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Article

Connecting the Dots: Transcriptomic Approaches and Relationship between Myocardial Infarction and Breast Cancer

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Abstract. Myocardial infarction, resulting from coronary blood vessel blockage, inflicts lasting damage on the heart muscle. Meanwhile, breast cancer ranks among the most diagnosed cancers, causing millions of deaths annually. Mouse model research suggests that myocardial infarction induces systemic changes, fostering cross-disease communication that expedites breast cancer. Using GEO2R for transcriptomic analysis, Cytoscape for protein-protein interaction (PPI), and EnrichR for enrichment analysis, we explored the myocardial infarction-breast cancer relationship with datasets from GEO. We identified 3,300 differentially expressed genes, including 6 commonly upregulated and 18 commonly downregulated genes. PPI and enrichment analyses revealed RAD51 genes associated with homologous recombination pathways (P-value 0.02032). Additionally, 4 genes (RAD51, KIF4A, DTL, and DLGAP5) were linked to CD105+ endothelial cells (P-value 0.00002216), connecting myocardial infarction and breast cancer. Nevertheless, further testing is needed for accurate results and to support this study's transcriptomic analysis.

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1. Introduction

Myocardial infarction (MI), also referred to as a heart attack, is a condition impacting the arteries that provide blood to the heart muscle (myocardium), specifically known as coronary artery disease [1]. The region of the heart muscle deprived of blood flow or with significantly reduced blood flow, resulting in an inability to support the heart muscle's function, is termed infarction, and the overall process is referred to as myocardial infarction. Myocardial infarction (MI) results in damage to the heart muscle and systemic effects due to increased sympathetic activity from the central nervous system [2-3].

For instance, the release of cytokines like interleukin (IL)-1β, in conjunction with post-MI β3 adrenergic stimulation, triggers the activation of leukocyte progenitor cells in the bone marrow. This leads to a temporary increase in the number of innate immune effector cells, particularly monocytes, in both circulation and hematopoietic reservoirs [4]. Monocytes play a critical role in the tumor microenvironment, and higher levels of circulating monocytes are associated with unfavorable clinical outcomes in different types of cancer [5-6]. Monocytes and their derived macrophages have diverse roles in supporting tumors, including facilitating immune evasion, promoting angiogenesis, and enhancing the proliferation, migration, invasion, and metastasis of cancer cells [6-7].

In summary, a heart attack serves as a catalyst for acute pathological stress, hastening the growth of breast cancer. Mechanistically, it instigates a systemic host response, centrally governed by the innate immune system, facilitating detrimental cross-disease communication that promotes tumor development. Epigenetically, a heart attack alters myeloid cells in the hematopoietic reservoir, shifting them toward an immunosuppressive state, leading to monocytosis, a condition exploited by tumors to enhance cancer growth [4][6].

Further investigation is needed to fully comprehend the mechanisms underlying myocardial infarction-induced monocyte immunosuppression in breast cancer, including the roles of ischemia, sympathetic and parasympathetic regulation, emergency hematopoiesis, and innate immune training (e.g., IFN and IL-1b/inflammasome regulation) [8-9]. Studies in mouse models suggest that myocardial infarction induces systemic changes, triggering inter-disease communication that accelerates breast cancer progression [4].

Breast cancer is currently one of the most frequently diagnosed cancers and the fifth leading cause of cancer-related deaths, with an estimated 2.3 million new cases worldwide according to GLOBOCAN 2020 data [10]. Breast cancer ranks first in terms of the most prevalent cancers in Indonesia and is a major contributor to cancer-related deaths. Procedures and screening programs for prevention are crucial to minimize the likelihood of breast cancer incidence and facilitate early treatment implementation. Current projections indicate that by 2030, the annual global number of newly diagnosed cases will reach 2.7 million, while the number of deaths will be approximately 0.87 million [11-13].

Lately, high-throughput sequencing has been widely employed for prognosis evaluation, molecular diagnosis, and target discovery. One such developed study is called transcriptomic, which explores the entire set of RNA transcribed by the genome of specific tissues or cell types at various developmental stages and/or under specific physiological conditions [14-15]. Subsequent transcriptomic analysis unveils regulatory processes occurring in tissues, ultimately providing guidance in disease diagnosis and clinical therapy [14].

One of the databases utilized for transcriptomic analysis is the Gene Expression Omnibus (GEO). The GEO database encompasses extensive and diverse gene expression patterns related to diseases, along with various key genes that can be utilized to explore disease initiation and progression. GEO data can also be used to investigate correlations between pathogenesis and molecular mechanisms, holding significant clinical relevance in disease research [16-17]. Therefore, we attempt to use GEO expression profiles to identify new biomarkers for diagnosis and therapy.

In this study, we obtained gene expression patterns of human myocardial infarction and breast cancer from the GEO database. The data acquired from GEO were then processed using GEO2R to obtain Differentially Expressed Genes (DEGs). These DEGs were subsequently used for protein-protein interaction (PPI) network analysis between myocardial infarction and breast cancer. Next, the gene expression data were processed using EnrichR to examine which pathways and cell types are associated with these genes. In summary, in this study, we provide evidence regarding the correlation between myocardial infarction and breast cancer.

2. Experimental Section

2.1. Materials

The dataset search was conducted using the GEO database (https://www.ncbi.nlm.nih.gov/geo/) with keywords "breast cancer" and "myocardial infarction". Subsequently, 2 datasets were selected, namely GSE24519 and GSE185645, and DEG analysis was performed using the GEO2R feature available in the GEO database. The results obtained were then used to create a Venn diagram using InteractiVenn (https://www.interactivenn.net/). The intersection of upregulated and downregulated genes was selected for Protein-protein Interaction analysis using the String feature in Cytoscape software version 3.10.1. Hub genes were identified using the CytoHubba feature in Cytoscape software version 3.10.1. Enrichment analysis was conducted using pathway, ontologies, and cell types features in the EnrichR database (https://maayanlab.cloud/Enrichr/). The research followed the flowchart depicted in Figure 1.

