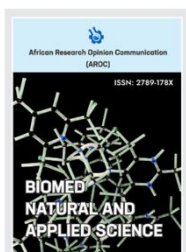


RESEARCH ARTICLE

In Silico Analysis of RNA-Seq Data Identifies IORT-Induced Downregulation of Neuroactive Signaling and Glycosylation Pathways in Breast Cancer

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ABSTRACT

Background: Intraoperative radiation therapy (IORT) delivers a single, high-dose radiation dose to the tumor bed during breast-conserving surgery. While clinically effective, its molecular impact remains unclear. This study aimed to characterize gene expression changes induced by IORT in hormone receptor-positive, HER2-negative breast cancer. **Methods:** RNA-seq data from GSE253650, including samples from patients with and without IORT (n = 11 per group), were analyzed using GEO2R. Differentially expressed genes were identified (adjusted p < 0.05, |log2FC| ≥ 1). Downregulated genes were evaluated using GO and KEGG enrichment via cluster Profiler in R. **Results:** We identified 1,662 differentially expressed genes, including 787 downregulated in IORT-treated tissues. Enrichment analyses revealed suppression of neuroactive ligand-receptor signaling, ion channel activity, glycosylation, and RNA processing. Affected GO terms included sialylation, synaptic membrane organization, and spliceosomal complex components. These molecular changes align with histologic and immune features observed in IORT-treated samples. **Conclusion:** IORT induces transcriptomic suppression of pathways critical for signaling and RNA regulation. These changes may promote a less permissive and more immunogenic tumor microenvironment, offering insight into IORT's therapeutic mechanisms.

Keywords: Intraoperative radiation therapy; Breast cancer; Transcriptomics; Gene expression profiling; Tumor microenvironment

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1.0 Introduction

Cancer, diabetes, and cardiovascular diseases are leading global health burdens, responsible for millions of deaths annually. Current treatments include chemotherapy, insulin therapy, and cardiovascular drugs, but their limitations have driven interest in natural products such as flavonoids and polyphenols, which offer anti-inflammatory and antioxidant effects [1-3]. A common thread in these diseases is oxidative stress—an imbalance between reactive oxygen species and antioxidant defenses—which contributes to cell damage, inflammation, and disease progression. Natural antioxidants [4], by restoring redox balance, may enhance conventional therapies and improve clinical outcomes. Breast-conserving surgery (BCS), followed by adjuvant radiation therapy, is a well-established standard of care for patients with early-stage breast cancer [5].

This approach offers oncologic control equivalent to mastectomy while preserving breast tissue and minimizing surgical morbidity [6]. In recent years, intraoperative radiation therapy (IORT) has emerged as a promising alternative or adjunct to traditional external beam radiation therapy (EBRT) [7]. IORT delivers a single, high-dose fraction of ionizing radiation directly to the tumor bed immediately after tumor excision, during surgery. This targeted

approach limits radiation exposure to surrounding healthy tissue and enables the completion of radiotherapy in a single session, thereby improving patient convenience, compliance, and quality of life [8].

Despite its clinical advantages, the biological and molecular consequences of IORT remain incompletely characterized. Unlike fractionated EBRT, which gradually induces DNA damage and tumor cell death over weeks [9], IORT combines the biological effects of high-dose radiation with the mechanical and inflammatory stress of surgical resection in a single acute event.

This simultaneous exposure to surgical trauma and radiation may trigger unique tissue responses, particularly within the irradiated tumor bed, that are not observed with standard radiation delivery. Understanding these responses is critical for optimizing treatment efficacy and identifying biomarkers that predict benefit or resistance to IORT [10].

Several studies have described the histological effects of IORT, including localized fibrosis, cellular atypia, and immune infiltration [11]. However, comprehensive transcriptomic profiling of irradiated tissue following IORT has been limited. Moreover, it remains unclear whether IORT induces specific gene expression programs that mediate tumor control, immune activation, or tissue remodeling. Prior histopathological reports have identified features such as squamous metaplasia and squamous metaplasia with atypia (SMwA) in IORT-treated specimens, suggesting that radiation can induce notable morphological changes within the tumor-adjacent epithelium [12]. Whether these changes reflect a protective response, a regenerative phenomenon, or a precursor to secondary pathology remains a subject of investigation.

