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A review on monocarboxylate transporter: an emerging target for treating breast cancer

Nandhini.K*

**Department of Pharmacology, PSG College of Pharmacy, Coimbatore, Tamil Nadu, India.*

Abstract:

This review article has greater dimension on various breast cancer types and their associated factors involved in treatment. Breast cancer cell line (MCF7) and triple-negative breast cancer cells (MDA-MB-231) are more concentrated in this study, revealing a new target called monocarboxylate transporter (MCT). MCT comprises a family of 14 members, but MCT1 and MCT4 are highly significant in determining cancer growth and inhibition status. MCT plays an important role in physiological and pathological processes. It controls the lactate exchange and other MCT between glycolysis and stromal or endothelial cells, as lactate serves as a metabolic fuel for cancer cells. They promote angiogenesis, play as an immunosuppressive metabolite. MCT1 exhibits over-expression in glycolytic cancer types that mediate glucose, pyruvate transportation. It enhances oxidative metabolism and decreases proliferation. This review clarifies the action of MCT in cancer cells, importance and clarity behind MCT1 and MCT4 as proton symporters. Hence, MCT1 and MCT4 are found to be a potential target in cancer diagnosis and prognosis.

Key words: breast cancer, lactate, monocarboxylate transporter

INTRODUCTION:

Breast cancer is a complex disease entity with different biological characteristics and clinical behaviour. According to American Cancer society "Breast cancer starts when cells in the breast begin to grow out of control. These cells usually form a tumour that can often be seen on an x-ray or felt as a lump. The tumour is malignant (cancer) if the cells can grow into (invade) encompassing tissues or spread (metastasis) to distant areas of the body. Breast cancer occurs almost entirely in women, but men can get breast cancer, too". Breast cancer is one of the most common cancers in the world and the foremost cause of cancer-related death among women.

As per GLOBOCAN 2012, 1.7 million new patients were diagnosed with breast cancer globally, whereas estimates of the year 2008, the incidence of carcinoma has accrued by a lot of than 2 hundredth and mortality rate has accrued by close to 14 July. Moreover, it has evolved as awfulassociate cause of death due to cancer in less developed countries. In India, close to 1000 girls are diagnosed with carcinoma with a case fatality magnitude relation of four-hundredth. It shows that the Republic of India has become a rustic of high carcinoma connected deaths worldwide.(1)

Many clinical and pathological features are outlined to predict outcome and treatment response in breast cancer. These features includes patient age, neoplasm stage, axillary lymphnode involvement, lymphovascular invasion, microscopic anatomy grade, hormonal and human epidermal growth factor receptor (HER receptor) status. Breast cancer has been found to occur one in four of all the cancers in women. This may probably due to sudden changes in the lifestyle of people and relatively scanty clinical facilities to combat this disease. The high occurrence of breast cancer among urban women can be correlated to several factors including having sex later, have fewer children, and breastfeed them less than the rural women which ultimately increases their exposure to oestrogen, and afterwards,risk of having breast cancer elevates greatly. Indian women also tend to have a western diet, which leads to obesity and high alcohol ingestion. Both of these factors contribute vastly to enhance the chance of breast cancer. (2)

The subtypes were characterised on the basis of expression Estrogen receptor (ER), Progestin receptor (PR), and human epidermal growth issue receptor two (HER2). The subtypes are as follows, luminal A (ER+/PR+HER2−, low Ki67 (14%), HER2 (ER−, PR−, HER2+), Basal-like (ER−, PR−, HER2−).

