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Comparison of the Efficacy of Photodynamic Therapy Versus Cisplatin Application

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Abstract

Introduction: Photodynamic therapy (PDT) is a photochemical treatment that involves the use of light and photosensitizer. This method is applied as a therapeutic approach against several types of cancer. The main aim of this study is to compare the efficacy of PDT with that of cisplatin (a well-known chemotherapy agent) through protein-protein interaction (PPI) network analysis.

Methods: Gene expression profiles of human melanoma A375 cells from the Gene Expression Omnibus (GEO) were selected for analysis via directed PPI network analysis. The significant differentially expressed genes (DEGs) were identified and assessed based on co-expression interactions. The critical DEGs were introduced by considering out-degree and in-degree values.

Results: Two directed PPI networks for upregulated and downregulated DEGs were constructed. TP53 was identified as a critical upregulated gene in response to cisplatin in comparison with PDT. EGFR, PPARG, MMP9, PTGS2, FOXO1, and RUNX2 were highlighted as the crucial downregulated genes due to the effect of cisplatin on the gene expression of the treated cells.

Conclusion: Cisplatin directly targets key cellular functions such as cell growth, differentiation, migration, and invasion. It seems that the combination of cisplatin and PDT is a suitable method for treating cancers because cisplatin targets the key genes responsible for cancer development, while PDT intensifies the effect of cisplatin and reduces its side effects.

Keywords: Photodynamic therapy; Cisplatin; Protein-protein interaction; Differentially expressed genes; Cancer treatment.

Introduction

Photodynamic therapy (PDT) is known as a treatment based on photochemical administration, which includes the application of light and photosensitizers. It is an efficient method with low side effects. This therapeutic option is suggested as a suitable approach in various fields, including cardiology, immunology, urology, pneumology, dentistry, ophthalmology, oncology, and dermatology.[1] Another agent used in chemotherapy against cancer is cisplatin. It has been widely used in the chemotherapy of various types of cancer, such as carcinomas and sarcomas. There is documentation regarding its effective therapeutic properties, particularly its ability to promote apoptosis. Despite its effectiveness, there is evidence of harmful side effects that have limited its application for prolonged use.[2] The combination of cisplatin and PDT is suggested to enhance the efficacy of the therapeutic protocol while attenuating the associated side effects.[3]

A gene expression profile study is an appropriate method for evaluating the efficacy and side effects of a therapeutic

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approach. Experts have studied the effectiveness of PDT against various diseases through gene expression profile analysis.[4,5] In such studies, the targeted genes are identified and analyzed using bioinformatics tools to highlight the critical individuals. One method for studying gene expression profiles is protein-protein interaction (PPI) network analysis. The genes, as nodes, are connected to their neighbors based on their interactions. Since each gene interacts with surrounding genes based on its function and properties, it plays a specific role in the network.[6,7] Wu et al evaluated gene expression changes in cisplatin-resistance oral squamous cell carcinomas using PPI network analysis. They identified NOTCH1, JUN, CTNNB1, CEBPA, and ETS1 as critical genes associated with cisplatin resistance in drug-resistant oral squamous cell carcinoma cell lines.[8] Dai et al reported the application of PDT for the treatment of systemic lupus erythematosus via PPI network analysis. The final targets of PDT in systemic lupus erythematosus were identified as AKT1, TNF, ALB, CASP3, EGFR, STAT3, HSP90AA1, SRC, HRAS, and MMP9.[9] Directed PPI networks include nodes that are linked through different interactions such as activation, co-expression, or inhibition. This type of PPI network is an appropriate tool to screen for crucial genes among a set of individuals.[10] In the present study, the gene expression profiles of human melanoma A375 cells in the presence of cisplatin and after the administration of PDT were downloaded from Gene Expression Omnibus (GEO) and analyzed via directed PPI network analysis, considering co-expression interactions, to explore the different molecular mechanisms of both PDT and cisplatin as anticancer agents.

Methods

Data Collection

To assess the antitumor properties of PDT, we searched for data on cisplatin and PDT in the GEO database. Data regarding the effect of cisplatin and PDT on gene expression in human melanoma A375 cells, recorded as GSE163377, were analyzed (https://www.ncbi.nlm.nih.gov/geo/geo2r/?acc=GSE163377). As described in a related article,[11] the cells were treated with 50 µM Cisplatin (CDDP, Sigma) (one of the common concentrations of Cisplatin in cellular apoptosis investigation), and for the hypericin-based PDT (Hyp-PDT) conditions, the cells were incubated for 16 hours with 150 nM hypericin (Enzo Life Sciences) in a full medium, followed by the removal of hypericin and irradiation with a fluence of 2.70 J/cm^2. The library strategy, source, selection, and instrument model were RNA-Seq, transcriptomic, cDNA, and Illumina NexSeq 500, respectively (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSM4977810).

