MCT4 has a potential to be used as a prognostic biomarker - a systematic review and meta-analysis

Arslaan Javaeed,1 Sanniya Khan Ghauri2

1Department of Pathology, Poonch Medical College, Rawalakot; 2Department of Emergency Medicine, Shifa International Hospital, Islamabad, Pakistan

Abstract

The role of several metabolic changes, such as hypoxia and acidosis, in the tumour environment has captured the attention of researchers in cancer progression and invasion. Lactate transport is one of the acidosis-enhancing processes that are mediated via monocarboxylate transporters (MCTs). We conducted a systematic review and meta-analysis to investigate the expression of two cancer-relevant MCTs (MCT1 and MCT4) and their potential prognostic significance in patients with metastasis of different types of cancer. Studies were included if they reported the number of metastatic tissue samples expressing either low or high levels of MCT1 and/or MCT4 or those revealing the hazard ratios (HRs) of the overall survival (OS) or disease-free survival (DFS) as prognostic indicators. During the period between 2010 and 2018, a total of 20 articles including 3831 patients (56.3% males) were identified. There was a significant association between MCT4 expression (high versus low) and lymph node metastasis [odds ratio (OR)=1.87, 95% confidence interval (CI)=1.10-3.17, P=0.02] and distant metastasis [OR=2.18, 95%CI=1.65-2.86, P<0.001] and the correlation remained significant for colorectal and hepatic cancer in subgroup analysis. For survival analysis, patients with shorter OS periods exhibited a higher MCT4 expression [hazard ratio (HR)=1.78, 95%CI=1.49-2.13, P<0.001], while DFS was shorter in patients with high MCT1 [HR=1.48, 95%CI=1.04-2.10, P=0.03] and MCT4 expression [HR=1.70, 95%CI=1.19-2.42, P=0.003] when compared to their counterparts with low expression levels. Future research studies should consider the pharmacologic inhibition of MCT4 to effectively inhibit cancer progression to metastasis.

Introduction

The genomic revolution over the past three decades has dramatically advanced our knowledge about the molecular and metabolic mechanisms of cancer and improved several aspects in relation to understanding, diagnosing, and treating multiple primary cancers. However, the inherent features of genomic and cellular changes of malignant cells are often perplexing. The rate, timing, and sites of these evolutionary changes are unpredictable and they are seemingly dependent on the cellular genomic makeup as well as the specific pressures placed on it. Such advances in cancer diagnosis have led to remarkable benefits in treatment outcomes when the disease is detected early. Nevertheless, the development of a metastatic phenotype represents a real challenge and is deemed the most lethal attribute of a malignancy. Reports have revealed that metastasis contributes to approximately 90% of all cancer-related deaths. Additionally, there is a variation in patients’ prognosis according to the distant organ. For instance, based on the Surveillance, Epidemiology and End Results database, breast cancer patients with bone metastasis had a favourable prognosis, while those with metastasis in the brain or multiple sites had the poorest prognosis. Furthermore, distant tumours are not suitable indications for surgical or radiological therapies and they are resistant to chemotherapeutic agents.

