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Different Response Capability To IFN-ATreatment Between Cervical Squamous Carcinoma Cells and Adenocarcinoma Cells

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Keywords:

Cervical Cancer; Interferon Alpha; Bioinformactics; Apoptoasis; Type I Interferon Signaling

1. Abstract

1.1. Objective

This study aimed to compare the difference of interferon alpha (IFN-α) therapeutic effect between cervical squamous cell carcinoma (CSCC) and cervical adenocarcinoma (CA).

1.2. Methods

Data were obtained from TCGA and GEO databases. The differentially expressed genes (DEGs) of mRNAs were screening by Limma package of R software. The functional enrichment analysis was performed using TCGA and GEO databases. The anti-tumor assay in vitro using CCK8, TUNEL and Annexin V-PI apoptosis assays.

1.3. Results

The up-regulated DEGs in CSCC were associated with response to type I interferon, cellular response to type I interferon and type I interferon signaling pathway (all items P<0.05) using GO and KEGG enrichment analysis compared with CA. Furthermore, the GSEA analysis demonstrated that hallmark interferon alpha response (FDR=0.011, P=0.016) is differentially enriched in CSCC compared with CA. In addition, we found that IFN-α inhibited SiHa cells more potently than that of Hela cells in vitro, indicating the higher p-STAT1 levels of tumor cell-intrinsic Type I interferon signaling pathways in SiHa cells.

1.4. Conclusion

Our findings suggest that CSCC was associated with Type I interferon signaling compared with CA. The anti-proliferative ability of IFN-α for CSCC cells is higher than that of CA cells.

2. Introduction

Cervical cancer is the fourth most common female malignant tumor, with an estimated 604,000 new cases and 342,000 deaths worldwide in 2020 [1]. At present, surgery and concurrent chemotherapy and radiation therapy are the main treatment methods for early-stage and locally invasive cervical cancer. Immunotherapy, including anti-PD-L1, anti-PD-1, and anti-CTLA4, has become a promising anti-cancer strategy that offers hope for improved cancer treatment and survival [2-4]. However, the use of these immunotherapy for the treatment of cervical cancer shows no satisfactory results [5]. Thus, we need to further explore the potential tumorigenesis mechanism of cervical cancer, and new drug targets should be developed.Over the past decade, the molecular mechanisms of interferons regulating effective host immunological responses to tumor cells have proved. Type I IFNs has become an effective therapeutic method against multiple malignancies, such as breast cancer, melanoma, and renal carcinoma [6-8]. The three types of interferons showed the different features of molecular mechanisms

through physiological responses including antiviral response, immunomodulatory or antitumor effects and autoimmunity [9]. For Type I IFNs (IFN-α, IFN-β), they can directly act on tumors via inhibiting the proliferation of tumor and inducing apoptosis [10,11]. The underlying mechanism may be that the Type I signaling pathway mediates distinct downstream signal activation, such as JAK/STAT pathway [12]. The different activation of pathways also induces specific downstream biological effects. They also have indirect anti-tumor activities, through priming immune cells to regulate the function of T cells and promote clearance of tumor cells [13].Nowadays, the treatment with IFN-α (by itself or as part of combination therapy) shows encouraging clinical response and significant clinical benefit. In a large of randomized controlled trials, IFN-α therapy in melanoma has effectively improved the progression free survival and overall survival [14]. However, systemic IFN-α treatment does not achieve satisfying results as an anti-tumor modality in cervical cancer because of poor survivability of regimes for patients [15].As we know, cervical cancer is mainly classified into three histological types, including CSCC, CA, and adenosquamous carcinoma. Although several research indicated that IFN-α can induce apoptosis of cervical cancer cells, lacking of specific study about differences of IFN-α treatment on CSCC and CA. Our findings suggest that CSCC was associated with Type I interferon signaling compared with CA. The ability of inhibiting CSCC cells proliferation is higher than that of CA cells in IFN-α treatment. These findings motivate us to provide novel guidance for the clinical application of IFN-α.

3. Methods

3.1. Data acquisition and Analysis

The TCGA-CESC RNA-seq and clinical data were downloaded from the UCSC Xena platform (https://xenabrowser.net/datapages/) and Genotype-Tissue Expression (GTEx) cervical RNA-Seq data, as normal tissue samples, were downloaded from the GTEx Portal. The cervical cancer gene expression data comprising the GSE7803 (Platform: GPL96), GSE9750 (Platform: GPL96), GSE63514 (Platform: GPL570) and GSE138080 (Platform: GPL4133) datasets were downloaded from GEO (https://www.ncbi.nlm. nih. gov/geo/). The Limma package (3.42.2) of R software was used to screen the differential expression of mRNAs (threshlolds: p.adj <0.05, |log2(fold change)|≥1). The XIANTAO (https:// www.xiantaozi.com) and ASSISTANT for Clinical Bioinformatic (wwww.aclbi.com) platform was used to data analysis and produce the figures.

3.2. Functional Enrichment Analysis

To further confirm the underlying function of differential genes, the Gene Ontology (GO) functional enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were conducted. To better uncover the biological functions of differential genes, ClusterProfiler package (3.14.3) in R was employed to analyze the GO function of potential targets and enrich the KEGG pathway. "p.adj < 0.05" was considered statistically significant. All analysis was finished in XIANTAO online website.

