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Research Progress of SLC38A5 in Disease Progression

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Abstract: The family of membrane proteins known as amino acid transporters (AAT) is responsible for regulating the transmembrane transportation of amino acids. Featuring 458 transporters grouped into 65 families, the solute carrier (SLC) superfamily is the largest family of transport proteins. Every family plays a crucial part in cellular physiology and exhibits unique substrate specificity and tissue distribution aspects. In order to preserve intracellular metabolic homeostasis, they control the absorption and efflux of crucial molecules such as ions, glucose, fatty acids, and amino acids. They are also essential for differentiation, cell division, and signal transmission. SLC38A5 (also called SNAT5, SN2), a member of the SLC family, has steadily gained attention in recent years as research has become more thorough. The X chromosome contains the gene that codes for SLC38A5, which is a sodium-dependent neutral amino acid transporter with 11 transmembrane domains. It makes it easier for sodium ions and amino acids to move across the membrane simultaneously. It is involved in a variety of cellular processes, and illnesses like cancer, neurodegenerative diseases, and metabolic disorders are intimately linked to its abnormal expression or malfunction. Its distinct function in the development of disease has drawn more and more attention. This article examines new research on SLC38A5 in immunology, metabolic disorders, cancer, and neurodegenerative diseases that was found using databases like Web of Science and PubMed. We provide an overview of SLC38A5 biology in this review, focusing on new discoveries on its function in the development of disease. The structure, distribution, physiological activities, and properties of SLC38A5 are all covered in this discussion, along with its pathogenic roles and potential therapies in particular diseases.

Keywords: SLC38A5; Membrane Protein; Amino Acids; Disease Progression.

1. Background

As for now the health of human beings is still severely endangered by disease. We now have a deeper grasp of diseases at different cell types and tissue levels thanks to the ongoing advancements in modern science and medicine. The occurrence and progression of many diseases are closely linked to a number of fundamental events, including gene mutations, the activation of aberrant signaling pathways, an imbalance in the regulation of the cell cycle, and aberrant immune function, according to additional research on the molecular mechanism and biological features of diseases. Cellular malfunction brought on by these aberrant occurrences quickens the course of the illness. Drug therapy, physical therapy, gene therapy, and immunotherapy are just a few of the significant advances in the field of disease treatment that we have accomplished in recent decades, but there are still many obstacles to overcome. To increase the treatment impact and decrease side effects, it is therefore very critical to identify novel therapeutic targets and approaches. In this regard, SLC38A5 is a promising new target in the field of illness treatment since its aberrant expression or functioning is intimately linked to the progression of several diseases, including cancers and disorders of the nervous system. The present state of SLC38A5 research in the course of disease is summed up in this article. It is intended that a thorough investigation of the role of SLC38A5 in illness progression would yield fresh concepts and sources for the study and management of associated conditions.

2. Basic Characteristics of SLC38A5

2.1. Gene Localization

In the GenBank database, the nucleotide sequence of human SLC38A5 gene has been almost completely detailed determined, the gene has a specific number AF196972, and is located in the short arm of the X chromosome 11 region 23 band, that is, Xp11.23 position [1].

2.2. The Encoded Membrane Protein Domain

SLC38A5 encodes a membrane protein with 11 transmembrane helical domains [1], which is a systemic N sodium coupled Amino acid transporter named "SLC38A5", also known as "amino acid-coupled Na^+/H^+ exchanger (SN2)", which is composed of 472 amino acids. The thorough investigation of the HepG2 hepatocyte cDNA collection led to this discovery. Through cloning and sequence analysis, researchers were able to determine the gene structure of SLC38A5, from which the human SN2 cDNA sequence was successfully extracted; the whole length of this sequence was 2667 base pairs [1]. The database included this result, which was assigned the number AF276889. The essential structural foundation for SLC38A5's transporter function is these transmembrane regions. SLC38A5 can be found on the cell membrane and offer channels for the transport of amino acids and other substrates because they cross the membrane and create a structural framework that is comparatively stable.

