Journal of Complementary Medicine Research, ISSN: 2146-8397 Vol. 14, No. 6, 2023(pp. 384-392)
RESEARCH ARTICLE WWW.JOCMR.COM

CLINICAL RELEVANCE OF DRUG RESISTANCE GENES IN BREAST CANCER

Pooja Bhadoriya, Research Scholar, Malwanchal University, Indore

Dr. Shreya Nigoskar, Professor, Department of Bio-chemistry, Malwanchal

University, Indore

ABSTRACT

One defining feature of cancer cells is metabolic pathway dysregulation, which prevents them from meeting their bioenergetic and biosynthetic demands. By comparing CERK and SPHK1 gene expression in the local and TCGA cohorts, we were able to confirm the aforementioned results and establish their clinical significance in breast cancer. The importance of CERK and SPHK1 as biomarkers for diagnosis and prognosis in breast cancer patients is further supported by their associations with metastatic markers MMP-2 and MMP-9 as well as medication resistance marker genes ABCC1 and ABCG2. Finding clinically relevant biomarkers was a breeze with the help of lipidomic investigations and multivariate analysis.

KEYWORDS: Clinical, Drug, Genes, Breast, and Cancer

INTRODUCTION

The purpose of this research was to catalog and evaluate lipid species in breast cancer survivors. Finding clinically relevant biomarkers was a breeze with the help of lipidomic investigations and multivariate analysis. To further support the potential of lipids as biomarkers in breast cancer, we have evaluated the protein expression of the representative genes and established their association with clinical features. Little is known about the role of lipid metabolism in breast cancer, despite its importance in other malignant tumors. We also need more information on the connection between lipids and breast cancer, as well as the function of treatment resistance and metastatic indicators.

Solubility in non-polar solvents and structure of long hydrocarbon chains are the fundamental distinctions between lipids and other macromolecules such as carbohydrates, proteins, and nucleic acids. Different classes, subgroups, and subsets of eukaryotic and prokaryotic lipid molecules are found within each of the eight categories that are based on physical and chemical features.

The functional aspects of lipids at several physiological levels, including metabolism, signaling pathways, spatial control, and interactions with other "Omics," provide a significant obstacle to system-scale lipid research. The goal of lipidomic mapping is to provide a comprehensive picture of lipids in living systems, including all interactions between lipids, metabolic pathways, and proteins. It enhances our comprehension of system biology in health and illness by integrating proteomics, genomes, and metabolomics.

Because lipids are not part of the DNA code, it is difficult to determine how many different types of chemicals make up the lipidome. Lipids typically consist of two main building components, ketoacyl or isoprene subunits, which are combined during condensation. Lipid biosynthesis and metabolism, on the other hand, are very diverse. There are hundreds of different lipid species that may be produced by combining different backbone, headgroup, and acyl chains in lipid biosynthesis.

Lipidomics is a rapidly evolving field that calls for improved analytical methods, as well as strategic sample processing and integrated computing resources. Recent technological advancements have made lipidomic research a promising new field for the identification of biomarkers with potential applications in preventative and predictive medicine. Focusing on lipid-protein interactions, this review examines methods for studying lipids in both healthy and unhealthy states.

Because lipids are not part of the DNA code, it is difficult to determine how many different types of chemicals make up the lipidome. Lipids typically consist of two main building components, ketoacyl or isoprene subunits, which are combined during condensation. Lipid biosynthesis and metabolism, on the other hand, are very diverse. There are hundreds of different lipid species that may be produced by combining different backbone, headgroup, and acyl chains in lipid biosynthesis. Better analytical methods, tactical sample processing, and integrated computing tools are all necessary due to the dynamic nature of lipidomics.

LITERATURE REVIEW

Zhiyong et.al (2024) Despite the prevalence of acute kidney damage (AKI), there is currently no medication that targets this particular illness. The importance of changes linked to lipids in AKI has been extensively studied. In order to keep the kidneys healthy, lipid metabolism is crucial. Lipids do more than only provide energy; they also help build the renal microenvironment and renal bio membranes. Signal transduction is a key regulatory mechanism in many important biological processes, including cell proliferation, differentiation, cell death, autophagy, and the epithelial-mesenchymal transition; lipids and their metabolites play an active role in this process. This study shifts the emphasis from chronic kidney disease to acute kidney injury (AKI) lipid metabolic anomalies, as most prior research has concentrated on CKI.