3.3. Gene Set Enrichment Analysis (GSEA)

A ranked gene set enrichment analysis was performed using the R package ClusterProfiler. For the RNA sequencing data, the ranked gene lists were constructed from all expressed genes, in which the ranking value was calculated as–sign[(log2FC)*log(p.adj)] and all expressed genes were analyzed using the Hallmarks and c2.cp. v7.2.symbols.gmt datasets. Gene sets with "False discovery rate (FDR)<0.25 and p.adjust<0.05" were regarded as significant. All analysis was finished in XIANTAO online website.

3.4. Cell Cultures

Human cervical cancer cell line (HeLa and SiHa) were obtained from the Cell Bank, Type Culture Collection,Chinese Academy of Sciences (CBTCCCAS). HeLa were cultured in high-glucose (4.5g/l) Dulbecco's Modified Eagle's Medium (DMEM) (Gibco) supplemented with 10% heat-inactivated fetal bovine serum (Gibco), 1% penicillin and streptomycin (Sigma) at 37℃ in 5% CO2. SiHa were cultured in Minimum Essential Medium (MEM) (Gibco) supplemented with 10% heat-inactivated fetal bovine serum (Gibco), 1% penicillin and streptomycin (Sigma) and 1% L-Glutamine (Solarbio) at 37℃ in 5% CO2.

3.5. Cell Viability Assay

HeLa or SiHa cells were seeded in a 96-well plate with a density of 5000 per well and treated with 1, 10, 100, 1000, 10000 and 100000 IU/ml IFN-α for 48 hours. After replacing the culture medium with a fresh medium, Cell Counting Kit-8 (CCK8) (Promega) was added, and the cells were incubated at 37℃ for 1 hour. The absorbance at 450nm was assessed using a SpectraMax M3 plate reader.

3.6. Annexin V-PI Apoptosis Analysis

HeLa or SiHa cells were seeded in a 6-well plate with a density of 150,000 per well and treated with 1000 IU/ml IFN-α for 48 hours. After treatment, all of the adherent and floating cervical cancer cells were collected and gently washed them tiwce with PBS (Gibco) before resuspending them in 200 μL of binding buffer from an apoptosis analysis kit (Solarbio). After incubating with Annexin V-FITC an propidium iodide (PI) in test tubes, the cells were subjected to flow cytometry analysis.

3.7. TUNEL Staining Assay

HeLa or SiHa cells were seeded in a 6-well plate with a density of 150,000 per well and treated with 1000 IU/ml IFN-α for 48 hours. After treatment, TUNEL staining was utilized to evaluate the apoptosis in cervical cancer cells by using the DeadEnd™ Colorimetric TUNEL System (Promega). The cells were incubated with proteinase-K for 15min. After being washed with PBS, the

cells were incubated with TUNEL reaction mixture for 1 h at 37°C. The nuclei of the cells were stained with PI (Solarbio) and observed using a fluorescence microscope (ZEISS).

3.8. Western Blotting

Protein extraction was performed using RIPA reagent (Solarbio). Lysis protein was collected and NanoDrop2000 system (Thermo Scientific) was adopted to adjust protein concentrations. All primary antibodies (Proteintech) were used at 1:1000 ratio and incubated at 4°C overnight, and secondary antibodies (Proteintech) were used at 1:5000 ratio and incubated at room temperature for 1 h. Images were collected using the Imaging System (Tanon 5200 Multi) with ECL and analyzed by ImageJ.

3.9. Statistical Analysis

All statistical analyses were performed using the R statistical package (R version 3.6.3) unless otherwise stated. The differences between the two independent groups were analyzed using Student's t test (unpaired, two-tailed).

4. Results

4.1. TCGA Analysis: Identification of DEGs Between CESC and Normal Samples

A total of 2,526 upregulated and 3,099 downregulated DEGs were identified from 253 Cervical squamous cell carcinoma (CSCC) samples compared with 22 normal samples. Meanwhile, 3,043 upregulated and 2,526 downregulated DEGs were identified from 53 cervical adenocarcinoma (CA) samples in comparison to 22 normal samples. The heat map and volcano plot of each gene expression profile data was shown in (Figure 1). These results suggested that the DEGs may have a crucial role in the tumorigenesis and progression of both CSCC and CA.

