International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 01-16 www.ijprajournal.com ISSN: 2249-7781

Monocarboxylate Transporters (SLC16): Role in Prostate Cancer

Ruchita R. Kachhadiya, Dr. Mustakim M. Mansuri
M.Pharm, Ph.D, Asst. Professor
Department of pharmacology l. M. College of pharmacy ahmedabad-380009
Department of Pharmacology, L. M. College of Pharmacy, Navrangpura, Ahmedabad - 380009, Gujarat, India.

Date of Submission: 20-08-2021 Date of Acceptance: 03-09-2021

ABSTRACT :
Monocarboxylate transporters (MCTs) are transmembrane proteins involved in the transportation through the plasma membrane of monocarboxylates that tend to play an important role in solid tumours, but the role of MCTs is largely unknown in prostate cancer. Prostate cancer (PCa) is a disorder with high rates of morbidity and mortality, requiring new approach to be discovered.In a variety of cancers, MCTs 1 and 4 are overexpressed, and current research has concentrated on transporter inhibition as a novel therapeutic strategy in cancers. They may have a functional characterization, potential significances for diagnosis and treatment, and may affect the progression and prognosis of this cancer. To find studies responding to our query, we reviewed literature published in various databases and search engines. MCTs have a close correlation with PCa, which contributes to their glycolytic and acid-resistant metabolism phenotype. MCT2 is an early detection biomarker, and MCT4 is a poor prognosis and resistance biomarker. Finally, by reducing cell proliferation, MCT1 and MCT4 have a profile as a possible therapeutic target. In conclusion, MCTs play an important role in PCa, so they should be taken into account in subsequent research to classify clinically relevant tools that contribute to reducing the burden of the disease.

KEY WORDS : Monocarboxylate Transporters, Prostate cancer, Glycolytic Metabolism

INTRODUCTION :

1.1 MONOCARBOXYLATE TRANSPORTERS (MCT) –

The Monocarboxylate transporters(MCTs) categorized under solute carrier transporters (SLC) superfamily,and they all are the members of SLC16 gene family. SLC family which are necessary for the transport of short-chain monocarboxylates, pyruvate and lactate(MCT1-MCT4) are reported to transport product of glycolysis), ketone bodies, hormones and supplements over the plasma membrane is necessary for metabolism of starch, fat etc.[1–5]

- Due to its wide range of substrate specificity, It plays an important role in physiology and equilibrium of endogenous moiety. MCT family consists of total 14 members and two individuals are from sodium-dependent MCT family such as SMCTs 1/ 2 and SLC5A8/12. Out of all 14MCT members, only MCT1, MCT2, MCT3 and MCT4 are found to promote the transport of proton-linked monocarboxylates, another two members are MCT5 and MCT6 are expressed in gastrointestinal region as it has an ability to transfer drugs such as bumetanide, nateglinide and probenecidetc,(6,7) MCT7 is a ketone bodies transporter(8) as well as MCT10 (SLC16A10) is also known as T-type amino acid transporter(TAT) as its role is to transport an Aromatic amino acids and MCT8(SLC16A2) transports Thyroid hormones.(4) MCT9 is a carnitine transporters(9)and MCT12 is known as creatine transporter.(10)

- Monocarboxylate transporters(MCTs) are differentiated based on cDNA separation and homology sequencing, MCTs are shown to be their distribution in various tissues and they are associated with regulation of key cellular processes, for example, glycolysis, fatty acid homeostasis and other metabolic pathways.(2,11)MCTs also has a key function as a therapeutic targets and in disease pathology. A few members of MCTs are interesting targets and biomarkers for different grade of cancer because of they are found to be elevated in tumour cells.Monocarboxylate transporters(MCT) plays important role in cancer cell proliferation and regulation.(12)

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 01-16 www.ijprajournal.com ISSN: 2249-7781

➢ Mainly MCT1, MCT2, MCT3 and MCT4 are majorly studied in prognosis of Cancer and they shows major participation in the field of clinical pharmacology12. In many of the carcinomas such as colon cancer, glioblastoma, breast cancer, prostate cancer, pancreatic cancer and renal cell carcinoma has been shown that an expression of MCT1, MCT2, and MCT4 are abnormal.(13,14)

➢

1.2 STURCTURE AND LOCATION OF MONOCARBOXYLATE TRANSPORTERS(MCT) –

➢ According to Hydrophobicity plots, a geography model for all MCT isoforms having 12 transmembrane (TM) α-helices with less conserved intracellular C-terminal and N-terminal along with wide loop between transmembrane domain 6 and TM- 7.(4,15)

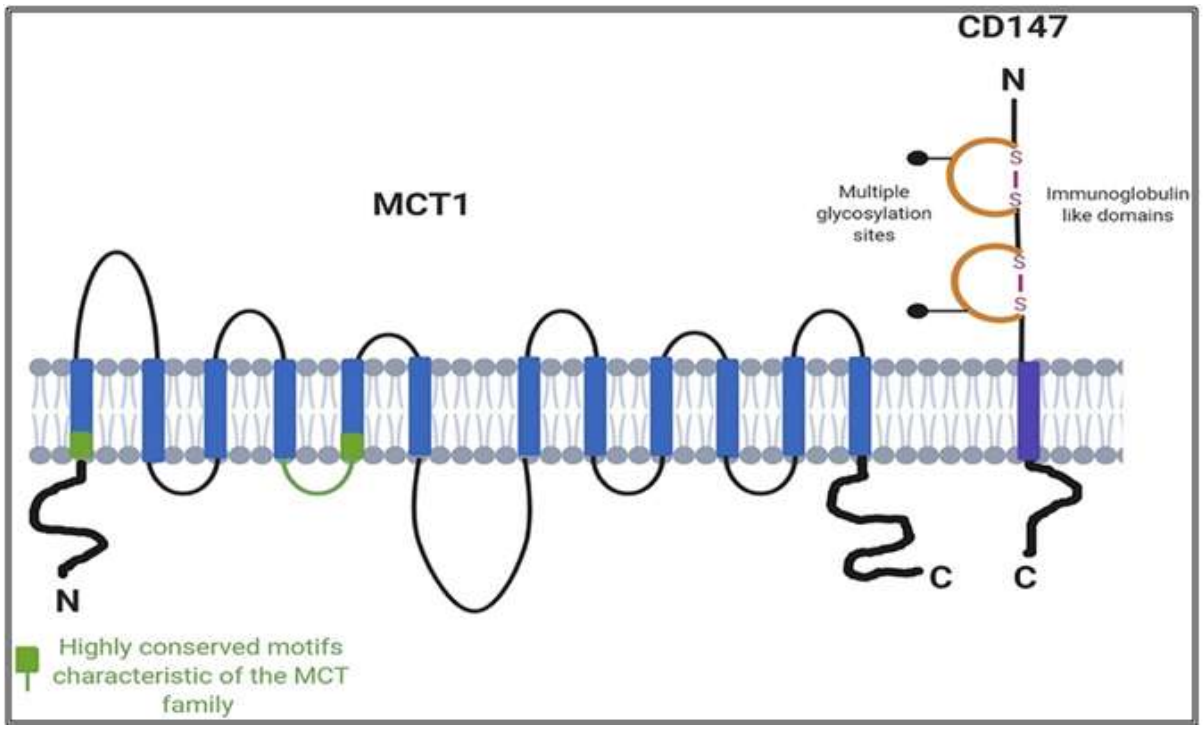


Figure 1: The proposed topology of the MCT family members. CD147, the ancillary protein that associates with MCT1 and MCT4, is also shown. The N and C termini and the large loop between transmembrane domains 6 and 7 show the greatest variation between family members, whereas the TMDs themselves are highly conserved.(16)

➢ Instead, For accurate targeting , functional expression and for appropriate trafficking to attend their function at plasma membrane, a few members of monocarboxylate transporters are dealing with an highly glycosylated anciliary protein. Specifically, Basigin also called CD-147, has been reported that interaction with MCTs 1, MCT3, MCT4, MCT11, and MCT12 mostly by non-covalent interactions. Another ancillary protein is Embigin, also called gp70, it is a member of the Ig superfamily and Interestingly, MCT2 has exhibited to make a complex with Embigin.(17–21)MCT8 acts as a Homodiemerbecause MCT8 don't require its interaction with glycosylated ancillary protein to give its functional expression and activity.(22)