In this study, we aimed to systematically characterize the transcriptomic landscape of breast tissues exposed to IORT using RNA-sequencing data from the GSE253650 dataset [12]. This dataset includes re-excision specimens from hormone receptor-positive/HER2-negative breast cancer patients who either received or did not receive IORT during initial surgery. By comparing gene expression profiles between IORT and non-IORT cohorts across histologically normal and metaplastic regions, we sought to identify radiation-induced molecular signatures, with a particular focus on pathways involved in immune modulation, apoptosis, epithelial differentiation, and tissue remodeling.

Furthermore, we performed functional enrichment analyses to uncover the biological processes and signaling networks perturbed by radiation. These findings provide new insights into the molecular impact of IORT on the tumor microenvironment and may inform the development of combination strategies that harness or enhance radiation-induced effects in early-stage breast cancer.

2.0 Methods

2.1 Data Source and Study Design

Transcriptomic data were obtained from the publicly available Gene Expression Omnibus (GEO) database under accession number GSE253650 [12]. This dataset comprises high-throughput RNA-sequencing (RNA-seq) profiles derived from re-excision breast tissue specimens of patients with hormone receptor-positive (HR+)/HER2-negative breast cancer. Patients were divided into two groups based on intraoperative radiation therapy (IORT) exposure: those treated with IORT ($n = 11$) and those who underwent breast-conserving surgery without IORT ($n = 11$). The tissue samples analyzed included histologically normal regions, as well as areas of squamous metaplasia (SM) and squamous metaplasia with atypia (SMwA), enabling comprehensive comparison of the radiation-induced molecular landscape.

2.2 Differential Expression Analysis via GEO2R

Differential gene expression analysis between IORT-treated and untreated samples was performed using GEO2R, an interactive web-based tool provided by the NCBI GEO portal. GEO2R utilizes the limma (Linear Models for Microarray Data) package within the R programming environment (Bioconductor) to compare expression profiles between user-defined experimental groups [13]. For this analysis, the IORT and non-IORT sample groups were explicitly defined using the sample annotation table. Log₂-transformed normalized expression values were used for statistical comparison.

Genes were filtered and ranked based on adjusted p-values (Benjamini-Hochberg method) to correct for multiple hypothesis testing. A gene was considered differentially expressed if it met the criteria of adjusted p-value < 0.05 and absolute log₂ fold change ≥ 1 . GEO2R automatically computes mean expression levels, fold changes, raw and adjusted p-values, and signal variability across samples.

2.3 Visualization of Differential Expression

To visually assess the differential expression landscape, the GEO2R output was exported and plotted using R (version 4.3.0). A volcano plot was generated to display the distribution of log₂ fold changes against the negative log₁₀ of adjusted p-values, enabling the clear identification of significantly upregulated and downregulated genes in response to intraoperative radiation therapy. Additionally, an MA plot was constructed to depict the log₂ fold change as a function of the average log-transformed expression level, providing insight into the expression variability across genes with different abundance levels.

To ensure data quality and normalization consistency, boxplots of normalized expression counts were plotted for all samples across the IORT and non-IORT groups, demonstrating comparable distributions and minimal batch effects. Lastly, a histogram of adjusted p-values was created to evaluate the global statistical significance distribution, revealing an overrepresentation of low p-values indicative of strong biological signal within the dataset.

2.4 Gene Ontology and Pathway Enrichment Analysis

Genes significantly downregulated in the IORT-treated group were further subjected to functional enrichment analysis. Enrichment of Gene Ontology (GO) terms—including Biological Process (BP), Molecular Function (MF), and Cellular Component (CC)—as well as Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways, was performed using the clusterProfiler package (v4.6.2) in R.

Gene symbols were converted to Entrez Gene IDs using the org.Hs.eg.db annotation database. Over-representation analysis was conducted using the enrichGO() and enrichKEGG() functions with Benjamini–Hochberg adjustment, and significance thresholds were set at adjusted p-value < 0.05. Results were visualized as dot plots using custom ggplot2-based scripts to display gene count, enrichment significance, and p-value gradients.

