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Transcriptomic Profiling and In Silico Drug Repurposing Reveal BIRC5 and AURKA as Actionable Targets in Triple-Negative Breast Cancer

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ABSTRACT

Triple negative breast cancer is an aggressive malignancy lacking targeted therapies. To uncover new therapeutic strategies, we analyzed RNA- Seq data from nine paired TNBC and adjacent normal tissues. We identified 2,329 differentially expressed genes, with 1,012 upregulated and 1,317 downregulated. Upregulated transcripts such as BIRC5, CDC20, and XRCC2 were strongly enriched in cell cycle progression, DNA repair, and mitotic regulation, consistent with the hyperproliferative nature of TNBC. Conversely, reduced expression of EGR3, SOCS2, SLC7A2, NLGN1, and NTRK2 indicated suppression of cytokine-mediated signaling, immune regulation, and neurotrophin-related pathways, reflecting immune evasion and loss of differentiation cues. Network analysis pinpointed BIRC5 and AURKA as key hub genes. Structure-based screening of FDA-approved compounds revealed nebivolol, a β_1-adrenergic blocker, as a potential inhibitor of both proteins. Collectively, our findings reveal a dual transcriptomic strategy in TNBC, characterized by the activation of proliferative programs alongside suppression of immune-related pathways. Through integrative in silico analyses, we identify nebivolol as a potential repurposed therapeutic candidate. However, these results are computational and hypothesis-generating in nature, requiring rigorous experimental and clinical validation before any translational application.

1. Introduction

Breast cancer is the most frequently diagnosed cancer among women worldwide, accounting for approximately 23-25% of all female cancers. Among its subtypes, triple-negative breast cancer (TNBC), represents a significant global health burden, accounting for 10-25% of all breast cancers worldwide [1,2]. TNBC is defined by the absence of estrogen receptor, progesterone receptor, and Human Epidermal Growth Factor Receptor 2 (HER2) overexpression [2]. The disease exhibits aggressive behavior with poor overall prognosis, frequent local recurrence, and organ metastases [3]. Since TNBC doesn't have receptors that we can target with drugs, chemotherapy is the go-to treatment. Fortunately, TNBC tends to respond well when chemo is given before surgery, often wiping out all detectable cancer cells, which is a good sign for the patient's prognosis.

Drug repurposing represents a promising strategy to address the challenges of oncology drug development, particularly for triple-negative breast cancer (TNBC). It offers significant potential by leveraging existing drugs' known safety profiles and mechanisms of action [4,5]. Traditional cancer drug development is costly, time-consuming, and has low success rates [6,7] Computational approaches enable systematic identification of repurposing candidates (5). The REpurposing Drugs in Oncology (ReDO) project specifically investigates off-patent non-cancer drugs for oncological applications, providing cheaper, effective, and safer therapeutic options [4]. Specifically, High-throughput RNA sequencing has revolutionized cancer transcriptome profiling by enabling comprehensive analysis of gene expression differences between tumor and normal tissues [8]. RNA-seq provides

unprecedented resolution in estimating gene expression with reduced signal noise compared to traditional methods, facilitating the identification of differentially expressed genes that distinguish tumor from normal samples [9]. Systematic workflows have been developed to process RNA-seq data from raw reads to system-level analyses, incorporating popular differential expression tools like DESeq2 and functional enrichment platforms such as GSEA for biological interpretation [10]. These transcriptomic approaches offer crucial insights into cancer biology by linking cellular phenotypes to molecular underpinnings and revealing potential biomarkers and therapeutic targets [8].

Therefore, the primary objective of this study is to elucidate key molecular drivers, dysregulated pathways, and potential therapeutic targets in triple-negative breast cancer (TNBC) through comprehensive transcriptomic analysis of RNA-seq data derived from matched normal and tumor samples. By performing differential gene expression profiling followed by Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses, we prioritized high-confidence oncogenes and tumor suppressors for therapeutic exploration (Fig.1.). While transcriptomic studies of TNBC exist, few have directly bridged molecular discovery with the identification of clinically actionable drugs. Our study addresses the research gap of the limited translation of transcriptomic insights into clinically actionable therapies through integrating in silico drug repurposing approaches to prioritize FDA-approved compounds targeting dysregulated genes. By bridging molecular discovery with therapeutic mapping, the proposed pipeline facilitates biomarker identification and accelerates the evaluation of druggable candidates, thereby advancing precision oncology and enhancing translational relevance in aggressive cancer treatment.