Metastasis is a complicated, multiphasic process in which the primary tumour cells invade the surrounding tissues due to hypermotility, intravasate into the blood circulation, disseminate to reach a capillary bud, permeate the blood vessels to reach a contiguous organ (extravasation), and finally colonise in the distant target and form a micrometastasis through angiogenesis and proliferation, which ultimately reflects as a macroscopic tumour. Several molecular mechanisms have been investigated in the literature regarding initiation of cancer cell metastasis, revealing a potential involvement of genetic mutations, tumour necrosis, immune escape, promoting blood circulation, and increased rates of glycolysis. Actually, the latter mechanism was initially demonstrated in 1924 through the accelerated engagement of cancer cells in glycolytic cascades, even in normoxic conditions. Intracellular lactate should be exported out of cancer cells to avoid cellular acidosis and apoptosis. Large amounts of lactic acid are produced via glycolysis leading to increased acidity in the extracellular environment. Additionally, lactate has been identified as a remarkable source of energy in cancer. To this end, the role of monocarboxylate transporters (MCTs) could be critical. Fourteen members belong to the MCT family (SLC16A) and they transport pyruvate, lactate and ketone across the cell membrane.
MCT1 (encoded by the SLC16A1 gene) and MCT4 (SLC16A3) export monocarboxylates coupled with a proton and they play a regulatory role on intracellular pH in cells relying on high glycolysis rates, such as red blood cells, skeletal muscle cells and tumour cells.10,11 Both MCT1 and MCT4 are expressed variably in normal and malignant cells. For instance, on a specific immunoreactivity (IR) score ranging between 0 (no IR) to 4 (strong IR), Froberg et al.12 revealed weak MCT1 IR in the microvessels and ependymocytes of normal human brain tissue, while it was strongest for high-grade glial neoplasms, astrocytoma, and glioblastoma multiforme when compared to the IR of low-grade glial neoplasms (2.8333 vs 1.0833, P=0.000). A consistently used method in the literature to semiquantitatively evaluate IR has shown that the majority of breast tumour cells were strongly IR to MCT1 (79.2% versus 33.3% in normal cells) and to MCT4 (95.5% versus 46.7%).13 However, the knowledge linking MCT1 and MCT4 expression and metastasis, as a major life-threatening condition, is still unclear. Herein, this review has provided a systematic insight into the association between the occurrence of metastasis and the expression of both MCT1 and MCT4 in different types of cancer to further characterise the impact of their targeted inhibition as a therapeutic approach. Furthermore, the integrative role of both proteins as prognostic biomarkers for survival in patients with cancer was analysed statistically.

Materials and Methods

Search strategy and study selection

The main search strategy was designed according to the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).14 A comprehensive search process was conducted on the following scientific databases: PubMed, Embase, Google Scholar and Web of Science for studies published between January 1st, 2010 and November 24th, 2018. The main search was conducted in PubMed using the keywords: (“monocarboxylate transporter1” OR “MCT1”) AND (“metastasis”) AND (“prognosis” OR “survival” OR “predict”) and (“monocarboxylate transporter4” OR “MCT4”) AND (“metastasis”) AND (“prognosis” OR “survival” OR “predict”) and the same terms were subsequently utilised in other databases. The bibliographies of the retrieved articles were searched for additional studies for inclusion. Two independent authors performed the search process and any disagreement was resolved by discussion.

Eligibility criteria

The included studies should report their results based on the pathological examination of MCT1 and/or MCT4 in clinical cohorts and the outcomes should be categorised according to their expression levels into either low or high. Studies reporting data about the association between MCT expression and lymph node metastasis (LNM) and/or distant metastasis (DM) were considered. Additionally, given the significant association between LNM and lymphovascular invasion,15,16 the latter was deemed an indicator of LNM during data collection in relation to MCT expression. For prognostic significance, articles should provide the hazard ratios (HRs) and 95% confidence intervals (CIs) for overall survival (OS) or disease-free survival (DFS). Studies were excluded if they provided insufficient data to be extracted. In addition, review articles, case reports, cell culture-based studies, preclinical experiments, case reports, non-English articles and systematic reviews were not eligible for inclusion.

Data extraction

The following data were extracted for each individually included study: author name(s), date of publication, the type of primary cancer, the investigated MCT(s), number of patients, number of patients with metastasis along with exhibiting high or low expression levels, and the total number of patients in each group. Data relevant to metastasis to lymph nodes or distant organs and tissues were also extracted. Furthermore, HRs and their corresponding minimum and maximum 95% CIs were also collected, including the methods by which they were analysed. If both univariate analysis and multivariate analysis were used in a given study, the survival data of multivariate analysis were preferably included.

Quality assessment

The Newcastle-Ottawa quality assessment scale17 was employed for the assessment of included studies. Such a tool entails a scoring system ranging between 0 (bad) and 9 (excellent) for certain criteria pertinent to the study groups, such as selection, comparability, and outcomes. Studies were deemed of a high quality if the total score was ≥6.

