opinion on Therapeutic Targets*

DOI: 10.1080/14728222.2018.1511706

Lactate transporters as therapeutic targets in cancer and inflammatory disease

Valentina Pucino[1], Danilo Cucchi[1] and Claudio Mauro[1,2]

[1]William Harvey Research Institute, Barts and The London School of Medicine & Dentistry, Queen Mary University of London, London, UK

[2]Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

Correspondence: Claudio Mauro

C.Mauro@bham.ac.uk

Keywords: lactate, lactate transporter, inflammation, metabolism, immunity, cancer

Abstract

Introduction: Inflammation is associated with the accumulation of lactate at sites of tumour growth and inflammation. Lactate initiates tissue responses contributing to disease. We discuss the potential of targeting lactate transporters in the treatment of cancer and inflammatory conditions.

Areas covered: Lactate is the product of glycolysis, which is considered to be a waste metabolite and a fuel for oxidative cells. It is also an active signalling molecule with immunomodulatory and angiogenic properties. They are the consequence of lactate binding to membrane receptor(s) or being transported through specific carrier-mediated transporters across the cellular membrane. Carriers are distinct in proton-linked monocarboxylate transporters (MCTs) and Na+-coupled electrogenic transporters (SMTCs), expressed by several tissues including immune system, endothelium and epithelium. Several tumours and inflammatory sites (i.e., arthritic synovium, atherosclerotic plaque) show accumulation of lactate and altered expression of its transporters, thus suggesting a role of this metabolite in cancer and inflammatory disorders. We review the most recent evidence on lactate biology, focusing on transporter expression and function in health and disease.

Expert opinion: Lactate-initiated signalling is gaining attention for its implications in cancer and inflammation. This review deals with the therapeutic potential of targeting lactate transporters and drugs that are already in clinical use for cancer and discusses the opportunity to develop new therapeutics for inflammatory disease based on recent findings.

Article Highlights:

1. Lactate is a main carbon source for biosynthetic pathways
2. Lactate is an immunomodulatory metabolite
3. Lactate transporters are expressed at different levels in immune, endothelial, epithelial and cancer cells
4. Expression of lactate transporters is up-regulated in some cancers and inflammatory disorders
5. Targeting lactate transporters is a therapeutic avenue that may lead to reduced inflammation and promote anti-cancer immunotherapy

1. Introduction - Lactate biology

Lactate is produced from pyruvate by the enzyme lactate dehydrogenase (LDH) in an NADH-dependent reaction. Its production occurs mainly in the cytoplasm under hypoxic conditions (fermentation) or even in the presence of normal oxygen concentration as a consequence of high glycolytic activity, such as in proliferating cells (we refer to this phenomenon as aerobic glycolysis, or Warburg effect, from the name of the scientist who first described it in cancer cells (1)). The production of lactate is important to replenish the pool of NAD+ necessary to maintain the flux of glycolysis. Lactate can be oxidised back to pyruvate and fed in to the TCA cycle or used as a fuel source for gluconeogenesis in the liver (2).

Lactate is present in solution in two distinct forms: as acid (i.e. lactic acid) at low pH, or as an ion salt (i.e. sodium lactate) at higher pH, with a dissociation constant (pKa) of 3.86. Lactate transfer across the plasma membrane happens through specific solute carrier transporters that we describe in more details in a separate section of this review. The physiological concentration of lactate, in blood and healthy tissues, is about 1.5-3mM (3), but in pathological conditions, such as atherosclerosis, rheumatoid arthritis and cancer, can peak at 10-30mM (4-6).

For many years lactate has been regarded merely as a waste product. Nowadays, emerging evidence has rehabilitated it to a major carbon source fuelling metabolic pathways as well as a proper signalling molecule able to orchestrate a variety of biological processes.

Many recent findings come from the field of cancer biology, because of the observation that in the cancer microenvironment lactate concentration can rise up to 20-30 mM (4, 5). Lactate is able to promote migration and growth of cancer cells (7, 8) and, in some cancerous cells, is also utilized as a substrate for the synthesis of lipids (9).

In a paper published in Cell in 2017, Faubert et al. investigated the fate of lactate in human lung cancer. Using intra-operative infusions of 13C-labeled nutrients, they were able to analyse the pattern of enrichment of labelled metabolites directly within the tumour (in this case lung tumours). The infusion of [U-13C] glucose showed a different pattern of enrichment in the cancer tissue as compared to the benign lung, with an excess of labelled lactate (rather than other upstream glycolytic metabolites) within the tumour. Interestingly, the infusion of 13C-lactate caused not only the accumulation of labelled lactate itself in the tumour, but also of labelled pyruvate, alanine and TCA cycle intermediates, showing that lactate was actively being used to supply the TCA cycle. The authors confirmed these findings in xenograft mouse models, but we believe the most important conclusion of the research was that comparing the contributions of lactate and glucose to the TCA cycle in the grafted tumours, the former turned out to make a much larger contribution than the latter. This effect was more dramatic when tumours were grown orthotopically in the lung rather than subcutaneously, suggesting a specific contribution of the tissue of residence of the tumour. Importantly, MCT1-deficient tumours showed a lower labelling of lactate-derived metabolites, underlining the importance of this lactate transporter (10).

Later in 2017, Hui et al. published another important piece of research in Nature demonstrating the role of lactate in fuelling the TCA cycle, both in normal and cancerous tissues. Analysis of the flux of circulating metabolites in mice showed that lactate is a major source of carbon for the TCA cycle; the infusion of 13C-lactate, in fed and fasted mice, showed extensive labelling of TCA cycle metabolites in all tissues, and in lung and pancreatic tumours the contribution of circulating lactate to the activity of TCA cycle was greater than that of glucose. These findings demonstrate that lactate is a substrate

of the TCA cycle both in normal and cancerous tissues, as well as that glycolysis and TCA cycle are uncoupled at the level of lactate, thus allowing the independent regulation of the two processes which also happen in a tissue-specific manner (11).

The effects of lactate are not only due to its ability to feed metabolic pathways, but also to its ability to trigger a signalling pathway via its receptor Gpr81. This is a surface lactate receptor involved in the regulation of lipolysis (12) but also in cancer cell survival (13). Feng et al., recently showed that lactate, through Gpr81, is able to regulate the expression of PD-L1 in human lung cancer cells. PD-L1 is the ligand of PD1, a receptor expressed on the membrane of activated T cells, responsible for reduced proliferation and effector function of T cells, and a major target for cancer immunotherapy (14). The authors show that lactate upregulates the expression of PD-L1 at a transcriptional level, in a Gpr81-dependent manner, and this upregulation leads to suppression of the effector function of T cells in co-culture experiments. Overall, the data point to a role for lactate in the tumour escape from immune-surveillance (15).