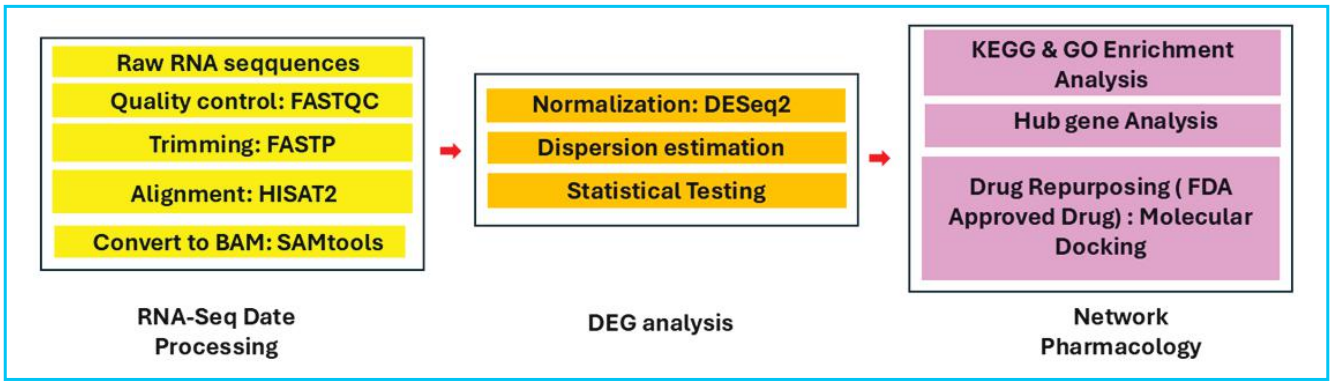


Fig.1. An Integrated Bioinformatics and Computational Biology Pipeline for Identifying Therapeutic Targets and Repurposing Drugs in Triple-Negative Breast Cancer (TNBC)

2. Materials and Methods

2.1 RNA-Seq Date Processing

RNA-seq data (GSE183947) from nine paired TNBC and adjacent normal tissues were retrieved from GEO, converted to FASTQ with the SRA toolkit, quality-checked (FASTQC), and trimmed (FASTP; Phred <20, length <50 bp discarded). Clean reads were aligned to GRCh38 using HISAT2, converted to BAM (SAMtools), and quantified at the gene level with feature Counts (Ensembl release 105).

2.2 Differential Expression Analysis

DESeq 2 was used for differential gene expression analysis. Low-count genes (total counts <50) were filtered, normalization was performed via the median-of-ratios method. Significantly dysregulated genes were identified by applying a false discovery rate (FDR) adjusted p-value threshold of padj < 0.05 and an absolute log2 fold-change threshold of >1.

2.3 Quality Assessment

Data quality was validated through dispersion plots, (principal component analysis) PCA, and sample-to-sample heatmaps. Dispersion estimates were visualized to confirm the appropriateness of the negative binomial model. Sample-level integrity was evaluated via PCA and heatmap visualization of sample-to-sample distances using variance-stabilized transformed data. Additionally, heatmaps of z-score normalized counts and R log transformed for the top 10 most significant genes

confirmed consistent expression patterns within condition groups and revealed clear transcriptional differences between normal and tumor samples.

2.4 Functional Enrichment

Volcano plots were generated, and the top 5 upregulated and downregulated genes passing stringent thresholds (|log2FC| > 2, p-value < 0.0001) were highlighted. Expression patterns of candidate biomarkers across samples were visualized using z-score normalized heatmaps. Differentially expressed genes (DEGs) were subjected to Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis using the **clusterProfiler (v4.4.4)** package in R. Enriched terms were considered significant at adjusted p-value < 0.05 and absolute log2 fold change > 1. Both **Biological Process (BP)** and **Molecular Function (MF)** categories were analyzed to capture regulatory changes in TNBC.

2.5 Protein-Protein Interaction and Hub Genes

The protein -protein interaction network was constructed after taking 300 most statistically significant DEGS into the STRING database, having a combined score of >0.4 as cutt off point. After STRING analysis, cytoscape (version 3.9.1), an open-source bioinformatics software platform used for network analysis. MCODE which is a plug in of cytoscape was used in identifying significant modules. Moreover, top 10 hub genes were calculated using the cytohubba plugin of cytoscape according to the most robust algorithm MCC.