Statistical analysis

The meta-analysis was performed using RevMan 5.3 software (Review Manager, the Cochrane Collaboration, Oxford, United Kingdom). The pooled effects were estimated using HRs and their 95% CI for prognostic data, while odds ratio (OR) and their 95% CIs were used for analysing the relationship between low or high MCT expression levels and LNM or DM. The I² statistic test was utilized to quantify the heterogeneity between studies, where a significant heterogeneity was considered at I²>50% and subsequently a random-effect model should be used. If not, a fixed effect model was applied. The subgroup analysis was done for LNM and DM and their association with MCT1 and/or MCT4 expression according to sample size (<150 versus ≥150), cancer type, and quality score (<7 versus ≥7). Significant relationships were estimated at a P value<0.05.

Results

Outcomes of the search process

Figure 1 depicts the main findings of the search process. A total of 4322 records were initially obtained, from which 250 duplicates were identified across different scientific databases. With an additional three articles identified in the reference lists of the attained articles, 4075 records were screened for eligibility. Subsequently, 4053 articles were excluded through the screening of titles and abstracts, and the remaining 25 studies were thoroughly evaluated for inclusion. Ultimately, 20 articles met the inclusion criteria.

Characteristics of the included studies

Table 1 demonstrates a chronologically ordered list of the included studies, which were published between 2010 and 2018. A total of 3831 patients (56.3% males) with different types of cancers were investigated. Colorectal cancer (CRC) was the most frequently studied type (in four studies) followed by hepatic cancer in three studies.22-24 Both MCT1 and MCT4 were investigated in six studies,21,25-29 while the remaining articles investigated either of them. All studies used immunohistochemistry (IHC) assays to quantify MCT expression. Five studies did not reveal their data relevant to MCT1 and/or MCT4 expression in metastasis, yet they were included as they reported the survival outcomes in patients
with tumours expressing such MCTs. For quality assessment, all included studies scored equal to or greater than 6, indicating that all of them were of a high quality.

**Expression of MCT1 and MCT4 in lymph node metastasis**

There was a significant heterogeneity between a total of 9 studies that demonstrated LNM with the expression of MCT1 and MCT4 (I^2=77% and 63%, respectively). Interestingly, there was a significant association between MCT4 expression (high versus low) and LNM (OR=1.87, 95%CI=1.10–3.17, P=0.02, Figure 2B). However, such a relationship was unremarkable for high MCT1 expression, although LNM in gallbladder cancer showed a significant elevation of MCT1 expression (Figure 2A). The lack of significant effect of high MCT1 expression was still evident with subgroup analysis according to sample size, cancer type and quality score (Table 2).

**Expression of MCT1 and MCT4 in distant metastasis**

As with LNM, metastasis to distant organs was significantly associated with high MCT4 expression as compared to low expression (OR=2.18, 95%CI=1.65–2.86, P<0.001, I^2=42%, Figure 2D). This association remained significant in colorectal and liver cancer, as per the results of subgroup analysis (Table 1). The overall effect of high MCT1 expression was not associated with DM, although higher odds ratios were shown in distant metastatic tumours in patients with clear cell renal cell carcinoma (ccRCC) and gallbladder cancer (Figure 2C). Remarkably, a significant association between high MCT1 expression and DM in small-sized studies, which analysed less than 150 samples (OR=20.64, 95%CI=2.58–164.89, P<0.001, Table 1). The relationship between MCT1 and/or MCT4 expression and prognosis