Manju et.al (2023) A diverse class of substances insoluble in water but soluble in organic solvents are known as lipids. In addition to their role in nutrition, lipids serve several additional purposes. Getting the proper kinds of lipids in your diet is crucial, since there is a wide variety of lipids found in nature. A number of biomolecules are essential to cellular structure and function, including lipids. The seeds and fruits of some plants are the primary places to get dietary lipids since that's where they are usually kept. Researching lipid metabolism and variety is crucial. This chapter provides a concise overview of lipids, including their many structures and activities, as well as the nomenclature and categorization of fatty acids. The processes, enzyme functions, and organelles that make up lipid metabolism are all covered in this chapter. Since fatty seeds mostly store as oils, studying their catabolism is important for understanding how they germinate. The stored lipids in fatty seeds do not serve as an immediate energy source.

Erich et.al (2022) An annual oilseed plant, camelina is becoming more popular as a cover crop for biofuels. Lipid metabolism and other plant metabolic processes can only be understood with a firm grasp of gene regulatory networks (GRNs). In this work, we use an expanding number of gene expression datasets to identify TFs involved in the regulation of Camelina lipid metabolism. Our research has uncovered around 350 transcription factors that are strongly associated with genes linked to lipids (LRGs). The MYB, AP2/ERF, bZIP, and bHLH families include several members of these transcription factors, including numerous homologs of renowned Arabidopsis lipid and seed developmental regulators. We used DNA affinity purification sequencing (DAP-seq) to find DNA-binding sites and predicted target genes for 16 of the 22 tested transcription factors after we prioritized the top 22 for further confirmation.

Dr Sumanta et.al (2019) Saturated lipid oxidation, ketogenesis, production of fatty acids and lipids, cholesterol metabolism, and hormonal control of lipid metabolism are all aspects of lipid metabolism. Atherosclerosis, fatty liver, and hypercholesterolemia are all symptoms of improper lipid metabolism. Because they are not soluble in water, lipids are often found in compartmentalized forms within cells, such as adipocyte membrane-associated lipids or triacylglycerol droplets, or they are transported in plasma in conjunction with proteins, such as albumin or lipoprotein particles. Nonpolar solvents can be used to extract lipids from tissues. The hydrophobic barrier is provided by lipids, which also serve as the body's primary energy source.

Renqiang et.al (2022) coronary artery disease (CAD) is induced in part by hyperlipidaemia. Coronary artery disease patients' lipid metabolic patterns as well as pertinent clinical and molecular characteristics were the focus of this investigation. Methods The present investigation utilized information obtained from the Gene Expression Omnibus (GEO) database to create a novel CAD classification according to the gene expression profile of genes involved in lipid metabolism. Nonnegative matrix factorization clustering was used for this purpose. The research also used bioinformatics to delve into the subgroups' inherent biological and clinical traits. Final Product the Gene Expression Omnibus database was queried for data pertaining to 615 samples, which were then linked to relevant clinical information.

RESEARCH METHODOLOGY

Patients with breast cancer who had surgical resection at the Department of Surgery Dept, SAMC & PGI, Indore, had their tumors and surrounding normal tissues removed. With the approval of the Institutional Ethics Committee at SAMC and PGI in Indore, as well as the informed permission of the participants, the samples were collected. Both the local cohort and the publicly accessible cancer genome atlas (TCGA) were used in the investigation Using ice-cold PBS as a flush, the breast tissues were dissected and then fixed in 10% neutral buffered formalin. Sections of 5µm thickness were cut from the paraffin-embedded tissue using a microtome. the mixture was incubated at 48ºCover the night. To break down glycerophospholipids, 75 µl of a solution of 1 M KOH in CH3OH was added after cooling, and the mixture was then placed in a shaking incubator at 37°C for 2 hours.