➢ Immunoglobulin superfamily includes both Basigin (EMMPRIN) as well as Embigin and comprise of a few extracellular immunoglobulin domain and one transmembrane domain relying upon the splice variation.(15)

➢ Additionally, two highly conserved motifs TM1 and TM5, which has a role in the conformational changes and molecular dynamics of MCTs. By utilizing the designated Escherichia coli glycerol-3-phosphate carrier crystal structure

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 01-16 www.ijprajournal.com ISSN: 2249-7781

(1PW4), a few3D structures of the MCTs are suggested from homology-based modelling approaches.(5)(23,24)

Sr. no	Gene Family	Transporters	Tissue localization
1	SLC16A1	MCT1	Present in almost all tissues
2	SLC16A7	MCT2	Liver, kidney, heart, skeletal muscle, brain, spleen, testis, pancreas
3	SLC16A8	MCT3	Retinal Pigmented Epithelium
4	SLC16A3	MCT4	Kidney, skeletal muscle, heart, lung
5	SLC16A4	MCT5	Liver, kidney
6	SLC16A5	MCT6	Kidney, intestine
7	SLC16A6	MCT7	Kidney
8	SLC16A2	MCT8	Liver, kidney, adrenal gland, brain, choroid plexus, ovary, thyroid gland, placenta, uterus
9	SLC16A10	MCT10	Liver, kidney, intestine, lung,
10	SLC16A11	MCT11	Liver, kidney, lung
11	SLC16A12	MCT12	Kidney, liver, lung
12	SLC16A13	MCT13	Kidney, intestine, lung
13	SLC16A14	MCT14	Peripheral blood mononuclear cells, kidney

Table 1 : Tissue distribution of all members of SLC16 superfamily (monocarboxylate Transporters from 1 to 14)

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 01-16 www.ijprajournal.com ISSN: 2249-7781

1.3 MONOCARBOXYLATE TRANSPORTERS (MCT) IN HEALTH AND DISEASE-

- **MCT1-4 :** MCT 1– MCT4 has a key physiological function is regulatethe intracellular pH and transport of monocarboxylate such as lactate.(2)The different grade of cancers, including breast cancer, bone cancer, colon cancer, and renal metastasis has an elevated expression of MCT1 and MCT4.(25)Elevated expression of MCTs in cancer cells helps to maintain required pH for tumor growth and their proliferation.(11)(12) In cancer cells, increasd level of MCTs has reported to worsen the condition of various types of cancers such as, bladder cancer(MCT1) as well as prostate cancer(MCT4).(25)MCT2 reported to play its role in prostate cell proliferation as it is potential biomarker in prostate cancer.(26)In cancer cell lines, blocking of the expression of MCTs resulted in inhibition of the cell proliferation.(27) Few studies demonstrate that some common cancers are characterized by protein expression of MCT1-MCT4.(12,28,29) In cancer treatment, Blocking of MCT1 and MCT4 gaining more interest because of its key role in maintaining oxidative and glycolysis cancer cell metabolism and energy production, also called Warburg Effect.(30,31)
- **MCT1** : It shows ubiquitous distribution and mutation in MCT1 causes many diseases, like exercise induced hyper-insulinemia (hypoglycemic disorder) is a result of mutation in promotor region of MCT1.(32) MCT1 has been also shown to increase bioavailability of few drug like gabapentin, because of its higher expression in intestine.(3)MCT1 has significant role in dietary regulatory pathways that is investigated from diet-induced obesity in preclinical haplo-insufficient mouse model.(33)Certainly there is a strong relationship between oxidative capacity as well as expression level of MCT1 in muscle fibres.(34,35) MCT1 has a role in brain, as it transports monocarboxylates through the blood brain barrier for uptake into neurons via MCT1 or MCT2, these monocarboxylates are utilized by red skeletal muscle as a respiratory fuel.(36)

- **MCT2** : It has a more restricted protein expression pattern having high affinity, and it is majorly expressed in neurons, testis, liver, kidneys, pancreas, heart, colon and stomach because of these tissues rely upon substrate uptake as fuel for oxidative phosphorylation as well as substrate for gluconeogenesis or lipogenesis.(37)
- MCT2 has been reported to potential functional and clinical importance with male spermatology and infertility.(38) In korean men, it was studied that two single nucleotide polymorphisms (rs10506398 and rs 10506399) has correlation with increased incidence of infertility.(3)
- MCT2 is an ideal candidate to target cancer cell metabolism as it has a greater affinity than MCT1 for monocarboxylates like lactate and pyruvate. MCT2 expression in different types of cancer cells shows that it is expressed mainly in cytosol proposing its presence within intracellular organelles like Mitochondria, as well as protein expression of MCT2 location in peroxisomes of prostate cancer cells and it is connected to malignant transformation process.(12,39)
- MCT2 is a potential biomarker for prostate cancer but it was also reported to expressed in other cancerous tumors like colon cancer, breast cancer, lung cancer. In one investigation suggesting that MCT2 showed similarity with alpha-methayl-acyl-CoA recemase(AMACR) which is already well-known biomarker for prostate cancer.(26,40) Studies demonstrated that MCT2 also takes a part in Neurodegeneration as its expression is quite higher in neurons as compared to other brain cells.(26)
- **MCT3 :** It is expressed mainly in Choroid Plexus Epithelium as well as Retinal Pigmented Epithelial (RPE)Cells and it is detected at the basal membrane.(41–43) MCT3 has also role in regulation of lactate transport at baso-lateral membrane of RPE, maintenance of ionic balance, pH balanceand controlling wound healing in the RPE.(44,45) At the retinal pigment epithelium MCT3 has a role to transport L-lactate out of the retina because Retina is extremely active at metabolic level and level of lactate is very high in the Retina. Although still less focused on MCT3 compared to MCT1, MCT2 and MCT4.(45)
- In response of injury and cell separation, MCT3 found to be expressed on the human as well as chicken fetal retinal pigmented epithelial cell culture.(45) MCT3 acts as a biomarker For modified Retinal pigmented epithelium, due to its differentiated level of expression. Down-regulated expression level of MCT3 is detected during Retinal pigmented epithelium cell damage, also there is elevated expression of MCT3 when re-establishment of cell-cell contacts occurs. So, the re-expression of MCT3 is totally relies upon structure of basement membrane cell-cell contact.(45)

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 01-16 www.ijprajournal.com ISSN: 2249-7781