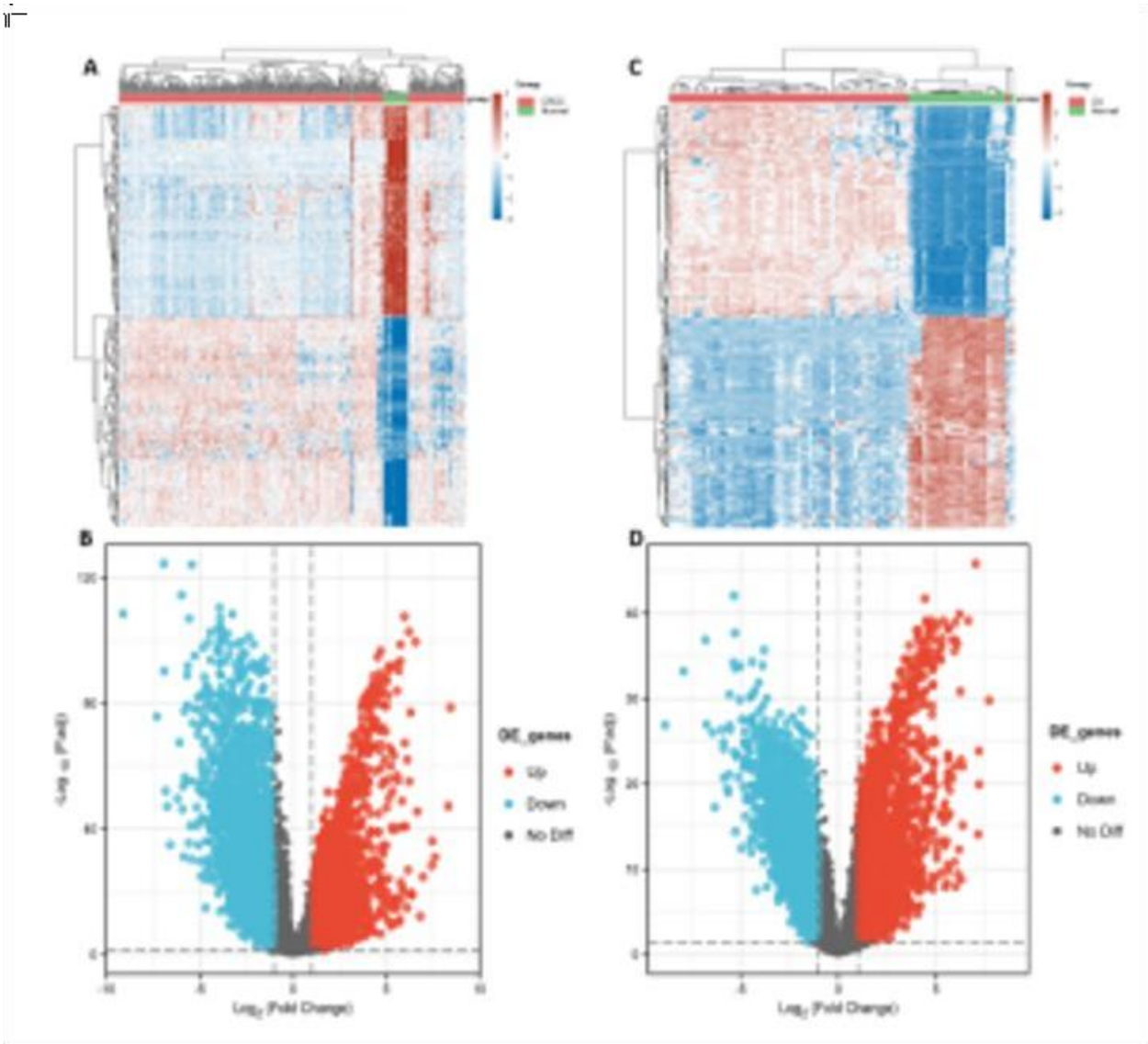

Figure 1: Gene expression profile data in CESC samples and normal ones. (A) Heatmap of differential gene expression in TCGA datasets (CSCC vsNormal). (B) Volcano plots of differential gene expression in TCGA datasets (CSCC vsNormal). (C) Heatmap of differential gene expression in TCGA datasets (CA vsNormal). (D) Volcano plots of differential gene expression in TCGA datasets (CA vsNormal). CSCC: cervical squamous cell carcinoma; CA:cervical adenocarcinoma.

4.2. TCGA analysis: Enrichment Analyses

To explore the functions of these DEGs, GO functions analysis results showed that the upregulated genes in CSCC were related to cellular response to type I interferon, type I interferon signaling and response to type I interferon (Figure 2). Similarly, the upregulated DEGs were also enriched in cellular response to type I interferon, type I interferon signaling and response to type I interferon terms for BP (Figure 2). To provide additional evidence that type I interferon as a key component, we tested the significant molecular pathways using GSEA analysis. As expected, the results indicated that whether CSCC or CA, both of which was predominantly associated with hallmark interferon alpha response, reactome interferon on alpha beta signaling and reactome interferon signaling (Figure 2). We thus considered that type I interferon associated pathway was necessary for the progression of cervical cancer.