Studies that investigated the survival analysis for MCT1 and MCT4 expression were based on a total of 1943 and 1853 patients’ samples, respectively. Compared with low MCT4 expression, high MCT4 expression was significantly associated with poor prognosis.
as revealed by shorter OS times (HR=1.78, 95%CI=1.49-2.13, P<0.001, Figure 3B) without heterogeneity between the included studies (I²=37%). However, survival analyses of the effects of high MCT1 expression revealed insignificant effects on prognosis and the studies were significantly heterogeneous (P=0.13, I²=81%, Figure 3A). For DFS, MCT1 expression was studied only among 166 patients while MCT4 expression was analysed among 1355 patients. Both MCT1 and MCT4 expression were obviously associated with higher HRs, indicating poor prognosis. The relationship was stronger for MCT4 despite the significant heterogeneity

![Figure 2. Forest plot of the relationship between lymph node metastasis and the expression of MCT1 (A) and MCT4 (B) as well as the relationship between distant metastasis and the expression of MCT1 (C) and MCT4 (D).](image-url)
between studies (HR=1.70, 95%CI=1.19-2.42, P=0.003, I²=71%) while the relationship in two studies reporting their HRs for DFS in solid tumours was less apparent (HR=1.48, 95%CI=1.04-2.10, P=0.03, I²=0%, Figure 3C and D).

Discussion

The biological implication of proton-dependent MCTs emerges from their integrative roles in transporting short-chain fatty acids, lactate and pyruvate in a variety of cells, including malignant cells, and thus MCTs have multiple pathologic implications. Given the importance of monocarboxylate compounds, including lactate, as well as pH homeostasis for the glycolytic metabolic pathways in cancer cells, it is not surprising that the relevant MCTs have gained increasing attention in cancer biology and its potential progression to a metastatic phenotype. Focusing on the latter aspect, increased lactate levels are significantly associated with metastasis in a considerable number of cancer types, such as cancers of the cervix, rectum, and head and neck. Actually, lactate can be involved in the signalling pathways of angiogenesis, immune system inhibition, and resistance to radiotherapy. For the implication of lactate transporters, this study has demonstrated that high MCT4 expression was consistently associated with LNM and DM in different types of cancer and yielded a remarkable shortening of OS and DFS. However, cancer metastasis was not associated with elevated MCT1 expression and it induced a poor prognostic effect only in DFS analysis (Table 3).

The variation in expression between both proteins could be explained by the relatively increased tendency of MCT4 expression.

Table 2. Subgroups analysis for the association between metastasis and the studied MCTs.

| Variable | MCT1 | | | MCT4 | | |
|---|---|---|---|---|---|---|
| | Samplesize | Studies | Model (I²%) | HR [95% CI] | P | Studies | Model (I²%) | HR [95% CI] | P |
| LNM | | | | | | | | | |
| Sample size | <150 | 2 | R (83) | 1.22 [0.39, 3.89] | 0.73 | 5 | R (56) | 3.26 [1.48, 7.19] | 0.003 |
| | ≥150 | 2 | R (86) | 2.93 [0.28, 30.16] | 0.37 | 3 | F (0) | 1.09 [0.76, 1.56] | 0.66 |
| Cancer type | Breast cancer | 1 | R (N/A) | 0.67 [0.33, 1.38] | 0.28 | 1 | R (N/A) | 0.92 [0.31, 2.74] | 0.89 |
| | CRC | - | - | - | - | 2 | R (68) | 1.64 [0.72, 3.71] | 0.24 |
| | Other types | 3 | R (72) | 2.31 [0.85, 6.30] | 0.10 | 5 | R (73) | 2.69 [1.05, 6.92] | 0.04 |
| Quality score | ≥7 | 4 | R (77) | 1.65 [0.68, 3.98] | 0.26 | 7 | R (63) | 1.74 [1.04, 2.91] | 0.04 |
| | <7 | - | - | - | - | 1 | R (N/A) | 16.66 [0.88, 315.27] | 0.06 |
| DM | | | | | | | | | |
| Sample size | <150 | 1 | R (N/A) | 20.64 [2.58, 164.89] | <0.001 | 4 | F (0) | 4.67 [2.27, 9.63] | <0.001 |
| | ≥150 | 3 | R (87) | 1.42 [0.22, 9.02] | 0.71 | 6 | F (41) | 1.88 [1.40, 2.54] | <0.001 |
| Cancer type | CRC | 1 | R (N/A) | 0.27 [0.11, 0.65] | 0.003 | 2 | F (0) | 3.38 [1.92, 5.96] | <0.001 |
| | HCC | - | - | - | - | 3 | F (0) | 1.78 [1.20, 2.65] | 0.004 |
| | Other types | 3 | R (77) | 7.31 [0.79, 67.51] | 0.08 | 5 | R (65) | 2.79 [0.87, 8.99] | 0.09 |
| Quality score | ≥7 | 3 | R (90) | 1.67 [0.25, 11.33] | 0.60 | 7 | R (55) | 2.57 [1.40, 4.70] | 0.002 |
| | <7 | 1 | R (N/A) | 24.17 [1.39, 419.06] | 0.03 | 3 | F (0) | 1.76 [1.11, 2.79] | 0.02 |