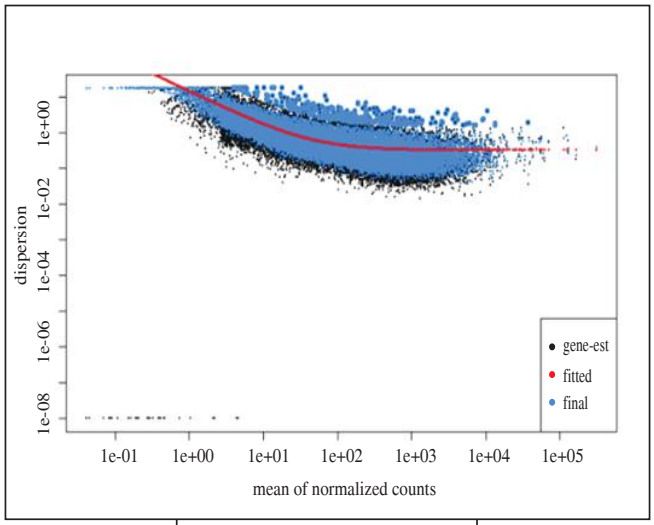
2.7 Drug Repurposing

Druggable hub genes AURKA and BIRC5 were prioritized. FDA-approved drugs targeting their functional domains were screened using PyRx. Molecular docking was performed in AutoDock Vina, and binding poses were evaluated in Discovery Studio and PyMOL.

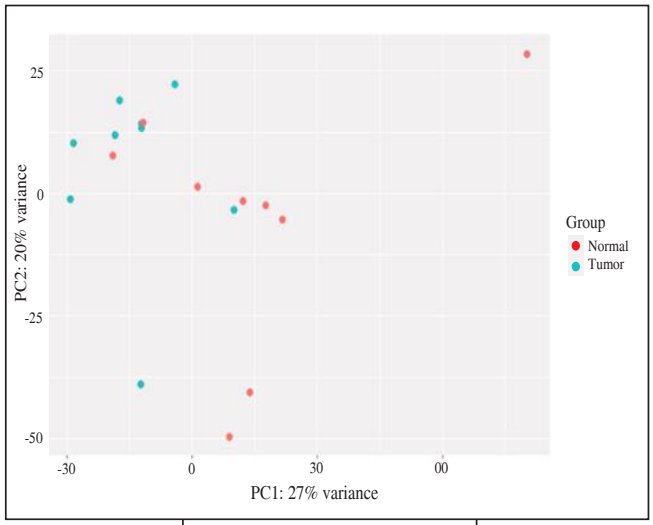
3. Results and Discussion

3.1 Quality Assessment of RNA-Seq Data

Quality control confirmed the robustness of the dataset. Dispersion plots showed appropriate variance modeling, while PCA revealed clear separation between tumor and normal samples (PC1: 27%, PC2: 20%), indicating strong biological variance (Fig.2).



1 (A)



1 (B)

Fig.2. (A) Dispersion plot showing modeled variance versus mean expression levels. (B) PCA plot demonstrating clustering of tumor and normal samples along PC1 and PC2.

2.6 Differential Gene Expression Analysis

Analysis identified 2,329 DEGs (1,012 upregulated, 1,317 downregulated; |log2FC| > 1, padj < 0.05). Stringent thresholds (|log2FC| > 2, p < 0.0001) highlighted a high-confidence subset, with BIRC5, CDC20, XRCC2, and H2BC5-AS1 among the top upregulated and NLGN1, EGR3, SLC7A2, and SOCS2 among the top downregulated genes (Fig. 3).