The ability of lactate to interfere with the response of the immune system against tumours was previously reported by the Kreutz' group. In 2007 they showed how tumour derived-lactic acid inhibits the proliferation and cytokine production of cytotoxic CD8+ T cells, while also dampening their cytolytic activity (16). The same group later showed that lactic acid also inhibits the production of TNF by human monocytes and decreases their glycolytic activity (17). More recently they published in Cell Metabolism a comprehensive analysis of the effects of lactic acid on immune surveillance against cancer (18). The authors generated melanoma cell lines with reduced expression of Ldha and observed a reduced rate of tumour growth as compared to controls. Upon analysis of the immune infiltrate, they found Ldha-low tumours bearing more immune cells, particularly CD8+ T cells producing IFNγ and granzyme B. This increase in the activity of CD8+ T cells was due to reduced production of lactic acid. Indeed the authors showed that lactic acid impairs both function and survival of T and NK cells. They went on to address a mechanism behind this phenotype. The lactic

acid produced by the tumour was taken up by T cells, causing a decrease in their intracellular pH that led to a drop in ATP production. This caused an impairment of the T cell functions, as a consequence of reduced NFAT activity, which is involved in the transcriptional control of IFNγ (18).

Along similar lines, the work published by Colegio et al. in 2014 showed that the lactic acid produced by tumours (lung carcinoma and melanoma) is able to induce the expression of Vegf and Arg1 in tumour-associated macrophages (TAMs), in a HIF1α-dependent manner. Moreover, lactic acid was also able to polarize TAMs toward a M2-like phenotype, thus enabling the establishment of a permissive microenvironment for tumour growth (5).

In the context of the tumour microenvironment, lactate plays a role not just in the crosstalk between cancer and immune cells, but also between cancer cells on one side and endothelium and stromal fibroblasts on the other side. Vegran and co-workers demonstrated that in the tumour microenvironment the lactate produced in large part by the cancer cells is taken up by endothelial cells (EC) leading to NFkB activation and consequent production of IL8, which in turn drives EC migration and neo-angiogenesis supporting tumour growth (19). Similarly and in agreement with (5), Sonveaux et al. showed that lactate is also able to activate HIF1 in EC, increasing the production of pro-angiogenic factors (bFGF and VEGFR2), thus overall stimulating angiogenesis; the inhibition of MCT1 is sufficient to abrogate the pro-angiogenic effect of lactate (20). Lactate is also important in the interplay between cancer and stromal cells. Fiaschi et al. have identified a lactate shuttle between human prostate cancer cells and cancer associated fibroblasts (CAF): the physical interaction between cancer cells and fibroblasts leads to the differentiation of the latter to CAF; these cells show high glycolytic activity with generation of lactate, elevated expression of MCT4 and stabilisation of HIF1. The lactate produced and released by CAF is then taken up by cancer cells through the transporter MCT1 and it is metabolised in the mitochondria, sustaining cancer growth. The disruption of this shuttle via pharmacological inhibition or genetic silencing of MCT1 inhibits cancer proliferation both in vitro and in vivo (21).

Diverse subsets of T cells show different metabolic requirement, with cytotoxic and effector T cells relying more on glycolysis for proliferation and cytokines production (22, 23) and, conversely, regulatory T cells (Tregs) being more dependent on oxidative phosphorylation (OXPHOS) (24, 25). Recently, Angelin et al. demonstrated that Foxp3 is able to reprogram the metabolism of Tregs, allowing them to cope better in low-glucose, high-lactate microenvironments. They found that the transcription factor Foxp3 promotes the increase of the oxygen consumption rate in inducible Tregs (iTregs) and also the production of reactive oxygen species (ROS); moreover Foxp3 is able to suppress the activity of Myc by binding to its promoter and reducing the expression of Myc-dependent transcripts, most of which are involved in the regulation of glycolysis. Foxp3 was also found to be able to regulate the direction of the LDH reaction in favour of the oxidation of L-lactate to pyruvate, leading to decreased production of lactate by Tregs (as compared to conventional T cells). Tregs can sustain exposure to lactate with better efficiency than effector and cytotoxic T cells, which are instead impaired by it: effector cells require NAD+ replenishment to sustain the flux of glycolysis, but the excess of utilization of lactate by LDH depletes the available pool of NAD+, leading to a decreased glycolytic flux; Tregs instead possess higher levels of NAD+ and due to their intrinsic metabolism are less affected by reduced glycolysis. The authors discuss that this adaptation could be detrimental in the tumour microenvironment, where the high concentration of lactate may inhibit anti-tumour immunity without affecting the regulatory component, which can further dampen the immune response against the tumour (26).

Recent evidence shows that lactate plays a crucial role also in the orchestration of the immune response in inflammatory conditions. In 2016, Peng et al. formally demonstrated that LDHA activity is necessary in CD4+ T cells to sustain aerobic glycolysis and express interferon-γ (IFN-γ), thus allowing a proper differentiation to the T helper 1 (Th1) subset. The authors found that genetic deletion of LDHA in CD4+ T cells reduced significantly glucose consumption, promoting a shift towards an oxidative metabolism, and, more importantly, led to a reduction of IFN-γ expression. The reduction of INF-γ transcripts (along with many others), was due to an overall decrease of histone

acetylation. Histone acetylation requires acetyl-coenzyme A (acetyl-CoA), but in the absence of LDHA, the consequent increased flux of the TCA cycle does not allow the export of acetyl-CoA from the mitochondria to the cytosol, reducing the pool of acetyl groups. These data demonstrate that LDHA regulates INF-γ production in Th1 cells through a fine-tuned epigenetic mechanism of histone acetylation coupled with the cellular metabolism (27).

Lactate is also involved in the production of IL17 and differentiation to the Th17 subset. In 2011, Yabu et al. showed how lactic acid enhances the production of IL23/IL17 by CD4+ T cells, acting as a pro-inflammatory signal (28). More recently, Haas et al. showed that sodium lactate is able to modulate T cell effector function by promoting the up-regulation of IL17 expression. They also showed that lactate affects the migratory capabilities of CD4+ T cells, thus causing their retention in the site of inflammation. These findings have an important impact on the understanding of the role of lactate in the inflammatory site, such as the inflamed synovium in rheumatoid arthritis, where lactate may act as an inflammatory signal leading to entrapment of CD4+ T cells and stimulation of IL17, thus perpetrating the inflammatory process. Interestingly, all these effects are mediated via a specific sodium lactate transporter, SLC5A12, which is expressed on the membrane of CD4+ T cells (6).

Overall lactate may induce an immune suppressive response in cancer yet act as an inflammatory signal in inflammatory conditions. The different response may be due to the context-dependent availability of nutrients and competition for them by the cellular constituents of the microenvironment (further discussed in Expert Opinion Section).

Lactate is also important in the physiology of the brain, through the astrocyte-neuron lactate shuttle (ANLS). This lactate exchange was first described in 1994 and highlights the existence of lactate-producing cells (astrocytes) and lactate-consuming cells (neurons): in this model, the neurotransmitter glutamate released in the synapse triggers glucose uptake and therefore lactate production by astrocytes; lactate is then utilised by neurons as a source of energy (29). For a more

detailed description of the role of lactate in the brain, both as a metabolite and a signalling molecule, we point the reader to a recent review (30).

Taken together, it is clear that lactate is not just an end-product of metabolism, but rather a source of carbons and, more importantly, a signal that affects the behaviour and the differentiation of many different cell types, especially at the interface between cancer and immune cells and in inflammatory diseases. In the following sections of this review we focus on the role of the different lactate transporters for their biological roles and as putative therapeutic targets.