Table 3. The biological implications of MCT1 and MCT4.

| Item | MCT1 | MCT4 | Reference |
|---|---|---|---|
| Main substrate | Lactate, pyruvate, butyrate, acetoacetate, β-hydroxybutyrate, XPI3512, GHB | Lactate, pyruvate, acetoacetate, β-hydroxybutyrate | Halestrap et al.45 Pierre and Pellerin46 |
| Tissue expression | Kidney, stomach, intestine, liver, heart, skeletal muscle, prostate, testis, eye, lung, placenta, blood and brain | Skeletal muscle, kidney, liver, brain, stomach, testis, eye, leukocytes, placenta, lung, heart, blood, chondrocytes | Halestrap et al.45 Pierre and Pellerin46 Pellerin et al.47 |
| Targeting drugs/inhibitors | - AZD3965 (Cayman Chemical Company) - 7ACCC (Cayman Chemical Company) - Syrosingopine (INDOFINE Chemical Company, Inc.) | Syrosingopine | Curtis et al.48 Halford et al.49 Corbet et al.50 Benjamin et al.51 |
| Clinical relevance of aberrant expression | - Multiple cancers (colon, breast, prostate, pancreas, glioblastoma, cervix) | - Multiple cancers (colon, breast, prostate, pancreas, ccRCC) | - Obesity, RA | Thibault et al.52 Tosur et al.53 Balasubramaniam et al.54 Fisel et al.55 |

Cancer type: ccRCC, clear cell renal cell carcinoma; EIHI, exercise induced hyperinsulinism; IBD, inflammatory bowel disease; RA, rheumatoid arthritis.
Figure 3. Forest plot depicting the relationship between the overall survival and the expression of MCT1 (A) and MCT4 (B) as well as the relationship between disease-free survival and the expression of MCT1 (A) and MCT4 (B).
sion in cells exhibiting high rates of glycolysis, such as cancer cells, when compared to MCT1.\textsuperscript{11} In vitro experiments have, to a degree, supported this finding through a significant MCT4 upregulation in the stroma of cancer-associated fibroblasts when they were cultured with breast cancer cell lines, due to activation of hypoxia-inducible factor-1a (HIF-1a), while MCT1 protein expression was only limited to epithelial cancer cells.\textsuperscript{36,57} Importantly, the correlation between HIF-1a and MCT4 is of great relevance since the former is a potent regulator of the metabolic switch in metastatic tumour cells.\textsuperscript{36,59} The involvement of the MCT4-inducing transcription factor, HIF-1a, in metastasis has been identified in several critical aspects, including stem cell maintenance, angiogenesis, metabolic reprogramming, metastasis and cancer cell invasion,\textsuperscript{60} while disruption of HIF-1a activity in mice injected with triple-negative breast cancer cells led to favourable effects on LNM and DM to the lungs.\textsuperscript{61}