Pre-evaluation Analysis

The gene expression profiles of treated A375 cells treated with cisplatin after 20 hours were compared with those exposed to PDT for the same duration using the GEO2R program (A statistical program associated with the GEO database). Sample separation was assessed via Uniform Manifold Approximation and Projection (UMAP) analysis. A volcano plot was generated to show the significantly upregulated and downregulated differentially expressed genes (DEGs). The number of significant DEGs compared to the total dysregulated genes was illustrated using a Venn diagram. The significant DEGs were identified based on an adjusted P value of <0.05. Since the name and properties of the uncharacterized genes were not identified, these DEGs were excluded from further investigation. The significant DEGs were filtered based on a fold change of >2. No additional filtration was administrated.

Directed Protein-Protein Interaction Analysis

The upregulated and downregulated selected DEGs were assessed using directed PPI network analysis through the CluePedia plugin of Cytoscape software. The nodes were connected based on co-expression interactions, and the main connected components of the networks were evaluated to identify the critical genes. The main connected component of the downregulated directed PPI network was analyzed using CluePedia to identify the actor genes and the most highly regulated individuals. The analyzed sub-networks were visualized and laid out based on out-degree and in-degree values.

Statistical Analysis

The significant DEGs were identified based on the adjusted p-value of less than 0.05.

Results

UMAP analysis revealed that the treated cells with cisplatin are completely separated from the cells exposed to PDT (see Figure 1). This finding indicates a different mechanism of

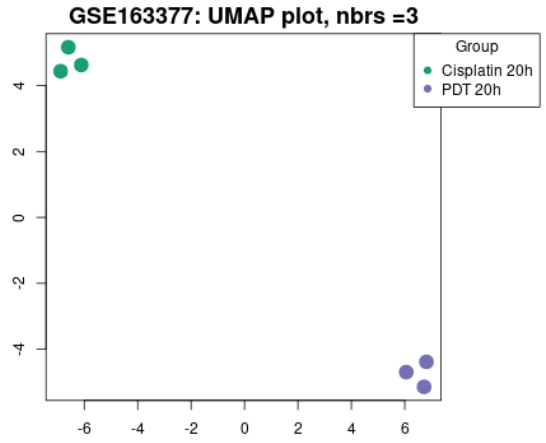

Figure 1. Uniform Manifold Approximation and Projection Plot Related to the Comparison of the Gene Expression Profiles of Treated Cells With Cisplatin Versus the Exposed Samples to PDT

action for cisplatin compared to PDT against tumors. The dysregulated genes and significant DEGs were visualized via the volcano plot. As depicted in Figure 2, there are many significant DEGs that discriminate between the two sets of studied gene expression profiles. A total of 9483 significant DEGs and 16 111 total dysregulated genes are presented in Figure 3. After filtering for significant DEGs, we selected 4028 genes, including 1859 upregulated DEGs and 2169 downregulated DEGs, for further analysis.

The upregulated selected DEGs were included in a directed PPI network. The main connected component of the network is presented in Figure 4. As depicted in Figure 4, TP53 serves as the central node of the constructed network. For more detail, TP53 and its first neighbors are shown in Figure 5. The first neighbors of TP53 include (1) 25 positively co-expressed genes, (2) four negatively co-expressed genes, (3) nine genes that are either positively or negatively co-expressed, (4) nine genes that downregulate TP53, and finally, (5) six DEGs that either upregulate or downregulate TP53. However, the members of the last group may have a reciprocal regulatory effect with TP53.

Similar to the upregulated DEGs, the downregulated genes were assessed via directed PPI. The main connected component of the analyzed PPI network is shown in Figure 6. While the main connected component of upregulated DEGs had a significant central node (TP53), the main connected component of the downregulated genes had several central genes. Considering the "out-degree" value which refers to the issued directed edges from a node and the "in-degree" parameter which denotes the entered edges into a node, the nodes of the network of downregulated DEGs were visualized (see Figures 7 and 8). As depicted in Figures 7 and 8, EGFR, PPARG, MMP9, HMOx1, and RUNX2 appear as prominent nodes in the network, while PTGS2, FOXO1, RUNX2, MMP9, PTHLH, ZEB1, EGFR, and CXCL8 are highlighted as the most significant DEGs under regulation.