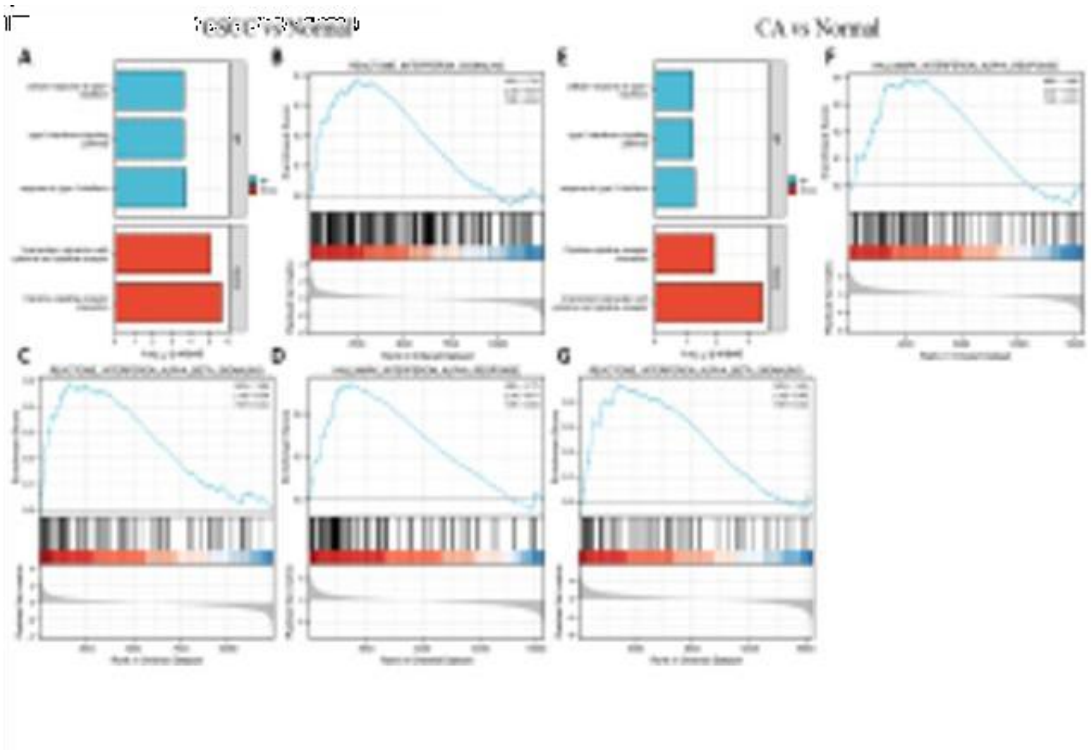

Figure 2: Enrichment analyses of DEGs in CESC. (A) GO and KEGG analysis for upregulated DEGs between CSCC and normal. (B-D) The Interferon related pathways of GSEA results across the CSCC. (E) GO and KEGG analysis for upregulated DEGs between CA and normal. (F-G) The Interferon related pathways of GSEA results across the CA.

4.3. GEO Analysis: Identification of DEGs Between CESC and Normal Samples

Furthermore, we examined the GEO database and excavated the data from four mRNA expression profile datasets (GSE7803, GSE9750, GSE63514 and GSE138080). The details of each GEO dataset were given in (Table 1). A total of 380 upregulated and 353 downregulated DEGs were identified in GSE7803 dataset. The 406 upregulated and 1200 downregulated DEGs were identified in GSE9750 dataset. From the GSE63514 dataset, we found that a total of 1804 upregulated and 1052 downregulated DEGs. In GSE138080 dataset, the 502 upregulated and 668 downregulated DEGs were discovered (Figure 3).

Table 1: Details of the GSE datasets.

Accession Numbers	GSE7803	GSE9750	GSE63514	GSE138080
Platform	Affymetrix Human Genome U133A Array	Affymetrix Human Genome U133A Array	Affymetrix Human Genome U133 Plus 2.0 Array	Agilent-014850 Whole Human Genome Microarray 4x44K G4112F
Samples				
Tumor	cervical squamous cell carcinomas : 21	cervical squamous cell carcinomas : 33	cervical squamous cell carcinomas : 28	cervical squamous cell carcinomas : 10
Normal	cervical epithelium : 10	cervical epithelium : 24	cervical epithelium : 24	cervical epithelium : 10