Among the above classification, triple-negative breast cancer(TNBC)(i.e., basal-like) is an aggressive subtype that is defined by lack of expression of ER and PR as well as the absence of overexpressed or amplified HER2. Triple-negative breast cancer (TNBC) were characterized by an absence of the estrogen (ER) and progesterone (PR) receptors, as well as the human epidermal growth factor receptor 2 (HER2/HER) and accounts for about 20% of all breast cancer cases. The absence of the three receptors significantly reduces targeted treatment options for patients with TNBC and studies have shown that TNBC and HER-2 over-expression breast cancer have a higher local recurrence and distant metastasis rates than other types (3). Prevalence of TNBC in India ranged from 27% to 35% across studies, with a summary estimate of 31%. It is comparable to the prevalence seen in African American women and is more than twice the rate seen in white women. Some study also found a higher prevalence of premenopausal breast cancer, grade 3 disease, and larger tumour size, all of which are associated with triple-negative disease. Because TNBC is known to be more aggressive than other breast cancer subtypes, higher prevalence of TNBC could be a contributing factor to the high fatality rate of patients with breast cancer in India. (4)

MCT, monocarboxylate transporter is a family of proton linked plasma membrane transporter that carries one carboxylate group eitherlactate or pyruvate across all biological membranes. It plays an essential role in carbohydrates, fat, protein metabolism, and they were rapidly transported across the cell membrane. These were also noted as solute carrier family, SLC16 that are close

enough to the characteristics of sequence motifs. All the family has transmembrane helices with a large cytosolic loop between 6 and 7. It is a novel oncogene on chromosome X22-24 which are amplified in a T cell lymphoma. This review is based on the compilation of various research work done in breast cancer inclusive of in-vitro, in-vivo and clinical aspects. This review aims to elaborate the research work of various authors on monocarboxylate transporter gene and their subsequent evaluation of cancer cells.

Effect of polyphenols in breast cancer cell lines:

Polyphenols are phenolic compounds that were generally found as a result of secondary metabolism. Polyphenols are found in fruits, vegetables, beverages and wine as the major source in the human diet. Because of its antioxidant property, polyphenols play a significant role in chronic diseases such as diabetes mellitus, cardiovascular diseases and cancer. Currently, MCT1 is the major glucose and lactate transporters in cancer and considered as the potential therapeutic target in the 21st century for cancer treatment. Being nontoxic, the dietary polyphenols were associated with the protective mechanism against cancer. In-vitro studies on polyphenols have proved that they act as specific inhibitors of glucose uptake against breast cancer cell lines by interfering with GLUT and SGLT family. Polyphenols found to inhibit cancer cells by flavanone naringenin that inhibits insulin-stimulated glucose uptake through MAPK pathway.Polyphenols showed a chemo protective effect against breast cancer cell lines during cellular lactate uptake through MCT1. As this MCT1 made a breakthrough because of the accumulation of lactate in the extracellular medium leading to the symbiotic relation of glycolytic and oxidative tumour cells that mutually regulate metabolites. Further, in-vivo studies were carried out to analyse the anti-metabolic potential of polyphenols. (5)

In-vitro investigation of breast cancer cells on MCT1 gene:

In-vitro investigation ofMCF7-MCT1 cells had overexpression of MCT1 gene with a slight elevation in estrogen receptor-α, DNA synthesis and growth in response to estradiol on comparing with empty vector control (MCF7-EV). N1, N4 and N7 are the clones used to compare the inhibition of breast cancer on cells. The invasiveness of the three clones varied significantly with 50% FBS where N1 being least aggressive on comparing to MCF7-EV. Gene expression studies have proved that estradiol-dependent decrease of ERα levels in MCF7-MCT1 cells whereas ERα degradation by fulvestrant. Although there has been a great difference in estradiol compared to MCF7-EV and parental MCF7 cells, there was no statistical significance on combination studies. They contribute to the pathogenesis and progression through two important routes such as inhibition of apoptosis and promotion of angiogenesis with a decline in Thrombospondin-1 (TSP1). (6)