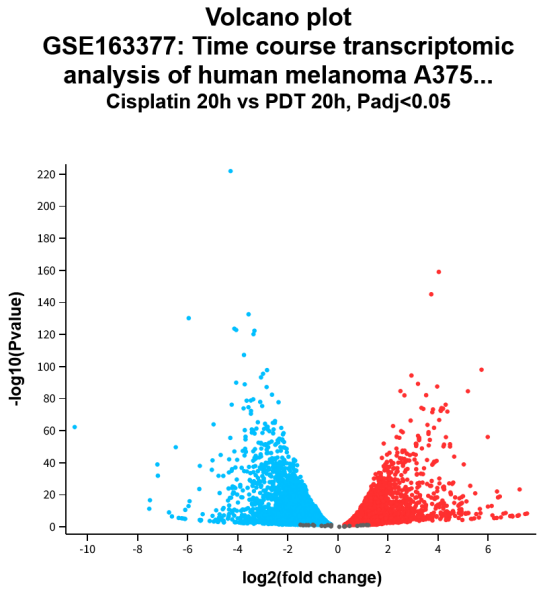

Figure 2. Volcano Plot Presentation of the Significant Up-regulated and Down-regulated DEGs

Discussion

Pre-evaluation analysis revealed significant differences between the antitumor molecular mechanism of cisplatin and PDT. The findings align with the investigation by Javani Jouni et al, which indicates that the combination of cisplatin and PDT is a suitable cancer therapy strategy. According to this report, the combined method is associated with minimal side effects, suggesting a potentially favorable therapeutic index for patients with cancer.[3] They showed that the application of PDT decreases the half maximum inhibitory concentration (IC50) of cisplatin by two-fold, indicating a synergistic interaction that enhances the efficacy of cisplatin while mitigating its toxicity. Significant differences in gene expression changes of the cells under the two conditions (application of cisplatin and PDT), including a statistical dysregulation of 9483 genes (see Figure 3), further support the distinct antitumor properties of each treatment.

As depicted in Figure 4, the upregulation of TP53 by cisplatin, relative to PDT, is a key point associated with the antitumor function of both therapies. The tumor suppressor TP53 is a well-known gene that regulates various cellular processes, such as DNA damage repair, cell cycling/cell senescence, cell death, and metabolic adaptation, all of which collectively help to counteract tumorigenesis.[12] Notably, results indicate that TP53 is inhibited by numerous first neighbor genes (see Figure 5), yet it remains significantly upregulated. The most significant finding in the network of upregulated genes is the upregulation of at least 25 DEGs, positively regulated by TP53 (see Figure 5).

The interplay between TP53 and its network of targets significantly impacts cancer cell behavior. For example, the upregulation of FUCA1, which encodes α-L-fucosidase, correlates with TP53 activity and has implications for glycosylation processes that affect tumor

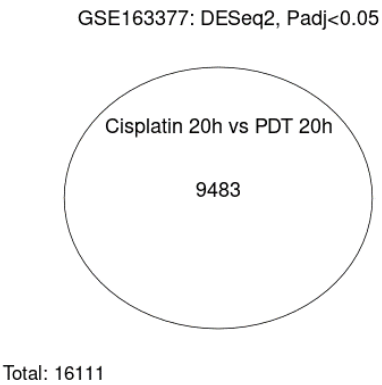

Figure 3. Venn Diagram Including 9483 Significant DEGs Versus 16 111 Dysregulated Genes. The significant DEGs are identified based on an adjusted *P* value < 0.05