- **MCT4 :** It is expressed in a vast number of tissues along with elevated expression level, as it is found to be expressed in those tissues which are highly dependent on glycolysis like tumor tissues, astrocytes, gastrocnemius muscle, white blood cells, white muscle fibres as well as in mammalian cell cultures. MCT4 is also detected in kidney, human placenta and small intestine.(4)(15,34)(35) The primary molecule which is transported by MCT4 is L-lactate and MCT4 is a minimal binding capacity transporter, MCT4 acts as a possible biomarker for different cancer types and its prognosis and treatment approach.(12)
- An activation of HIF-α caused by oxidative stress, because of this mechanism MCT4 protein expression is induced in breast cancer cell lines co-cultured with cancer associated fibroblast.(46,47) There are many protein expressions elevated in cancer cells, in that location of MCT1 is detected to epithelial cells of cancer and MCT4 is localized in stromal cells. Previously it was assessed that MCT4 acts as crucial target for treatment and prognosis of cancer, MCT4 perform its function by inhibiting homeostasis between metabolic coupling to adjacent cancer cells with the use of energy produced by lactate, this mechanism is called ''Reverse Warburg Effect''.(30,31) MCT4 exhibits its key function in cell viability and cell growth in one study that was done to investigate 17 breast cancer cell lines,because of these findings it was detected that MCT4 has a key role in cancer cell proliferation in cancer cell lines it would be a current approach for cancer therapy.(30)
- Due to DNA methylation occurs in the promoter Zone of MCT4 gene in Clear cell renal cell cancer and thereby, protein expression of MCT4 gene is elevated in patients with Clear cell renal cell carcinoma.(13) As reported that worsening of this condition is correlated with death because of carcinomas like pancreatic cancers, data suggested that more MCT4 gene expression is associated with lethality of disease. DNA methylation as well as imbalance in expression level of MCT4 gene is a potential biomarker to determine the ccRCC pathology.(48) All of the mechanism suggests that in aerobic and glycolytic Adenocarcinomas, elevated protein expression level of MCT4 indicates that adeno cell cancers and squamous non-small cell lung cancers are metabolically different.(49) This evidence suggests that MCT4 acts as a tool for disease prognosis and it is an important parameter to target a new strategy for treatment of glycolytic and metabolically active carcinomas as MCT4 can have an ability to inhibit the function and proliferation of cancer cells.
- **MCT 5 :**Earlier MCT5 is notable as MCT4 but due to further modification by researchers on its structure, it is well known as MCT5 nowadays and it is also identified as SLC16A4. Location of MCT5 in the human body at intestinal portion particularly at the basolateral membrane of the colon, liver, kidney, ovary, brain, muscle, placenta and heart.(50,51) when the pathologic condition occurs like colorectal cancer(CRC), there is a level of MCT5 that gets elevated remarkably. These findings indicate that MCT5 has an important role in gastrointestinal carcinomas.(50) MCT5 also has a protective function in many types of viral disease as it has a capacity to act as a viral reproduction resistance factor.(16) Although MCT5 has a minimal role in the pathogenesis of human disease and its health, investigation on the MCT5 has to be needed because a number of studies related to genes are very less performed. Orphan transporters are those who have an unknown role in human health and disease which includes MCT5, MCT13 and MCT14.(22).
- **MCT 6 :**As like MCT5, there is a limited study performed on MCT6 protein that is also present in the human intestine.(51) MCT6 has a very little role in the normal healthy individual as well as any pathological condition. As it's expression is found in the bowel region of humans, MCT6 has a capacity to modify absorption of few drugs such as nateglinide by various pathways.(6,7) MCT6 is a xenobiotic transporter as it is able to improve its substrate specificity towards some molecules like probenecid, bumetanide, prostaglandins and nateglinide.(16)
- **MCT7 :** It is closely connected to various human tissues such as brain, prostate, pancreas, muscle and liver from which MCT7 has a major role in transporting molecules from the Liver.(8) MCT7 plays a key function in the transfer of ketone bodies like B-hydroxybutyrate, as it is known as ketone bodies transporter. Previous study on preclinical models showed that MCT7 has a crucial part in liver disease as it is reported in zebrafish model of hepatic steatosis which is caused by genetic mutation or loss of function of MCT7 and as a result of regulating the function of MCT7 showed simultaneously curing of hepatic steatosis.(8) In the above study MCT7 shown to transport ketone bodies from the liver, mainly exported ketone body was B-hydroxybutyrate. From the above findings, MCT7 has a key role in

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 01-16 www.ijprajournal.com ISSN: 2249-7781

ketone bodies regulation intracellularlythereby, it can reduce the excess production of Triglycerides.

- **MCT8 :** It is a thyroid hormone transporter. Because of its aptitude to transfer a thyroid hormone, it is one of the most examined transporters from all MCTs. An Allan Herndon Dudley Syndrome (AHDS), a X-linked mental retardation neurological syndrome which is caused by MCT8 gene mutations. Due to mutation of MCT8 gene there is a reduction of cellular uptake of thyroid hormone thereby, increases the level of thyroid hormones like triiodothyronine (T3) in serum.(52–57) Different types of thyroid hormones like Diiodithyronine (T2), Triiodothyronine (T3), Tetraiodothyronine (T4) have been uptakenneuronally by MCT8. Although, further research required to finalize the role of MCT8 to promote the transfer of thyroid hormone out of the Blood Brain Barrier (BBB), as it was reported in one study that MCT8 gene expression is present in cerebral microvessels of humans.(58) Some symptoms like weakness, Muscle dysplasia, Hypotonia, Thyroid hormone imbalance in blood are caused by alteration in the MCT8 mRNA gene expression.(54) All of the above pathological conditions was seen in the preclinical study in MCT8 gene deficient mouse models. Such models can be an applicable approach to study these types of diseases and associated irregularities caused by imbalance of Thyroid hormones as well as MCT8 malfunction.(56)(52)
- **MCT 9 :**Main function of MCT9 is to transport the carnitine, as it is also known as a carnitine transporter. Many MCTs are associated with glycosylated ancillary proteins to perform their role and expression but this mechanism is unknown for MCT9 till date. MCT9 is localized in tissue like Kidney particularly on the Proximal Convoluted Tubule(PCT) epithelial cells.(59) It was confirmed that Carnitine is transferred by MCT9 but insufficient data are available for the substrate urate. There are limited sources about the clinical relevance of MCT9, although MCT9 affects the level of Serum Uric Acid (SUA) by its functional mechanism to cause the disease like gout by elevating the concentration of SUA but it is not properly explained.(9)According to the study, having mutation in MCT9 mRNA is directly correlated to higher risk of gout by exchange in amino acids such as lysine residue to threonine residue at the position of 258 amino acid.(3) For identifying the role of MCT9 to maintain the balance in urate level, one study is to be performed pre-clinically in the genetic model of knockout mice to check in-vivo activity of MCT9.
- **MCT10 :** It mainly transports the amino acids therefore it is also called T-type amino acid transporter. To a little extent, MCT10 has an ability to transport thyroid hormones such as Triiodothyronine (T3).(60) In this mechanism of MCT10, one study reported the correlation of the imbalance in thyroid hormone and MCT10 which showed to reduce the T3 concentration in plasma caused by SNP in the gene MCT10.(61) Out of all above roles of MCT10 there is evidence from invivo preclinical study that explain the importance of MCT10 to keep the equilibrium between liver amino acids and circulating amino acid levels.(62) Non-alcoholic steatohepatitis (NASH), a disease associated with the fluctuation of the gene expression of MCT10, as it was clearly reported that NASH is caused by decrease in the gene expression of MCT10, that will upregulate the concentration of aromatic amino acid in the sample of NASH liver patient.(63) One study showed that decreased level of SLC16A10 gene expression is directly associated with the development of Non-alcoholic Fatty Liver Disease (NAFLD). although, the above mechanism involved in these pathological conditions is not clearly explained yet.(63)
- **MCT11 :** It is also known as SLC16A11 and it is localized in many human tissues such as skin, ovary, pancreas, retinal pigmented epithelium, breast, lung and choroid plexus.(3) The contribution and role of MCT11 is majorly in development of Type-2 Diabetes mellitus (T2DM), therefore MCT11 can be a novel target for T2DM therapy. Genome Wide Association Study (GWAS) conducted from the different regional patients of T2DM showed decreased activity of MCT11 intracellularly. there is an increased risk of T2DM with the genetic mutation in the MCT11 mRNA region.(21)(64,65) Another study of adults and children also reported that missense mutation in the gene MCT11was resulted in development of the Type-2 Diabetes.(66)From the above findings, we can conclude that genetic mutation in MCT11 is directly related to the higher risk of Type-2 Diabetes Mellitus.
- **MCT12 :** It is a member of the SLC16 gene family and known as creatine transporter.(10) The human tissues which are having positive expression of the gene MCT12 are kidney, testis, lungs and various regions of the eye like retinal pigmented epithelium, lens etc.(67) One of the cases in 2008 related to mutation (nonsense) in the

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 01-16 www.ijprajournal.com ISSN: 2249-7781

gene MCT12 observed in a swiss family having an eye disability like juvenile cataract, glucosuria as well as microcornea.(20,67) Hence, the above case suggests that MCT12 gene translational efficiency is regulated, so it can be correlated to the Age-related eye disorders.(68) On another hand, MCT12 also has a role in renal function impairment, as it was reported that transport of creatine as well as its precursors like guanidinoacetate is majorly affected by MCT12, this activity was determined by research on analysis of mutation in sodium-glucose cotransporter 2 (SGLT2, SLC5A2), substrate specificity and selectivity.(69) In the above study, it is still difficult to catch the proper mechanism of how MCT12 affects the concentration of guanidinoacetate. Another case of the swiss family in which renal glucosuria is present, further it was shown that mutation happened in the region of the MCT12, SGLT2. A role of basigin in this case is that basigin-MCT12 interaction will promote the age-related cataract because basigin has an ability to upregulate the decreased activity of MCT12.(70) On the same disorder like cataract, the study performed preclinically in the rats of genetically modified MCT12 gene. as a result of this study it was determined that the mutation in MCT12 in the human would cause formation of cataract because of an inability to trafficking at the plasma membrane as well as due to misfolded proteins, where as the complete loss of vision was detected in the transposon-modified MCT12 in rats.(3) From the above findings it was indicated that the difference in eye disability is from species to species. Further development is required to determine the mechanism of MCT12 to affect the equilibrium of guanidinoacetate.