Likewise, Gallagher et al.\textsuperscript{62} have reported that MCT1 was the most predominant MCT member in normal breast tissue, while the metastatic MDA-MB-231 cells showed high MCT4 expression. The authors suggested that several genes that encode glycolytic transporters may contribute to such expression patterns, such as GLUT1.\textsuperscript{63} Meijer et al.\textsuperscript{64} have revealed a difference in the expression of MCT4 and GLUT1 between highly-glycolytic adenocarcinomas and squamous cell non-small-cell lung cancer. In addition, MCT4 can act synergistically with its chaperone protein CD147, which is a known inducer of extracellular matrix metalloproteinase, in cancer cells to promote metastasis via lowering the pH of the tumour microenvironment and increasing the rates of degradation of extracellular matrix through enhancing lactate efflux. The elevated co-expression of MCT4, CD147 and GLUT1 has been also identified in papillary renal cell carcinoma\textsuperscript{64} whereas other reports emphasized the potential role of MCT4 and CD147 expression in the metabolic remodelling of prostate\textsuperscript{65} and pancreatic cancers.\textsuperscript{66}

Besides its role in metastasis biology, the current study revealed that MCT4 is regarded as a clinical biomarker of cancer-related mortality. MCT4 was significantly expressed and associated with higher tumour grades as well as poorer clinical outcomes in patients with breast cancer, oral squamous cell carcinoma, and ccRCC.\textsuperscript{34,67,68} Although MCT1 was upregulated in multiple types of cancer, such as prostate and breast cancer,\textsuperscript{65,69} its association with poor prognostic markers was only significant in melanomas.\textsuperscript{70} Following lactate transport via MCT1, it is oxidized to pyruvate which accumulates in cancer cells and suppresses prolyl-hydroxylase 2, leading to activation of HIF-1 and NF-xB.\textsuperscript{71} Both factors can supposedly have a role in inducing metastasis.\textsuperscript{72,73}

In line with the biological relevance and prognostic role of MCT4, and to a less extent MCT1, it is essential that one assesses their potential in targeted cancer therapies as either single anticancer agents or in combination with other chemotherapeutic drugs. As such, several MCT inhibitors have been developed, such as AR-C155858 and 7ACC2.\textsuperscript{74,75} In addition, recent evidence has shown that AZD3965, an MCT1 inhibitor, has led to intracellular lactate accumulation in 120 samples of diffuse large B-cell lymphoma which expressed low levels of MCT4.\textsuperscript{76} However, Bola et al.\textsuperscript{77} found that gastric and small cell lung cancer cells employed a compensatory mechanism by increasing the rate of reliance on glucose as a source of energy, as demonstrated by glycolytic flux analysis, thereby AZD3965 can be effective only in the hypoxic areas of tumours. In the context of metastasis, migration and invasion of cancer cells could be disrupted via downregulation or pharmacological inhibition of MCT1 or MCT4, as shown in multiple experimental studies.\textsuperscript{72,78-80}

This meta-analytic approach to the impact of lactate-transporting MCTs in metastatic progression may highlight the importance of these proteins and further encourage conducting reliable investigations aimed at reducing the burden of metastasis. However, some limitations might affect the interpretation of the outcomes. Analysis of MCT expression by IHC might be based on different methodological approaches in terms of relying on heterogeneous antibodies or the arbitrary scoring methods. This could be resolved by methodological validation and using unified commercial reagents. The number of studies concerned with the survival analysis of MCT1 expression might be insufficient to reveal a statistical significance. Finally, the variation in sample sizes and methodological flaws between studies might lead to a reported statistical heterogeneity in several instances.

Conclusions

In conclusion, we have shown that MCT4 is highly expressed in the metastasis of several types of cancers, such as colorectal and hepatic cancer. This effect is mediated by promoting lactate transport that enhances the invasion and migration of metastatic cells. An increase in the expression levels of MCT4, and to a less extent MCT1, in patients with cancer was also correlated with poor prognosis. However, formal confirmatory evidence that MCT inhibition can reduce metastasis and mortality is still lacking. This highlights the importance of developing relevant therapeutic interventions that target these proteins and their pertinent molecular pathways.

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