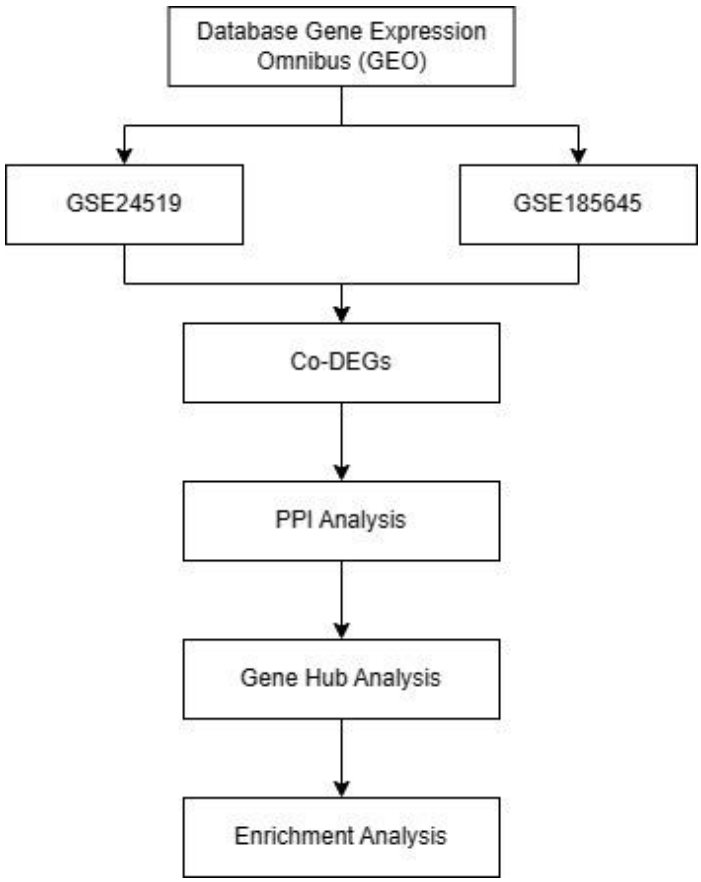

Figure 1. Schematic/Flowchart of research

2.2. Tips

2.2.1 Data Abstraction

We obtained gene expression datasets, GSE24519 and GSE185645, from the Gene Expression Omnibus (GEO). The GSE24519 dataset contains information gathered from platelets of 34 patients with myocardial infarction and 4 healthy individuals. Meanwhile, the GSE185645 dataset consists of data collected from 15 patients diagnosed with triple-negative breast cancer and 1 healthy individual.

2.2.2 Identification of Differentially Expressed Genes (DEGs)

The GSE24519 and GSE185645 datasets were then analyzed using GEO2R to identify differentially expressed genes (DEGs). Gene expression fold change was the parameter used to assess changes in gene expression. The gene expression fold change was evaluated with a log2FC value considered as the threshold for DEGs in both datasets. Genes with a log2FC > 1 were defined as upregulated, while genes with a log2FC < -1 were defined as downregulated [18]. After obtaining the DEG results, a Venn diagram analysis was conducted to obtain the intersecting genes from both upregulated and downregulated sets. The genes at the intersection were used for further analysis.

2.2.3 Construction of Protein–Protein Interaction (PPI) Network

The data derived from identifying DEGs underwent further analysis through Protein-Protein Interaction (PPI) examination. Using Cytoscape software (version 3.9.1), we constructed the PPI association between myocardial infarction and breast cancer. Cytoscape is an open-source bioinformatics platform utilized for visualizing molecular interaction networks. The analysis of protein-protein interactions was conducted using the Search Tool for the Retrieval of Interacting Genes (STRING) plugin within Cytoscape, and proteins with a STRINGDB value exceeding 0.7 were chosen [18]. To pinpoint hub genes, we employed the CytoHubba app in Cytoscape, employing a combined method with a score surpassing 0.7 and sorting by degree [19].

2.2.4 Enrichment Analysis

The data obtained from Protein–Protein Interaction was further subjected to enrichment analysis using EnrichR (https://maayanlab.cloud/Enrichr/). The analyses conducted include pathways, gene ontology, and cell Types.

3. Results and Discussion

3.1 Identification of Differentially Expressed Genes (DEGs)

From the GSE24519 dataset, 4,482 DEGs were obtained from healthy and myocardial infarction samples. Subsequently, gene duplicates were removed, resulting in 2,832 DEGs, comprising 734 upregulated genes and 2,098 downregulated genes. From the GSE185645 dataset, 1,284 DEGs were obtained from healthy and breast cancer samples. After removing gene duplicates, 468 DEGs were obtained, consisting of 311 upregulated genes and 157 downregulated genes. A Volcano Plot was used to visualize DEGs using GEO2R (Figure 2).

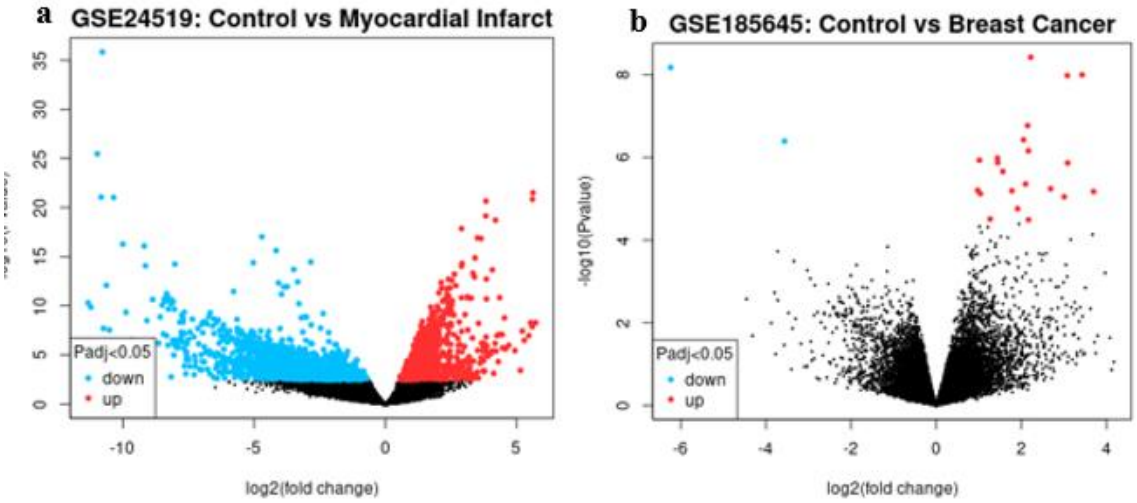

Figure 2. (a) The volcano plot illustrates the DEGs (Differentially Expressed Genes) contrasting the normal and myocardial infarction samples in the GSE24519 dataset. (b) Similarly, another volcano plot showcases the DEGs comparing the normal and breast cancer disease samples in the GSE185645 dataset. In these plots, upregulated genes are denoted by red dots, no significant genes by black dots, and downregulated genes by blue dots.