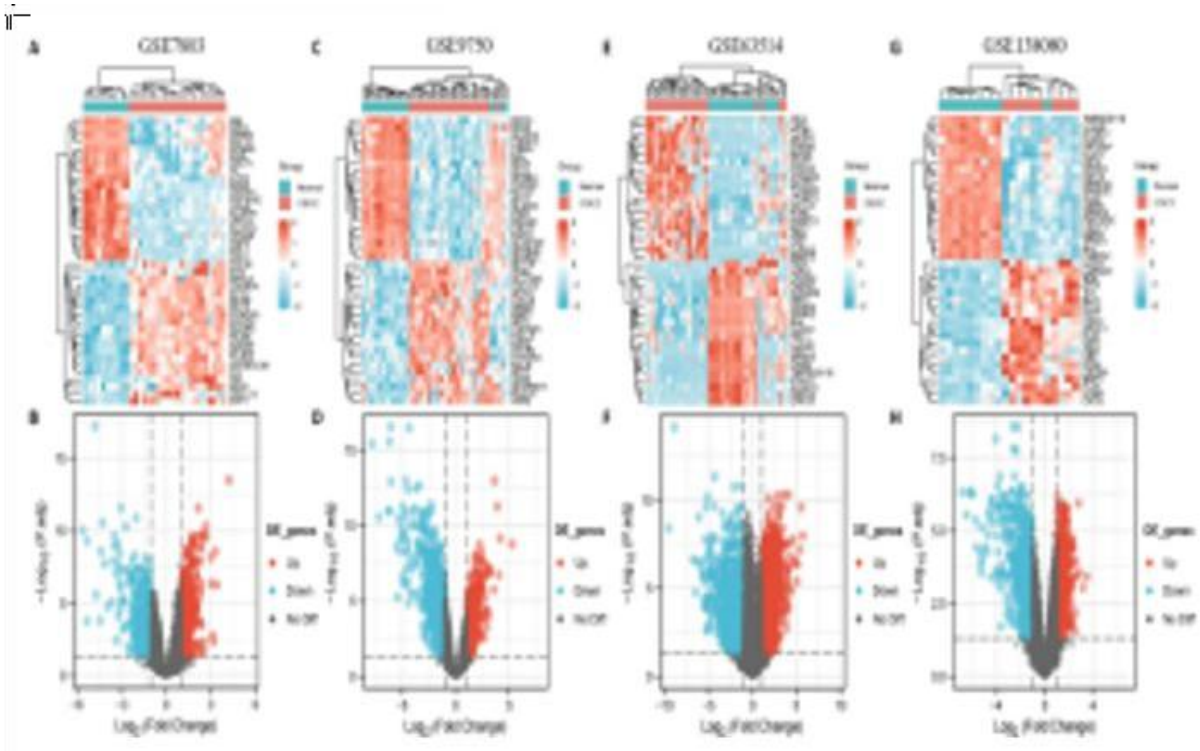

Figure 3: Gene expression profile data in GEO datasets. (A, C, E, G) The heatmap of top20 DEGs in GEO datasets (GSE7803, GSE9750, GSE63514 and GSE13808). (B, D, F, H) Volcano plots of differential gene expression in GEO datasets (GSE7803, GSE9750, GSE63514 and GSE13808).

4.4. GSE analysis: Enrichment Analyses

We are further to discuss the functions of DEGs, GO function analysis results indicated that the upregulated genes in CSCC were related to cellular response to type I interferon, type I interferon signaling and response to type I interferon in four GEO detasets (Figure 4). Furthermore, we evaluated the significant molecular pathways by GSEA analysis (Figure 5). This result was consistent with previous results.

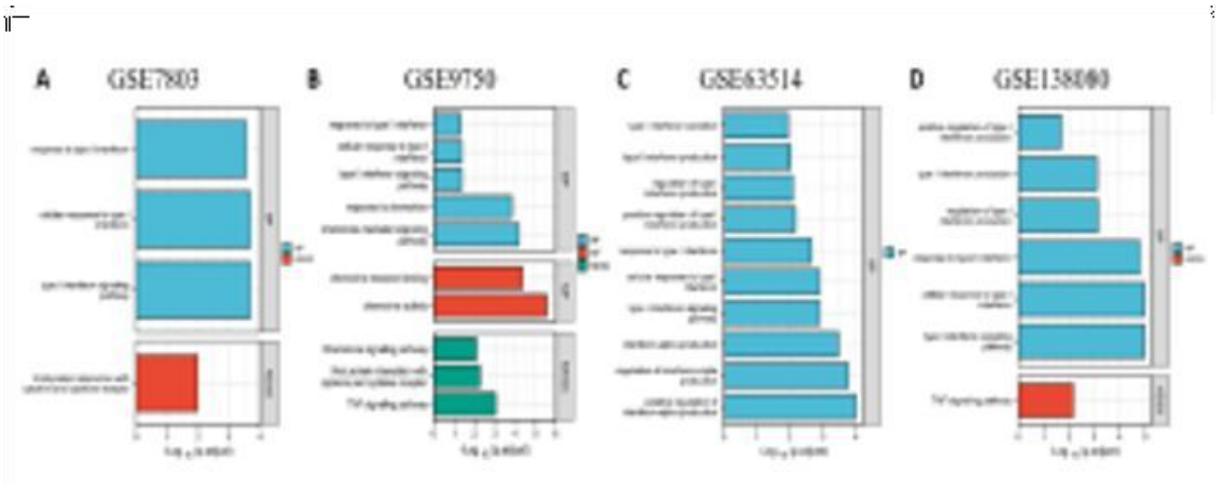

Figure 4: GO and KEGG analysis of upregulated DEGs. (A-D) GO and KEGG analysis for upregulated DEGs between CSCC and normal from GEO datasets (GSE7803, GSE9750, GSE63514 and GSE13808). BP:biological process; MF:molecular function.