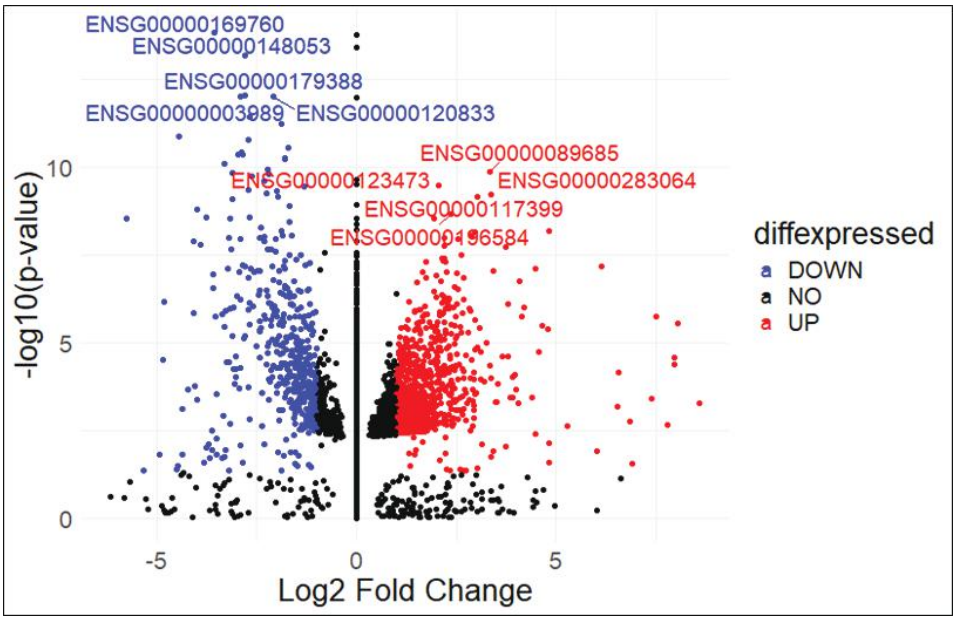


Fig.3. Volcano Plot of Differentially Expressed Genes. Volcano plot illustrating the distribution of differentially expressed genes between tumor and normal samples. The x-axis represents the log2 fold change (log2FC), and the y-axis represents the −log10(p-value). Genes with log2FC > 2 or log2FC < −2 and p-value < 0.0001 were considered significantly differentially expressed. The top five significant genes are labeled with their Ensembl gene IDs.

3.2 Clustering and Heatmap Analysis

A heatmap of the top 10 DEGs (r log transformed) demonstrated distinct expression patterns between tumor and normal samples (Fig.4).

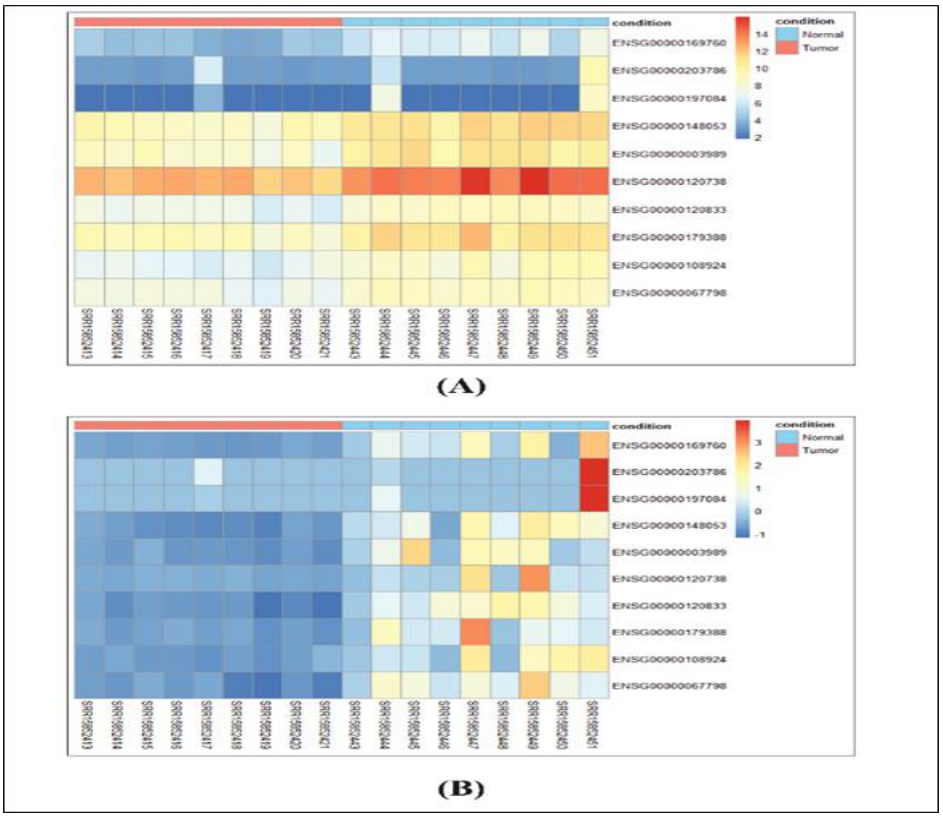


Fig. 4. (A) Heatmap of top 10 DEGs across tumor and normal samples (rlog Transformed). (B) Z-score normalized expression profiles demonstrating consistent separation of sample groups.

Z-score normalization confirmed that tumor samples exhibited consistent overexpression of oncogenes (e.g., *BIRC5, CDC20*) and suppression of tumor suppressors (*EGR3, SOCS2*).