DATA ANALYSIS

A subfamily of transporters known as ATP-binding cassette transporters (ABC transporters) facilitates the cellular release of lipids and other medicines. In both the local and TCGA cohorts, we examined the expression of two important drug transporters, ABCC1 and ABCG2, in tumor and surrounding normal breast tissues (n=31). Figure 1 A shows that there was a statistically significant increase in ABCC1 levels in tumor tissue compared to neighboring normal tissue in the local cohort (*p=0.035). A notable increase in the expression of ABCC1 in tumor tissue was also shown by TCGA data (***p<0.0001), as seen in Figure 1 C. Figure 1 B shows that in the local cohort, there was no statistically significant difference in the levels of ABCG2 between tumor and nearby normal tissue. In contrast, Figure 1 D shows that in the TCGA cohort, normal tissue levels were considerably higher than tumor levels.

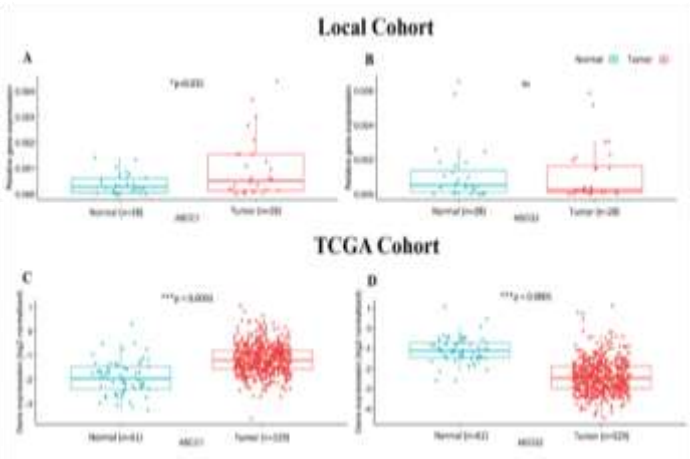

Figure 1 Evaluation of breast cancer patients' gene expression profiles related to drug transporters.

The local cohort has A. ABCC1, B. ABCG2, and C. ABCC1, D. ABCG2; the TCGA cohort has the same.

Using ROC curve analysis, we found out how well ABCC1 and ABCG2 could distinguish tumors from nearby normal tissue. There is strong evidence that ABCC1 might be used as a diagnostic tool for breast cancer patients, according to the AUC values from both the local cohort (Figure 2 A) and the TCGA cohort (Figure 2 C). In the local cohort, there was no significant AUC value for ABCG2 expression (Figure 2 B). In contrast, ABCG2 showed a very significant result and an excellent AUC value in the TCGA cohort (Figure 2 D). further shows that ABCG2 may have great promise as a breast tumor tissue discriminator, according to its excellent sensitivity and specificity values.

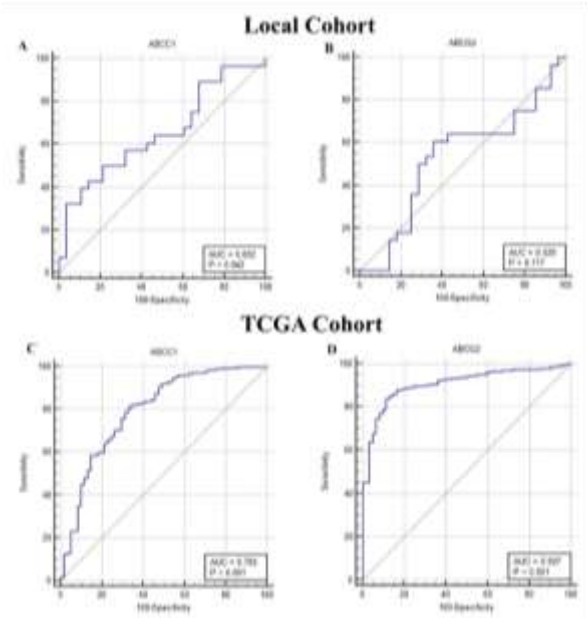

Figure 2 Results from the ROC analysis for A. ABCC1, B. ABCG2 in the local cohort and C. ABCC1, D. ABCG2 in the TCGA cohort

Table 1 Sensitivity and specificity of drug resistance genes

Cohort	*Genes*	AUC (95% CI)	Sensitivity	Specificity
Local Cohort	*ABCC1*	0.652 (0.513-0.774)	39.29%	89.29%
	ABCG2	0.529 (0.391-0.664)	60.71%	64.29%
TCGA Cohort	*ABCC1*	0.795 (0.760- 0.827)	80.91%	67.21%
	ABCG2	0.907 (0.880 -0.929)	83.74%	88.52%

The current research found that ABCC1 levels were considerably increased in nodal positive (*p=0.02), late-stage (*p=0.034) (Figure 3 E) and Ki67 (*p=0.034) (Figure 3 F) patients. Nevertheless, there was no discernible variation in ABCG2 expression across different clinical groupings (Figure 3).