The Venn diagram of DEGs in the GSE24519 and GSE185645 datasets is presented in Figure 3. The Venn diagram was created using InteractiVenn (http://www.interactivenn.net/). As seen in the diagram, there are 6 common upregulated genes and 18 common downregulated genes. Details of these common genes are presented in Table 1.

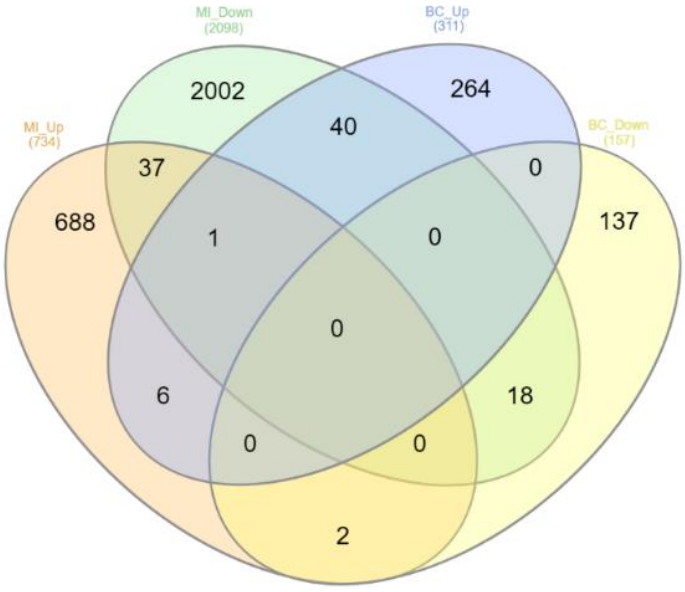

Figure 3. The Venn diagram displays the shared Differentially Expressed Genes (DEGs) identified in both the GSE24519 and GSE185645 datasets. MI refers to myocardial infarction, BC refers to breast cancer, up refers to genes that are upregulated, and down refers to genes that are downregulated.

Table 1. Differentially Expressed Genes (DEGs) undergoing upregulation and downregulation from GSE24519 and GSE185645.

No	Gene Symbol	Fold Change		Gene Title
		GSE24519	GSE185645	
Upregulated				
1	RNPC3	1.159122	1.2583518	RNA Binding Region (RNP1, RRM) Containing 3
2	LALBA	5.730219	1.1724460	Lactalbumin Alpha
3	GRIA4	2.799473	1.6798127	Glutamate Ionotropic Receptor AMPA Type Subunit 4
4	PLAT	1.049796	1.6860090	Plasminogen Activator, Tissue Type
5	CAV1	1.034316	1.8854793	Caveolin 1
6	SLC14A1	2.113529	2.4922122	Solute Carrier Family 14 Member 1 (Kidd Blood Group)
Downregulated				
1	CDC20	-2.060426	-2.4131244	Cell Division Cycle 20
2	DLGAP5	-4.997760	-2.1822216	DLG Associated Protein 5
3	PLK1	-5.575303	-2.1333261	Polo Like Kinase 1
4	UHRF1	-3.760185	-2.0945975	Ubiquitin Like with PHD and Ring Finger Domains 1
5	NUF2	-1.904452	-1.9604079	NUF2 Component of NDC80 Kinetochore Complex
6	MELK	-1.901047	-1.9406213	Maternal Embryonic Leucine Zipper Kinase
7	PCLAF	-2.006673	-1.9144413	PCNA Clamp Associated Factor
8	DTL	-1.035308	-1.8734744	Denticleless E3 Ubiquitin Protein Ligase Homolog
9	MCM10	-1.544612	-1.7609496	Minichromosome Maintenance 10 Replication Initiation Factor
10	MSR1	-1.577223	-1.7540946	Macrophage Scavenger Receptor 1
11	HJURP	-1.445792	-1.7338288	Holliday Junction Recognition Protein
12	KIF4A	-3.904573	-1.7234835	Kinesin Family Member 4A
13	KIF14	-1.133570	-1.6418602	Kinesin Family Member 14
14	BGN	-1.381430	-1.5240925	Biglycan
15	H1-5	-3.174134	-1.4331959	H1.5 Linker Histone, Cluster Member
16	BLM	-3.383173	-1.4321137	BLM RecQ Like Helicase
17	RAD51	-1.115733	-1.2453268	RAD51 Recombinase
18	H2BC4	-1.601743	-1.1862764	H2B Clustered Histone 4

3.2 Construction of Protein–Protein Interaction (PPI) Network

To investigate the association of DEGs, a PPI network was constructed using the STRING plugin in Cytoscape software. Fourteen proteins with a STRINGDB score > 0.7 were obtained. These proteins are DLGAP5, NUF2, MELK, PCLAF, PLK1, BLM, DTL, KIF14, CDC20, KIF4A, HJURP, MCM10, UHRF1, and RAD51 (Figure 4). For hub gene identification, we employed a combined method using CytoHubba. Ten proteins have a combined score > 0.7, with NUF2 and MELk having the highest degree, followed by KIF4A, DLGAP5, RAD51, PCLAF, HJURP, DTL, CDC20, and PLK1 (Figure 5).

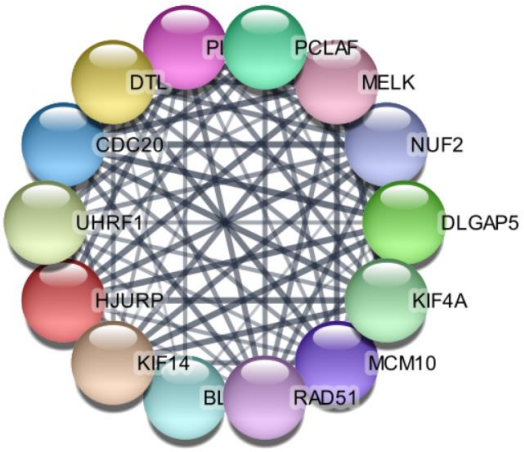

Figure 4. The Protein-Protein Interaction (PPI) network illustrates the interactions among the Differentially Expressed Genes (DEGs) identified in both the GSE24519 and GSE185645 datasets.