2.5 Data Availability

The GSE253650 dataset is publicly accessible via the NCBI GEO portal (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE253650>). Raw count files and normalized expression matrices were obtained from the GEO2R interface or directly from the supplementary files.

3.0 Results

3.1 Differential Gene Expression in Intraoperative Radiation Therapy in Breast Cancer

To investigate the molecular consequences of intraoperative radiation therapy (IORT) in hormone receptor-positive (HR+), HER2-negative breast cancer, we analyzed RNA-sequencing data from the GSE253650 dataset. This study involved matched re-excision specimens from patients treated with IORT (n = 11) and those who underwent breast-conserving surgery without radiation (n = 11). The samples comprised normal breast tissue and regions showing squamous metaplasia (SM) or squamous metaplasia with atypia (SMwA), allowing for the capture of cellular and histological alterations induced by radiation.

Differential gene expression analysis revealed substantial transcriptomic changes associated with IORT exposure. A total of 1,662 genes were significantly dysregulated, including 875 upregulated and 787 downregulated genes (adjusted p-value < 0.05). Volcano plot visualization highlighted a pronounced bifurcation in gene regulation, with numerous genes displaying log₂ fold changes greater than ± 2 , underscoring the robust impact of radiation on gene expression (Fig. 1a). An MA plot further confirmed that the expression shifts spanned a wide range of mean expression values, suggesting that both lowly and highly expressed transcripts were affected (Fig. 1b).

3.2 Sample Quality and Data Distribution

To ensure the technical robustness of the differential expression analysis, we examined the distribution of normalized counts across all samples. Log-transformed count distributions (Fig. 1c) revealed uniformity in expression profiles between IORT and non-IORT groups, suggesting minimal batch effects and effective normalization.

Additionally, the histogram of adjusted p-values (Fig. 1d) displayed a strong bias toward significance, with an overrepresentation of low p-values consistent with true biological signal rather than statistical noise.