PROSTATE CANCER (PCA)–

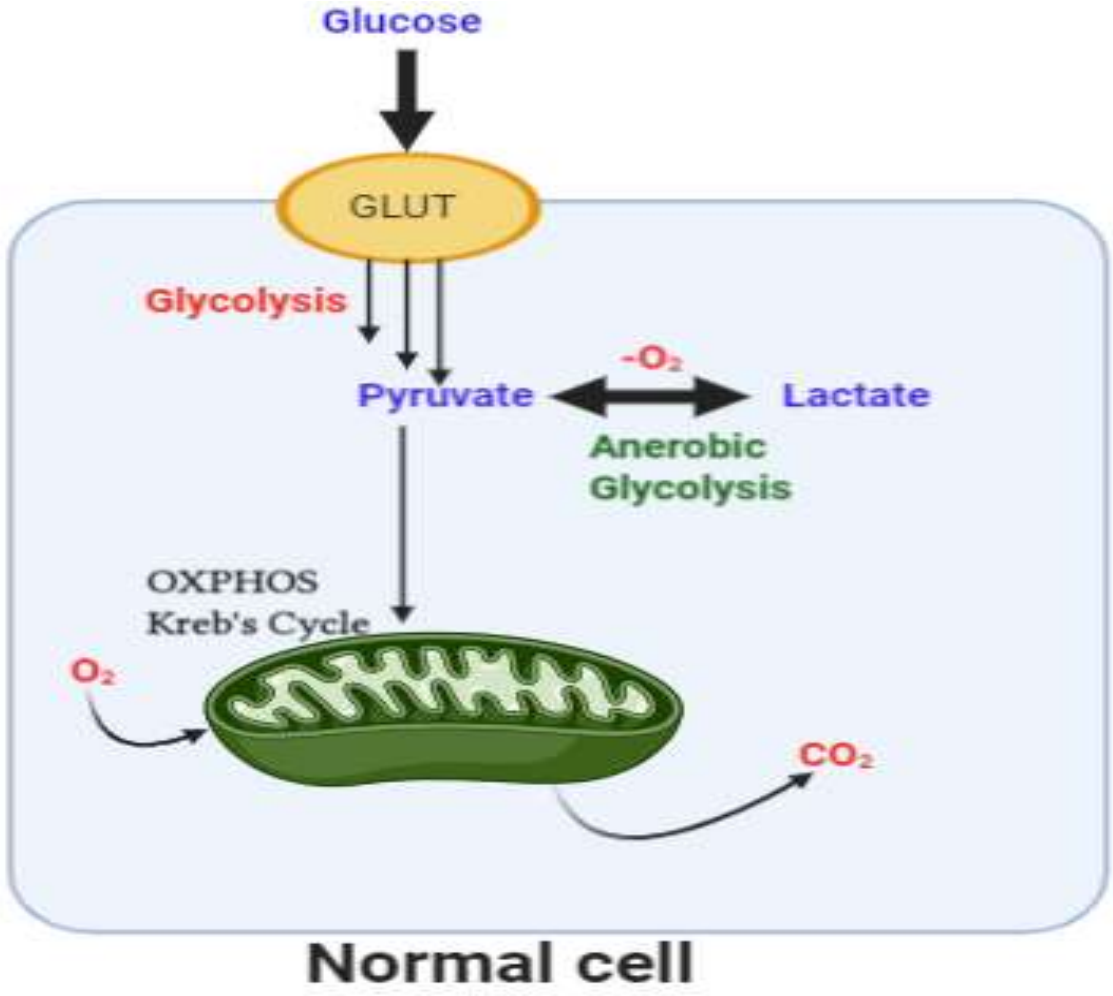
- Prostate cancer is the oncological disease of the prostate gland, a gland that produces a seminal fluid in men. Worldwide, Prostate cancer is one of the most common types of cancer having a mortality burden globally which has a higher prevalence in those nationalities who are already in the developed stage. Prostate cancer is divided in various stages depending upon its severity like low grade PCa and high grade PCa. In the diagnosis of PCa patients also have some challenges like to perform needle biopsy or radical prostatectomy can be difficult at all.
- There are many treatments available such as hormonal therapy, radiation therapy, prostatectomy and chemotherapy that are given based on the stage of the PCa.These all treatments are only giving temporary relief to symptoms/ illness, although there is around 30% chances of the recurrence and metastasis of the PCa.(71) For the metastatic castration resistant prostate cancer (mCRPC) , androgen deprivation therapy that are currently available but canalso lead to disease remission and tumor in the prostate gland becomes more resistant to other treatments. There are some medications like Enzalutamide(72) and Abiraterone(73) which act by targeting androgen receptors to increase the life span of the patient significantly.(74)

1.4 METABOLISM IN NORMAL CELLS AND IN CANCER CELLS :

- Cancer cells uses glucose in the different way from the normal cells, by using glycolytic pathways in aerobic as well as in anaerobic condition and produce a larger amount of lactic acid known as ‘’Warburg Effect’’. Therefore, one can target energy metabolism of cancer cells for treating PCa might be a useful therapeutic approach for PCa.(75) By utilizing more glucose, cancer cells cause an increase in the level of lactic acids that can lead to an either primary or metastatic cancer observed in almost all common cancers.(76) Therefore glycolytic metabolism can be a critical factor to understand the proliferation of the cancer cells. Hence, to permanently treat the PCa, there is a need to research newer therapies that can be a better treatment for PCa patients.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 01-16 www.ijprajournal.com ISSN: 2249-7781

Figure 2: Glycolytic metabolism in Normal cell



- Due to higher glycolytic rate there is a higher amount of glucose is taken up by cancer cells and produce large amount of lactate.proliferation of cancerous cells leads to decreased anti-proliferative properties of host cells because of lactic acid will cause an acidic microenvironment of the cell to the pH 6-6.5 pH. This acidic microenvironment is favourable condition for the proliferative cancer cells

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 01-16 www.ijprajournal.com ISSN: 2249-7781