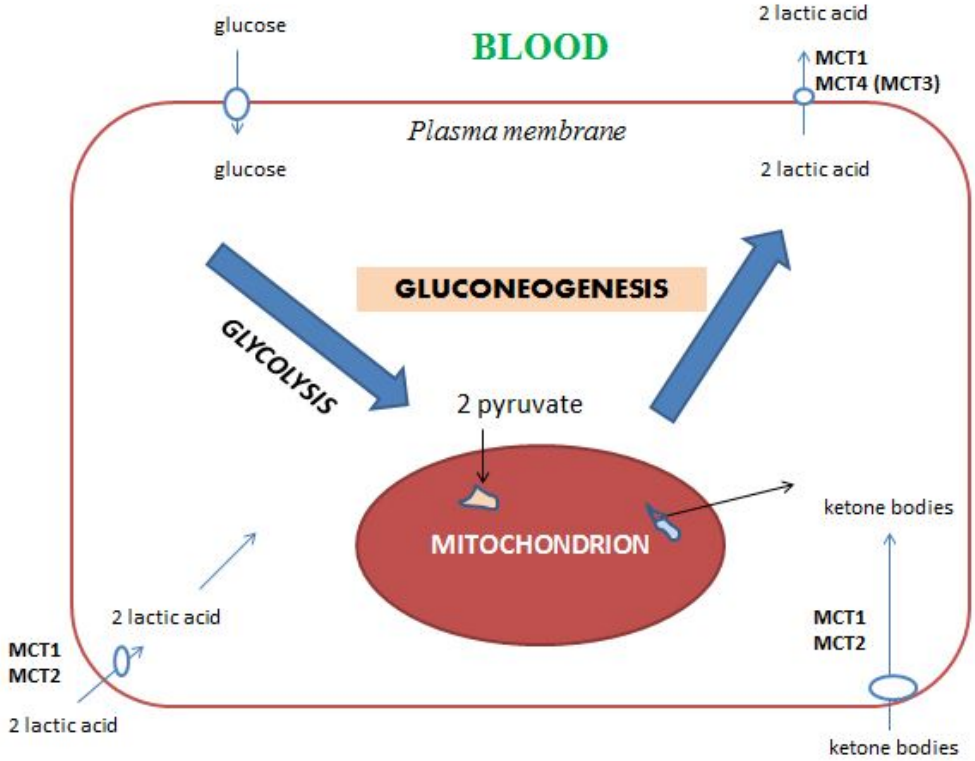

Figure 1: Role of monocarboxylate transporters in metabolism. No single cell may carry the complete metabolic pathway, the uptake of lactate (oxidation) and ketone bodies (gluconeogenesis) may vary depending upon the tissues. Under hypoxic conditions, glycolytic metabolism utilizes MCT4 but MCT3 fulfils the function. Further, lactic acid gets exported in any MCT isoforms, generally MCT1.

Hypoxia, acidosis and mitochondrial defect are the major reason for the increased glycolysis leading to a greater incidence of malignancy and drug resistance. In assistance to it, lactate production and efflux via monocarboxylate transporter are essential for the survival of the glycolytic cells. Emmprin were found to stimulate drug resistance, ErbB2 activation and anchorage-independent growth in a hyaluronan dependent manner. Such disturbance of hyaluronan interactions by treating it with small oligomers containing hyaluronan inhibits lactate secretion. Also, these oligomers have caused MCT1 and MCT4 to dissociate from CD44 and Emmprin to localize intracellularly. On addition of Alexa488- conjugated CD44 antibody to the medium. After fixation, actin filaments are allowed to stain with phalloidin which confirmed that CD44 has localised within the cells after treatment with oligomers. Later, on treatment with latrunculin (an actin polymerization inhibitor) leads to clustering of CD44 at the membrane and in contrast decreases the oligomer induced internalization. (7)

Various studies have supported that overexpression of MCT1 and CD147 has a significant correlation with poor histological parameters propounding the possible role of MCT1 in Triple-negative Breast Cancer. WST assay supports that concentration-dependent inhibition of lactate uptake and cell growth by AR-C155858 (selective MCT1 inhibitor) molecule was found to act in nM. Eventhough, no changes in migration and invasion at 10nM concentration, there was a significant reduction in glucose consumption and lactate efflux (8). The effect of AR-C155858 was found to be less likely potential than other drug regimen. The author has suggested that preclinical models with better dosing regimens and combination therapy can provide greater insight into the new MCT1 inhibitor efficacy. (9)