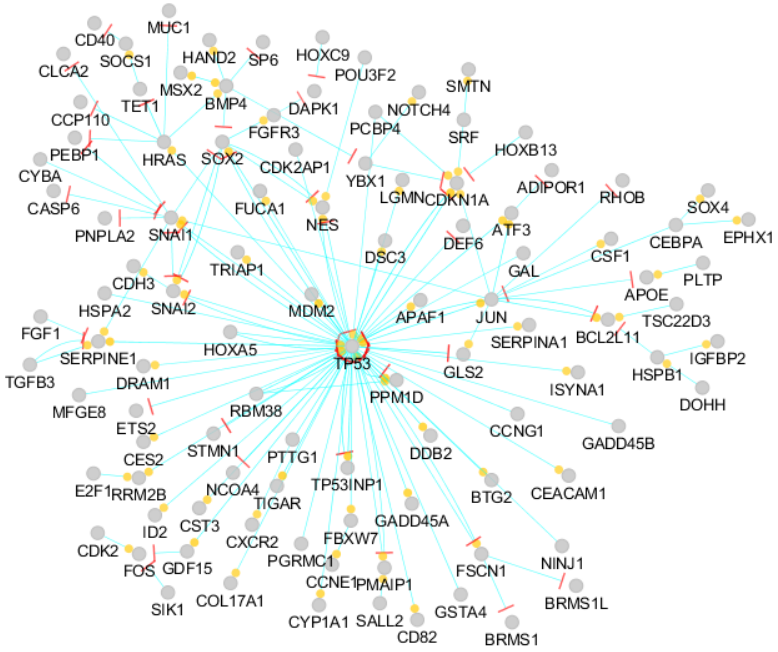

Figure 4. The Main Connected Component of the Directed PPI Network of the Selected Upregulated DEGs. Nodes are connected via co-expression action

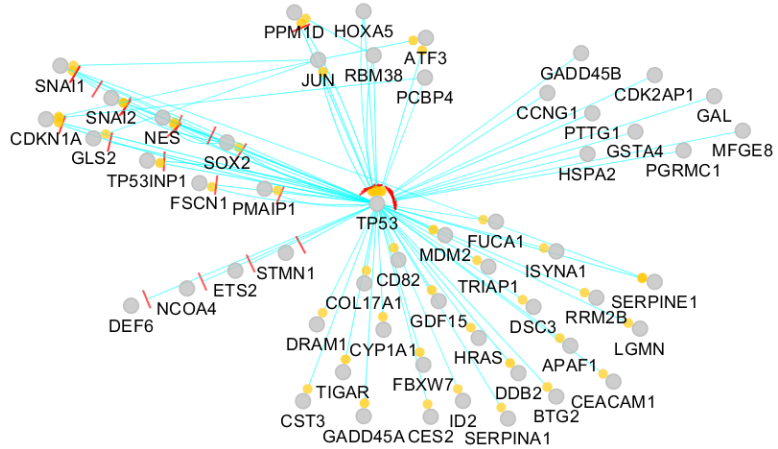

Figure 5. TP53 and its First Neighbors. The positively and negatively co-expressed genes associated with TP53 are pointed by the yellow round and red tips respectively

progression.[13] Similarly, COL17A1, identified as a target of TP53, has been shown to inhibit breast cancer cell migration and invasion, further underscoring the role of TP53 in modulating tumor aggressiveness.[14] Additionally, the relationship between TP53 and CYP1A1 involves regulatory mechanisms that influence the metabolic response to chemotherapy, illustrating the multifaceted role of TP53 in cancer biology.[15,16]

In contrast to the upregulated PPI network, the downregulated PPI network is characterized by several central genes (see Figure 6). As shown in Figure 7, EGFR is highlighted as a prominent player in the downregulated PPI network. The mutation and/or overexpression of EGFR are frequently associated with various human cancers, and its downregulation by cisplatin indicates the agent's effectiveness in disrupting key oncogenic pathways.[17] The potential for therapeutic intervention targeting EGFR is further supported by studies demonstrating that the downregulation of this receptor can enhance the apoptotic response to chemotherapeutic agents.[18]

The second downregulated gene is PPARG. Zaytseva et al published a study on the impact of PPARG downregulation on the suppression of cell growth and the induction of apoptosis in breast cancer cells.[18] Li et al have introduced PPARG as a suitable drug target against breast cancer.[19]

The third gene in the downregulated network is MMP9. Joseph et al published a study on the correlation between the upregulation of MMP9 and shorter patient survival in breast cancer.[20] The downregulation of MMP9, known for its role in promoting metastasis, suggests a