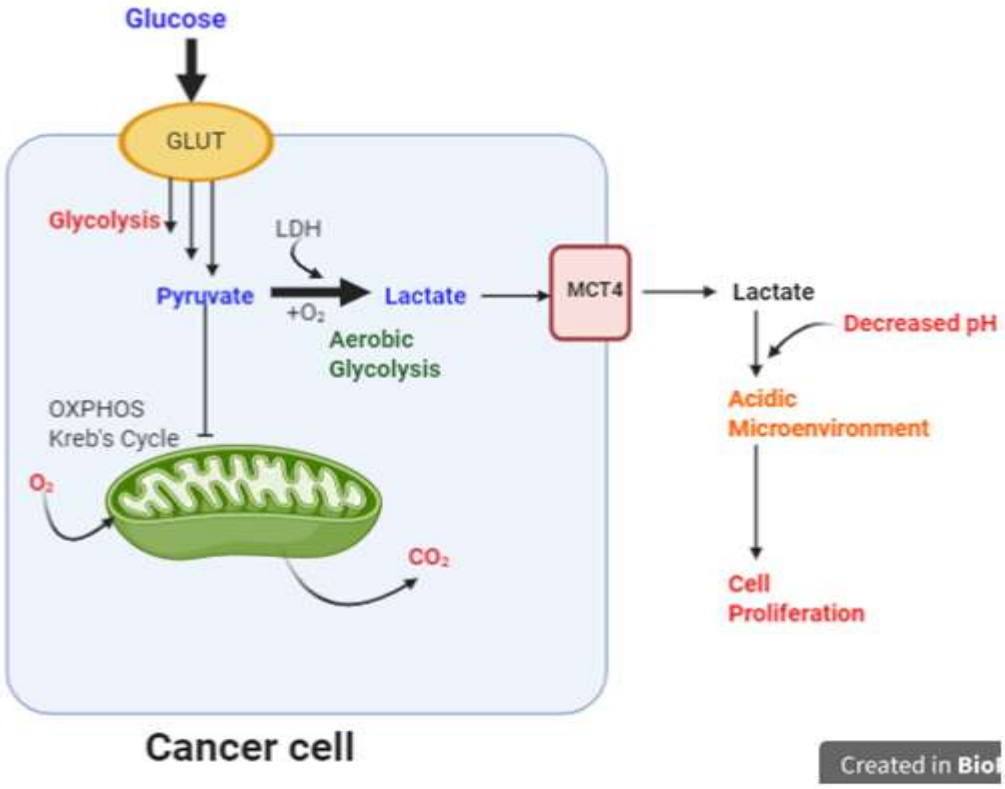


Figure 3 : Glycolytic metabolism in Cancerous cells

- There are different pathways for glycolytic metabolism in normal cells and cancerous cell, targeting this energy metabolism can be an useful approach to further develop new therapies. For example in cancerous cells, elevated level of lactic acid because of higher rate of lactic acid production because of higher glycolytic rate, this produced lactic acid is a primary cause of proliferation of metastatic cells. In most of common cancers cells are undergoes abnormal glutamine use, leads to higher production of lactic acid that is responsible for acidic microenvironment. This is all which are depends on Warburg effect that includes in cancerous cells are undergoes aerobic mitochondrial metabolism to glycolytic metabolism.

1.5 ROLE OF MONOCARBOXYLATE TRANSPORTERS IN CANCER CELL METABOLISM

- Monocarboxylate transporters take a part in the metabolic pathways of cancerous cells and their proliferation by the way of transportation of molecules like lactic acid, therefore to regulate these metabolic processes MCTs can be an important tool to develop novel drug therapies in clinical and experimental fields. Lactic acid plays a major role in tumour cell proliferation, as it induces acidic environment of pH 6-6.5 and higher pH will impact on the immune imbalance leading to complete inhibition of the anti-cancer immunity of the host cells.(77) An ATP generated by cancerous cells by anaerobic metabolism rather than through the Krebs cycle (TCA cycle) also in the absence of oxygen. Those cells that support this metabolic pathway will also produce a higher amount of lactic acid by utilizing more glucose while normal cells are consuming lactate for their source of energy. Therefore, lactic acid secreted by cancerous cells will make an acidic microenvironment that becomes a favourable condition for competition of the cancerous cells. MCTs are involved in this glycolytic metabolism at the stage of lactic acid production and its transport mainly by one of the member of MCTs such as MCT4, as it can be an beneficial approach to achieve an objective in the clinical field.(77)

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 01-16 www.ijprajournal.com ISSN: 2249-7781

1.6 ROLE OF MONOCARBOXYLATE TRANSPORTERS IN PROSTATE CANCER :

- All the Cells of Advanced prostate cancer consists of higher amount of lactic acid due to its higher rate of aerobic glycolysis and prostate tumour cells equilibrate the lactate production intracellular although activity of MCTs are directly related to the severity of the PCa and exacerbate this pathological condition. The Cells may gathered the unwanted noxious metabolic yields more rapidly by inhibiting the efficacy of MCTs. Lactate transporters are distributed mainly in almost all prostate cancer cells that suggests the role of this transporters as an indicator of prognosis and diagnosis of Prostate cancer as a novel future beneficial target for PCa.(12)(78)
- Out of the all MCTs, MCT1 as well as MCT4 are mainly participating with progression of various types of cancers as they are expressed in more than 90% of carcinoma cells.(12)(11) On silencing these transporters, different anabolic-catabolic as well as any functional or biological changes can takes place. Any alteration in activity of MCT1 and MCT4 related to metabolism of cancerous cells of PCa and they have a great correlation with PCa cell proliferation. For example, there are elevated level of intracellular lactate in absence of oxygen by alteration or blocking the activity of MCT4 and this alteration may increase the susceptibility of the cancerous cells over a drugs like Docetaxel. On other hand, elevated expression of MCT1 affects directly to the cell cycle as it blocks the G2 or M phase of the cell cycle and the process of elimination of toxic by-products of the metabolic process directly affected by increased activity of MCT4.(79) MCT4 is distributed in PCa cell invasion, MCT2 is distributed in lesions of neoplastic intraepithelial cells and MCT1 is expressed in non-cancer cells of epithelial layer.
- Above arrangement of these cells specifies that MCTs is an important player of various stages of Prostate cancer.(80)

1.7 INVOLVEMENT OF MONOCARBOXYLATE TRANSPORTES IN PROGNOSIS AND DEVELOPMENT OF PCa:

- MCTs are distributed in various patterns in various tissues reported in different grades of cancer also with different degree of expansion, this may give us an understanding the involvement of MCTs in prognosis and severity of Prostate cancer. In prostate cancer, elevated expression of MCT4 is directly correlated with Gleason tumour stage and invasion, elevated prostate specific antigen, biochemical recurrence and poor prognosis.(80,81)In addition, pT3 refers to the carrier transporter between the tumor and stromal cells and poor clinical outcomes are based on the expansion of MCT4 and MCT1 expression in the fibroblasts associated with the disease.(82)In addition, expression of MCT1 and MCT4 are also present in prostate intraepithelial neoplasia in tumor cells and MCT2 and AMACR tumors. As a result, they are associated as potential biomarkers and are involved in threatening change and progression of infection. On the other hand, the presence of MCT1 in limited tumors and MCT4 in stronger tumors indicates that metabolism occurs.(81)
- Interestingly, by blocking the pharmacological activity of MCT1 has profoundly affected prostate carcinoma cell existence and tumor development. A xenographic model-explicit MCT4 expression inhibition prompted a decrease in secretion of lactic acid, glycolyticmetabolism, and neuroendocrine PCa multiplication.(83) Likewise, there are comparable findings in castration resistant PCa cells.(77) The exact calculation of the direction of MCTs in PCa is therefore still usually obscure. Nonetheless, most exploratory research indicates a trend towards the beneficial effect of MCTs as a therapeutic target.
- In the androgen-resistant cell lineages, MCT1 and MCT4 overexpress. Quieting and altering have opposite consequences and the viability of healthy cells is removed. MCT4 overexpression is also present in the mutilation of healthy malignant growth cells(84) and docetaxel-safe cells.(85)(86) The modification of MCT4 by brief ribonucleic corrosive meddling represses the production and activates apoptosis of PCa cells that are healthy for mutilation.(87)

1.8 THERAPEUTIC INVOLVEMENTS OF MCTs IN PCa:

- The specific complication of prostate cancer cell metabolism, to find out either lactic acid or carrier molecules which is the best

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 01-16 www.ijprajournal.com ISSN: 2249-7781

therapeutic target for PCa that is a difficult task.(88) Hence, it is still challengeable to select a suitable target that could characterize a specific metabolic pathway involved in prostate cancer.(81,89) As mentioned previously, that many of studies has been done to find out the role of MCTs in PCa either by modifying or blocking the expression of MCT1 and MCT4. These studies concluded that prostate cancer cell lines survival reported in both Hypoxic and normoxic condition.(88)

- On opposite side, Some studies also reported that by silencing the expression of the MCT1 affects the viability of the prostate cancer cell and causes tumour development.(81,90)
- Beause of MCTs are majorly involved in glycolytic cellular metabolism of cancerous cells, MCTs becoming promising agent for therapeutically targeting Prostate cancer tumour growth. Few molecules that has an Anti-glycolytic activity like 3-bromopyruvate, iodoacetate, dichloroacetate are served as a substrate for MCTs. MCTs not only applicable when it is inhibited, another function of MCTs as a carrier for some recently developed anti-cancer drugs, that is proven by various in-vivo and in-vitro experiments.(14)
- Besides aboves functions of MCTs, They are also reported to be involved in resistance, e.g. in androgen-resistance cell lines MCT1 as well as MCT4 has been over expressed. Both Modifications and silencing of the MCTs expression has an different effects that either increased or decreased survival of the resistant PCa cells. To bring out apoptosis as well as inhibit cancerous cell propagation, can be done by various changes in expression of MCT4 either silencing or by few modifications by using of SiRNA or by Anti sense oligonucleotides(ASO).(87)