Regulation of MCT1 expression was proved to have a direct link between p53 function and also mediates lactate inward and outward fluxes in tumour cells under hypoxic conditions. It was found to alter the MCT1 mRNA stabilization by directly interacting with the MCT1 gene. Though such speculations are observed, few changes in mRNA expression were not supported with excessive presence off excess extracellular lactate on gene transcripts in MCF-7 and MDA-MB-231. The elevated basal expression of p53 levels was noted with a gain-of-function p53 mutation on stimulation under hypoxic conditions. Lactate uptake serves as an alternative fuel for respiration after reconversion of lactate into pyruvate with the assistance of LDHB/LDHA ratio being highly compatible. The cells growth was seen even after lacking glucose, the gene was found to recapitulate under reversal of lactate transport. Also, it was proved COX4 as an adaptation to optimise the respiratory chain under normoxia.(10)

Human mesenchymal stem cells obtained from bone marrow-derived stromal cells has been proved to show a great role in tumour progression markedly under hypoxic conditions. It was seen that MDA-MB-231 cells had a greater reduction in breast cancer growth under hypoxic conditions than containing 20% oxygen and obtains lactate with signalling pathways boosted by TLR4 receptor and through NF-κB pathway to ameliorate migration. The transcriptional studies were mediated through MCT1 and MD2 (a co-receptor for TLR4). The lactate efflux weresquired by MCT1 interaction with various binding partners like CD147 and CD44 giving a great exploration for the studies utilizing MCT1 inhibitors. Further Cancer-Associated Fibroblasts plays an influential role in tumour progress in regards with metabolic co-operation. In contrast to other studies of lactate uptake under aerobic condition, the study was aimed to suggest that the reverse Warburg effect was not significant in all tumour conditions. The greater detailed study on CAFs and tumour cells can figure out the exact metabolic interactions. (11)

New paradigms have proposed as the cells on mitochondrial metabolism were found to produce the ketone bodies, which serves as a fuel for cells for conversion of ketone to acetyl-CoA. It also utilizes to upregulate the enzymes that are necessary for the discovery of “druggable” target in treating cancer. By treating on MCF7 cells, ketones were widely coupled for transcriptional profile into order to generate a prognostic marker(12)**.** One such biomarker is stroma Cav-1 in a lethal tumour condition for breast, prostate cancer and melanoma (13). Samples of human mammary fat pad rand lung tissues showed elevated ketone bodies with Cav-1 (-/-). The above were confirmed that ketones are responsible for tumour production. Though the in-vitro studies paved a way for the identification of biomarkers, it is equally important to researchthe clinical related findings. (12).

MCF-7 cells and R3230Ac (obtained from adenocarcinoma of rats) were found to reveal that the lactate production in breast cancer cells profoundly has greater metabolic activity. MDA-MB-231 was also subjected to the same study but could not reveal the activity. The manipulations and catabolic activity are accompanied through CHC (alpha-cyano-4-hydroxycinnamate), which is an MCT1 inhibitor that are more likely to kill the breast cancer cells even in the presence of high lactate. It were furthermore found that CHC has well tolerated the in both the cell lines either ± lactate revealing off-target effects. Though MDA-MB-231 cells had less activity, expression of MCT4 was found to be high than when compared to the other two cell lines on the expression of MCT1 (14). The above activities were determined in all possible conditions such as hypoxia, high concentrations and under aerobic conditions. (15)

PTEN gene is a gene with a crucial role upon mutation or deletion, leading to genomic cancer cell transformation or metastatic potential in human cancer cells. This augments PI3K/AKT activation in breast, ovarian and few other cancers (16)**.** The determination of MCT1 activity on cancer, it was noted that MCT1 stimulates PI3K and Src activation. PTEN gene ablation further stimulated over expression of MCT1 and causes stimulated and activation of EGFR, AKT and Src. MCT1 promotes PTEN degradation through a ubiquitin-proteosome pathway in p53 independent activity. It could elucidate the molecular

interaction, helps in identifying strategies with Src hyper-activation, itself serving as a therapeutic target. (17)