3.3 Functional Enrichment Reveals Cell Cycle and Chromatin Remodeling Pathways

The GO Analysis revealed enrichment in cell cycle processes such as mitotic division and chromosome segregation, while molecular function terms included chromatin structure and DNA helicase activity. KEGG pathways highlighted the cell cycle and p53 signaling, consistent with proliferative and checkpoint dysregulation in TNBC (Fig.5).

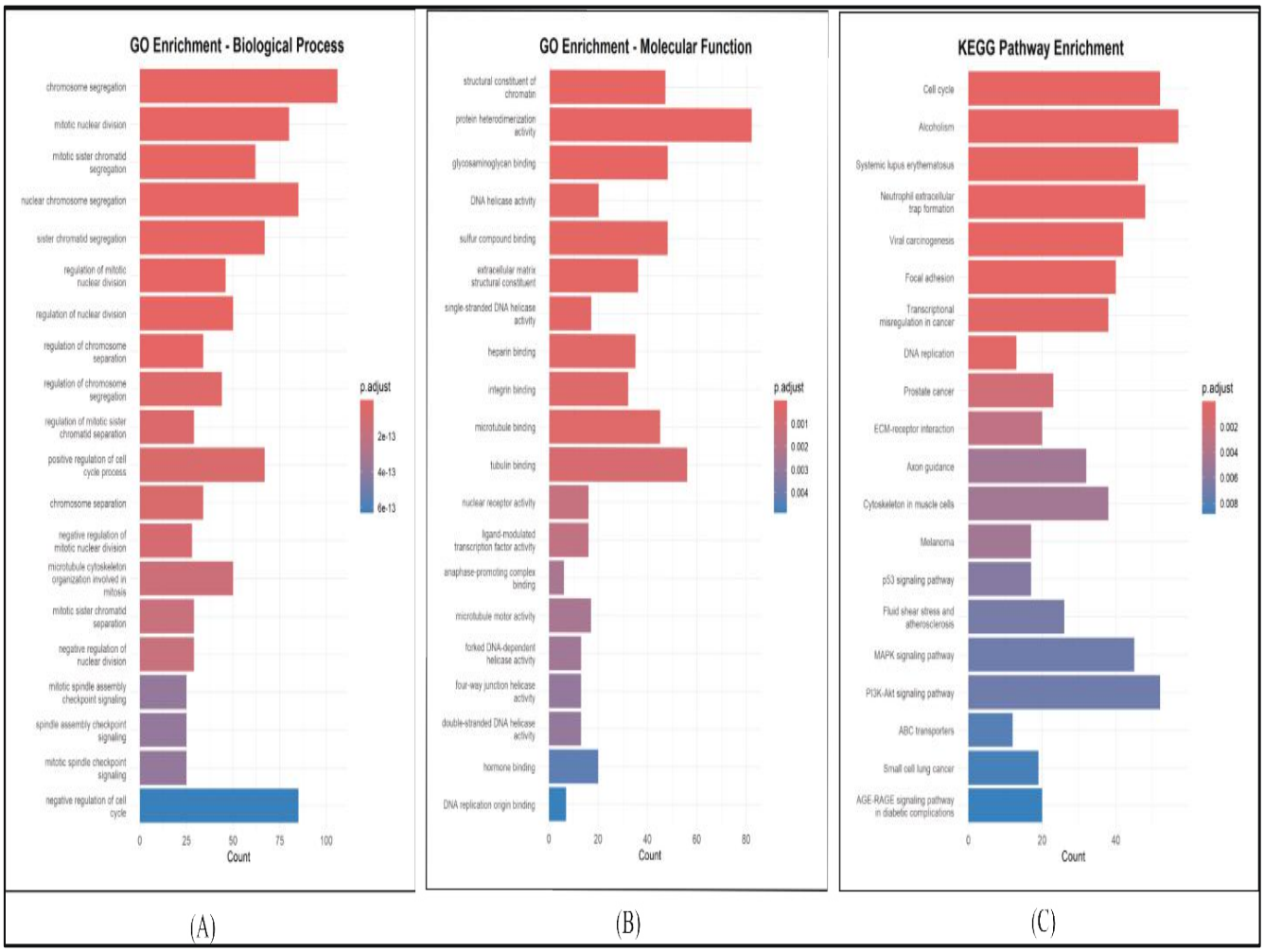


Fig. 5. GO and KEGG enrichment analysis of differentially expressed genes (DEGs).A)Gene Ontology (GO) enrichment for Biological Processes (BP),(B) GO enrichment for Molecular Functions (MF), and (C) Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment.The bar plots represent significantly enriched GO terms and KEGG pathways, with bar lengths corresponding to the number of genes (Count) associated with each category. Colors indicate the adjusted p-value (p.adjust), with darker colors representing more significant enrichment.