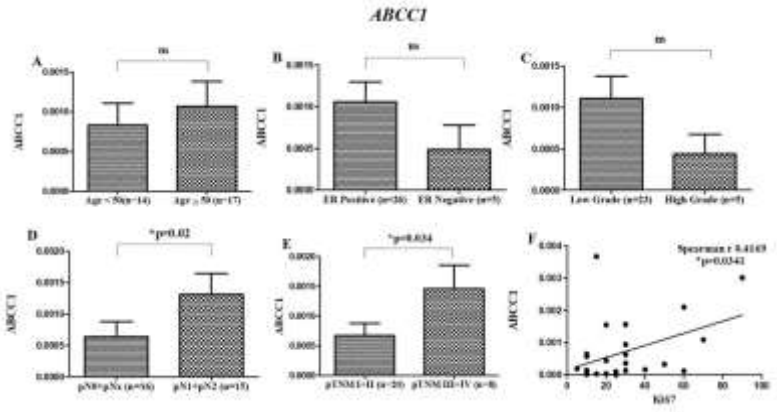

Figure 3 Expression of the ABCC1 gene in breast tumor tissues and its association with many clinicopathological variables.

Section A: Age B: Endocrinological Status C: Grade D: pN Stage E: pTNM Stage F: Ki67 correlation

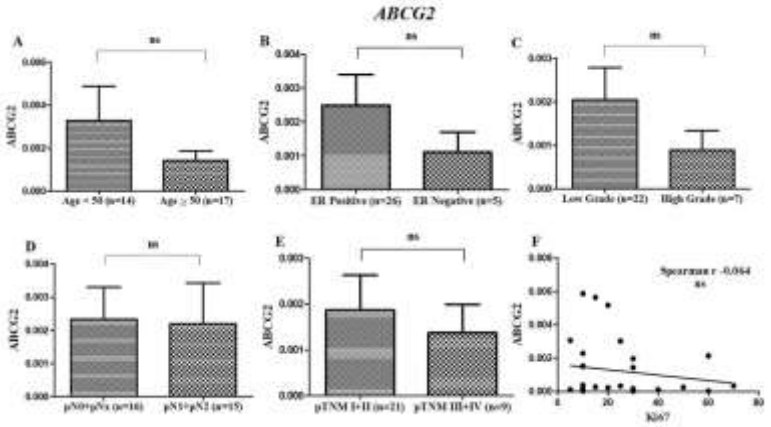

Figure 4 Expression of the ABCG2 gene in breast tumor tissues and its association with many clinicopathological variables.

A. Years Lived B. Emergency Room Present Condition C. Academic Level The association between Ki67 and stages D, E, and F of Ptnm

Figure 5 B shows that the expression of ABCG2 was not significantly different between the tumor and the neighboring normal tissue. In addition, no correlation was seen between ABCG2 expression and any of the clinicopathological variables (Figure 5). There was a statistically significant increase in ABCC1 levels in tumor tissue compared to normal tissue that was nearby (**p=0.0012) (Figure 5 C). Figure 5 shows that there was no statistically significant association between ABCC1 and any of the clinical variables tested.

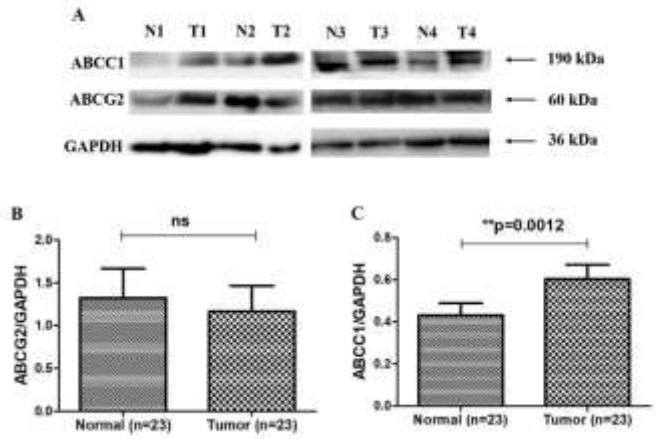

Figure 5 Breast cancer patients' ABCG2 and ABCC1 protein expression.