MCF7 and MDA-MB-231 cells were co-cultured with fibroblasts and observed for localization caused due to MCT1 and MCT4 gene expression. Their major reason for the onset includes oxidative stress on treating with N-Acetyl Cysteine, being responsible for the prevention of upregulation of MCT4 gene. The results were determined on cancer-associated fibroblasts indicating the selective localization on stromal cells but in contrast, MCT1 was confined to epithelial cells, thus placing at different cellular compartments. According to this, other research has proved for the upregulation of MCT4 under hypoxic conditions known as HIFI target (18). Reverse Warburg effect and the uptake of lactate were furthermore helpful for the prognostic identification of cancer, especially the loss of stromal Cav-1 in breast cancer. On evaluating the transcriptional genomic profile, it was identified that activation of two transcriptional factors- HIFI and NF-κB had a great role. (19)

A link between an aberrant P-Cadherin expression, hypoxic, glycolytic and acid-resistant breast cancer were identified in breast cancer stem cell using *in-vitro* methods because of it is hypoxia resistant and has preponderant glycolytic metabolism. Hypoxia conditions are brought to limelite because of its tendency for cell survival, pluripotency, stemness and proliferation of stem cells. Though P-Cadherin is an established marker, their adaptation for other conditions such as stress, lactic acidosis was reprogrammed for the treatment. The expression of P-Cadherin and HIF-α in breast cancer were demonstrated, and interestingly HIF-α stabilization promotes P-Cadherin expression and modulates GLUT1, CAIX AND MCT1 with no alteration in CDH3 mRNA levels on co-treating with $CoCl_2$. A new interaction between P-Cadherin and CD147 were found proving P-Cadherin has invasive nature in breast cancer by activation through MMP1 and MMP2. (20) (21)

Daunorubicin- induced cytotoxicity (DNR) were tested through 3-bromopyruvate (3-BrPA), a hexokinase inhibitor that enhances anti-tumour activity in breast cancer cells. DNR involves MCT1 on drug accumulation and efflux of MCF7 and MDA-MB-231 cancer cells. Cancer cells are more likely to undergo a glycolytic pathway for energy generation than normal cells and eventually cause resistance because of atypical expression of ABC transporter responsible for drug expulsion (22). Recent studies have proved that MCT1 is more likely to be involved in MCF7 cells on western blot studies than other aggressive breast cancer cell types.3-BrPA caused apoptosis and also damaged mitochondrial membrane potential with significant production of ROS, reactive oxygen species. (23)

Hypoxic conditions were maintained to enhance glycolytic metabolism and impair oxidative phosphorylation. Cells experienced lactate shuttle or shift in hypoxia with increased lactate secretion in MDA-MB-231 and BT20 cells. This exposed the expression of MCT1 or MCT4 to efflux or export lactate. MDA-MB-468 was found to express better than MDA-MB-231on silencing the gene MCT4 with greater reduction of tumour size. (24)

Coumarin and coumarin derivatives are synthesized and proved to be an anticancer drug by inhibiting via MCT1. The metabolic activity of cancer cells occurred through various possible pathways. Parameters such as bioavailability, hepatic clearance, drug efflux, monolayer permeability are analysed. Better stability, absorption and low efflux ration were reported confirming its use for cancer treatment. (25)

MDA-MB-231 cells are highly aggressive and metastatic which, were profoundly seen for its usage of glucose and metabolic variability. On comparing MDA-MB-231 and MCF7 cells, it was found that glycolysis and lactic acid release had increased in the former cells. MDA-MB-231 has higher mRNA expression of glucose transporter (GLUT1) and $NADH/NAD^+$ ratio than MCF7. MCT1 and MCT4 have significant activity in the expression of cancer cells, but MCT1 had greater osteoclast differentiation than others. Also MCT1 impaired lactate-promoted osteoclast activity, enhancing type I collagen resorption. 7ACC2, an MCT1 inhibitor exhibited a delayed growth of cervical cancer (26) and AZD39965 being a dual MCT1 and MCT4 inhibitors proved its activity over various cancer. (27) (28)