CONCLUSION :

The SLC16 family of transporters represents a significant group of 14 membrane proteins important for the disposition of both xenobiotics and endogenous compounds. Given their extensive tissue distribution and broad range of substrates. Of particular note, protein expression of MCTs is present in critical tissues for elimination and absorption, including the liver, kidney, intestines, and the blood brain barrier. The importance of members of the SLC16 family, including MCT1–4 and MCT8, is now well recognized. Of note, MCTs 1 and 4 are overexpressed in cancers, and inhibition of these transporters represents a current area of investigation as a chemotherapeutic strategy in cancers. Other MCT isoforms are less characterized, but ongoing studies indicate that MCT6 transports xenobiotics such as bumetanide, nateglinide, and probenecid, whereas MCT7 has been characterized as a transporter of ketone bodies. MCT8 and MCT10 transport thyroid hormones, and recently, MCT9 has been characterized as a carnitine efflux transporter and MCT12 as a creatine transporter. Expressed at the blood brain barrier, MCT8 mutations have been associated with an X-linked intellectual disability, known as Allan-Herndon-Dudley syndrome. MCTs play an essential role as potential determinants of diagnosis, prognosis, progression, and treatment of PCa. We found that the progression and prognosis of PCa are closely related to the expression of MCT1 and MCT4, highlighting the importance of MCT4 as a possible biomarker of PCaprogression and aggressiveness. Finally, the findings on the inhibition of MCT1 and MCT4 that could contribute to being therapeutic targets open a new research opportunity.

ABBREVIATIONS :

MCT – Monocarbpxylate Transporters
PCa – Prostate Cancer
SLC – Solute Carrier Transporter Family
SMCT – Sodium Dependent MCT Family
TAT – T-Type Amino Acid Transporters
TMD – Trans membrane Domain
CD147 – Cluster of Differentiation 147
AMACR – Alpha Methyl CoA Racemase
ccRCC – Clear Cell Renal Cell Carcinoma
CRC – Colorectal Cancer
AHDS – Allan Herndon Dudley Syndrome
SUA – Serum Uric Acid
NASH – Non Alcoholic Steato Hepatitis
NAFLD – Non Alcoholic Fatty Liver Disease
T2DM – Type-2 Diabetes Mellitus
SGLT – Sodium Glucose Co Transporter
GWAS – Genome Wide Association Study

REFERENCES

[1]. Halestrap AP, and Price NT, “The proton-linked monocarboxylate transporter (MCT) family: Structure, function and regulation” Biochemical Journal. 1999.
[2]. Halestrap AP, “The SLC16 gene family-Structure, role and regulation in health and disease” Molecular Aspects of Medicine. 2013.

[3]. Jones RS, and Morris ME, "Monocarboxylate Transporters: Therapeutic Targets and Prognostic Factors in Disease" Clin. Pharmacol. Ther. 2016;
[4]. Halestrap AP, and Meredith D, "The SLC16 gene family - From monocarboxylate transporters (MCTs) to aromatic amino acid transporters and beyond" Pflugers Archiv European Journal of Physiology. 2004.
[5]. Price NT, Jackson VN, and Halestrap AP, "Cloning and sequencing of four new mammalian monocarboxylate transporter (MCT) homologues confirms the existence of a transporter family with an ancient past" Biochem. J. 1998;
[6]. Murakami Y, Kohyama N, Kobayashi Y, Ohbayashi M, Ohtani H, Sawada Y, et al., "Functional characterization of human monocarboxylate transporter 6 (SLC16A5)" Drug Metab. Dispos. 2005;
[7]. Kohyama N, Shiokawa H, Ohbayashi M, Kobayashi Y, and Yamamoto T, "Characterization of monocarboxylate transporter 6: Expression in human intestine and transport of the antidiabetic drug nateglinide" Drug Metab. Dispos. 2013;
[8]. Hugo SE, Cruz-Garcia L, Karanth S, Anderson RM, Stainier DYR, and Schlegel A, "A monocarboxylate transporter required for hepatocyte secretion of ketone bodies during fasting" Genes Dev. 2012;
[9]. Suhre K, Shin SY, Petersen AK, Mohney RP, Meredith D, Wägele B, et al., "Human metabolic individuality in biomedical and pharmaceutical research" Nature. 2011;
[10]. Abplanalp J, Laczko E, Philp NJ, Neidhardt J, Zuercher J, Braun P, et al., "The cataract and glucosuria associated monocarboxylate transporter MCT12 is a new creatine transporter" Hum. Mol. Genet. 2013;
[11]. Halestrap AP, and Wilson MC, "The monocarboxylate transporter family-Role and regulation" IUBMB Life. 2012.
[12]. Pinheiro C, Longatto-Filho A, Azevedo-Silva J, Casal M, Schmitt FC, and Baltazar F, "Role of monocarboxylate transporters in human cancers: State of the art" Journal of Bioenergetics and Biomembranes. 2012.
[13]. Fisel P, Kruck S, Winter S, Bedke J, Hennenlotter J, Nies AT, et al., "DNA methylation of the SLC16A3 promoter regulates expression of the human lactate transporter MCT4 in renal Cancer with consequences for clinical outcome" Clin. Cancer Res. 2013;
[14]. Baltazar F, Pinheiro C, Morais-Santos F, Azevedo-Silva J, Queirós O, Preto A, et al., "Monocarboxylate transporters as targets and mediators in cancer therapy response" Histology and Histopathology. 2014.
[15]. Halestrap AP, "The monocarboxylate transporter family-Structure and functional characterization" IUBMB Life. 2012.
[16]. Felmlee MA, Jones RS, Rodriguez-Cruz V, Follman KE, and Morris ME, "Monocarboxylate transporters (SLC16): Function, regulation, and role in health and disease" Pharmacological Reviews. 2020.
[17]. Wilson MC, Meredith D, Manning Fox JE, Manoharan C, Davies AJ, and Halestrap AP, "Basigin (CD147) is the target for organomercurial inhibition of monocarboxylate transporter isoforms 1 and 4: The ancillary protein for the insensitive MCT2 is embigin (gp70)" J. Biol. Chem. 2005;
[18]. Poole RC, and Halestrap AP, "Interaction of the erythrocyte lactate transporter (monocarboxylate transporter 1) with an integral 70-kDa membrane glycoprotein of the immunoglobulin superfamily" J. Biol. Chem. 1997;
[19]. Kirk P, Wilson MC, Heddle C, Brown MH, Barclay AN, and Halestrap AP, "CD147 is tightly associated with lactate transporters MCT1 and MCT4 and facilitates their cell surface expression" EMBO J. 2000;
[20]. Castorino JJ, Gallagher-Colombo SM, Levin A V., Fitz PGG, Polishook J, Kloeckener-Gruissem B, et al., "Juvenile cataract-associated mutation of solute carrier SLC16A12 impairs trafficking of the protein to the plasma membrane" Investig. Ophthalmol. Vis. Sci. 2011;
[21]. Rusu V, Hoch E, Mercader JM, Gymrek M, von Grotthuss M, Fontanillas P, et al., "Type 2 Diabetes Variants Disrupt Function of SLC16A11 through Two Distinct Mechanisms" Cell. 2017;
[22]. Fisel P, Schaeffeler E, and Schwab M, "Clinical and Functional Relevance of the Monocarboxylate Transporter Family in Disease Pathophysiology and Drug Therapy" Clinical and Translational Science. 2018.
[23]. Wilson MC, Meredith D, Bunnun C, Sessions RB, and Halestrap AP, "Studies on the DIDS-binding site of monocarboxylate

transporter 1 suggest a homology model of the open conformation and a plausible translocation cycle" J. Biol. Chem. 2009;

[24]. Ovens MJ, Manoharan C, Wilson MC, Murray CM, and Halestrap AP, "The inhibition of monocarboxylate transporter 2 (MCT2) by AR-C155858 is modulated by the associated ancillary protein" Biochem. J. 2010;

[25]. Park SJ, Smith CP, Wilbur RR, Cain CP, Kallu SR, Valasapalli S, et al., "An overview of MCT1 and MCT4 in GBM: small molecule transporters with large implications." Am. J. Cancer Res. 2018;