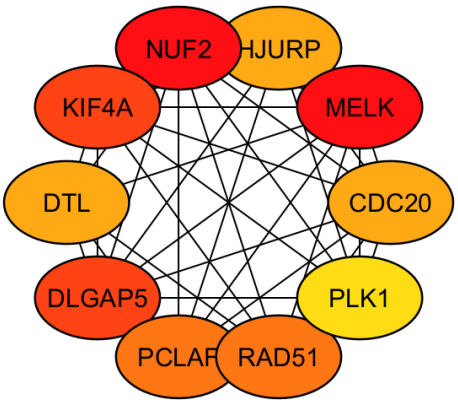

Figure 5. Identification of hub genes.

3.3 Enrichment Analysis

The results of the enrichment analysis are shown in Table 2. From the Pathways analysis based on KEGG 2021 Human, 10 proteins resulting from the PPI are associated with homologous recombination. Gene ontology analysis covering biological processes, molecular functions, and cellular components indicates that 10 proteins are associated with the biological process of microtubule cytoskeleton organization involved in mitosis, the molecular function of ubiquitin ligase activator activity, and the cellular component spindle.

Biological processes encompass the biological goals to which genes or their products contribute. These processes may entail one or multiple coordinated molecular functions and often entail chemical or physical changes. Molecular functions encompass biochemical activities, such as specific binding to ligands or structures, performed by gene products. Unlike molecular functions, which describe what is done without indicating where or when it happens, cellular components denote the cellular locations where gene products are active [20-21]. Reactome analysis indicates that these 10 proteins are associated with phosphorylation of emi1 R-HAS. The results from the Cell Types analysis based on the Human Gene Atlas show that the 10 proteins resulting from the PPI are associated with CD105+ endothelial.

Table 2. Pathways associated with 14 proteins.

Analysis	Name	P-value
Pathway	Homologous recombination	0.02032
Biological process	Microtubule Cytoskeleton Organization Involved in Mitosis	1.415e-8
Molecular function	Ubiquitin Ligase Activator Activity	0.002997
Cellular component	Spindle	0.000002361
Reactome	Phosphorylation of Emi1 R-HSA	0.000003371
Cell types	CD105+ endothelial	0.00002216

The results from the PPI indicate that there are 10 genes with strong interactions are involved in the homologous recombination pathway based on enrichment analysis with a P-value of 0.02032. Homologous recombination (HR) has been associated with both myocardial infarction (MI) and breast cancer. Homologous recombination is a DNA repair pathway associated with myocardial infarction. RAD51 is one of protein that essential for homologous recombination repair [22-23]. Based on the DEG identification results, RAD51 are downregulated in cases of myocardial infarction and breast cancer. The decrease in RAD51 expression correlates with homologous recombination deficiency (HRD), which represents a phenotype where cells cannot efficiently mend double-strand DNA breaks through the homologous recombination repair mechanism. HRD is linked to various cancer types, such as breast cancer [24-26].

Microtubule Cytoskeleton Organization involves in mitosis biological process of myocardial infarction. It highlights that cardiac microtubules, which are part of the non-sarcomeric cytoskeleton in cardiomyocytes, play essential roles in intracellular cargo delivery, mechanical signal transmission, membrane system shaping, and the organization of myofibrils and organelles. Alterations to the microtubule cytoskeleton have been observed in heart failure, impacting cardiac function and structure [27-29]. Microtubule organization involves on breast cancer progression. It emphasizes that alterations in microtubule stability and tubulin isotypes correlate with poor prognosis and chemotherapy resistance in breast cancer and other tumors [30]. Microtubules and associated proteins regulate critical cellular processes, such as migration and invasion, making them potential targets for cancer therapy. Elevated α-tubulin acetylation in metastatic and basal-like breast cancer cells promotes adhesion and invasive migration. Microtubule organization crucially influences breast cancer progression by regulating cell growth, movement, and stress responses [31-32]

Kif4A is a protein that has been studied in the context of various diseases, including myocardial infarction and breast cancer. In the case of breast cancer, research has focused on the role of Kif4A in doxorubicin-induced apoptosis and its association with the breast cancer susceptibility gene product BRCA2 [33]. Specifically, Kif4A has been implicated in DNA damage response and/or DNA repair pathways in breast cancer. It has also been evaluated as a potential prognostic biomarker for breast cancer classification [34-35].

As for its connection to myocardial infarction, there is limited direct evidence available in the provided search results. However, Kif4A is known to play important roles in the regulation of eukaryotic cell mitosis, which is relevant to various diseases, including cancer, but its specific link to myocardial infarction is not well-documented. NUF2, a protein associated with the regulation of cell division, has been found to be elevated in breast cancer and other types of cancer, such as human osteosarcoma and pancreatic tumor [36]. However, there is no direct evidence linking NUF2 to myocardial infarction. The research suggests that NUF2 may serve as a potential immunological and prognostic marker for breast cancer and other cancers [37-38]. While there is extensive research on the role of various genes and proteins, including NUF2, in different types of cancer, the specific connection between NUF2 and myocardial infarction is not well-established based on the available search results. Therefore, further research would be needed to determine the potential relationship between NUF2 and myocardial infarction.

Polo-like kinase 1 (PLK1) is a protein crucial for regulating cellular processes like the cell cycle and division. Studies have linked PLK1 to both myocardial infarction and breast cancer. Regarding myocardial infarction, elevated PLK1 levels have been linked to mitigating myocardial ischemia-reperfusion injury in rats through inducing mitophagy and controlling the p-AMPK/FUNDC1 axis. Moreover, PLK1 is recognized as a key regulator of heart regeneration in zebrafish and is indispensable for cardiomyocyte proliferation. In the context of breast cancer, PLK1 has been found to induce the mitophagy of breast cancer cells and promote cell proliferation [39-40].

However, the specific link between PLK1, myocardial infarction, and breast cancer is a complex area of study that requires further research to fully understand the interplay between PLK1 and these two conditions. DLGAP5, also known as HURP, has been found to be highly expressed in breast cancer specimens and associated with poor prognosis in breast cancer patients [41]. However, there is no direct evidence linking DLGAP5 to myocardial infarction based on the available search results. The research suggests that DLGAP5 may act as a potential oncogene in breast cancer [42]. While there is extensive research on the role of various genes and proteins in different diseases, the specific connection between DLGAP5, myocardial infarction, and breast cancer is not well-established based on the available search results. Therefore, further research would be needed to determine the potential relationship between DLGAP5, myocardial infarction, and breast cancer.