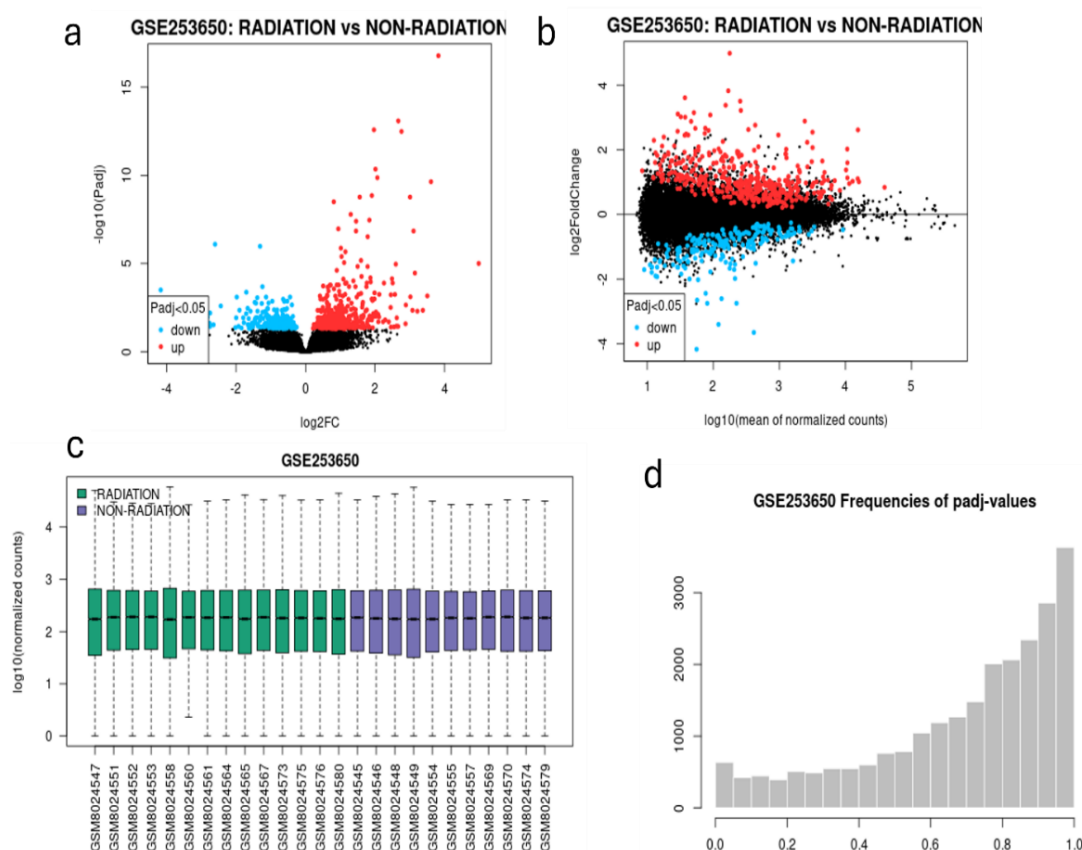


Figure 1. Transcriptome-wide differential expression in breast tissue following intraoperative radiation therapy (IORT). (a) Volcano plot displaying $\log_2$ fold change versus $-\log_{10}$ adjusted p-value for all genes analyzed. Red points indicate significantly upregulated genes and blue points denote significantly downregulated genes ($\text{adjusted } p\text{-value} < 0.05$, $|\log_2FC| \geq 1$). (b) MA plot showing $\log_2$ fold changes as a function of mean expression, highlighting the widespread transcriptomic shifts induced by IORT. (c) Boxplot of normalized expression counts across all IORT and non-IORT samples, confirming comparable expression distributions and effective normalization. (d) Histogram of adjusted p-values indicating enrichment of low p-values and strong biological signal across the dataset.

3.3 Biological Processes Suppressed by IORT

Gene ontology enrichment analysis of the downregulated gene set revealed selective suppression of biological processes involved in cellular signaling and ionic regulation. GO Biological Process (BP) terms significantly enriched among downregulated genes included *sialylation*, *magnesium ion homeostasis*, *positive regulation of potassium ion transport*, and *regulation of presynaptic membrane potential* (Figure 2). These findings indicate that radiation therapy impairs transcriptional programs crucial for maintaining ionic gradients, signaling fidelity, and possibly intercellular communication within the tumor bed.

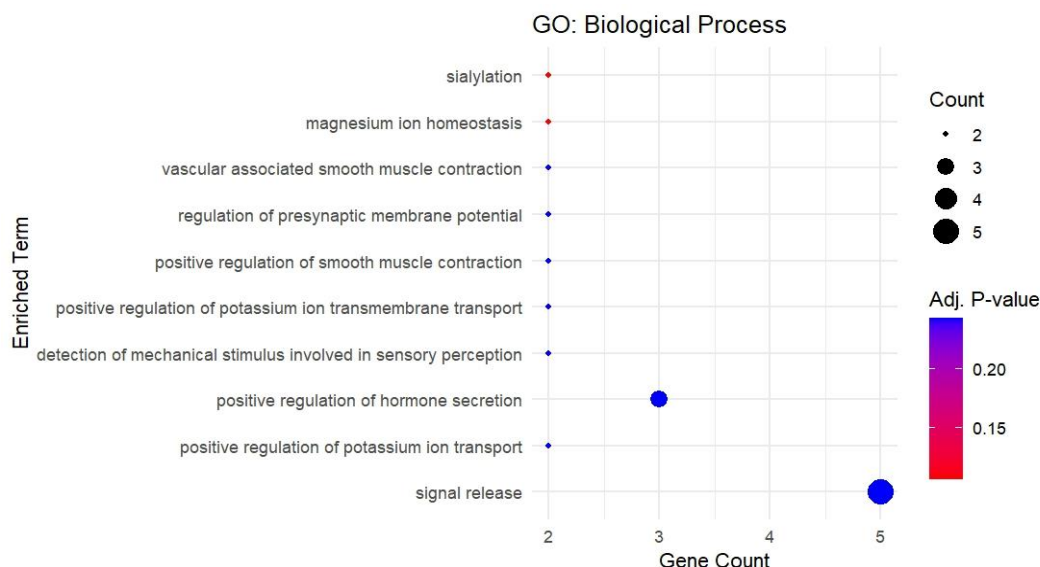


Figure 2. GO Biological Process enrichment of downregulated genes in IORT-treated breast tissue. Top enriched biological processes include sialylation, magnesium ion homeostasis, regulation of presynaptic membrane potential, and potassium ion transport. Dot plot displays gene counts, significance (adjusted p-values), and enrichment magnitude based on clusterProfiler output.