2.3. Chemical Properties and Physiological Functions

SLC38A5 plays a crucial part in c sodium-amino acid transporter family and can be observed on all cell membranes and organelle membranes [2]. It has the ability to move sodium ions and amino acids from the extracellular space to the intracellular space via the transmembrane [3], stabilizes amino acids by controlling the differential of amino acid concentration between different cells, and is also a neutral amino acid transporter in cooperation with sodium ions [4]. Meanwhile, in order to maintain the charge balance, sodium and hydrogen ions trade places across the membrane.

SLC38A5 controls cell growth and proliferation and has a role in energy metabolism, protein synthesis, and cell signaling. Cancer, disorders of the neurological system, inflammation of the skin similar to psoriasis, and other illnesses are intimately linked to its aberrant expression and function. Furthermore, research has demonstrated that XBP1, a crucial transcription factor in the IRE1 pathway, increases its transcriptional activity when the ER is under stress. Activated XBP1 can also up-regulate the expression of SLC38A5, which alleviates ER stress by promoting protein synthesis and folding and maintaining intracellular amino acid balance [5]. This may be related to the increased demand for amino acids and special metabolic characteristics of tumor cells.

2.4. Tissue Distribution and Cell-Specific Expression

Amino acid transporters (ATT) can be observed in almost all mammalian cells. It is mostly facilitated by solute carriers (SLCs) genes [6], including 11 SLC gene families, such as SLC38, which include members that encode amino acid transporters [7]. SLC38A5 is expressed in almost all mammalian tissues. However, its expression level is higher in some specific tissues. According to human protein mapping (HPA) database (https://www.proteinatlas. org/ENSG00000017483-SLC38A5 / tissue, on December 20, 2024), The SLC38A5 gene is localized in the cytoplasm, plasma membrane and vesicles [8-10]. In tissue expression, SLC38A5 is not only highly expressed in the pancreas, but also widely distributed in the digestive tract, brain, liver, bone marrow, placenta, sex organs, lung, kidney, muscle and other tissues [1,11-13]. The expression level of SLC38A5 is different in different cells. Especially in basal respiratory cells, plasma cells, exocrine gland cells, red blood cells, neurons and astrocytes [12,14]. It was also found that the expression of SLC38A5 was abnormally increased in some tumor cells [13,15], and the same results were obtained in the Gene Expression Profile Interaction Analysis (GEPIA) database. (http: // gepia. cancer-pku.cn/ detail. php?gene =SLC38A5, accessed 20 December 2024), suggesting that SLC38A5 has a critical function in these tissues and cells.

3. The Role of SLC38A5 in Relevant Diseases

3.1. Regulation of SLC38A5 Expression in Malignant Tumors

SLC38A5 plays a crucial function in the control of expression in malignant tumors and is intricately associated with the metabolic processes of cancer, emerging as a focal point in contemporary cancer research. Research indicates that SLC38A5 is significantly upregulated in cancer, facilitating the transport and catabolism of glutamine, which produces α-ketoglutarate (α-KG) and subsequently activates the serine-glycine-one-carbon (SGOC) pathway. This system produces serine and glycine, supplying nucleotides and methyl donors, so facilitating the fast proliferation, DNA/RNA synthesis, and oxidative stress response of cancer cells [16], demonstrating its significance in the metabolic control of neoplastic cells.

In triple-negative breast cancer, SLC38A5 is specifically increased and promotes macropinocytosis, a novel function intimately associated with the nutrition acquisition and proliferation of cancer cells [17]. This may pertain to SLC38A5's effective transport of amino acids, including glutamine, during macropinocytosis, hence augmenting the nutrients acquired in the process. Moreover, SLC38A5 in triple-negative breast cancer cells participates in the mechanisms of oxidative stress and the development of ferroptosis. Chloroxamine demonstrates potential therapeutic benefits by inhibiting SLC38A5 and the transporter SLC7A11 [18].