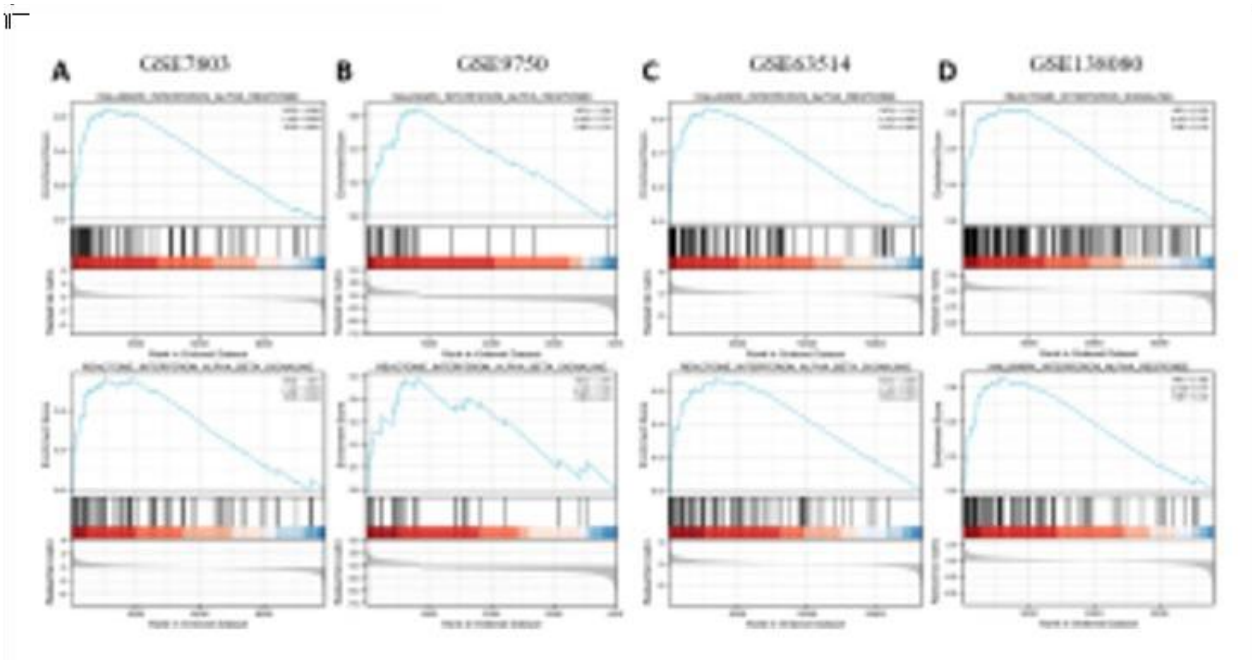

Figure 5: The results of GSEA analysis. (A-D) The significant pathways of GSEA results across the CESC and normal from GEO datasets.

4.5. Identification of DEG between CSCC and CA

We used TCGA datasets to identify the DEGs between CSCC and CA. A total of 601 upregulated and 943 downregulated DEGs were identified from 253 CSCC samples compared with 53 AC samples (Figure 6). Then we explored the potential function of upregulated genes, GO enrichment analysis of biological process annotations showed that the upregulated genes were positively associated with several tumor-promoting properties, including response to type I interferon, cellular response to type I interferon and type I interferon signaling pathway (Figure 6). Interestingly, we also found that the upregulated genes were related to Cytokine-cytokine receptor interaction in KEGG pathway analysis. Moreover, the similar results were obtained in GSEA analysis, such as hallmark interferon alpha response (Figure 6).

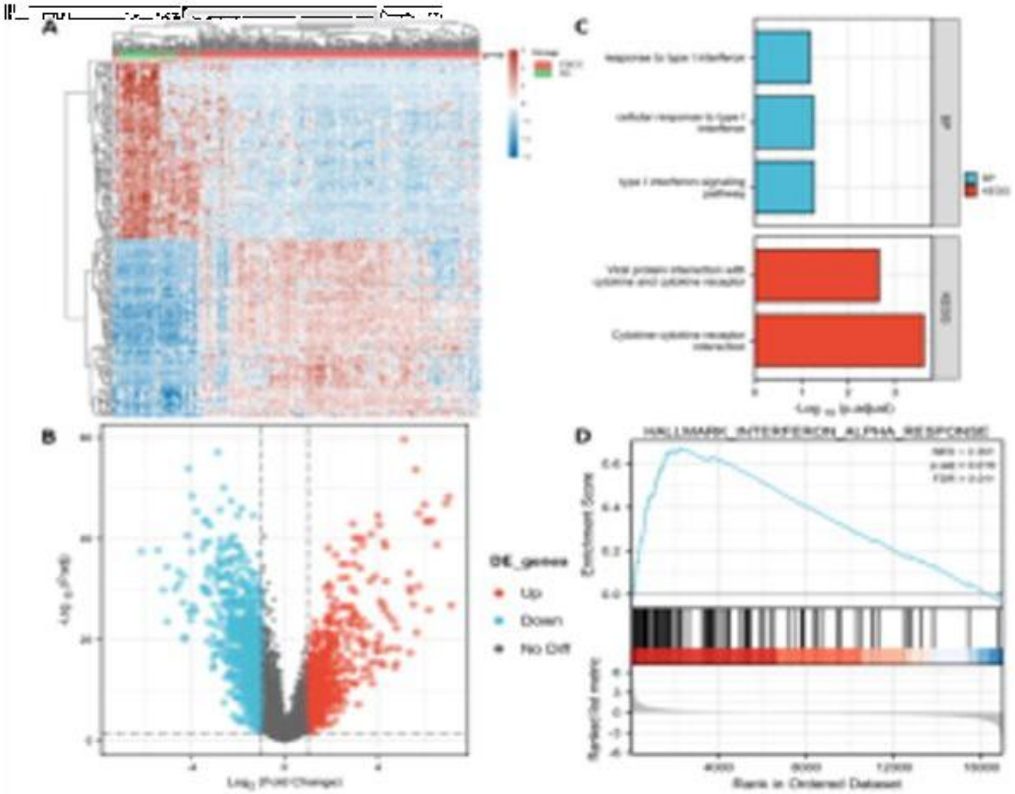

Figure 6: Identification of DEG and Enrichment analyses between CSCC and CA. (A) Heatmap of differential gene expression in TCGA datasets (CSCC vsCA). (B) Volcano plots of differential gene expression in TCGA datasets (CSCC vsCA). (C) GO and KEGG analysis for upregulated DEGs.