3.4 Suppression of Receptor-Mediated Signaling Functions

At the molecular function (MF) level, the downregulated gene set was enriched for terms such as *neuropeptide receptor activity*, *adrenergic receptor activity*, *sialyltransferase activity*, and *voltage-gated monoatomic ion channel activity* (Figure 3). This pattern suggests a coordinated downregulation of genes encoding membrane-bound receptors and enzymes involved in neuromodulatory and hormonal signaling. The suppression of these functions may contribute to reduced tumor cell adaptability and disrupted tumor-stromal interactions in irradiated tissues.

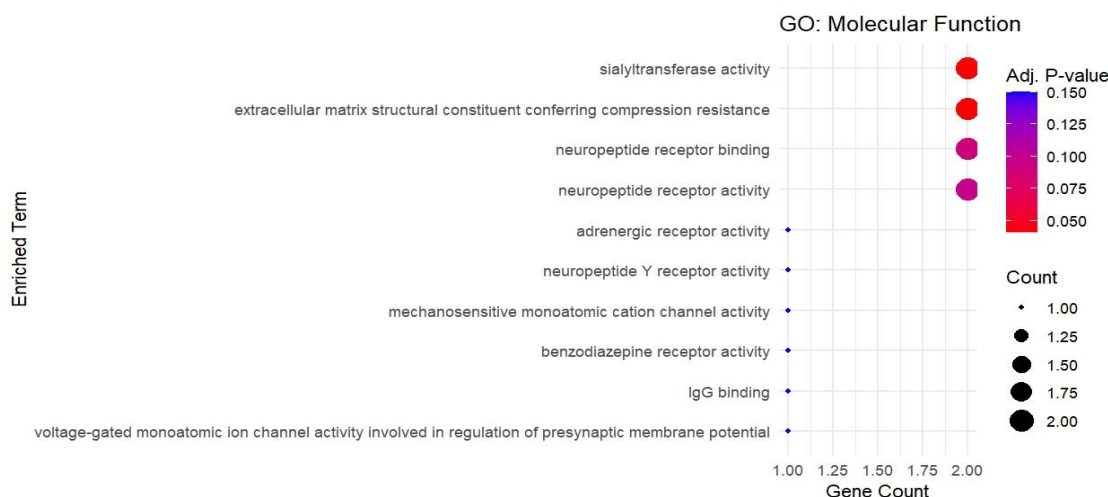


Figure 3. GO Molecular Function enrichment of downregulated genes following IORT. Functional categories such as neuropeptide receptor activity, sialyltransferase activity, adrenergic receptor signaling, and ion channel activity were significantly suppressed. Dot plot illustrates the most enriched molecular functions, ranked by adjusted p-value and gene set size.

3.5 Radiation-Associated Loss of RNA and Synaptic Machinery

Enrichment of GO Cellular Component (CC) terms further highlighted the suppression of synapse-associated structures and RNA processing machinery. Notably, downregulated genes were significantly localized to components such as the *GABA-ergic synapse*, *synaptic membrane*, *Golgi lumen*, and the *spliceosomal snRNP complex* (Figure 4). These results suggest that IORT diminishes the transcriptional support for synaptic connectivity and post-transcriptional regulation, potentially impairing protein synthesis and trafficking in both tumor and surrounding stromal cells.