A. Spots that represent B. ABCG2 density-metric analysis and C. ABCC1 levels in neighboring tumor and normal tissues

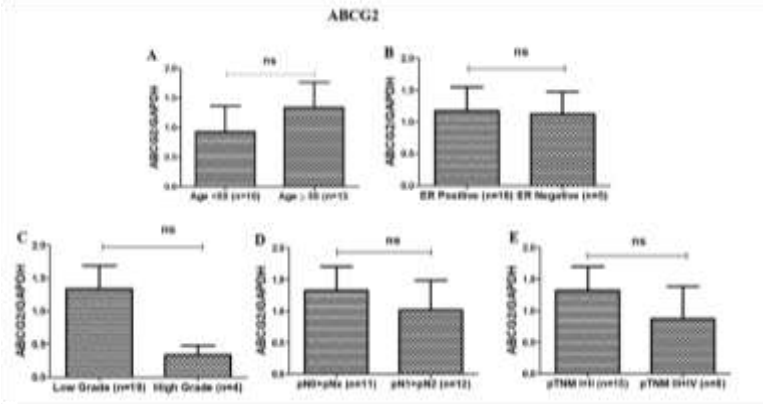

Figure 6 Various clinicopathological categories' ABCG2 levels compared using densitometry between tumors.

A. Years Lived B. Emergency Room Present Condition C. Academic Level Stages D and E of pTNM

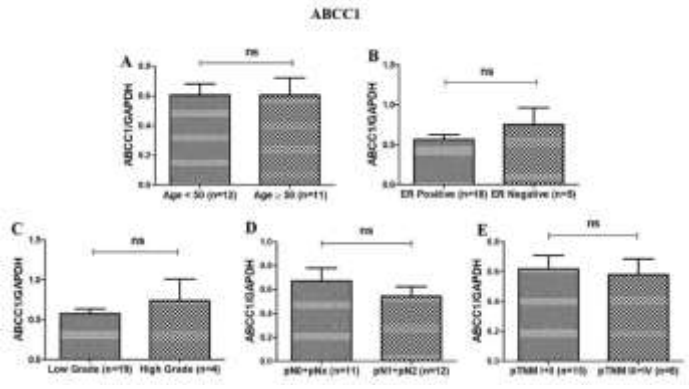

Figure 7 Various clinicopathological categories' ABCC1 levels compared using densitometry between tumors.

A. Years Lived B. Emergency Room Present Condition C. Academic Level Stages D and E of pTNM

CONCLUSION

Studying the expression of drug transporter genes. In order to assess the possible diagnoses. Clinicopathological features and drug transporter gene correlation. Pharmacological transporter protein expression in breast cancer patients. After breast cancer patients had their tumors surgically removed, the surrounding normal tissues and tumors were gathered to help achieve these goals. Tissues from breast tumors have far higher levels of ABCC1 mRNA expression compared to normal tissues nearby. Nodal positivity, advanced pTNM stage, and a high Ki67 index were additional characteristics associated with breast cancer patients with high ABCC1 levels. Patients with breast cancer who had surgical resection at the Department of Surgery Dept, SAMC & PGI, Indore, had their tumors and surrounding normal tissues removed.