2. Lactate transporters

2.1 Monocarboxylate transporters (MCTs)

Monocarboxylate transporters (MCTs) include 14 transmembrane proteins encoded by the SLC16A gene family. According to the Milton Saier classification (http://www.tcdb.org), MCTs belong to the monocarboxylate porter (MCP) family, which in turn is part of the facilitator superfamily (MFS). MCTs have been identified in all eukaryotic organisms and can transport a wide variety of substrates (31) (Table 1).

MCT1-4 are proton-linked transporters responsible for transport across the plasma membrane of several monocarboxylate metabolites, such as pyruvate, L-lactate and ketone bodies (acetoacetate and D-β-hydroxybutyrate) together with a proton (32, 33). Other identified MCTs are MCT8 which shows high affinity for the thyroid hormones T3 and T4, and MCT10/TAT1, a transporter of aromatic amino acids (33, 34). MCT6 has been reported to facilitate the proton-linked transport of bumetanide (35). MCT7 has been implicated in the export of ketone bodies by hepatocytes (36).

MCT9 has been identified as a sodium- and pH-independent carnitine efflux transporter upon expression in Xenopus oocytes injected with [3H]-carnitine (37). The substrates and functions of the other MCT family members are yet not known.

MCTs are expressed in a wide range of tissues (such as brain, skeletal muscle, heart, bowel and liver) and display many physiological functions. In particular they play a pivotal role in the control of the central metabolism of glucose, gluconeogenesis, and activation of T-lymphocytes, spermatogenesis, pancreatic β cell activity, thyroid hormone metabolism and drug transport (31).

Among other functions, MCTs are important regulators of intracellular lactate and pH. Indeed, highly glycolytic cells, such as inflammatory and tumour cells, utilize MCT transporters to export lactate.

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 (SLC16A1) is responsible for its export across the plasma membrane in to the extracellular space (33, 38).

Lactate can be taken up from the extracellular space and used as a substrate to fuel metabolic pathways such as lipogenesis, gluconeogenesis, TCA cycle and oxidative phosphorylation (OXPHOS) (28, 10). Cells that utilize lactate may express different MCTs depending on tissues and species (33, 39-42).

In many cancer cells with an oxidative metabolic fingerprint, MCT1 is the most expressed MCT isoform (40, 43). However, in glycolytic cancer cells and other specific tissues such as white muscle fibres and astrocytes, MCT4 is expressed at higher level than MCT1 and mediates lactate export (40, 43, 45). Accordingly, there is increasing evidence in support of the shuttling of this metabolite between cells with different metabolic behaviours within the same tissue. Such phenomenon has been described in the skeletal muscle where glycolytic/white fibres export lactate through MCT4 and oxidative/red fibres import lactate through MCT1 to fuel the TCA cycle (46). A similar mechanism has been proposed to account for a metabolic symbiosis between glycolytic/hypoxic cancer cells and oxidative/oxygenated cancer cells in tumours (40). Notoriously in the brain, glycolytic

oligodendrocytes and astrocytes export lactate through MCT1 and MCT4 to fuel oxidative neurons expressing MCT2 (47-50).

2.2 Sodium-coupled transporter (SMCTs)

In contrast to MCTs, which function as H+-coupled electroneutral transporters, SMCTs function as Na+-coupled electrogenic transporter. The transport process is electrogenic as more than 1 Na+ is transported per transport cycle with a Na+/monocarboxylate substrate ratio of ≥2. Two members of the sodium-coupled monocarboxylate transporter family (SMCT) have been identified so far, the high-affinity transporter SMCT1 (SLC5A8) and the low-affinity SMCT2 (SLC5A12) (51, 3). The SMCT1/SLC5A8 gene was originally identified from a library of kidney cDNA as a close structural relative of the human Na/I symporter (SLC5A5) (51). Other than in the kidney, SLC5A8 has been subsequently detected in intestine, salivary gland, thyroid gland, brain, and retina (52). Substrates of SLC5A8 are similar to those of MCTs (53, 54). SLC5A8 mediates the transport of monocarboxylic acids such as lactate, pyruvate, propionate, butyrate, nicotinate, and short-chain fatty acids (Table 2).

The affinity of the transporter for these monocarboxylates is quite high, with a Michaelis constant in the range of 200–400 μM.

Less is known about SMCT2/SLC5A12. mRNA expression of SLC5A12 was detected in kidney, small intestine, and skeletal muscle and to a lesser level in brain and retina. Functional characterization of SLC5A12 suggested a substrate specificity similar to that of SLC5A8. However, the affinities of SLC5A12 for monocarboxylate substrates are approximately 35- to 80-fold lower than those of SLC5A8 (3).

In the kidney, SLC5A8 is expressed in the apical membrane of tubular epithelial cells in the S2-S3 proximal tubule segments. Here SLC5A8 is involved in renal reabsorption of lactate and pyruvate in a

sodium-dependent transport (55-58). Indeed, SLC5A8-deficient or knockout mice exhibit increased urinary excretion of lactate (59). Renal SLC5A12 is localized at the brush border with higher expression in the initial part of the proximal tubules and gradually decreasing toward the S3 segment. Thus, the proximal convoluted tubules provide low and high affinity transporters in the upper and lower proximal tubules, respectively.

In the brain, SLC5A8 exhibits a neuron-specific distribution and may mediate cellular uptake of lactate and ketone bodies, the primary energy substrates of neurons (60), while SLC5A12 is specifically expressed by astrocytes. Besides its physiological functions, several reports suggested a tumour suppressing role for SLC5A8. High frequency of aberrant methylation or down-regulation of the SLC5A8 gene has been observed in human colon cancer, papillary thyroid carcinomas, pancreatic cancer, prostate tumour, acute myeloid leukemia, and glioma formation (52, 61, 62). Interestingly, Li et al. found that the exogenous SLC5A8 was able to suppress the proliferation of colon cells carrying the defective allele, thus suggesting that SLC5A8 inactivation confers a selective advantage to neoplastic colon epithelial cells (62). The mechanisms of this effect remain to be explored.

In the bowel, SLC5A8 is expressed differentially in the lumen-facing apical membrane of colonic and intestinal epithelial cells, while SLC5A12 is expressed primarily in the small intestinal tract (63, 53).

Recently these transporters have been also linked with the function of immune cells. Interestingly, SLC5A12 has been identified to be expressed by human and murine lymphocytes. In particular it was found that SLC5A12 is selectively expressed on the surface of $CD4^+$ but not of $CD8^+$ T cells (6, 64, 65). Whether immune cells express SLC5A8 is yet not known.

3. MCTs in cancer and immunity

MCTs, especially MCT1 and MCT4, are widely expressed in a variety of immune and cancer cells. In the tumour microenvironment, cancer cells produce high amount of lactate, which is extruded in the intercellular space via MCT4. Released lactate is then taken up by macrophages via

MCT1, promoting their polarization toward a TAM phenotype via the induction of HIF1⍰ and arginase 2. These effects induce neo-angiogenesis, via vascular endothelial growth factor (VEGF) production, and ultimately promote tumour growth (5).