3.4 Protein-Protein Interaction and Identification of Hub genes:

The STRING-based PPI network (295 nodes, 1008 edges) identified CDC45, BIRC5, AURKA, TPX2, TRIP13, MYBL2, MCM4, ASPM, CDC6, and KIF4A as top hub genes (Fig.6).

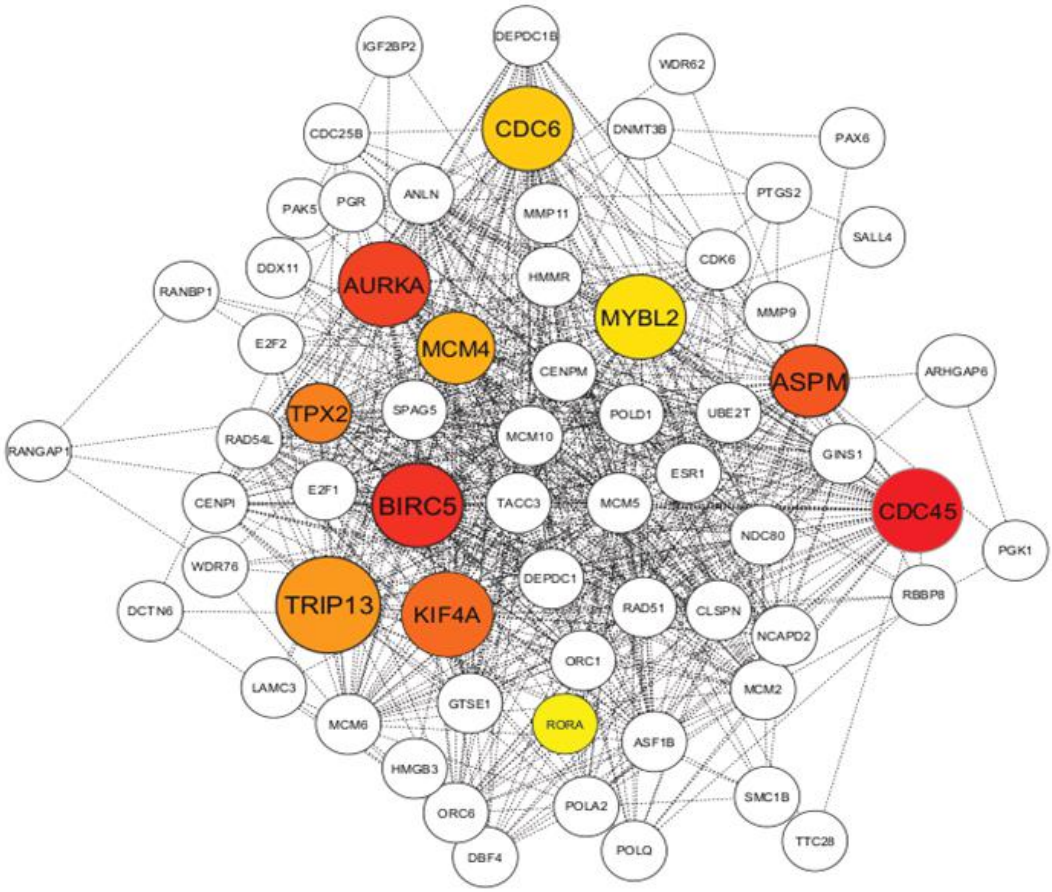


Fig. 6. Protein-Protein Interaction network of identified hub genes. Each node represents a gene/protein and edges represent interactions between them, Node color intensity indicates the degree of connectivity (red = highest degree, orange = intermediate, yellow = lower) with darker shades representing connectivity.

3.5 Virtual Screening against Targeted Proteins

Docking analysis of **BIRC5** and **AURKA** revealed strong binding pockets. Candidate FDA-approved drug Nebibovol demonstrated favorable hydrogen bonding, hydrophobic contacts, and electrostatic interactions within their active sites, supporting their potential as repurposed inhibitors (Fig. 7).