4.6. Antitumor Activity Both in Vitro

We performed CCK8 assay to determine the IC50 values of IFN-α on two cervical cancer cell subtypes (SiHa and Hela). Our results indicated that IFN-α inhibits cervical cancer cell growth in a dose-dependent manner. The viability of SiHa and Hela after treatment with various doses (1, 10, 100, 1000, 10000, and 100000 IU) of IFN-α for 48h was evaluated using the CCK8 assay (Figure 7). We calculated IC50 values based on CCK8 assay results, revealing that the IC50 of SiHa cells was 34,105 IU, while the IC50 of Hela cells was 103,850 IU. Notably, our fundings indicate that SiHa cells are more sensitive to IFN-α than Hela cells. We next examined whether IFN pathway associated-proteins have changes in mobility under exogenous stimulation of IFN-α. We tested various intracellular proteins (STAT1, STAT3, p-STAT1, and p-STAT3) that are key downstream components of signaling cascades. We found that higher levels of p-STAT1 and p-STAT3 protein expression in SiHa cells compared to Hela cells, indicating that the IFN-α pathway activation level in SiHa cells is stronger than that in Hela cells (Figure 7). Meanwhile, the function of p-STAT1 covers up the function of p-STAT3. We also considered the apoptosis of Hela and SiHa cells that was observed by flow cytormetry and TUNEL assays. The Annexin V-PI apoptosis assay exhibited that apoptoic cells in SiHa cells are significantly higher than that in Hela cells (Figure 7). Consistently, a similar pattern of cell apoptosis was detected by TUNEL assays in SiHa cells. Hence, the differences of IFN-α treatment were explained by the cross-talk of tumor cell-intrinsic pathways.

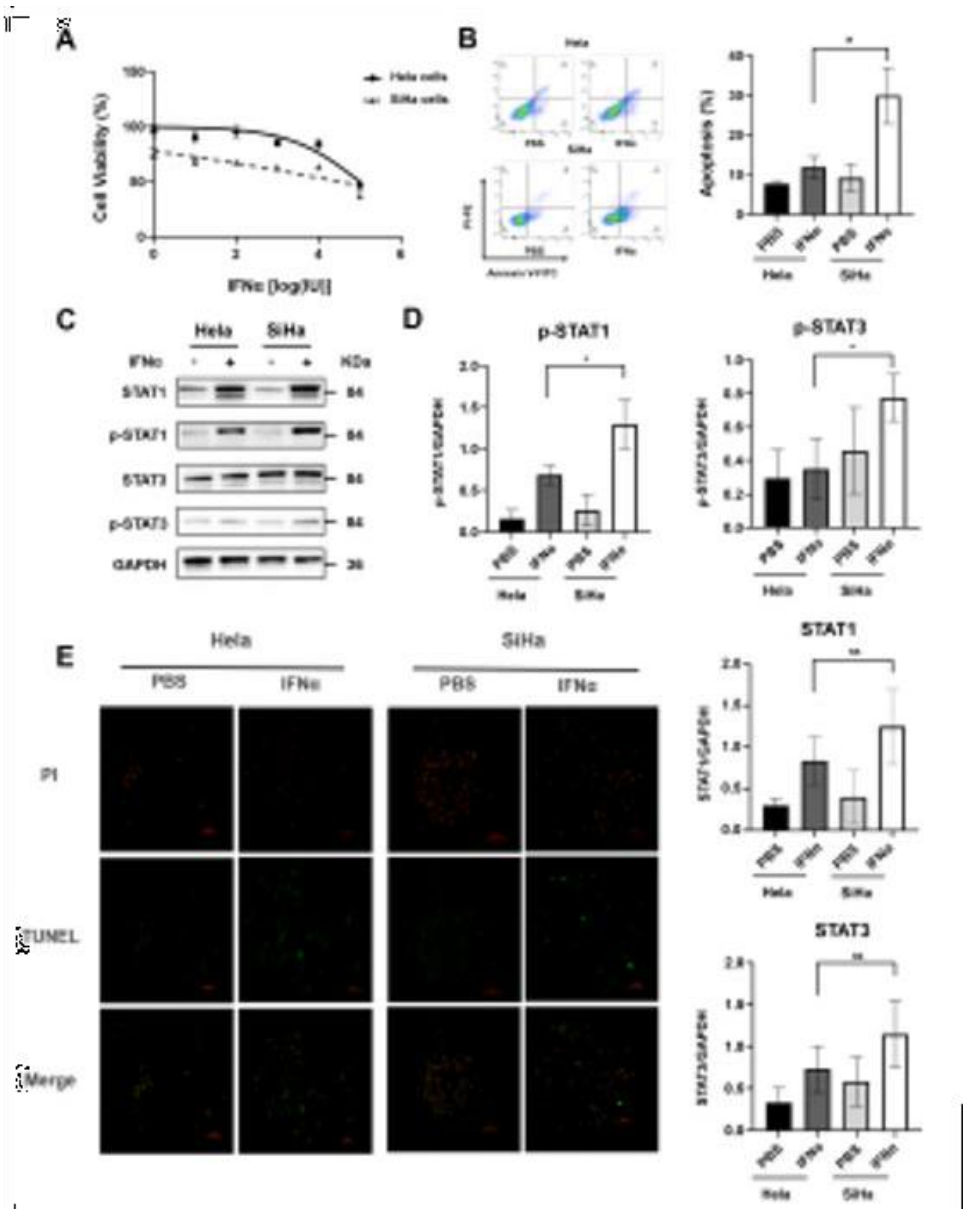

Figure 7: The antitumor effects of IFNα in vitro. (A) SiHa or Helacells were treated with IFNα for 48 h, and cell viability was analyzed by CCK-8 assay. (B) Annexin V/PI apoptoic analysis in Hela and SiHa cells treated with IFNα (1000 IU/ml). (C-D) The protein levels of STAT1, p-STAT1, STAT3 and p-STAT3 in Hela and SiHa cells treated with IFNα for 48 h measured by western blotting (upper panel). The grey values of the images were calculated using ImageJ. (E) TUNEL analysis of apoptotic Hela and SiHa cells following treatment with IFNα (1000 IU/ml).