The function of ubiquitin ligase activator activity in both myocardial infarction and breast cancer is complex. In myocardial infarction, the E3 ubiquitin ligase Peli1 has been associated with myocardial ischemia/reperfusion injury, hinting at its possible involvement in cardiac disorders. Moreover, the ubiquitin proteasome system, controlled by ubiquitin ligases, serves various roles in protein degradation, energy regulation, receptor uptake, hypertrophic response, apoptosis, and ischemia/reperfusion tolerance in cardiomyocytes, underscoring its importance in cardiac conditions [43-44].

Moreover, the NEDD4 family of ubiquitin ligases has been linked to cardiovascular disease, underscoring the wider role of ubiquitin ligases in heart-related disorders. Ubiquitin ligases like Siah2 and Peli1 have been linked to essential cellular functions, encompassing DNA damage, cellular arrangement, and polarity, suggesting potential relevance across various disease states, including cancer and heart attacks. Notably, the activity of Siah2 has been linked to decreasing the expression of C/EBPδ, a tumor suppressor involved in the advancement of breast cancer [45-46]. In breast cancer, the E3 ubiquitin ligase UCHL1 has been identified as a potential therapeutic target, with its dysregulation impacting the development of aggressive forms of breast cancer. Therefore, ubiquitin ligase activator activity is intricately linked to the pathophysiology of both myocardial infarction and breast cancer, playing a role in fundamental cellular processes and disease pathways [47-48].

The protein CDC20 is implicated in several cancer types, such as lung squamous cell carcinoma, breast cancer, and endometrial cancer. Elevated levels of CDC20 have been correlated with poorer outcomes in lung cancer, including non-small cell lung cancer (NSCLC). In breast cancer, increased

expression of CDC20 has been linked to reduced short-term survival rates, suggesting its potential as a prognostic biomarker. Additionally, increased expression of CDC20 is associated with increased chromosomal instability in various cancers, including breast cancer, colon cancer, and endometrial cancer [49-50]. Regarding myocardial infarction (MI), CDC20 showed notable enrichment in rat cardiomyocytes following MI, suggesting its likely role in the response to ischemic injury. Moreover, studies have indicated that CDC20 modulates cardiac hypertrophy by influencing LC3-dependent autophagy, which is relevant to MI [51-52]. In summary, CDC20 is implicated in the prognosis and development of various cancers, including breast cancer, lung cancer, and endometrial cancer. Additionally, there is ongoing research on the potential link between Pkm2 and myocardial infarction.

The spindle cellular component is associated with both myocardial infarction and breast cancer. In myocardial infarction, the involvement of cardiac macrophages, which exhibit a spindle-shaped and elongated appearance, plays a crucial role in the inflammatory cascade following the sudden loss of cardiomyocytes. This cascade leads to cardiac fibrosis and heart failure [53-54]. In breast cancer, the spindle cellular component is associated with spindle cell carcinoma, an infrequent subtype distinguished by predominant spindle-shaped cells. Spindle cell carcinoma encompasses diverse elements such as in situ or ductal, lobular, squamous, or mixed infiltrating carcinoma. It is characterized by sizable, well-defined tumors, frequently exhibiting cystic formations. Generally, the prognosis is favorable, marked by low expression of estrogen receptor (ER) and progesterone receptor (PR), and relatively rare occurrences of lymph node metastasis. Timely detection and suitable treatment are imperative for favorable outcomes [55-56].

The Reactome pathway "Cell Cycle" (R-HSA) is linked to both myocardial infarction and breast cancer. In terms of myocardial infarction, genes related to inflammation and the cell cycle have been recognized as potential biomarkers for diagnosing and predicting acute myocardial infarction. This indicates a potential involvement of the cell cycle in the pathophysiology of myocardial infarction [57]. In the case of breast cancer, the regulation of the cell cycle by non-coding RNAs (ncRNAs) has been shown to affect the efficiency of CDK4/6 inhibition, which is a key pathway in cancer development and treatment [58-59].

Additionally, circular RNAs (circRNAs) have been found to regulate cell cycle-related genes and promote the growth of estrogen receptor-positive breast cancer cells, further highlighting the role of the cell cycle in breast cancer development and progression [60]. These findings indicate that the cell cycle, as represented by the "Cell Cycle" (R-HSA) pathway, is intricately linked to the pathogenesis of myocardial infarction and breast cancer. Dysregulation of the cell cycle, influenced by various genetic and molecular factors, can contribute to the development and progression of these conditions [61-62]. Further research into the specific mechanisms underlying the involvement of the cell cycle in myocardial infarction and breast cancer is warranted to identify potential therapeutic targets and diagnostic markers.

The results of the enrichment analysis referring to cell types indicate that there are 6 genes, namely BLM, RAD51, KIF4A, MCM10, DTL, and DLGAP5, associated with CD105+ Endothelial cell type with a P-value of 1.020e-7. The results in this study differ from those obtained by Graeme using a mouse model. Graeme's research indicated that myocardial infarction and breast cancer are related through Ly6Chigh monocytes [4]. CD105+ endothelial cells are a subtype of endothelial cells expressing the CD105 protein on their cell surface. CD105 (Endoglin) is a cell membrane glycoprotein dominantly expressed in various cell types within the vascular system, with higher expression in developing endothelial cells. It is involved in blood vessel development and serves as a robust marker of neovascularization [63-64].

Endoglin increases in heart failure due to excessive pressure, heart failure due to volume overload, and acute myocardial infarction. It is currently known that endoglin is involved in several physiological processes and malignancies. CD105 has been studied in relation to breast cancer, and a 2004 study published in Clinical Cancer Research found that CD105 expression in breast carcinoma

tissue microarrays was associated with neoangiogenesis, or the formation of new blood vessels in tumors [65-67]. CD105 exhibits greater specificity in assessing microvessel density (MVD) within tumor tissues compared to broad endothelial markers like CD31, CD34, and von Willebrand factor (vWF). The assessment of neovascularization using CD105 is closely associated with prognostic indicators in breast cancer [68].

4. Conclusion

In summary, employing a range of bioinformatics tools for gene expression analysis, we constructed a protein-protein interaction (PPI) network linking myocardial infarction and breast cancer. Our results indicate a significant association between myocardial infarction and breast cancer via homologous recombination pathways and CD105+ endothelial cell types. Further validation through in vitro and in vivo studies is warranted to confirm our findings. These results could serve as a basis for future investigations into the molecular mechanisms underlying the connection between myocardial infarction and breast cancer.

References

[1] Ali, S., Ishaq Dar, M., A. Rather, R., & Afroze, D. (2020). Cell Cycle and Factors Involved in Inhibition or Progression of Breast Cancer. In *Breast Cancer Biology*. IntechOpen.