MCT1 expression has been reported in a variety of human malignancies including head and neck, lung, stomach, colon, prostate and cervix, as well as gliomas (40, 66-68). MCT1 has also been proposed to be the most important isoform responsible for lactate transport across the plasma membrane in breast and bladder cancer, non-small cell lung carcinomas (NSCLC) and ovarian carcinomas (69,70).

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 (66-69).

Recently, Pertega-Gomes and Baltazar (71) reported a correlation between the expression of MCT1, MCT2 and MCT4 and the different stages of prostate cancer progression. MCT1 and MCT2 play a role in tumour maintenance, whereas MCT4 increases tumour aggressiveness. MCT2 was also proposed as a biomarker for prostate cancer (71). In another study focused at NSCLC, Eilertsen et al. proposed MCT1 as a biomarker for prognostic and survival (70). The co-expression of GLUT1 and MCT1 and of GLUT1 and MCT4 was found to be a negative prognostic factor associated with poor disease-specific survival.

MCT2 and MCT4 show a high intracellular expression. This suggests a possible role of these transporters in mediating lactate and/or pyruvate transport across the membranes of intracellular vesicles or organelles (45, 69).

Lactate transporters have been described in inflammatory sites such as rheumatoid arthritis (RA) synovium (6, 65). Here lactate is produced by highly glycolytic local cells such as fibroblast-like synovial cells as well as infiltrating immune cells (i.e. lymphocytes, and macrophages).

Unlike in tumours where lactate plays a key role in promoting cancer cell migration and growth, in inflammatory sites lactate activates a stop migration signal leading to the local entrapment of T cells

(72, 6). This phenomenon is due to the interaction of sodium lactate and lactic acid with the transporters SLC5A12 and SLC16A1/MCT1 which are selectively expressed on the surface of $CD4^+$ and $CD8^+$ subsets, respectively (6) (Figure 1). Sodium lactate-mediated inhibition of $CD4^+$ T cell migration is regulated via lactate interference with metabolic pathways (64, 72). Sodium lactate via SLC5A12 prompts $CD4^+$ T cells to start producing higher amounts of pro-inflammatory cytokines, in particular IL17A, while lactic acid causes impairment of $CD8^+$ T cell-mediated killing through SLC16A1/MCT1 (6, 16, 73). Lactate also promotes T cell retention in the inflamed tissue and exacerbates the process of chronic inflammation (i.e. synovial tissue) (6) (Figure 1).

Similar to cancer cells, highly proliferating RA synovial fibroblasts (RASFs) express high levels of MCT4, thus promoting synovial fluid acidification (74) (Figure 1). Silencing of MCT4 led to inhibited proliferation of RASFs and reduced the severity of arthritis in the mouse model of collagen-induced arthritis (CIA) (74). Accordingly, other authors found that MCT4 is required for macrophage activation upon TLR2 and TLR4 stimulation. MCT4 knockdown led to enhanced intracellular accumulation of lactate and decreased glycolysis in LPS-treated macrophages reducing their active response during inflammation (Figure 1) (75). This evidence suggests a potential role of lactate transporter inhibitors in the therapy of RA.

4. MCT/SMCT Inhibitors

Targeting lactate transporters has become a promising therapeutic avenue in oncology (76) and is also gaining attention in inflammatory disorders. A recent study found that blocking the lactate transporter MCT1 reduces the proliferation of breast cancer cells co-expressing MCT1 and MCT4 (77, 78) and reduces HIF-1 induced angiogenesis and tumour growth (20).

Several MCT inhibitors have been identified, although with only relative specificity for the various MCT isoforms. The first inhibitors identified were 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 analogues (32). Other inhibitors with a higher affinity for MCTs,

have been developed more recently (79). In this regard, 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 (78, 80). Draoui et al. have recently identified several new compounds belonging to the 7-aminocarboxycoumarine family that potently inhibit MCTs (82).

Interestingly, 7-(N-benzyl-N-methylamino)- 2-oxo-2H-chromene-3-carboxylic acid (7ACC2) was further reported to be an inhibitor of lactate uptake that does not inhibit lactate export (82).

Samuvel et al. reported that alpha-cyano-4-hydroxycinnamic acid, an inhibitor of monocarboxylate transporters, blocks lactate-augmented inflammatory gene expression and NFkB activity in human macrophages, indicating that lactate transport through monocarboxylate transporters is required for macrophage effector functions (83). Besides MCTs, proton-sensing GPCRs such as T cell death-associated gene 8 (TDAG8) have been shown to be important for the modulation of T cells in an acidic tumour environment and during inflammation (84, 85).

Lonidamine is an anti-spermogenic agent with anti-neoplastic activity; recently, it has been demonstrated that this drug inhibits lactate transport by MCT1, MCT2 and MCT4, providing an explanation to its anti-tumour effect (86, 87). Immunomodulatory drugs, such as thalidomide and its derivatives (lenalidomide and pomalidomide), have also been shown to act on the expression of MCT1 in myeloma cells, in vitro and in vivo: Eichner et al. demonstrated that these drugs destabilise the transmembrane complex CD147-MCT1, which is important in sustaining angiogenesis, proliferation and invasion of cancer cells, pointing out to the importance of lactate export and the efficacy of MCTs inhibition as an anti-cancer therapy (88).

Much less is known about SMCT inhibitors. Blocking SLC5A12 with a commercial antibody has revealed a great potential in promoting T cell egress from the inflamed site in a murine model of zymosan-induced peritonitis. More specifically, Phloretin (MCT1 inhbitor), an anti-Slc5a12 antibody or an isotype control antibody were injected intra-peritoneally in mice. Anti-Slc5a12 antibody caused

a significant reduction of $CD4^+$ T cells in the peritoneum in comparison to an isotype control antibody, while having no effect on CD8+ T cells. In contrast, phloretin promoted a significant decrease of CD8+ T cells in the peritoneum but did not show any effect on $CD4^+$ T cells. This suggests a peculiar specificity of these lactate transporter inhibitors targeting different T cells subsets (6).

Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and salicylic acid, and uricosuric drugs like probenecid, have also shown some inhibitor effects over MCT/SMCT substrates, such as hydroxybutyric acid (GHB), limiting their uptake (89, 90).

5. Expert opinion

For many years lactate has been considered a bystander product of glycolysis, produced during hypoxia or by highly proliferative cells. Only recently it has become to receive some consideration as a signalling metabolite. Its role in cancer biology and immunity is getting into the spotlight nowadays. The breakthrough that lactate plays an important role in the interplay between inflammation, cancer, metabolism and immunity together with the characterization of lactate transporters being expressed by a variety of cells (i.e. immune, stromal and cancer cells) has opened a new area of research and novel potential therapeutics. The emerging evidence that solid cancers deprive the tumour environment of glucose and enrich it with lactate which in turn depresses effector and cytotoxic T cell functions while promoting suppressive Treg cells, has also shed lights on new immunosuppressive therapy approaches, based on potentiating Treg cell activity, in conditions where Treg cell functionality is overthrown (i.e. autoimmunity, transplantation). On the other side, in cancer this can offer a new potential therapeutic approach based on targeting cancer metabolism that can reduce detrimental Treg cells in favour of effector T cells enhancing anti-tumour response (26) (Figure 1).