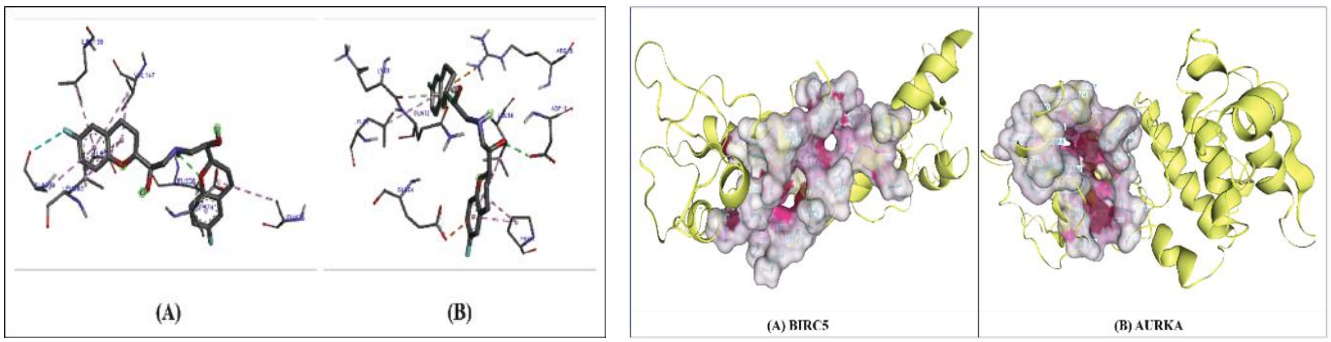


Fig. 7. Binding Pockets of BIRC5 (Survivin) and AURKA (Aurora Kinase B) are visualized using surface representation. The protein backbone is shown in yellow ribbon representation. Molecular Surfaces highlight the potential ligand binding cavities in grey. Key amino acid residues forming the binding site are labeled in cyan. Hydrophobic and Polar regions within the binding pocket are indicated by pink and light coloring shading respectively indicating the physiochemical environment important for ligand interaction.

4. Discussion

Triple Negative breast cancer is defined by the lack of three receptors: Estrogen Receptor (ER-), Progesterone Receptor (PR-), and overexpression of Human Epidermal Growth Factor Receptor (HER2-) (11). This makes it ineffective to use Hormonal Therapy or HER-2 targeted therapy, which are successful in other breast cancer subtypes [12,13]. While current standards of care include chemotherapy, immunotherapy, and PARP inhibitors, their efficacy is often limited by intrinsic or acquired resistance, systemic toxicity, and the profound heterogeneity of TNBC [12]. Addressing the pressing need for novel and innovative therapeutic strategies against TNBC, we used a comprehensive RNA-seq approach on matched TNBC tumor and normal adjacent tissues to identify key transcriptomic changes. Our results not only deepen understanding of TNBC biology but also point toward actionable strategies, highlighting drug repurposing opportunities against critical hub genes such as BIRC5 and AURKA.

The differential expression analysis revealed over 2300 genes with significant dysregulation. Upregulated genes such as BIRC5, CDC20, XRCC2, and STIL highlight the dominance of mitotic control, chromosomal segregation, and DNA damage repair in driving uncontrolled proliferation. BIRC5 (survivin) is a well-known breast cancer proliferation marker, and its high expression correlates with poor survival [14]. CDC20 overexpression has been associated with tumor aggressiveness, and several mitotic inhibitors (e.g., Apcin, Aurora kinase inhibitor VX-680) have been shown to block TNBC proliferation [15]. Elevated XRCC2 expression, which participates in homologous recombination repair of DNA double-strand breaks, may predict poor prognosis with PARP inhibitor therapy, thereby implying the need for alternative therapeutic strategies [16,17]. In TNBC cell lines, STIL overexpression drives proliferation and confers cisplatin resistance, whereas STIL knockdown sensitizes cells to DNA-damaging therapy [18–20]. H2BC6-AS1, a long noncoding RNA antisense to a histone gene, shows differential expression in TNBC and may represent a novel biomarker. Further studies are needed to determine whether H2BC6-AS1 modulates histone expression or contributes to oncogenic progression in TNBC.

In contrast, several tumor-suppressive and immune-related genes were downregulated in TNBC. EGR3 and SOCS2, which are generally associated with favorable outcomes in ER-positive breast cancers, showed reduced expression, consistent with the aggressive biology of TNBC [21–23]. Loss of SLC7A2, an arginine transporter required for T-cell activation, may help explain the limited efficacy of immunotherapies in this setting [21–23].