[2] Ashburner, M., Ball, C. A., Blake, J. A., Botstein, D., Butler, H., Cherry, J. M., Davis, A. P., Dolinski, K., Dwight, S. S., Eppig, J. T., Harris, M. A., Hill, D. P., Issel-Tarver, L., Kasarskis, A., Lewis, S., Matese, J. C., Richardson, J. E., Ringwald, M., Rubin, G. M., & Sherlock, G. (2000). Gene Ontology: tool for the unification of biology. *Nature Genetics*, *25*(1), 25–29.

[3] Attachaipanich, T., Chattipakorn, S. C., & Chattipakorn, N. (2024). Current evidence regarding the cellular mechanisms associated with cancer progression due to cardiovascular diseases. *Journal of Translational Medicine*, *22*(1), 105.

[4] Bedford, L., Lowe, J., Dick, L. R., Mayer, R. J., & Brownell, J. E. (2011). Ubiquitin-like protein conjugation and the ubiquitin–proteasome system as drug targets. *Nature Reviews Drug Discovery*, *10*(1), 29–46.

[5] Borys, F., Joachimiak, E., Krawczyk, H., & Fabczak, H. (2020). Intrinsic and Extrinsic Factors Affecting Microtubule Dynamics in Normal and Cancer Cells. *Molecules*, *25*(16), 3705.

[6] Caporizzo, M. A., Chen, C. Y., & Prosser, B. L. (2019). Cardiac microtubules in health and heart disease. *Experimental Biology and Medicine*, *244*(15), 1255–1272.

[7] Caporizzo, M. A., & Prosser, B. L. (2022). The microtubule cytoskeleton in cardiac mechanics and heart failure. *Nature Reviews Cardiology*, *19*(6), 364–378.

[8] Charpin, C., Dales, J.-P., Garcia, S., Carpentier, S., Djemli, A., Andrac, L., Lavaut, M.-N., Allasia, C., & Bonnier, P. (2004). Tumor Neoangiogenesis by CD31 and CD105 Expression Evaluation in Breast Carcinoma Tissue Microarrays. *Clinical Cancer Research*, *10*(17), 5815–5819.

[9] Clough, E., & Barrett, T. (2016). *The Gene Expression Omnibus Database* (pp. 93–110).

[10] Consortium, T. G. O. (2001). Creating the Gene Ontology Resource: Design and Implementation. *Genome Research*, *11*(8), 1425–1433.

[11] Deng, Y., Li, J., Zhang, Y., Hu, H., Wan, F., Min, H., Zhou, H., Gu, L., Liao, X., Zhou, J., & Zhou, J. (2023). NUF2 Promotes Breast Cancer Development as a New Tumor Stem Cell Indicator. *International Journal of Molecular Sciences*, *24*(4), 4226.

[12] Feng, C., Zhang, Y., Wu, F., Li, J., Liu, M., Lv, W., Li, C., Wang, W., Tan, Q., Xue, X., Ma, X., & Zhang, S. (2023). Relationship between homologous recombination deficiency and clinical features of breast cancer based on genomic scar score. *The Breast*, *69*, 392–400.

[13] Hakiminia, F., Jannat Alipoor, F., Keshavarz, M., & Asadi, M. H. (2023). LncRNA PNKY Is Upregulated in Breast Cancer and Promotes Cell Proliferation and EMT in Breast Cancer Cells.

Non-Coding RNA, *9*(2), 25.
[14] Hausenloy, D. J., Bøtker, H. E., Ferdinandy, P., Heusch, G., Ng, G. A., Redington, A., & Garcia-Dorado, D. (2019). Cardiac innervation in acute myocardial ischaemia/reperfusion injury and cardioprotection. *Cardiovascular Research*, *115*(7), 1167–1177.
[15] Hu, Q., & Huang, T. (2023). Regulation of the Cell Cycle by ncRNAs Affects the Efficiency of CDK4/6 Inhibition. *International Journal of Molecular Sciences*, *24*(10), 8939.
[16] Jeong, J., Suh, Y., & Jung, K. (2019). Context Drives Diversification of Monocytes and Neutrophils in Orchestrating the Tumor Microenvironment. *Frontiers in Immunology*, *10*.
[17] Jian, Y., Zhou, X., Shan, W., Chen, C., Ge, W., Cui, J., Yi, W., & Sun, Y. (2023). Crosstalk between macrophages and cardiac cells after myocardial infarction. *Cell Communication and Signaling*, *21*(1), 109.
[18] Karra, H., Repo, H., Ahonen, I., Löyttyniemi, E., Pitkänen, R., Lintunen, M., Kuopio, T., Söderström, M., & Kronqvist, P. (2014). Cdc20 and securin overexpression predict short-term breast cancer survival. *British Journal of Cancer*, *110*(12), 2905–2913.
[19] Kitada, M., Hayashi, S., Matsuda, Y., Ishibashi, K., Oikawa, K., & Miyokawa, N. (2014). Spindle cell carcinoma of the breast as complex cystic lesion: a case report. *Cancer Biology & Medicine*, *11*(2), 130–133.
[20] Koelwyn, G. J., Newman, A. A. C., Afonso, M. S., van Solingen, C., Corr, E. M., Brown, E. J., Albers, K. B., Yamaguchi, N., Narke, D., Schlegel, M., Sharma, M., Shanley, L. C., Barrett, T. J., Rahman, K., Mezzano, V., Fisher, E. A., Park, D. S., Newman, J. D., Quail, D. F., … Moore, K. J. (2020). Myocardial infarction accelerates breast cancer via innate immune reprogramming. *Nature Medicine*, *26*(9), 1452–1458.
[21] Kubota, A., & Frangogiannis, N. G. (2022). Macrophages in myocardial infarction. *American Journal of Physiology-Cell Physiology*, *323*(4), C1304–C1324.
[22] Li, X., Zhang, L., Yi, Z., Zhou, J., Song, W., Zhao, P., Wu, J., Song, J., & Ni, Q. (2022). NUF2 Is a Potential Immunological and Prognostic Marker for Non-Small-Cell Lung Cancer. *Journal of Immunology Research*, *2022*, 1–22.
[23] Li, Y., Wei, J., Sun, Y., Zhou, W., Ma, X., Guo, J., Zhang, H., & Jin, T. (2023). DLGAP5 Regulates the Proliferation, Migration, Invasion, and Cell Cycle of Breast Cancer Cells via the JAK2/STAT3 Signaling Axis. *International Journal of Molecular Sciences*, *24*(21), 15819.
[24] Liu, Y., Li, J., Xu, N., Yu, H., Gong, L., Li, Q., Yang, Z., Li, S., Yang, J., Huang, D., Xue, Y., Xue, G., Liu, J., Chen, H., Zhang, R., Li, A., Zhao, Y., Li, P., Li, M., … Cai, B. (2022). Transcription factor Meis1 act as a new regulator of ischemic arrhythmias in mice. *Journal of Advanced Research*, *39*, 275–289.
[25] Lu, L., Liu, M., Sun, R., Zheng, Y., & Zhang, P. (2015). Myocardial Infarction: Symptoms and Treatments. *Cell Biochemistry and Biophysics*, *72*(3), 865–867.
[26] Łukasiewicz, S., Czeczelewski, M., Forma, A., Baj, J., Sitarz, R., & Stanisławek, A. (2021). Breast Cancer—Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies—An Updated Review. *Cancers*, *13*(17), 4287.
[27] Mantovani, A., Allavena, P., Marchesi, F., & Garlanda, C. (2022). Macrophages as tools and targets in cancer therapy. *Nature Reviews Drug Discovery*, *21*(11), 799–820.
[28] Mao, S., Tian, S., Luo, X., Zhou, M., Cao, Z., & Li, J. (2021). Overexpression of PLK1 relieved the myocardial ischemia-reperfusion injury of rats through inducing the mitophagy and regulating the p-AMPK/FUNDC1 axis. *Bioengineered*, *12*(1), 2676–2687.
[29] Mekonnen, N., Yang, H., & Shin, Y. K. (2022). Homologous Recombination Deficiency in Ovarian, Breast, Colorectal, Pancreatic, Non-Small Cell Lung and Prostate Cancers, and the Mechanisms of Resistance to PARP Inhibitors. *Frontiers in Oncology*, *12*.
[30] Meurer, S. K., & Weiskirchen, R. (2020). Endoglin: An 'Accessory' Receptor Regulating Blood Cell Development and Inflammation. *International Journal of Molecular Sciences*, *21*(23), 9247.