Different is the context of inflammatory disorders where the competition for nutrients between stromal and immune cells may be more even and lead to a different response to lactate.

Indeed, in the presence of high concentration of lactate, such as in the rheumatoid arthritis synovium, T cells are unable to egress ending up "entrapped" in the inflammatory site (6, 64, 65). Here, T cells produce a high amount of pro-inflammatory cytokines contributing to the establishment of chronic inflammation. Indeed, the effect of lactate on T cells recapitulates the typical characteristics of inflammatory infiltrates, in particular tissue retention, local production of inflammatory cytokines and loss of cytolytic activity (6) (Figure 1).

A selective lactate transporter expression by CD4+- and CD8+-activated T cells may orchestrate their differential distribution in the inflamed tissues as well as affect their functional and migratory responses depending, for example, on the nature of the inflammatory exudate (i.e., more lactic acid versus sodium lactate) (91-93). Thus, modulating selective T cell subsets via targeting specific lactate transporters may provide novel tools to reduce inflammation and help to better understand the pathogenesis of inflammatory disorders.

The development of specific or pan-MCT/SMCT inhibitors capable of tissue specificity may be the ultimate goal to achieve targeted therapy. Little is currently known about the regulation of MCT/SMTCs expression and activity in different tissues and their regulation during inflammation or tumours. The generation of tissue/cell-specific MCT/SMTCs-deficient mice will enable exploiting MCT physiopathology and toxicity. MCTs/SMTCs substrate transport is another interesting area that should be further explored. Indeed, the discovery that MCTs can transport anticancer agents (i.e. 3-bromopyruvate, dichloroacetate and iodoacetate) across cell membranes (45) suggests that those substrates can also act as anticancer compounds. This can also lead to the identification and validation of biomarkers capable of predicting therapeutic responses.

Overall, we have provided a summary of the potential role of lactate that, via a distinctive signalling network, may promote pathogenic characteristic typical of the inflammatory or tumour “milieu”. Thus targeting lactate transporters may provide a promising tool to reduce inflammation and induce anti-cancer responses.

Funding

This paper was funded by British Heart Foundation, UK, Arthritis Research UK, Queen Mary Innovation Ltd (QMI), UK and Fondazione Cariplo, Italy

Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose

Table 1 - MCT transporters

MCT transporter	Common name	Substrate	Distribution
SLC16A1	MCT1	Lactate, pyruvate, ketone bodies	Ubiquitous
SLC16A2	MCT8	T2, rT3, T3, T4	Ubiquitous
SLC16A3	MCT4	Lactate, ketone bodies	Skeletal muscle, chondrocytes, leucocytes, testis, lung, brain, ovary, placenta, heart, leucocytes
SLC16A4	MCT5	N/A	Brain, muscle, liver, kidney, lung, ovary, placenta, heart
SLC16A5	MCT6	Bumetanide probenecid nateglinide	Kidney, muscle, brain, heart, pancreas, prostate, lung, placenta
SLC16A6	MCT7	Ketone bodies	Liver, brain, pancreas, muscle, prostate
SLC16A7	MCT2	Pyruvate, lactate, ketone bodies	High expression in testis, moderate to low in spleen, heart, kidney, pancreas, skeletal muscle, brain and leucocytes
SLC16A8	MCT3	Lactate	Retinal pigment epithelium, choroid plexus
SLC16A9	MCT9	Carnitine	Endometrium, testis, ovary, breast, brain, kidney, spleen, retina
SLC16A10	MCT10	N/A	Kidney (basolateral), intestine, muscle, placenta, heart
SLC16A11	MCT11	N/A	Skin, lung, ovary, breast, lung, pancreas, retinal pigment epithelium, choroid plexus
SLC16A12	MCT12	N/A	Kidney, retina, lung testis
SLC16A13	MCT13	N/A	Breast, bone marrow stem cells
SLC16A14	MCT14	N/A	Brain, heart, muscle, ovary, prostate, breast, lung, pancreas liver, spleen, thymus

HUGO nomenclature	Common name	Function	Distribution
SLC5A1	SGLT1	Na+/glucose or Na+/galactose	Gastrointestinal tract, liver, kidney, male tissues
SLC5A2	SGLT2	Na+/glucose	Kidney, male tissues
SLC5A3	SMIT1	Na+/myoinositol	Ubiquitous
SLC5A4	SGLT3	Glucose-sensitive Na+-channel	Gastrointestinal tract
SLC5A5	NIS	Na+/iodide	Gastrointestinal tract, endocrine tissues, female tissues
SLC5A6	SMVT	Na+/biotin or Na+/pantothenate	Ubiquitous
SLC5A7	CHT1	Na+/Cl−/choline	Low expression in gastrointestinal tract, kidney, endocrine tissues, female and male tissues
SLC5A8	SMCT1	Na+/monocarboxylate	Intestin, kidney (apical membrane of tubular epithelial cells), brain, salivary gland, thyroid gland
SLC5A9	SMT	Na+/mannose	Gastrointestinal tract
SLC5A10	N/A	Unknown	Kidney
SLC5A11	SMIT2	Na+/myoinositol	Gastrointestinal tract, kidney, female tissues, brain
SLC5A12	SMCT2	Na+/monocarboxylate	Small intestin, kidney, brain, retina, male tissues, lymphoid organs, leucocytes