Productions of H+ and CO2 ions are in large number during the metabolic and proliferative stage in cancer cells. Thus a dysregulation in aid-base metabolism plays a crucial role in correlation to breast cancer. Two positive correlation between NBCn1 and HER2 were found and the variant p95HER2 upregulates NBCn1 in both transcriptional and posttranscriptional mechanisms and also between PR status and NHE1 & NBCn1 expression. After various matches, MCT4 were correlated and the expressions were found as an independent prognostic marker, especially in TNBC cell lines. Knockdown cells showed decreased NBCn1 and MCT4. MDA-MB-231 cells exhibited MCT4 expression, but there was a significant lack of MCT1 expression. (29)

Alteration in miRNA (miR-342-3p) leads to downregulation in triple-negative breast cancer cell lines because of its intrinsic miRNA with a host gene. The expression pattern was set to correlate with all genes and found to regulate the transcriptional activity of estrogen receptor (ER). On examination of the loss of this gene in various cancers such as lung, breast, colorectal, etc., it not only induced apoptosis but also inhibited tumour growth, invasion, growth and proliferation. Increased level of MCT1 is generated as a hallmark in the basal subtype of breast cancer (30). Various alterations were notes in glycolysis and lactate uptake mechanism on inhibition of MCT1. This has also been demonstrated under hypoxia conditions and favours the modulation of expression of MCT1. (31)

N,N-dialkylcyanocinnamic acids are identified as a novel MCT1/4 inhibitor in breast cancer cell lines. Compound 9 is the lead compound to determine the anticancer activity. Various properties such as glycolysis, respiration and mitochondrial OxPhos inhibition were determined. The compound was subjected to inhibit glycolytic and

mitochondrial parameters. Also, it has disrupted mitochondrial function through the internalisation of cytoplasm. (32)

In-vivo investigation of breast cancer cells on MCT1 gene:

In-vivo experimentation was carried over through estrogen-dependent breast cancer model. After the amplification of MCT1 coding sequence to its respective clones with the forward 5V-CACCATGTTCAAGAAATTTGATGAA-3V and reverse primer 5V-TTTATATGTCTTCATATGCCACAGCC-3Vand cloned in the TOPO sites of pcDNA3.1/V5-histidine tag vector. For further subclones, the genes were amplified using PCR technique, digested, ligated into pLXSN. Later pLXSN empty vector and pLXSN-MCT-1-V5 histidine were transferred and made confluent. The process was continued by transfecting into nude mice at the mammary fat pads of ovariectomizedathymic mice in the presence of s.c.estradiol-release pellets. After the occurrence of cancer, the statistical significance was marginal in the MCF7-MCT-1 group. Wherein, transplanted cloned groups showed a better development of tumour growth after cell injection. It were also confirmed that there were no significant micrometastases in lung and liver tissues. MCF7-MCT-1 group with tumours were vascularized and less apoptotic when compared to MCF7-EV tumour groups. Changes in TSP-1 overexpression have registered under hypoxic conditions in MCT-1, noting that one of the hypoxia-induced transcription factors is responsible for the action. (6)

Murine 4T1 breast cancer tumour modelwere conducted on BALB/c mice by knocking down MCT1 via shRNA in 4T1 cells with decreased lung metastasis on breast cancer xenograft where the tumour was implanted subcutaneously in mice. Such knockdown has caused a greater impact of delayed tumour growth expressing MCT1 and/ or MCT4. AR-C155858 on xenograft model has caused a delayed tumour growth at 30mg/kg, once daily for six days. Though the immune function effects were not demonstrated, the immunosuppressive action of AR-C155858 analogue, AZD3965 had an overall anti-tumour efficacy with a reported decrease in spleen weight. AR-C155858 was also found to have inhibitory activity against MCT2 along with decreased uptake of gamma-hydroxybutyric acid (GHB). (9)