In pancreatic cancer research, the expression level of SLC38A5 is markedly increased and is strongly associated with the malignant characteristics of tumor proliferation, invasion, and metastasis. Inhibiting SLC38A5 expression significantly suppresses the growth and survival of pancreatic cancer cells, suggesting it is a very potential therapeutic target.[19]. Notably, SLC38A5 also overcomes gemcitabine resistance in pancreatic cancer by regulating the process of ferroptosis, maintaining the intracellular antioxidant system, reducing the occurrence of ferroptosis, thereby enhancing the resistance of cancer cells. However, when the expression of SLC38A5 is inhibited, the sensitivity of pancreatic cancer cells to gemcitabine is restored [20], which provides a new solution to the problem of pancreatic cancer resistance. Besides, SLC38A5 plays a potential role in the molecular mechanism of the anticancer effect of BET protein family inhibitors either [21], and its expression may be related to certain specific responses of cancer cells.

Through bioinformatics analysis, certain experts have elucidated that SLC38A5 is a pivotal gene within the TGF-β signaling pathway in ovarian cancer, intricately linked to the immune response and prognosis of the disease [22], providing a theoretical basis for precision treatment of ovarian cancer. Through the advancement of technology, studies combining machine learning techniques and RNA sequencing data have also found that the SLC38A5-CCL5 signaling pathway is significantly upregulated in clear cell renal cell carcinoma, closely related to disease progression and poor prognosis [23].

SLC38A5 is prominently expressed in several tumor cells and facilitates tumor cell proliferation, survival, migration, and invasion via modulating amino acid absorption and metabolic reconfiguration. These discoveries have deepened the understanding of the metabolic mechanisms of cancer cells and provided new ideas and potential targets for the treatment of triple-negative breast cancer, renal cell carcinoma, pancreatic cancer, and other cancers. At the same time, they have also opened up new perspectives and strategies for the development of anticancer drugs, prognosis evaluation, and personalized treatment.

3.2. Association of SLC38A5 with Neurological Disorders

SLC38A5 is an amino acid transporter specifically expressed in astrocytes, playing a crucial role in the nervous system. Research indicates that SLC38A5 not only facilitates the release of glutamate from astrocytes for further metabolism into gamma-aminobutyric acid (GABA) by neurons but also serves as a transporter for various amino acids including glutamine, glycine, L-serine, histidine, alanine, cysteine, and asparagine [24-29]. Particularly, L-serine, a product synthesized through the glycolytic pathway in astrocytes, is indispensable for early brain development, promoting neuronal survival and dendrite formation [29].The expression pattern of SLC38A5 in different brain regions varies significantly across distinct developmental stages of the nervous system. Notably, its expression levels are

markedly elevated in critical areas such as the hippocampus, cortex, and cerebellum, suggesting its importance in the functional roles within these regions [30]. SLC38A5 knockout mice have developmental delays, motor impairments, and decreased concentrations of L-serine and D-serine in the brain. The behavioral impairments are markedly improved by L-serine supplementation, further validating the role of SLC38A5 as a selective serine transporter at the blood-brain barrier.[29].

Moreover, researchers have successfully isolated cerebral capillaries from individual neonatal mice using immunomagnetic bead separation technology (IMB) combined with ultracentrifugation, and compared the proteome of cerebral capillaries between neonatal and adult mice via liquid chromatography-tandem mass spectrometry (LC-MS/MS).It was found that the expression levels of SLC38A5 vary significantly across different age groups, with a marked increase observed in adult mice[31]. This reflects the dynamic changes in amino acid transport requirements during neural development. In vitro and in vivo experiments have shown that NH4+ treatment can disrupt the expression and function of SLC38A5 in astrocytes, an interference closely related to common neuropsychiatric symptoms seen in patients with hepatic encephalopathy, such as cognitive impairment and coma[32]. This finding reveals that dysfunction of SLC38A5 may contribute to the pathogenesis of neurological disorders.

Other researchers utilized bioinformatics analysis and experimental validation to identify a novel endoplasmic reticulum stress response element (ERSE). Under conditions of endoplasmic reticulum stress, this element is activated by X-box binding protein 1 (XBP1), leading to upregulation of SLC38A5 expression. The upregulation of SLC38A5 helps maintain glutamine supply, thereby supporting neuronal energy metabolism and antioxidant defense, mitigating endoplasmic reticulum stress-induced neuronal damage[33].

