Faculty of Science
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Evaluating Some Amino Acids Transporters as New Prognostic Biomarkers in Breast Cancer Patients

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6. SUMMARY, CONCLUSION AND RECOMMENDATIONS

6.1 Summary

Cancer is a complex and heterogeneous disease characterized by uncontrolled cell proliferation and the potential to spread to other tissues. Breast cancer (BC) is a common malignancy worldwide, with a significant number of cases diagnosed each year. Cellular heterogeneity within BC reflects the disease's natural history and altered cell populations' progression during carcinogenesis. Understanding the biology of BC subtypes and the role of amino acid transporters can aid in identifying potential therapeutic targets and improving patient outcomes. Targeting glutamine metabolism and amino acid transporters may offer new avenues for developing effective treatments of aggressive BC subtypes.

This study investigated the expression of ASCT2 and LAT1, two amino acid transporters, in BC patients and their association with various clinicopathological factors. ASCT2 and LAT1 play essential roles in BC by facilitating nutrient uptake as they function as antiporters and exchange amino acids across the plasma membrane. This partnership helps maintain amino acid equilibrium and supports tumor cell growth. The functional coupling of ASCT2 and LAT1 promotes extracellular glutamine efflux and leucine uptake, essential for mTOR activation and tumor cell growth. Glutamine metabolism is a crucial aspect of cancer cell metabolism and has been linked to poor prognosis and aggressive tumor behavior in BC. It represents a potential target for therapeutic intervention. Targeting these transporters using specific inhibitors has shown promise in limiting tumor growth.

This study found that ASCT2 and LAT1 expression were statistically significant associated with aggressive cancer pathological stage, larger tumor size, higher tumor grade, lymph node involvement, and lymphatic vascular invasion, suggesting their involvement in BC progression through this mechanism. There were no statistically significant associations between ASCT2 and LAT1 expression and age, type of surgery performed, tumor laterality, tumor site, tumor, tumor type, and molecular subtypes of BC. However, the triple positive, triple negative and HER2-enriched subtypes BC tended to have higher expression levels of ASCT2 and LAT1 compared to other subtypes.

ASCT2 and LAT1 expression correlated with hormone receptor status, HER2 status, and Ki-67 expression. ASCT2 and LAT1 were positively associated with estrogen receptor (ER) negativity and progesterone receptor (PR) negativity. The metabolic changes in hormone receptor-negative BC cells, such as increased glutamine utilization, might contribute to the upregulation of ASCT2 and LAT1. The correlation between ASCT2 and LAT1 expression and hormone receptor status might reflect the metabolic changes in hormone receptor-negative BC cells. Moreover, all cases with HER2 positivity showed high LAT1 and ASCT2 expression. High expression of both ASCT2 and LAT1 was significantly associated with increased Ki-67 expression, indicating a more aggressive tumor phenotype and poorer prognosis in BC. The positive correlation between ASCT2 and LAT1 expression and Ki-67 suggested their potential role in tumor growth and proliferation.

This study also found a significant co-expression between ASCT2 and LAT1 in BC patients and analyzed ASCT2 and LAT1 mRNA expression. Both transporters were upregulated in BC patients. The significant positive correlation between the expression of ASCT2 and LAT1 indicated their involvement in similar metabolic processes. Most cases showed a moderate staining score for both transporters, and supported their close relationship. The correlation between gene expression levels of ASCT2 and LAT1 was weaker compared to protein expression, highlighting the complex regulation of these transporters in cancer cells. The expression of ASCT2 and LAT1 might be linked to increased glutamine uptake by BC cells, which supported their increased metabolic demands and proliferation.

6.2. Conclusion

Current findings and results from previous studies suggest that ASCT2 and LAT1 are functionally linked in BC and that targeting both transporters could disrupt glutamine uptake and metabolism in cancer cells. Consequently, this leads to reduced proliferation and tumor growth, which may represent a promising therapeutic strategy for this disease. It is worth noting that this study is just one piece of the puzzle and should be considered alongside other research in the field. Further studies are needed to explore the correltation's underlying mechanisms, and to develop targeted therapies that can exploit these transporters' roles in cancer.

From the strength points of the study, it is one of the few cohort studies done on determining the level of expression of ASCT2 and LAT1 amino acid transporters in BC patients in Egypt. In addition, it examined the association of these transports' expression with other variables that are important for the choice of the targeted therapy and are also crucial prognostic factors for BC. Furthermore, this study adds to the growing body of evidence proposing that ASCT2 and LAT1 may have a vital role in cancer progression. Their expression levels may be useful as prognostic biomarkers and therapeutic targets. Nevertheless, it opens the door to future research on similar topics on BC patients and other cancer types in Egypt.

Study Limitations and Future Recommendations:

However, the current study had a few limitations: the small number of enrolled cases, the absence of randomization, the collection of samples from only one location, the different cancer stages without equal distribution, and the numerous types of used surgeries.

We recommend further molecular studies for ASCT2 and LAT1 genes at both the genetic and epigenetic levels to find mutations and their associations with over-expression on a larger size and homogenous sample distribution.