[31] Mondal, M., Conole, D., Nautiyal, J., & Tate, E. W. (2022). UCHL1 as a novel target in breast cancer: emerging insights from cell and chemical biology. *British Journal of Cancer*, *126*(1), 24–33.

[32] Moore, X. T. R., Gheghiani, L., & Fu, Z. (2023). The Role of Polo-Like Kinase 1 in Regulating the Forkhead Box Family Transcription Factors. *Cells*, *12*(9), 1344.

[33] Ng, B., Puspitaningtyas, H., Wiranata, J. A., Hutajulu, S. H., Widodo, I., Anggorowati, N., Sanjaya, G. Y., Lazuardi, L., & Sripan, P. (2023). Breast cancer incidence in Yogyakarta, Indonesia from 2008–2019: A cross-sectional study using trend analysis and geographical information system. *PLOS ONE*, *18*(7), e0288073.

[34] Olingy, C. E., Dinh, H. Q., & Hedrick, C. C. (2019). Monocyte heterogeneity and functions in cancer. *Journal of Leukocyte Biology*, *106*(2), 309–322.

[35] Orhan, E., Velazquez, C., Tabet, I., Sardet, C., & Theillet, C. (2021). Regulation of RAD51 at the Transcriptional and Functional Levels: What Prospects for Cancer Therapy? *Cancers*, *13*(12), 2930.

[36] Parker, A. L., Kavallaris, M., & McCarroll, J. A. (2014). Microtubules and Their Role in Cellular Stress in Cancer. *Frontiers in Oncology*, *4*.

[37] Parker, A. L., Teo, W. S., McCarroll, J. A., & Kavallaris, M. (2017). An Emerging Role for Tubulin Isotypes in Modulating Cancer Biology and Chemotherapy Resistance. *International Journal of Molecular Sciences*, *18*(7), 1434.

[38] Phyo, S. A., Uchida, K., Chen, C. Y., Caporizzo, M. A., Bedi, K., Griffin, J., Margulies, K., & Prosser, B. L. (2022). Transcriptional, Post-Transcriptional, and Post-Translational Mechanisms Rewrite the Tubulin Code During Cardiac Hypertrophy and Failure. *Frontiers in Cell and Developmental Biology*, *10*.

[39] Qi, J., Kim, H., Scortegagna, M., & Ronai, Z. A. (2013). Regulators and Effectors of Siah Ubiquitin Ligases. *Cell Biochemistry and Biophysics*, *67*(1), 15–24.

[40] Qian, H., Yang, L., Zhao, W., Chen, H., & He, S. (2018). A comparison of CD105 and CD31 expression in tumor vessels of hepatocellular carcinoma by tissue microarray and flow cytometry. *Experimental and Therapeutic Medicine*.

[41] Rakha, E. A., Brogi, E., Castellano, I., & Quinn, C. (2022). Spindle cell lesions of the breast: a diagnostic approach. *Virchows Archiv*, *480*(1), 127–145.

[42] Rossi, E., Bernabeu, C., & Smadja, D. M. (2019). Endoglin as an Adhesion Molecule in Mature and Progenitor Endothelial Cells: A Function Beyond TGF-β. *Frontiers in Medicine*, *6*.

[43] Shyu, K.-G. (2017). The Role of Endoglin in Myocardial Fibrosis. *Acta Cardiologica Sinica*, *33*(5), 461–467.

[44] Stewart, M. D., Merino Vega, D., Arend, R. C., Baden, J. F., Barbash, O., Beaubier, N., Collins, G., French, T., Ghahramani, N., Hinson, P., Jelinic, P., Marton, M. J., McGregor, K., Parsons, J., Ramamurthy, L., Sausen, M., Sokol, E. S., Stenzinger, A., Stires, H., … Allen, J. (2022). Homologous Recombination Deficiency: Concepts, Definitions, and Assays. *The Oncologist*, *27*(3), 167–174.

[45] Su, J., Gao, C., Wang, R., Xiao, C., & Yang, M. (2018). Genes associated with inflammation and the cell cycle may serve as biomarkers for the diagnosis and prognosis of acute myocardial infarction in a Chinese population. *Molecular Medicine Reports*.

[46] Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, *71*(3), 209–249.

[47] Supplitt, S., Karpinski, P., Sasiadek, M., & Laczmanska, I. (2021). Current Achievements and Applications of Transcriptomics in Personalized Cancer Medicine. *International Journal of Molecular Sciences*, *22*(3), 1422.