Research using spinal muscular atrophy (SMA) animal models revealed a considerable downregulation of SLC38A5 expression in key motor control-related brain areas[34]. including the spinal cord and cerebral cortex. This confirms the critical role of Slc38a5 in maintaining intracerebral amino acid homeostasis, synaptic development, and neuronal function. These studies demonstrate that SLC38A5 is widely expressed in the nervous system and participates in the transport and metabolism of neurotransmitters. Dysfunction of SLC38A5 may lead to various neurodevelopmental and metabolic abnormalities. Thus, triggering neurological diseases.

3.3. Potential Links Between SLC38A5 and Other Systemic Diseases

As an essential amino acid transporter, SLC38A5 exhibits potential connections and roles in various systemic diseases. In the retina, SLC38A5 is prominently upregulated in ganglion cells [35] and has been identified as a regulator of developmental and pathological retinal angiogenesis by modulating amino acid nutrient uptake and homeostasis in endothelial cells, thereby participating in angiogenic processes[36].

Regarding cutaneous inflammation, SLC38A5 enhances amino acid influx into dendritic cells (DCs), activating the mTOR signaling pathway, which subsequently promotes lysosomal biogenesis and acidification. Enhanced lysosomal acidification alters the intralysosomal environment, leading to enhanced antigen processing and presentation capabilities, thus eliciting a stronger immune response and exacerbating psoriasis-like dermatitis [37]. Knocking out SLC38A5 in murine models significantly alleviates symptoms of psoriasis-like skin inflammation, highlighting its potential role in cutaneous health and disease.

Furthermore, as the sole nutrient transporter discovered in mammalian intestinal crypt cells, SLC38A5 plays a crucial role by facilitating glutamine uptake [38], dependent on sodium gradients maintained by Na-K-ATPase[39,40]. In chronic enteritis models, SLC38A5 activation in crypt cells is associated with increased Na-K-ATPase activity. Experiments have demonstrated that Leukotriene D4 can indirectly affect SLC38A5 function by regulating Na-K-ATPase activity. Thus, it plays a significant role in chronic enteritis [38].

Researchers have found that SLC38A5 also plays a crucial role in the proliferation of pancreatic α-cells induced by glucagon receptor inhibition in skeletal muscle and islet cells. By regulating amino acid uptake and activating the mTORC1 signaling pathway, it promotes the proliferation of α-cells [26]. Meanwhile, SLC38A5 exhibits selective expression on the basolateral membrane of acinar cells. In studies of acute pancreatitis, decreased expression of SLC38A5 has been observed, suggesting a potential link to its function in pancreatic α-cells [41]. Collectively, these findings indicate that SLC38A5 may have potential associations and roles in various systemic diseases such as retinal disorders, psoriasis, chronic enteritis, and pancreatitis, providing new research directions for disease prevention and pathogenesis, and offering novel therapeutic strategies.

4. Conclusion

As a pivotal amino acid transporter, SLC38A5 plays critical roles in multiple biological processes including psoriatic inflammation, tumor metabolic regulation, mechanisms of chemoresistance, neurotoxicity, and angiogenesis. However, despite some progress, the precise mechanisms of SLC38A5's functions in various diseases remain unclear, hindering a comprehensive understanding of its roles. Recent advancements in bioinformatics analysis, metabolomics, transcriptomics, and gene editing technologies, along with the rapid development of databases, provide powerful tools for further exploring the functions and mechanisms of SLC38A5. Future research should focus on elucidating the specific mechanisms of SLC38A5 in diseases. In particular, its interaction network with other signaling pathways and molecules is of great importance. Meanwhile, the development of specific inhibitors targeting SLC38A5 is also critical. These studies are expected to provide new targets and strategies for the prevention, diagnosis, and treatment of related diseases, and may lead to new breakthroughs in cancer therapy, bringing benefits to cancer patients. We have reason to believe that in the future, more groundbreaking achievements will be made in the medical field, bringing greater benefits to patients.

5. Declarations

5.1. Ethics Approval and Consent to Participate:

Not applicable.

5.2. Consent for Publication:

Not applicable.

5.3. Availability of Data and Materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

5.4. Competing Interests:

The authors declare that they have no competing interests.

5.5. Authors' Contributions:

ZP collected relevant literatures on SLC38A5 and was a major contributor in writing the manuscript, JHC is responsible for making changes to the translation of the article, RQS guided the literature review and framework revision.

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