Table 2 - SMCT transporters

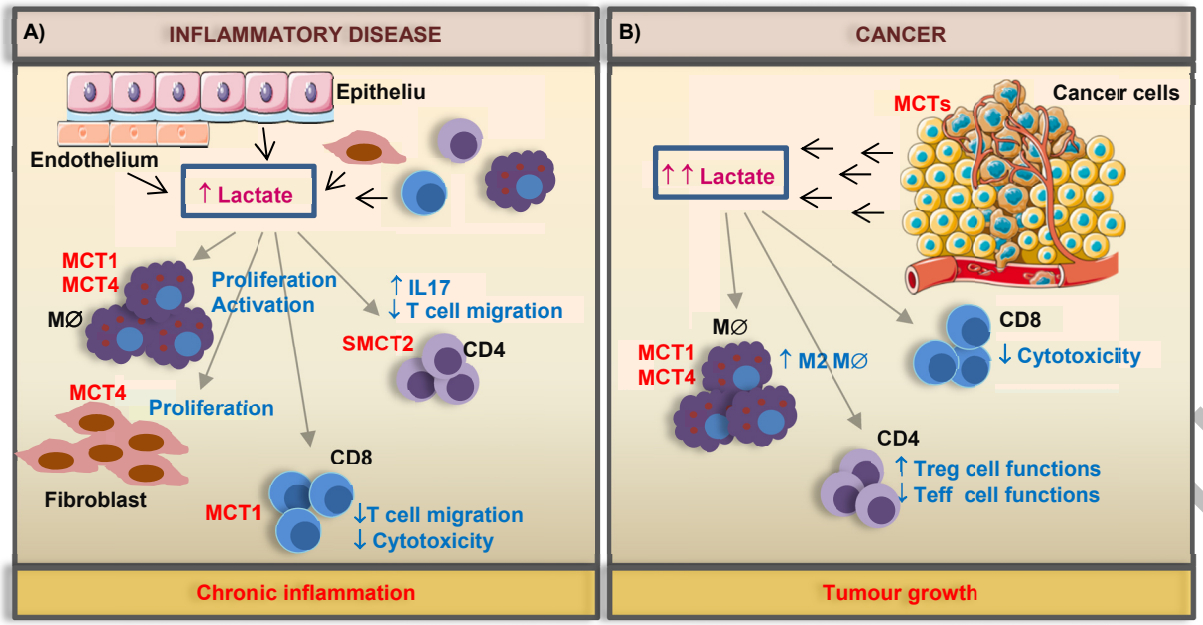

Figure 1. Accumulation of lactate occurs in the inflamed tissue and in the tumour microenvironment where it promotes chronic inflammation and tumour growth. A) During the inflammatory process immune cells sense (via specific transporters) and respond to the high levels of lactate that is produced by endothelial and epithelial cells as well as by the infiltrating immune cells, which all consume the available glucose. The sodium lactate transporter SMCT2 (SLC5A12) and the lactic acid transporter MCT1 (SLC16A1) are expressed by $CD4^+$ and $CD8^+$ T cells, respectively. MCT4 is expressed by fibroblasts and macrophages; the latter also display high levels of MCT1. Through these transporters, lactate modulates immune cell functions. In particular lactate promotes fibroblast proliferation as well as macrophage (MÆ) proliferation and activation. Lactate also inhibits T cell motility thus causing T cell entrapment in the inflamed tissue. There, in response to lactate $CD4^+$ T cells produce higher amounts of IL-17 and $CD8^+$ cytotoxic activity is affected. Overall these events promote chronic inflammation. B) Cancer cells express high levels of MCTs and release high amount of lactate in the tumour microenvironment, as the product of their pronounced glycolytic metabolism, which leaves infiltrating immune cells reliant on carbon sources other than glucose for their metabolism. There, lactate has an effect on wide range immune cell functions. It induces the switch of macrophages to an M2 phenotype via the transporters MCT1 and MCT4. It also promotes T cell differentiation to the Treg phenotype while suppressing Teff functions (i.e. cytokine production, cytotoxicity), thus leading to enhanced tumour growth.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers

1. Warburg O. On the origin of cancer cells. Science 1956;123:309–314

2. Cornell NW, Lund P, Hems R, et al. Acceleration of gluconeogenesis from lactate by lysine (short communication). Biochem J 1973;134:671–672

3. Srinivas SR, Gopal E, Zhuang L, et al. Cloning and functional identification of slc5a12 as a sodium-coupled low-affinity transporter for mono-carboxylates (SMCT2). Biochem J 2005;392:655–664 ****This study provides an overview of the distribution and function of SLC5A12**

4. Hirschhaeuser F, Sattler UG, Mueller-Klieser W. Lactate: a metabolic key player in cancer. Cancer Res 2011;71:6921–6925

5. Colegio OR, Chu NQ, Szabo AL, et al. Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. Nature 2014;513:559–563 ****This study**

demonstrates that lactic acid produced by the tumour drives the differentiation of tumour-associated macrophages

6. Haas R, Smith J, Rocher-Ros V, et al. Lactate regulates metabolic and pro-inflammatory circuits in control of T cell migration and effector functions. PLoS Biol 2015;13:e1002202 ****This study shows how lactate can modulate different T cell subset functions via lactate transporters selectively expressed on CD4+ and CD8+ T cells**

7. Baumann F, Leukel P, Doerfelt A, et al.(2009) Lactate promotes glioma migration by TGF-b2-dependent regulation of matrix metalloproteinase-2. Neuro Oncol 2009;11:368–380

8. Bonuccelli G, Tsirigos A, Whitaker-Menezes T, et al. Ketones and lactate "fuel" tumor growth and metastasis: evidence that epithelial cancer cells use oxidative mitochondrial metabolism. Cell Cycle 2010;9:3506–3514

9. Chen YJ, Mahieu NG, Huang X, et al. Lactate Metabolism is Associated with Mammalian Mitochondria. Nat Chem Biol 2016;12:937–943

10. Faubert B, Li KY, Cai L, et al. Lactate Metabolism in Human Lung Tumors. Cell 2017;171:358–371.e9 ****This study shows that lactate is a main carbon source in cancer cells and feeds the TCA cycle**

11. Hui S, Ghergurovich JM, Morscher RJ, et al. Glucose feeds the TCA cycle via circulating lactate. Nature 2017;551:115–118

12. Liu C, Wu J, Zhu J, et al. Lactate inhibits lipolysis in fat cells through activation of an orphan G-protein-coupled receptor, GPR81. J Biol Chem 2009;284:2811–2822

13. Roland CL, Arumugam T, Deng D, et al. Cell surface lactate receptor GPR81 is crucial for cancer cell survival. Cancer Res 2014;74:5301–5310

14. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell 2015;27:450-61.

15. Feng J, Yang H, Zhang Y, et al. Tumor cell-derived lactate induces TAZ-dependent upregulation of PD-L1 through GPR81 in human lung cancer cells. Oncogene 2017;36:5829-5839

16. Fischer K, Hoffmann P, Voelkl S, et al. Inhibitory effect of tumor cell-derived lactic acid on human T cells. Blood 2007;109:3812–3819

17. Dietl K, Renner K, Dettmer K, et al. Lactic acid and acidification inhibit TNF secretion and glycolysis of human monocytes. J Immunol 2010;184:1200–1209

18. Brand A, Singer K, Koehl GE, et al. LDHA-associated lactic acid production blunts tumor immunosurveillance by T and NK cells. Cell Metab 2016;24:657-671 ***This study explains how lactic acid inhibits the immune system in the tumour microenvironment**

19. Vegran F, Boidot R, Michiels C, Sonveaux P, Feron O. Lactate influx through the endothelial cell monocarboxylate transporter MCT1 supports an NF-kappaB/IL-8 pathway that drives tumor angiogenesis. Cancer Res 2011;71: 2550–60.

20. Sonveaux P, Copetti T, De Saedeleer CJ, et al. Targeting the lactate transporter MCT1 in endothelial cells inhibits lactate-induced HIF-1 activation and tumor angiogenesis. PLoS one 2012;7:e33418

21. Fiaschi T, Marini A, Giannoni E, Taddei ML, Gandellini P, De Donatis A, Lanciotti M, Serni S, Cirri P, Chiarugi P: Reciprocal metabolic reprogramming through lactate shuttle coordinately influences tumor-stroma interplay. Cancer Res 2012;72(19):5130–40.