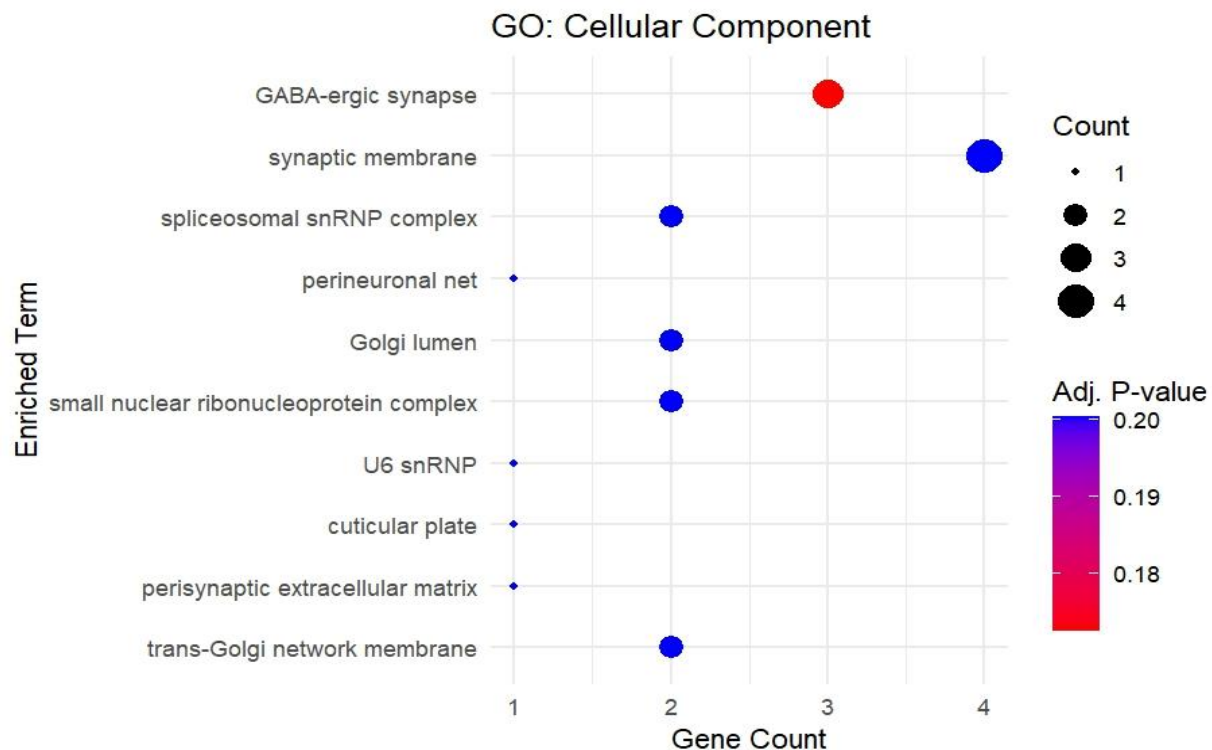


Figure 4. GO Cellular Component enrichment in response to intraoperative radiation. Downregulated genes were localized to key cellular compartments including the *GABA-ergic synapse*, *synaptic membrane*, *Golgi lumen*, and *spliceosomal snRNP complexes*. Visualization highlights structural components impacted by radiation-induced transcriptional suppression.

3.6 Disruption of Signaling and Structural Pathways by IORT

KEGG pathway analysis echoed the trends observed in GO enrichment, with downregulated genes mapping to critical signaling and structural pathways. Among the top enriched pathways were *neuroactive ligand-receptor interaction*, *cAMP signaling*, *spliceosome*, *cytoskeleton regulation in muscle cells*, and various glycosylation pathways including *N-glycan biosynthesis*. (Figure 5).

These findings reinforce the hypothesis that IORT elicits a broad suppressive effect on membrane signaling, transcriptional flexibility, and post-translational modification systems, all of which are critical for maintaining tumor cell plasticity and microenvironmental crosstalk.