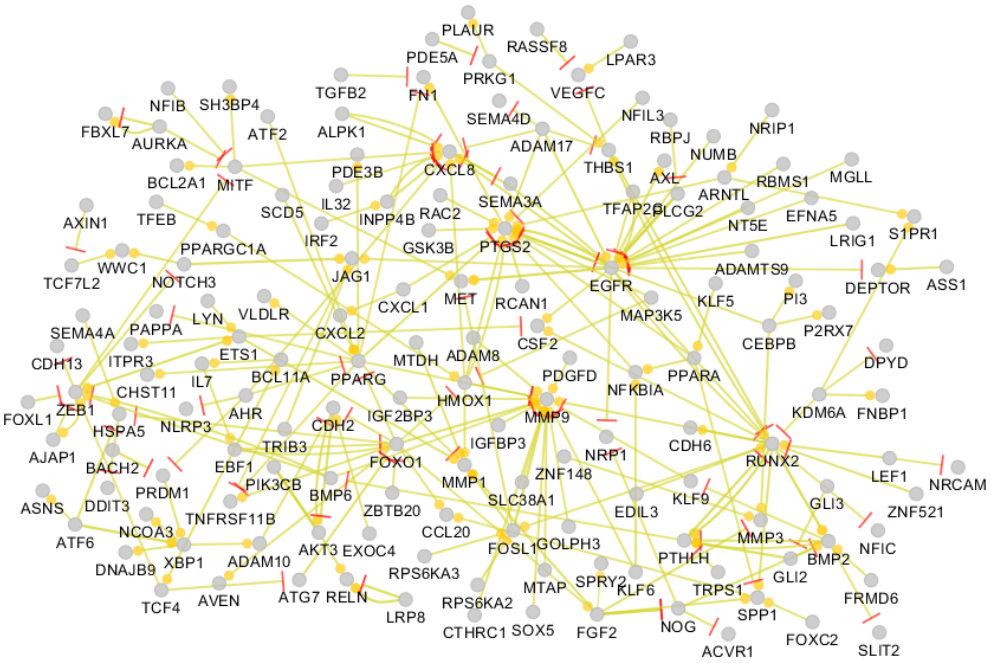

Figure 6. The Main Connected Component of the Directed PPI Network of the Selected Downregulated DEGs. Nodes are connected via co-expression action

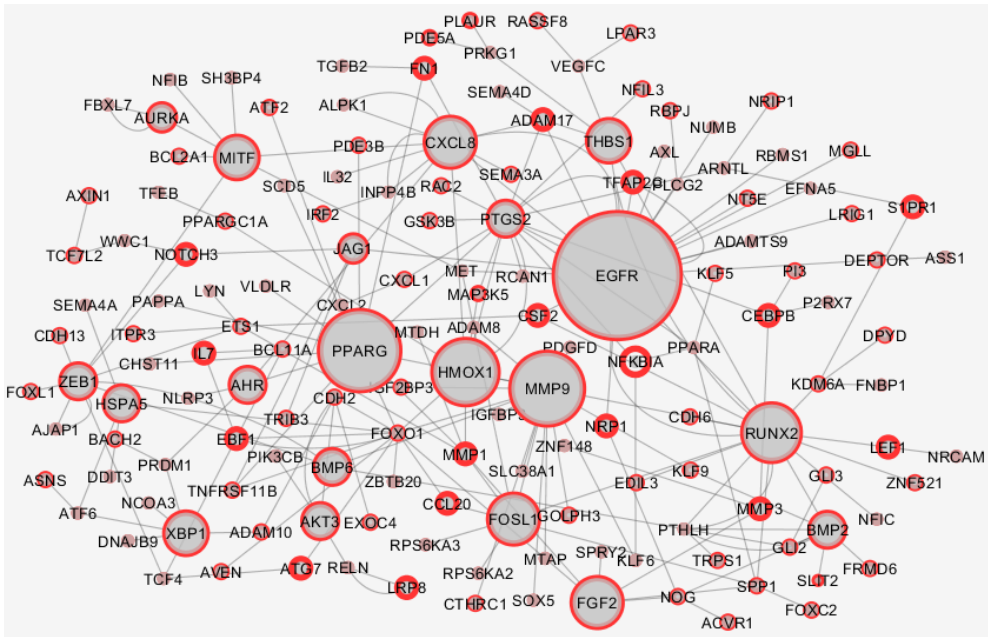

Figure 7. The Main Connected Component of the Directed PPI Network of the Selected Downregulated DEGs. Nodes are connected via co-expression action and layout based on out-degree value

strategic inhibition of invasion pathways by cisplatin, further corroborating its efficacy in controlling tumor progression.[20]

As depicted in Figure 8, PTGS2 is the most controlled gene in a downregulated network. The findings regarding PTGS2 reveal its regulatory role, where RUNX1-induced upregulation is implicated in cell growth, migration, and invasion, linking it to the metastatic potential of tumors.[21] Conversely, the downregulation of RUNX2 by cisplatin may contribute to the observed reduction in angiogenesis and metastasis, as RUNX2 is known to facilitate these processes in various cancers.[22,23] The detailed interactions among the downregulated genes suggest a coordinated response that collectively enhances the antitumor effects of cisplatin.