22. Chang CH, Curtis JD, Maggi LB, et al. Posttranscriptional control of T cell effector function by aerobic glycolysis. Cell 2013;153:1239–1251

23. Macintyre AN, Gerriets VA, Nichols AG, et al. The glucose transporter Glut1 is selectively essential for CD4 T cell activation and effector function. Cell Metab 2014;20:61–72

24. Michalek RD, Gerriets VA, Jacobs SR, et al. Cutting edge: distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4+ T cell subsets. J Immunol 2011;186:3299–3303

25. Gerriets VA, Kishton RJ, Nichols AG, et al. Metabolic programming and PDHK1 control CD4+ T cell subsets and inflammation. J Clin Invest 2015;125:194–207

26. Angelin A, Gil-de-Gómez L, Dahiya S, et al. Foxp3 Reprograms T Cell Metabolism to Function in Low-Glucose, High-Lactate Environments. Cell Metab 2017;25:1282-1293 ****This study demonstrates that Foxp3 allows Treg cells to be active in high-lactate environments**

27. Peng M, Yin N, Chhangawala S, et al. Aerobic glycolysis promotes T helper 1 differentiation through an epigenetic mechanism. Science 2016;14:481-484

28. Yabu M, Shime H, Hara H, et al. IL-23-dependent and –independent enhancement pathways of IL-17A production by lactic acid. Int. Immunol. 2011;23:29-41

29. Pellerin L, Magistretti PJ. Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. Proc. Natl. Acad. Sci. U.S.A. 1994;91: 10625–10629

30. Magistretti PJ, Allaman I. Lactate in the brain: from metabolic end-product to signalling molecule. Nat Rev Neurosci 2018;19(4):235-249

31. Pérez-Escuredo J, Van Hée VF, Sboarina M, Falces J, Payen VL, Pellerin L, Sonveaux P. Monocarboxylate transporters in the brain and in cancer. Biochim Biophys Acta. 2016;1863:2481-97

32. Halestrap AP, Price NT. The proton-linked monocarboxylate transporter (MCT) family: structure, function and regulation. Biochem J 1999;343:281–299 ***This study provides an overview of the structure, distribution and function of MCTs**

33. Halestrap AP, Meredith D. The SLC16 gene family-from monocarboxylate transporters (MCTs) to aromatic amino acid transporters and beyond. Pflugers Arch 2004;447:619–628.

34. Visser WE, Friesema EC, Visser TJ. Minireview: thyroid hormone transporters: the knowns and the unknowns. MolEndocrinol 2011;25:1–14

35. Murakami Y, Kohyama N, Kobayashi Y, et al. Functional characterization of human monocarboxylate transporter 6 (SLC16A5). Drug Metab Dispos 2005;33:1845–1851

36. Hugo SE, Cruz-Garcia L, Karanth S et al. A monocarboxylate transporter required for hepatocyte secretion of ketone bodies during fasting. Genes Dev 2012;26:282–293

37. Suhre K, Shin SY, Petersen AK, et al. Human metabolic individuality in biomedical and pharmaceutical research. Nature 2011;477:54–60

38. Halestrap AP, Wilson MC. The monocarboxylate transporter family—role and regulation. IUBMB Life 2012;64:109–119

39. Bonen A. The expression of lactate transporters (MCT1 and MCT4) in heart and muscle. Eur J Appl Physiol 2001;86:6–11

40. Sonveaux P, Végran F, Schroeder T, et al. Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice. J Clin Invest 2008;118:3930–3942

41. Van Hée VF, Pérez-Escuredo J, Cacace A, et al. Lactate does not activate NF-kB in oxidative tumor cells. Front Pharmacol 2015;6:228

42. Huang CK, Chang PH, Kuo WH, et al. Adipocytes promote malignant growth of breast tumours with monocarboxylate transporter 2 expression via β-hydroxybutyrate. Nat Commun. 2017 Mar 10;8:14706.

43. Kennedy KM, Scarbrough PM, Ribeiro A, et al. Catabolism of exogenous lactate reveals it as a legitimate metabolic substrate in breast cancer. PLoS One 2013;8:e75154

44. Ullah MS, Davies AJ, Halestrap AP. The plasma membrane lactate transporter MCT4, but not MCT1, is up-regulated by hypoxia through a HIF-1alpha-dependent mechanism. J Biol Chem 2006;281:9030–9037

45. Baltazar F, Pinheiro C, Morais-Santos F, et al. Monocarboxylate transporters as targets and mediators in cancer therapy response. Histol Histopathol 2014;29:1511–1524

46. Juel C, Halestrap AP. Lactate transport in skeletal muscle—role and regulation of the monocarboxylate transporter. J Physiol 1999;517:633–642.

47. Brooks, GA. Cell–cell and intracellular lactate shuttles. J Physiol 2009;587:5591–5600

48. Pellerin L, Magistretti PJ. Sweet sixteen for ANLS. J Cereb Blood Flow Metab 2012;32:1152–1166

49. Funfschilling U, Supplie LM, Mahad D et al. Glycolytic oligodendrocytes maintain myelin and long-term axonal integrity. Nature 2012;485:517–521

50. Saab AS, Tzvetanova ID, Nave KA. The role of myelin and oligodendrocytes in axonal energy metabolism. Curr Opin Neurobiol 2013;23:1065–1072

51. Rodriguez AM, Perron B, Lacroix L, et al. Identification and characterization of a putative human iodide transporter located at the apical membrane of thyrocytes. J Clin Endocrinol Metab 2002;87:3500Y3503 ***First identification of sodium-coupled transporters (SMCTs)**

52. Ganapathy V, Thangaraju M, Gopal E, et al. Sodium-coupled Monocarboxylate Transporters in Normal Tissues and in Cancer. AAPS Journal 2008;10:193-199 ***This study provides an overview of the distribution and functions of SMCTs**

53. Gopal E, Umapathy NS, Martin PM, et al. Cloning and functional characterization of human SMCT2 (SLC5A12) and expression pattern of the transporter in kidney. Biochim Biophys Acta 2007;1768:2690–2697

54. Morris ME, Felmlee MA. Overview of the proton-coupled MCT (SLC16A) family of transporters: characterization, function and role in the transport of the drug of abuse gamma-hydroxybutyric acid. AAPS J 2008;10:311-21

55. Barac-Nieto M, Murer H, Kinne R. Lactate-sodium cotransport in rat renal brush border membranes. Am J Physiol 1980;239:F496-506

56. Mengual R, Claude-Schlageter MH, Poiree JC, et al. Characterization of sodium and pyruvate interactions of the two carrier systems specific of mono- and di- or tricarboxylic acids by renal brush-border membrane vesicles. J Membr Biol 1989;108:197-205

57. Gopal E, Miyauchi S, Martin PM, et al. Transport of nicotinate and structurally related compounds by human SMCT1 (SLC5A8) and its relevance to drug transport in the mammalian intestinal tract. Pharm Res 2007;24:575–584

58. Yanase H, Takebe K, Nio-Kobayashi J, et al. Cellular localization of a sodiumdependent monocarboxylate transporter (Slc5a8) and the MCT family in the mouse kidney. Histochem Cell Biol 2008;130:957–966

59. Frank H, Gröger N, Diener M, Becker C, Braun T, Boettger T. Lactaturia and loss of sodium-dependent lactate uptake in the colon of SLC5A8-deficient mice. J Biol Chem 2008;283:24729-37

60. Martin PM, Gopal E, Ananth S, et al. Identity of SMCT1 (SLC5A8) as a neuron-specific Na+-coupled transporter for active uptake of L-lactate and ketone bodies in the brain. J Neurochem 2006;98:279–288