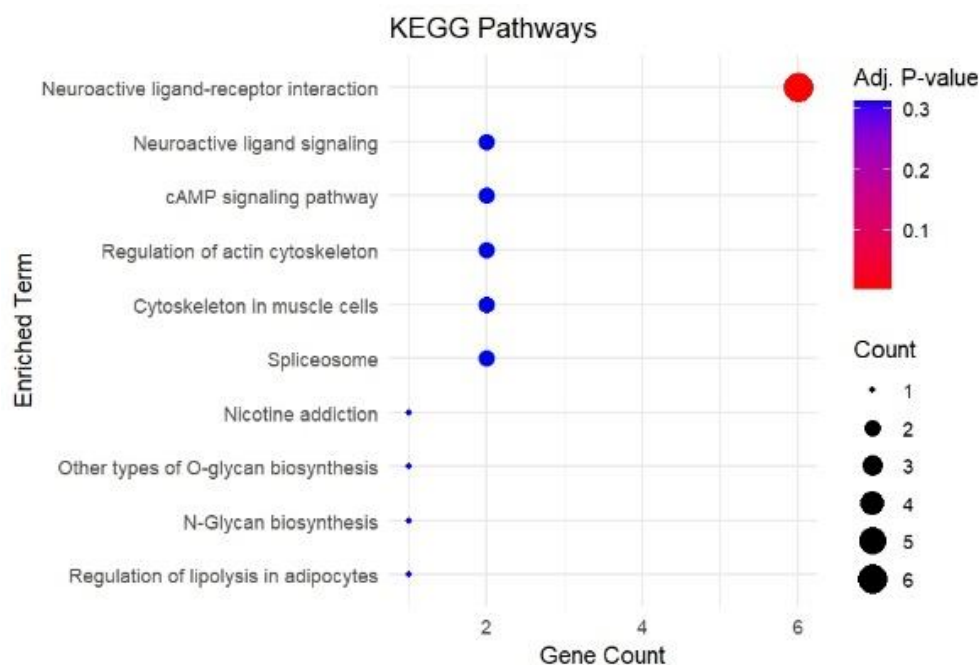


Figure 5. KEGG pathway analysis of downregulated genes in IORT-exposed samples. Radiation suppressed multiple signaling and biosynthetic pathways including neuroactive ligand-receptor interaction, cAMP signaling, spliceosome assembly, and glycosylation pathways. Dot plot reflects pathway significance and gene involvement based on KEGG enrichment.

4.0 Discussion

In this study, we investigated the molecular effects of intraoperative radiation therapy (IORT) in hormone receptor-positive, HER2-negative breast cancer using transcriptomic data from GSE253650. IORT is increasingly used as a targeted, single-dose radiation strategy that minimizes damage to surrounding healthy tissue while maintaining oncologic control [10]. Despite its clinical utility, the biological mechanisms underlying its efficacy remain poorly defined.

Our analysis revealed significant transcriptomic alterations in IORT-treated tissues, with 1,662 genes differentially expressed and nearly equal numbers of upregulated and downregulated genes. Enrichment analysis of downregulated genes indicated suppression of pathways involved in neuroactive ligand-receptor signaling, ion channel function, glycan biosynthesis, and RNA processing. Notably, genes related to neuropeptide and adrenergic receptor activity, voltage-gated ion channels, and sialylation were significantly suppressed. These pathways are increasingly recognized as critical modulators of tumor growth, cellular communication, and immune evasion in solid tumors, including breast cancer [14-19].

The observed downregulation of spliceosomal and glycosylation-related genes suggests that IORT may impair the tumor's ability to maintain transcriptomic and proteomic plasticity—both of which are essential for therapeutic resistance and progression [20]. These findings align with histological evidence of radiation-induced epithelial changes, such as squamous metaplasia with atypia (SMwA), previously described in the same cohort [7].

In parallel with recent reports showing increased immune cell infiltration in IORT-treated tissues [12], our data support the hypothesis that IORT may reprogram the tumor microenvironment to promote immunogenicity. The suppression of glycan processing, in particular, may enhance tumor antigen presentation and reduce immune masking [21].

In conclusion, although breast cancer is the most prevalent women cancer, due to exposure to many chemicals as well as genetic factors [21-22]. IORT induces broad transcriptional suppression across multiple oncogenic and immunomodulatory pathways. These findings shed light on the molecular underpinnings of IORT's therapeutic efficacy and suggest new opportunities to exploit these effects through rational combination therapies or biomarker-guided patient selection.

5.0 Conclusion

This study demonstrates that intraoperative radiation therapy (IORT) induces broad transcriptomic reprogramming in breast cancer tissue, characterized by the downregulation of genes involved in receptor signaling, ion transport, glycosylation, and RNA processing. These molecular changes may underlie the histological and immunological effects observed in IORT-treated tumors and suggest a shift toward a less permissive and more immunogenic tumor microenvironment. Our findings provide new insight into the biological mechanisms of IORT and lay the groundwork for future investigations into combinatorial strategies that harness these molecular effects to improve therapeutic outcomes in early-stage breast cancer.

Conflict of Interest: The author declares no conflict of interest.

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