REFERENCES

1. Zhang, Xiaoyu & Wu, Wen & Li, Yiming & Peng, Zhiyong. (2024). Exploring the role and therapeutic potential of lipid metabolism in acute kidney injury. Renal Failure. 46. 2403652. 10.1080/0886022X.2024.2403652.
2. Bhatla, Satish & Lal, Manju. (2023). Lipid Metabolism. 10.1007/978-981-99-5736-1_10.
3. Gomez-Cano, Fabio & Chu, Yi-Hsuan & Cruz-Gomez, Mariel & Abdullah, Hesham & Lee, Yun & Schnell, Danny & Grotewold, Erich. (2022). Exploring Camelina sativa lipid metabolism regulation by combining gene co-expression and DNA affinity purification analyses. The Plant Journal. 110. 10.1111/tpj.15682
4. Mondal, Dr Sumanta. (2019). UNIT-II: Lipid metabolism.
5. Liao, Yanhui & Dong, Zhenzhen & Liao, Hanhui & Chen, Yang & Hu, Longlong & Yu, Zuozhong & Xia, Yi & Zhao, Yuanbin & Fan, Kunpeng & Ding, Jingwen & Yao, Xiongda & Deng, Tianhua & Yang, Renqiang. (2022). Lipid metabolism patterns and relevant clinical and molecular features of coronary artery disease patients: an integrated bioinformatic analysis. Lipids in Health and Disease. 21. 10.1186/s12944-022-01696-w.
6. Xu, Jiesi & Huang, Xun. (2020). Lipid Metabolism at Membrane Contacts: Dynamics and Functions Beyond Lipid Homeostasis. Frontiers in Cell and Developmental Biology. 8. 10.3389/fcell.2020.615856.
7. Sandhir, Rajat. (2014). Metabolic Pathways: Lipid Metabolism. 10.1016/B978-0-12-384730-0.00200-7.
8. Guo, Yongjie & Shen, Kailin & Ge, Shuqing & Zheng, Qi & Gao, Jingchao & He, Xiaopo. (2025). Exploring the potential causal relationship between fatty acid metabolism ratios and major salivary gland carcinomas: A two-sample Mendelian randomization study. Medicine. 104. e41802. 10.1097/MD.0000000000041802.

9. Khan, Fahad & Elsori, Deena & Verma, Meenakshi & Pandey, Shivam & Rab, Safia & Siddiqui, Samra & Alabdallah, Nadiyah M & Saeed, Mohd & Pandey, Pratibha. (2024). Unraveling the intricate relationship between lipid metabolism and oncogenic signaling pathways. Frontiers in cell and developmental biology. 12. 1399065. 10.3389/fcell.2024.1399065.
10. Tkachenko, Oksana & Polishchuk, Iryna & Gorchakova, Nadiya & Zaychenko, Hanna. (2020). Metabolic syndrome and lipid metabolism disorders: Molecular and biochemical aspects. Acta Facultatis Medicae Naissensis. 37. 5-22. 10.5937/afmnai2001005T.
11. Maurotti, Samantha & Geirola, Nadia & Frosina, Miriam & Mirarchi, Angela & Scionti, Francesca & Mare, Rosario & Montalcini, Tiziana & Pujia, Arturo & Tirinato, Luca. (2024). Exploring the impact of lipid droplets on the evolution and progress of hepatocarcinoma. Frontiers in cell and developmental biology. 12. 1404006. 10.3389/fcell.2024.1404006.
12. Yang, Yueyi & Wei, Jieya & Li, Jiachi & Cui, Yujia & Zhou, Xuedong & Xie, Jing. (2021). Lipid metabolism in cartilage and its diseases: a concise review of the research progress. Acta biochimica et biophysica Sinica. 53. 10.1093/abbs/gmab021.
13. Wu, Xinyue. (2024). Lipid metabolism and insulin sensitivity. Theoretical and Natural Science. 46. 23-29. 10.54254/2753-8818/46/20240400.
14. dos Santos, Diandra & Souza, Josiany & Pimenta, Tatiana & Martins, Bárbara & Junior, Roberto & Butzene, Solenny & Tessarolo, Nayara & Lyra, Paulo & Victor Silva, Ian & Rangel, Leticia. (2023). The impact of lipid metabolism on breast cancer: a review about its role in tumorigenesis and immune escape. Cell Communication and Signaling. 21. 10.1186/s12964-023-01178-1.
15. Ahmad, Yusra & Seo, Dong & Jang, Younghoon. (2024). Metabolic Effects of Ketogenic Diets: Exploring Whole-Body Metabolism in Connection with Adipose Tissue and Other Metabolic Organs. International Journal of Molecular Sciences. 25. 7076. 10.3390/ijms25137076.