[26]. Pértega-Gomes N, Vizcaíno JR, Gouveia C, Jerõnimo C, Henrique RM, Lopes C, et al., "Monocarboxylate transporter 2 (MCT2) as putative biomarker in prostate cancer" Prostate. 2013;

[27]. Guan X, Rodriguez-Cruz V, and Morris ME, "Cellular Uptake of MCT1 Inhibitors AR-C155858 and AZD3965 and Their Effects on MCT-Mediated Transport of L-Lactate in Murine 4T1 Breast Tumor Cancer Cells" AAPS J. 2019;

[28]. Pérez-Escuredo J, Van Hée VF, Sboarina M, Falces J, Payen VL, Pellerin L, et al., "Monocarboxylate transporters in the brain and in cancer" Biochim. Biophys. Acta - Mol. Cell Res. 2016;

[29]. Baltazar F, Pinheiro C, Reis RM, Ricardo S, Longatto-Filho A, and Schmitt F, "Expression of monocarboxylate transporters 1, 2, and 4 in human tumours and their association with CD147 and CD44" J. Biomed. Biotechnol. 2010;

[30]. Baenke F, Dubuis S, Brault C, Weigelt B, Dankworth B, Griffiths B, et al., "Functional screening identifies MCT4 as a key regulator of breast cancer cell metabolism and survival" J. Pathol. 2015;

[31]. Witkiewicz AK, Whitaker-Menezes D, Dasgupta A, Philp NJ, Lin Z, Gandara R, et al., "Using the 'reverse Warburg effect' to identify high-risk breast cancer patients: Stromal MCT4 predicts poor clinical outcome in triple-negative breast cancers" Cell Cycle. 2012;

[32]. Otonkoski T, Jiao H, Kaminen-Ahola N, Tapia-Paez I, Ullah MS, Parton LE, et al., "Physical exercise-induced hypoglycemia caused by failed silencing of monocarboxylate transporter 1 in pancreatic β cells" Am. J. Hum. Genet. 2007;

[33]. Lengacher S, Nehiri-Sitayeb T, Steiner N, Carneiro L, Favrod C, Preitner F, et al., "Resistance to diet-induced obesity and associated metabolic perturbations in haploinsufficient monocarboxylate transporter 1 mice" PLoS One. 2013;

[34]. Juel G, and Halestrap AP, "Lactate transport in skeletal muscle - Role and regulation of the monocarboxylate transporter" Journal of Physiology. 1999.

[35]. Bonen A, "The expression of lactate transporters (MCT1 and MCT4) in heart and muscle" Eur. J. Appl. Physiol. 2001;

[36]. Pierre K, and Pellerin L, "Monocarboxylate transporters in the central nervous system: Distribution, regulation and function" Journal of Neurochemistry. 2005.

[37]. Fishbein WN, Merezhinskaya N, and Foellmer JW, "Relative distribution of three major lactate transporters in frozen human tissues and their localization in unfixed skeletal muscle" Muscle and Nerve. 2002;

[38]. Lee J, Lee DR, and Lee S, "The genetic variation in Monocarboxylic acid transporter 2 (MCT2) has functional and clinical relevance with male infertility" Asian J. Androl. 2014;

[39]. Valença I, Pértega-Gomes N, Vizcaino JR, Henrique RM, Lopes C, Baltazar F, et al., "Localization of MCT2 at peroxisomes is associated with malignant transformation in prostate cancer" J. Cell. Mol. Med. 2015;

[40]. Pértega-Gomes N, Vizcaino JR, Felisbino S, Warren AY, Shaw G, Kay J, et al., "Epigenetic and oncogenic regulation of SLC16A7 (MCT2) results in protein over-expression, impacting on signalling and cellular phenotypes in prostate cancer" Oncotarget. 2015;

[41]. Yoon H, Fanelli A, Grollman EF, and Philp NJ, "Identification of a unique monocarboxylate transporter (MCT3) in retinal pigment epithelium" Biochem. Biophys. Res. Commun. 1997;

[42]. Philp NJ, Yoon H, and Lombardi L, "Mouse MCT3 gene is expressed preferentially in retinal pigment and choroid plexus epithelia" Am. J. Physiol. - Cell Physiol. 2001;

[43]. Philp NJ, Yoon H, and Grollman EF, "Monocarboxylate transporter MCT1 is located in the apical membrane and MCT3 in the basal membrane of rat RPE" Am. J. Physiol. - Regul. Integr. Comp. Physiol.

1998;
[44]. Daniele LL, Sauer B, Gallagher SM, Pugh EN, and Philp NJ, "Altered visual function in monocarboxylate transporter 3 (Slc16a8) knockout mice" Am. J. Physiol. - Cell Physiol. 2008;
[45]. Gallagher-Colombo S, Maminishkis A, Tate S, Grunwald GB, and Philp NJ, "Modulation of MCT3 expression during wound healing of the retinal pigment epithelium" Investig. Ophthalmol. Vis. Sci. 2010;
[46]. Ullah MS, Davies AJ, and Halestrap AP, "The plasma membrane lactate transporter MCT4, but not MCT1, is up-regulated by hypoxia through a HIF-1α-dependent mechanism" J. Biol. Chem. 2006;
[47]. Whitaker-Menezes D, Martinez-Outschoorn UE, Lin Z, Ertel A, Flomenberg N, Witkiewicz AK, et al., "Evidence for a stromal-epithelial 'lactate shuttle' in human tumors: MCT4 is a marker of oxidative stress in cancer-associated fibroblasts" Cell Cycle. 2011;
[48]. Baek GH, Tse YF, Hu Z, Cox D, Buboltz N, McCue P, et al., "MCT4 Defines a Glycolytic Subtype of Pancreatic Cancer with Poor Prognosis and Unique Metabolic Dependencies" Cell Rep. 2014;
[49]. Meijer TWH, Schuurbiers OCJ, Kaanders JHAM, Looijen-Salamon MG, de Geus-Oei LF, Verhagen AFTM, et al., "Differences in metabolism between adeno- and squamous cell non-small cell lung carcinomas: Spatial distribution and prognostic value of GLUT1 and MCT4" Lung Cancer. 2012;
[50]. Lin WR, Chiang JM, Lim SN, Su MY, Chen TH, Huang SW, et al., "Dynamic bioenergetic alterations in colorectal adenomatous polyps and adenocarcinomas" EBioMedicine. 2019;
[51]. Gill RK, Saksena S, Alrefai WA, Sarwar Z, Goldstein JL, Carroll RE, et al., "Expression and membrane localization of MCT isoforms along the length of the human intestine" Am. J. Physiol. - Cell Physiol. 2005;
[52]. Wirth EK, Roth S, Blechschmidt C, Hölter SM, Becker L, Racz I, et al., "Neuronal 3′,3,5-triiodothyronine (T3) uptake and behavioral phenotype of mice deficient in Mct8, the neuronal T3 transporter mutated in Allan-Herndon-Dudley syndrome" J. Neurosci. 2009;
[53]. Trajkovic M, Visser TJ, Mittag J, Horn S, Lukas J, Darras VM, et al., "Abnormal thyroid hormone metabolism in mice lacking the monocarboxylate transporter 8" J. Clin. Invest. 2007;
[54]. Schwartz CE, May MM, Carpenter NJ, Rogers RC, Martin J, Bialer MG, et al., "Allan-Herndon-Dudley syndrome and the monocarboxylate transporter 8 (MCT8) gene" Am. J. Hum. Genet. 2005;
[55]. Dumitrescu AM, Liao XH, Best TB, Brockmann K, and Refetoff S, "A Novel Syndrome Combining Thyroid and Neurological Abnormalities Is Associated with Mutations in a Monocarboxylate Transporter Gene" Am. J. Hum. Genet. 2004;
[56]. Dumitrescu AM, Liao XH, Weiss RE, Millen K, and Refetoff S, "Tissue-specific thyroid hormone deprivation and excess in monocarboxylate transporter (Mct) 8-deficient mice" Endocrinology. 2006;
[57]. Friesema ECH, Ganguly S, Abdalla A, Manning Fox JE, Halestrap AP, and Visser TJ, "Identification of monocarboxylate transporter 8 as a specific thyroid hormone transporter" J. Biol. Chem. 2003;
[58]. Roberts LM, Woodford K, Zhou M, Black DS, Haggerty JE, Tate EH, et al., "Expression of the thyroid hormone transporters monocarboxylate transporter-8 (SLC16A2) and organic ion transporter-14 (SLCO1C1) at the blood-brain barrier" Endocrinology. 2008;
[59]. Habuka M, Fagerberg L, Hallström BM, Kampf C, Edlund K, Sivertsson A, et al., "The kidney transcriptome and proteome defined by transcriptomics and antibody-based profiling" PLoS One. 2014;
[60]. Johannes J, Braun D, Kinne A, Rathmann D, Köhrle J, and Schweizer U, "Few amino acid exchanges expand the substrate spectrum of monocarboxylate transporter 10" Mol. Endocrinol. 2016;
[61]. van der Deure WM, Peeters RP, and Visser TJ, "Genetic variation in thyroid hormone transporters" Best Practice and Research in Clinical Endocrinology and Metabolism. 2007.
[62]. Mariotta L, Ramadan T, Singer D, Guetg A, Herzog B, Stoeger C, et al., "T-type amino acid transporter TAT1 (Slc16a10) is essential for extracellular aromatic amino acid homeostasis control" J. Physiol. 2012;
[63]. Lake AD, Novak P, Shipkova P, Aranibar N,