In-vivo studies concern to the uptake of lactate from R3230Ac cells consumed glucose and lactate simultaneously leading to the conversion of lactate into alanine and glutamate observed in Fischer rats (LABC) locally advanced breast cancer. Lactate being the reliable indication for tumour progression, it has greater utilization in cancer growth. The MCF-7 cells and R3230Ac cells exhibit similar activity on studying the catabolic activity of lactate. Unveiling the study on these cells has explored the expression of MCT1 and MCT4 cells. The lactate was preferentially noted in oxygenated tumour site and highly seen at perinecrotic hypoxic tumour regions. Also, increased expression of HIF-α and angiogenesis has been noted (33). Hence, a lactate consuming phenotype can be used for treatment.

MCF7 and MDA-MB-231 cells were co-cultured with fibroblasts and experiments were made on laboratory animals. According to the hypothesis obtained from **Whitaker-Menezes et al**., (18) it was noted that ketones or lactate is significant in increasing the tumour growth and metastasis. This promoted mitochondrial biogenesis and phenocopies along with fibroblast co-culture. During the transcriptional gene expression study, the researchers noted a conversion of Acetyl CoA and enter into TCA cycle and oxidative phosphorylation (12). Hence, these expressions play a vital role in increasing the "stemness" of cancer cells.

Liu et al(23)proposed the study to assess the effect of 3-BrPA in Daunorubicin induced nude mice by injecting subcutaneously. It was indicated that 3-BrPA sensitizes tumours to DNR on mice revealing the accumulation of DNR in tumours. The whole animal body were subjected to bio-luminescence, where red fluorescence indicates the accumulation of DNR in tumour cells.

In-vivo studies exhibited a greater advantage over lactate efflux, supporting reduction in tumour formation and growth. It was tested on mammary fat pad of nude female mice which has been silenced of MCT gene. The tumour was then subjected to immunohistochemical and histological evaluations. Re-expression of MCT1 and CD147 at the plasma membrane in MDA-MB-468 tumour prevents a decrease in tumour growth. (24)

In-vivo tumour growth studies are subjected to coumarin derivatives and reported for their inhibitory activity against healthy CD-1 mice. The drug was found to be well tolerated with increased body weight and no side effects. This exhibited expressing MCT1 GL261-luc2 on xenograft mouse models upon MDA-MB-231 cells. These derivatives can be used as a single agent on MCT1 than MCT4 as it does not exhibit greater activity on breast cancer cells (25)

MDA-MB-231 *in-vivo*tumour xenograft model in mice has resulted in inhibition of tumour cells by acting through MCT1 gene expression using N,N – dialkylcyanocinnamic acids. Tumour cells were suspended and injected on the right flank of female SCID mice. It has been proved as a potential drug of choice in broad-spectrum anticancer agents. (32)

CONCLUSION

Great progress has been made in initiating and analysing the role of MCT1 and their isoforms in cancer treatment. This serves as a biomarker for cancer cells, especially in breast cancer that is focussed in this review. Though MCT1 and MCT4 had been well established, the other few isoforms are a concern for the research as it is not identified. It is because of the translocation seen and identified in MCT1 and not in others like MCT5/6/9/10/14. The other few isoforms like MCT7/11/13 are proton transporters. It is focussed on various pathways that are studied through in-vitro, in-vivo and clinical investigation adding up to the further gateway for the research and treatment in the field of discovery. It contributes to the progression and pathogenesis of breast cancer, angiogenesis through various pathways. The

lactate uptake and glycolytic pathway inhibition contribute to a greater level of understanding in treating triple-negative breast cancer cells. Corroborating the findings, MCT1 can be a promising potential biomarker and can be used as a target of choice for treating breast cancer.

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