[48] Thun, M. J., DeLancey, J. O., Center, M. M., Jemal, A., & Ward, E. M. (2010). The global burden of cancer: priorities for prevention. *Carcinogenesis*, *31*(1), 100–110.
[49] Tsao, C. W., Aday, A. W., Almarzooq, Z. I., Anderson, C. A. M., Arora, P., Avery, C. L., Baker-Smith, C. M., Beaton, A. Z., Boehme, A. K., Buxton, A. E., Commodore-Mensah, Y., Elkind, M. S. V., Evenson, K. R., Eze-Nliam, C., Fugar, S., Generoso, G., Heard, D. G., Hiremath, S., Ho, J. E., … Martin, S. S. (2023). Heart Disease and Stroke Statistics—2023 Update: A Report From the American Heart Association. *Circulation*, *147*(8).
[50] Verschuren, J. J. W., Trompet, S., Deelen, J., Stott, D. J., Sattar, N., Buckley, B. M., Ford, I., Heijmans, B. T., Guchelaar, H.-J., Houwing-Duistermaat, J. J., Slagboom, P. E., & Jukema, J. W. (2013). Non-Homologous End-Joining Pathway Associated with Occurrence of Myocardial Infarction: Gene Set Analysis of Genome-Wide Association Study Data. *PLoS ONE*, *8*(2), e56262.
[51] Wang, H., Lu, C., Li, Q., Xie, J., Chen, T., Tan, Y., Wu, C., & Jiang, J. (2014). The Role of Kif4A in Doxorubicin-Induced Apoptosis in Breast Cancer Cells. *Molecules and Cells*, *37*(11), 812–818.
[52] Wang, L., Liu, G., Bolor-Erdene, E., Li, Q., Mei, Y., & Zhou, L. (2021). Identification of KIF4A as a prognostic biomarker for esophageal squamous cell carcinoma. *Aging*, *13*(21), 24050–24070.
[53] Wang, X., Shi, N., Wu, B., Yuan, L., Chen, J., Ye, C., & Hao, M. (2022). Bioinformatics analysis of gene expression profile and functional analysis in periodontitis and Parkinson's disease. *Frontiers in Aging Neuroscience*, *14*.
[54] Willis, M. S., Bevilacqua, A., Pulinilkunnil, T., Kienesberger, P., Tannu, M., & Patterson, C. (2014). The role of ubiquitin ligases in cardiac disease. *Journal of Molecular and Cellular Cardiology*, *71*, 43–53.
[55] Wu, G., Zhou, L., Khidr, L., Guo, X. E., Kim, W., Lee, Y. M., Krasieva, T., & Chen, P.-L. (2008). A novel role of the chromokinesin Kif4A in DNA damage response. *Cell Cycle*, *7*(13), 2013–2020.
[56] Xian, F., Zhao, C., Huang, C., Bie, J., & Xu, G. (2023). The potential role of CDC20 in tumorigenesis, cancer progression and therapy: A narrative review. *Medicine*, *102*(36), e35038.
[57] Xie, Y.-P., Lai, S., Lin, Q.-Y., Xie, X., Liao, J.-W., Wang, H.-X., Tian, C., & Li, H.-H. (2018). CDC20 regulates cardiac hypertrophy via targeting LC3-dependent autophagy. *Theranostics*, *8*(21), 5995–6007.
[58] Xu, T., Dong, M., Li, H., Zhang, R., & Li, X. (2020). Elevated mRNA expression levels of DLGAP5 are associated with poor prognosis in breast cancer. *Oncology Letters*.
[59] Xu, W., Wang, Y., Wang, Y., Lv, S., Xu, X., & Dong, X. (2019). Screening of differentially expressed genes and identification of NUF2 as a prognostic marker in breast cancer. *International Journal of Molecular Medicine*.
[60] Yan, L., Cui, Y., & Feng, J. (2023). Biology of Pellino1: a potential therapeutic target for inflammation in diseases and cancers. *Frontiers in Immunology*, *14*.
[61] Yang, J., Tong, T., Zhu, C., Zhou, M., Jiang, Y., Chen, H., Que, L., Liu, L., Zhu, G., Ha, T., Chen, Q., Li, C., Xu, Y., Li, J., & Li, Y. (2022). Peli1 contributes to myocardial ischemia/reperfusion injury by impairing autophagy flux via its E3 ligase mediated ubiquitination of P62. *Journal of Molecular and Cellular Cardiology*, *173*, 30–46.
[62] Yang, X., Kui, L., Tang, M., Li, D., Wei, K., Chen, W., Miao, J., & Dong, Y. (2020). High-Throughput Transcriptome Profiling in Drug and Biomarker Discovery. *Frontiers in Genetics*, *11*.
[63] Yuan, Z., Li, Y., Zhang, S., Wang, X., Dou, H., Yu, X., Zhang, Z., Yang, S., & Xiao, M. (2023). Extracellular matrix remodeling in tumor progression and immune escape: from mechanisms to treatments. *Molecular Cancer*, *22*(1), 48.

[64] Zangouei, A. S., Zangoue, M., Taghehchian, N., Zangooie, A., Rahimi, H. R., Saburi, E., Alavi, M. S., & Moghbeli, M. (2023). Cell cycle related long non-coding RNAs as the critical regulators of breast cancer progression and metastasis. *Biological Research*, *56*(1), 1.

[65] Zhang, F., Li, L., & Fan, Z. (2022). circRNAs and their relationship with breast cancer: a review. *World Journal of Surgical Oncology*, *20*(1), 373.

[66] Zhang, Q., Wu, J., Bai, X., & Liang, T. (2020). Evaluation of Intra-Tumoral Vascularization in Hepatocellular Carcinomas. *Frontiers in Medicine*, *7*.

[67] Zheng, H., Qian, X., Tian, W., & Cao, L. (2022). Exploration of the Common Gene Characteristics and Molecular Mechanism of Parkinson's Disease and Crohn's Disease from Transcriptome Data. *Brain Sciences*, *12*(6), 774.

[68] Zhu, K., Li, X., Gao, L., Ji, M., Huang, X., Zhao, Y., Diao, W., Fan, Y., Chen, X., Luo, P., Shen, L., & Li, L. (2023). Identification of Hub Genes Correlated with the Initiation and Development in Chronic Kidney Disease via Bioinformatics Analysis. *Kidney and Blood Pressure Research*, *48*(1), 79–91.