FOXO1 is the second most significantly downregulated gene. The role of FOXO1 in cancer progression has been intricately linked to its regulatory effects on other key genes.[22] By inhibiting FOXO1 expression, cisplatin may disrupt the pro-tumorigenic signaling pathways that

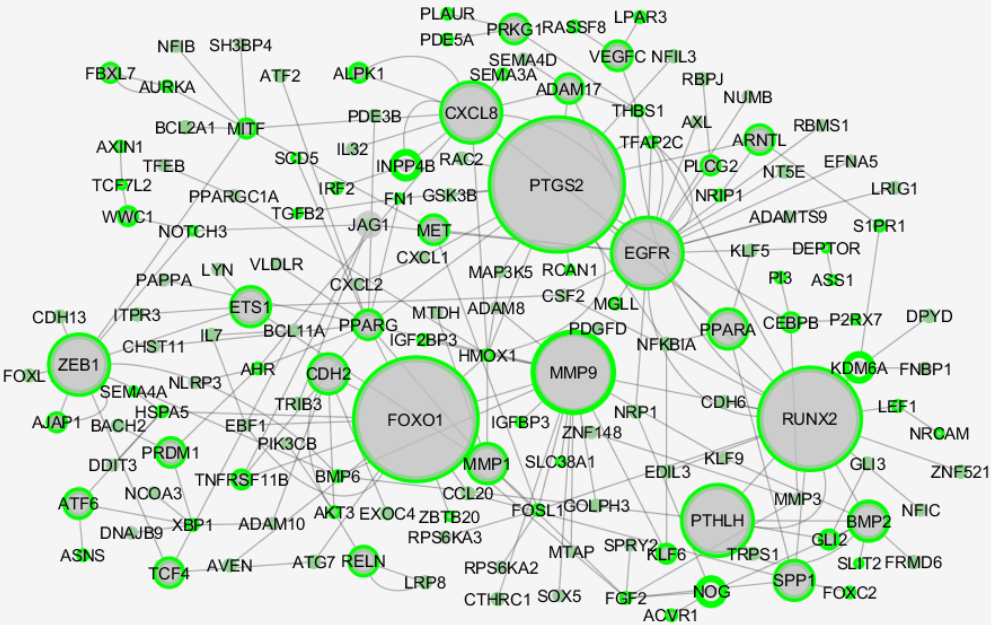

Figure 8. The Main Connected Component of the Directed PPI Network of the Selected Downregulated DEGs. Nodes are connected via co-expression action and layout based on in-degree value

facilitate cancer cell survival and proliferation, thereby contributing to its therapeutic potential.

While this study provides insights into the differential gene expression and network interactions induced by PDT and cisplatin in human melanoma A375 cells, several limitations must be acknowledged. First, the analysis relies on a single cell line, A375, which may not fully represent the diverse biological responses observed in other melanoma cell lines or in primary tumor samples. Additionally, the gene expression data obtained from the GEO may be influenced by batch effects or variations in experimental conditions that are not accounted for in our analysis. The directed PPI networks constructed here provide valuable insights but are inherently limited by the availability and quality of interaction data, which may not capture all relevant interactions. Furthermore, this study primarily focuses on gene expression changes without investigating downstream effects on protein levels or functional validation of the identified genes. Future studies incorporating multiple cell lines, functional assays, and in vivo models will be essential to validate the findings and explore the therapeutic potential of combining PDT and cisplatin in a broader context.

Conclusion

In conclusion, cisplatin controls tumor progression in a different way than PDT. The upregulation of TP53 and the downregulation of EGFR, PPARG, MMP9, PTGS2, FOXO1, and RUNX2 by cisplatin lead to significant alteration in cellular functions such as cell growth, differentiation, and migration and invasion. It can be suggested that the combination of cisplatin and PDT is a suitable method for treating cancer, as cisplatin targets key genes responsible for cancer development. Additionally, PDT seems to act as a complementary agent that intensifies the effect of cisplatin.

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Validation: Masoumeh Farahani.
Visualization: Mitra Rezaei.
Writing–original draft: Babak Arjmand, Fatemeh Daneshimehr.
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Competing Interests

The authors declare that they have no competing interests.

Ethical Approval

This project is approved via IR.SBMU.LASER.REC.1403.010 ethical code.

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