5. Discussion

In recent years, it has been reported that IFN-α can induce apoptosis of cervical cancer cells. Unfortunately, there have no study to compare the difference of IFN-α therapeutic effect on CSCC and CA. Our research revealed that the different effects of IFN-α treatment between CSCC and CA. Importantly, these findings motivated us to provide novel guidance for the clinical application of IFN-α. Nowadays, the type I interferon signaling played an important role in the occurrence and development of cancer.16 We found that type I interferon signaling was associated with cervical cancer (whether squamous cell carcinoma or adenocarcinoma) through GO and KEGG enrichment analyses. Furthermore, we further demonstrated the relationship between cervical cancer and type I interferon related signaling pathway via GSEA analysis. These results showed that the type I interferon signaling may be the key factor in progression of cervical cancer. At present, several studies have supported this view. Joseph M Gozgit et.al revealed that Inhibition of PARP7 lead to tumor regression in mouse lung cancer model, and induced tumor-specific adaptive immune memory depending on type I IFN signaling in tumor cells [17]. Liufu Deng et.al indicated that the radiation-mediated antitumor immunity by cytosolic DNA sensor cyclic GMP-AMP (cGAMP) synthase (cGAS) and STING pathway relied on type I IFN to exert its effect [18]. Another study demonstrated that IFN-α can upregulate PD-1 expression in CD8+ T cells via IFN-α-IFNAR1-JAK1-STAT3 signaling pathway in hepatocellular carcinoma [19]. Our findings illustrate the importance of type I interferon signaling in regulating anti-tumor effect for cancer. Thus, it may be that type I interferon signaling relate to the progression of cervical cancer.In our study, we were further to evaluate the difference between CSCC and CA. We identify the 601 upregulated DEGs, and explored the potential function of upregulated genes through GO enrichment analysis and GSEA analysis. The results of GO analysis indicated that upregulated DEGs were involved in interferon-related signaling pathway, and interferon alpha response are differentially enriched in CSCC group via GSEA analysis. Furthermore, anti-proliferation assays in Hela and SiHa cells demonstrated that IFN-α can repress proliferation of cervical cancer cells [20]. Nowadays, many previous studies indicated that IFN-α can induce apoptosis of cervical cancer cells and inhibit cervical cancer cells proliferation [20]. Found that the combination of IFN-α and TNFα on ME-180 human cervical cancer cells showed synergistic anticancer effects via STAT1-dependent pathway [21]. The other study also demonstrated that IFN-α can promote apoptosis of cervical cancer by activating intrinsic mitochondrial pathway and caspase-4-related endoplasmic reticulum stress-induced pathway [22]. However, these results did not investigate the difference of IFN-α therapeutic effect in different histological types of cervical cancer.Interestingly, our research found that the difference of IFN-α therapeutic effect between Hela and SiHa cells, representing adenocarcinoma and squamous cell carcinoma respectively, incubated with the same concentration of IFN-α. We guessed that the expression difference of IFN-α receptor in different cervical cancer cells may be an important factor in tumor response to IFN-α treatment. Reza F Saidi et.al indicated that IFN-α combined with gemcitabine in treating human pancreatic cancer on nude mice showed good therapeutic effect. This process was more prominent in MiaPaCa-2 cells that express the IFN-α receptors [23]. Moreover, another study also illustrated that Interferon tau can induce antiproliferative effect and apoptosis of BMK-16/myc cells in comparison with SiHa cells. These results were consistent with our result. Additionally, the difference of distinct biological behavior in respond to IFN-α needs to be investigated. The other possible key factor may be explained in a cross-talk of different pathways in tumor cells. In the tumor microenvironment, JAK/STAT3 signaling acts to drive the proliferation, angiogenesis, immunosuppression, and metastasis, while strongly suppressing the antitumor immune response [24,25]. On the contrary, JAK/STAT1/STAT2 pathway can promote the apoptosis, Chemokine secretion, immune activation [26,27]. Yong Li et.al found that the activation of ITGB3-c-SRC-STAT3 pathway can affect STAT1 activation to cause resistance to IFN-α-induced apoptosis in melanoma tumor-repopulating cells [28]. Therefore, the differences of IFN-α treatment were also explained by the cross-talk of tumor cell-intrinsic pathways.

6. Conclusion

Our research first reported that CSCC was enriched in Type I interferon signaling compared with CA. The ability of inhibiting CSCC cells proliferation is higher than that of CA cells in IFN-α treatment. These findings motivate us to provide novel guidance for the clinical application of IFN-α.

7. Funding Support

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