61. Park JY, Helm JF, Zheng W, et al. Silencing of the candidate tumor suppressor gene solute carrier family 5 member 8 (SLC5A8) in human pancreatic cancer. Pancreas 2008;36:e32-9

62. Li H, Myeroff L, Smiraglia D, et al. SLC5A8, a sodium transporter, is a tumor suppressor gene silenced by methylation in human colon aberrant crypt foci and cancers. Proc Natl Acad Sci USA 2003;100:8412–8417

63. Iwanaga T, Takebe K, Kato I, et al. Cellular expression of monocarboxylate transporters (MCT) in the digestive tract of the mouse, rat, and humans, with special reference to slc5a8. Biomed Res 2006;27:243–254

64. Haas R, Cucchi D, Smith J, et al. Intermediates of metabolism: from bystanders to signalling molecules. Trends Biochem Sci 2016;4:460-71

65. Pucino V, Bombardieri M, Pitzalis C, et al. Lactate at the crossroads of metabolism, inflammation, and autoimmunity. Eur J Immunol 2017;47:14-21

66. Kennedy KM, Dewhirst MW. Tumor metabolism of lactate: the influence and therapeutic potential for MCT and CD147 regulation. Future Oncol 2010;6:127–148

67. Pinheiro C, Longatto-Filho A, Azevedo-Silva J, et al. Role of monocarboxylate transporters in human cancers: state of the art. J Bioenerg Biomembr 2012;44:127–139

68. Miranda-Goncalves V, Honavar M, Pinheiro C, et al. Monocarboxylate transporters (MCTs) in gliomas: expression and exploitation as therapeutic targets. Neuro-Oncol 2013;15:172–188

69. Afonso J, Santos LL, Miranda-Goncalves V, et al. CD147 and MCT1-potential partners in bladder cancer aggressiveness and cisplatin resistance. Mol Carcinog 2015;54:1451–1466

70. Eilertsen M, Andersen S, Al-Saad S Y, et al. Monocarboxylate transporters 1–4 in NSCLC: MCT1 is an independent prognostic marker for survival. PLoS One 2014;9:e105038

71. Pertega-Gomes N, Baltazar F. Lactate transporters in the context of prostate cancer metabolism: what do we know? Int J Mol Sci 2014;15:18333–18348

72. Droge W, Roth S, Altmann A, et al. Regulation of T-cell functions by L-lactate. Cell Immunol 1987;108:405-41652

73. Mendler AN, Hu B, Prinz PU, et al. Tumor lactic acidosis suppresses CTL function by inhibition of p38 and JNK/c-Jun activation. Int J Cancer 2012;131:633-40

74. Fujii W, Kawahito Y, Nagahara H, et al. Monocarboxylate transporter 4, associated with the acidification of synovial fluid, is a novel therapeutic target for inflammatory arthritis. Arthritis Rheumatol 2015;67:2888-96 *This study shows efficacy of MCTs blockers in RA

75. Tan Z, Xie N, Banerjee S, et al. The monocarboxylate transporter 4 is required for glycolytic reprogramming and inflammatory response in macrophages. J Biol Chem. 2015 Jan 2;290(1):46-55.

76. Doherty JR and Cleveland JL. Targeting lactate metabolism for cancer therapeutics. J Clin Invest 2013;123:3685-92

77. Halestrap AP. Monocarboxylic acid transport. Compr Physiol 2013;3:1611–1643.

78. Hong CS, Graham NA, Gu W, et al. MCT1 Modulates Cancer Cell Pyruvate Export and Growth of Tumors that Co-express MCT1 and MCT4. Cell Rep. 2016 Feb 23;14(7):1590-1601.

79. Draoui N, Schicke O, Fernandes A, et al. Synthesis and pharmacological evaluation of carboxycoumarins as a new antitumor treatment targeting lactate transport in cancer cells, Bioorg Med Chem 2013;21:7107–7117

80. Ovens MJ, Manoharan C, Wilson MC, et al. The inhibition of monocarboxylate transporter 2 (MCT2) by AR-C155858 is modulated by the associated ancillary protein. Biochem J 2010;431:217–225

81. Doherty JR, Yang C, Scott KE, et al. Blocking lactate export by inhibiting the Myc target MCT1 Disables glycolysis and glutathione synthesis. Cancer Res 2014;74:908-20. ***This study shows efficacy of MCT blockers in cancer**

82. Draoui N, Schicke E, Seront C, et al. Antitumor activity of 7-aminocarboxycoumarin derivatives, a new class of potent inhibitors of lactate influx but not efflux. Mol Cancer Ther 2014;13:1410–1418

83. Samuvel DJ, Sundararaj KP, Nareika A, et al. Lactate boosts TLR-4 signalling and NFkB pathway-mediated gene transcription ind macrophages via monocarboxylate transporteres and MD-2 upregulation. J Immunol 2009;182:2476-84

84. Pilon-Thomas S, Kodumudi KN, El-Kenawi AE, et al. Neutralization of Tumor Acidity Improves Antitumor Responses to Immunotherapy. Cancer res 2016;76:1381-1390

85. Ishii S, Kihara Y, Shimizu T. Identification of T cell death-associated gene 8 (TDAG8) as a novel acid sensing G-protein-coupled receptor. J Biol Chem 2005;280:9083-7

86. Nancolas B, Guo L, Zhou R, et al. The anti-tumour agent lonidamine is a potent inhibitor of the mitochondrial pyruvate carrier and plasma membrane monocarboxylate transporters. Biochem J 2016;473(7):929–936.

87. Nath K, Guo L, Nancolas B, et al. Mechanism of antineoplastic activity of lonidamine. Biochim Biophys Acta. 2016 Dec;1866(2):151-162.

88. Eichner R, Heider M, Fernández-Sáiz V, et al. Immunomodulatory drugs disrupt the cereblon-CD147-MCT1 axis to exert antitumor activity and teratogenicity. Nat Med 2016 Jul;22(7):735-43.

89. Cui D, Morris ME. The drug of abuse gamma-hydroxybutyrate is a substrate for sodium-coupled monocarboxylate transporter (SMCT) 1 (SLC5A8): characterization of SMCT-mediated uptake and inhibition. Drug Metab Dispos 2009;37:1404-10

90. Emoto A, Ushigome F, Koyabu N, et al. H(+)-linked transport of salicylic acid, an NSAID, in the human trophoblast cell line BeWo. Am J Physiol Cell Physiol 2002;282(5):C1064-75.

91. Ene-Obong A, Clear AJ, Watt J, et al. Activated pancreatic stellate cells sequester CD8+ T cells to reduce their infiltration of the juxtatumoral compartment of pancreatic ductal adenocarcinoma. Gastroenterology 2013; 145: 1121–1132

92. Haworth O, Hardie DL, Burman A, Rainger GE, Eksteen B, et al. A role for the integrin alpha6-beta1 in the differential distribution of CD4 and CD8 T-cell subsets within the rheumatoid synovium. Rheumatology (Oxford) 2008;47:1329–1334.

93. Olloquequi J, Ferrer J, Montes JF, et al. Differential lymphocyte infiltration in small airways and lung parenchyma in COPD patients. Respir Med 2010;104:1310–1318.