Interestingly, we also identified suppression of NLGN1 and NTRK2, two genes not previously well-characterized in breast cancer. NLGN1 encodes a synaptic adhesion protein, and its aberrant expression has been implicated in tumor-microenvironment interactions and metastatic potential in certain cancers [24] NTRK2, a receptor for brain-derived neurotrophic factor (BDNF), has context-dependent roles, functioning as a driver of proliferation and survival in some tumors, while acting as a differentiation or stress-response factor in others. Their downregulation in TNBC suggests a distinct biology compared with other cancer types and raises the possibility that loss of neurotrophin/adhesion signaling may contribute to the immune-evasive and highly metastatic phenotype of TNBC [24,25].

Our findings further highlight why many patients with TNBC fail to benefit from existing therapies. Underexpression of SLC7A2, an arginine transporter required for effective T-cell responses, suggests that TNBC tumors may derive limited benefit from Immunotherapy [21]. Similarly, overexpression of BIRC5 has been strongly associated with resistance to both chemotherapy and radiotherapy through its potent anti-apoptotic effects [26,27]. In addition, elevated XRCC2, a DNA repair gene, indicates that PARP inhibitors may be less effective in this context due to enhanced homologous recombination proficiency [17]. Collectively, these features underscore the inadequacy of current treatment modalities for such tumors. In contrast, co-targeting BIRC5 and AURKA represents a rational therapeutic approach: both are overexpressed hub proteins that cooperate to maintain mitotic integrity and apoptosis resistance, and their simultaneous inhibition induces mitotic catastrophe while dismantling survival signaling.

Our in-silico study identified nebivolol, a third-generation β_1-adrenergic blocker, as a promising repurposed agent for TNBC, with strong binding to AURKA (−9.0 kcal/mol) and BIRC5 (−10.0 kcal/mol) [28-29].

Both proteins are critical oncogenic drivers: AURKA promotes uncontrolled proliferation and chemoresistance, while BIRC5 blocks apoptosis and correlates with poor survival [30,31]. Their dual inhibition could therefore synergistically suppress tumor growth and overcome resistance. Notably, nebivolol has already shown antitumor efficacy in preclinical models, including inhibition of TNBC cell invasion and migration [28], suppression of oxidative phosphorylation and angiogenesis [29], and induction of apoptosis and cell cycle arrest in melanoma 33, which suggests it may synergize with existing therapies. For example, nebivolol may sensitize TNBC cells to chemotherapy by weakening mitotic checkpoints, improve PARP inhibitor efficacy by counteracting XRCC2-mediated DNA repair, and enhance immunotherapy by modifying the tumor microenvironment. Clinical studies also suggest β-blocker use improves breast cancer outcomes. Our findings extend these observations by providing the first evidence that nebivolol may directly target AURKA and survivin, offering a mechanistic rationale for its repositioning in TNBC. While these findings are promising, they remain computational and require validation through biochemical assays, cellular experiments, and in vivo studies.

While our study provides a comprehensive transcriptomic overview, we acknowledge that the conclusions are tempered by a limited sample size (n = 9 paired tissues), which may affect the broader applicability of these findings. To strengthen the clinical relevance of the proposed biomarkers, future validation in larger, independent cohorts coupled with parallel protein-level assessment will be essential. Furthermore, functional studies are required to definitively establish the oncogenic roles of the candidate genes and to evaluate the anti-tumor efficacy of the suggested repurposed compounds in relevant preclinical models. Expanding this work through multi-omics approaches, such as proteomics, epigenomics, and single-cell sequencing, could also help unravel the full complexity of TNBC heterogeneity and uncover subtype-specific therapeutic vulnerabilities, ultimately guiding more precise treatment strategies.

5. Conclusions

We've found two key proteins, BIRC5 and AURKA, that act as major drivers of triple-negative breast cancer (TNBC). Our research suggests that an existing heart medication, nebivolol, could potentially be repurposed to treat this aggressive cancer because it shows a strong ability to block both targets. While this is a promising new strategy, it still needs to be tested in labs and clinical trials to see if it works in patients.

Authors' Contribution

S.S. (Sunbin Samin) conceived the idea, designed and performed the experiments, analyzed the results, and drafted the manuscript. M.H.U. (Mahima Haque Utsha) performed the experiments, contributed to data analysis, assisted in drafting the manuscript, and reviewed and edited the final version. Both authors have read and approved the manuscript.

Declaration of Competing interest

The authors declare there are no competing interests

Data Availability

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

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