Robertson DG, Reily MD, et al., "Branched chain amino acid metabolism profiles in progressive human nonalcoholic fatty liver disease" Amino Acids. 2015;

[64]. Kimura Y, Kobayashi M, Asari M, Higuchi I, Narumi K, Furugen A, et al., "Genetic variations in the monocarboxylate transporter genes (SLC16A1, SLC16A3, and SLC16A11) in the Japanese population" Drug Metab. Pharmacokinet. 2018;

[65]. Williams Amy AL, Jacobs Suzanne SBR, Moreno-Macías H, Huerta-Chagoya A, Churchhouse C, Márquez-Luna C, et al., "Sequence variants in SLC16A11 are a common risk factor for type 2 diabetes in Mexico" Nature. 2014;

[66]. Miranda-Lora AL, Cruz M, Molina-Díaz M, Gutiérrez J, Flores-Huerta S, and Klünder-Klünder M, "Associations of common variants in the SLC16A11, TCF7L2, and ABCA1 genes with pediatric-onset type 2 diabetes and related glycemic traits in families: A case-control and case-parent trio study" Pediatr. Diabetes. 2017;

[67]. Kloeckener-Gruissem B, Vandekerckhove K, Nürnberg G, Neidhardt J, Zeitz C, Nürnberg P, et al., "Mutation of Solute Carrier SLC16A12 Associates with a Syndrome Combining Juvenile Cataract with Microcornea and Renal Glucosuria" Am. J. Hum. Genet. 2008;

[68]. Zuercher J, Neidhardt J, Magyar I, Labs S, Moore AT, Tanner FC, et al., "Alterations of the 5'untranslated region of SLC16A12 lead to age-related cataract" Investig. Ophthalmol. Vis. Sci. 2010;

[69]. Dhayat N, Simonin A, Anderegg M, Pathare G, Lüscher BP, Deisl C, et al., "Mutation in the monocarboxylate transporter 12 gene affects guanidinoacetate excretion but does not cause glucosuria" J. Am. Soc. Nephrol. 2016;

[70]. Stä ubli A, Capatina N, Fuhrer Y, Munier FL, Labs S, Schorderet DF, et al., "Abnormal creatine transport of mutations in monocarboxylate transporter 12 (MCT12) found in patients with age-related cataract can be partially rescued by exogenous chaperone CD147" Hum. Mol. Genet. 2017;

[71]. Hutchinson L, "The Role and Therapeutic Significance of Monocarboxylate Transporters in Prostate Cancer" PQDT - UK & Ireland. 2017.

[72]. Ning YM, Pierce W, Maher VE, Karuri S, Tang SH, Chiu HJ, et al., "Enzalutamide for treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel: U.S. foodand drugadministrationdrug approval summary" Clin. Cancer Res. 2013;

[73]. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al., "Abiraterone and Increased Survival in Metastatic Prostate Cancer" N. Engl. J. Med. 2011;

[74]. Bianchini D, Lorente D, Rodriguez-Vida A, Omlin A, Pezaro C, Ferraldeschi R, et al., "Antitumour activity of enzalutamide (MDV3100) in patients with metastatic castration-resistant prostate cancer (CRPC) pre-treated with docetaxel and abiraterone" Eur. J. Cancer. 2014;

[75]. Zhang Y, and Yang JM, "Altered energy metabolism in cancer: A unique opportunity for therapeutic intervention" Cancer Biology and Therapy. 2013.

[76]. Koochekpour S, Majumdar S, Azabdaftari G, Attwood K, Scioneaux R, Subramani D, et al., "Serum glutamate levels correlate with gleason score and glutamate blockade decreases proliferation, migration, and invasion and induces apoptosis in prostate cancer cells" Clin. Cancer Res. 2012;

[77]. Choi SYC, Xue H, Wu R, Fazli L, Lin D, Collins CC, et al., "The MCT4 gene: A novel, potential target for therapy of advanced prostate cancer" Clin. Cancer Res. 2016;

[78]. Eidelman E, Twum-Ampofo J, Ansari J, and Siddiqui MM, "The metabolic phenotype of prostate cancer" Frontiers in Oncology. 2017.

[79]. Hutchinson L, Boyers A, Chadwick A, and Stratford I, "The impact of monocarboxylate transporter expression on metabolic function in prostate cancer cells" Eur. J. Cancer. 2016;

[80]. Pértega-Gomes N, Vizcaíno JR, Miranda-Gonçalves V, Pinheiro C, Silva J, Pereira H, et al., "Monocarboxylate transporter 4 (MCT4) and CD147 overexpression is associated with poor prognosis in prostate cancer" BMC Cancer. 2011;

[81]. Pértega-Gomes N, and Baltazar F, "Lactate transporters in the context of prostate cancer metabolism: What do we know?" International Journal of Molecular Sciences. 2014.

[82]. Pértega-Gomes N, Vizcaíno JR, Attig J,

Jurmeister S, Lopes C, and Baltazar F, "A lactate shuttle system between tumour and stromal cells is associated with poor prognosis in prostate cancer" BMC Cancer. 2014;

[83]. Choi SYC, Ettinger SL, Lin D, Xue H, Ci X, Nabavi N, et al., "Targeting MCT4 to reduce lactic acid secretion and glycolysis for treatment of neuroendocrine prostate cancer" Cancer Med. 2018;

[84]. Zhao Y, Butler EB, and Tan M, "Targeting cellular metabolism to improve cancer therapeutics" Cell Death and Disease. 2013.

[85]. Hao J, Chen H, Madigan MC, Cozzi PJ, Beretov J, Xiao W, et al., "Co-expression of CD147 (EMMPRIN), CD44v3-10, MDR1 and monocarboxylate transporters is associated with prostate cancer drug resistance and progression" Br. J. Cancer. 2010;

[86]. Hao J, Madigan MC, Khatri A, Power CA, Hung TT, Beretov J, et al., "In vitro and in vivo prostate cancer metastasis and chemoresistance can be modulated by expression of either CD44 or CD147" PLoS One. 2012;

[87]. Sun Q, Hu LL, and Fu Q, "MCT4 promotes cell proliferation and invasion of castration-resistant prostate cancer PC-3 cell line" EXCLI J. 2019;

[88]. Pertega-Gomes N, Felisbino S, Massie CE, Vizcaino JR, Coelho R, Sandi C, et al., "A glycolytic phenotype is associated with prostate cancer progression and aggressiveness: A role for monocarboxylate transporters as metabolic targets for therapy" J. Pathol. 2015;

[89]. Flavin R, Zadra G, and Loda M, "Metabolic alterations and targeted therapies in prostate cancer" Journal of Pathology. 2011.

[90]. Fiaschi T, Marini A, Giannoni E, Taddei ML, Gandellini P, De Donatis A, et al., "Reciprocal metabolic reprogramming through lactate shuttle coordinately influences tumor-stroma interplay" Cancer Res. 2012;