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Interleukin 6 in breast cancer: From metabolism to genomic profile

(Interlekina 6 en el cáncer de mama: Desde el metabolismo hacia el perfil genético)

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Abstract(english)

The overexpression of the proinflammatory cytokine IL-6 has been reported in breast cancer. Aim. To investigate the role of IL-6 in metabolism and breast cancer using public databases. We analyzed these data for the biological function of IL-6, expression, somatic mutation, and correlation in normal and breast cancer using bioinformatics skills. Within the Oncomine database, IL-6 represented reduced expression and showed no significant difference in the expression between breast cancer and normal controls. The mRNA upregulation frequencies of IL-6 in patients with breast invasive lobular carcinoma were higher (5.41%) than those in invasive breast carcinoma (1.82%). Our results revealed that in 1,084 breast cancer patients in the cBioPortal, IL-6 gene alteration frequencies showed that IL6 exhibited lower alteration frequency (1.1%), and gene amplification accounted for most changes. The rate of point mutations in IL6 in breast cancer was 0.42 in the COSMIC database. In conclusion the observed mRNA and mutation rate of IL6 may correlate with tumor burden, controlling breast cancer metastasis and impaired metabolism.

Keywords(english)

Interleukin 6, metabolism, cancer, genetics, breast cancer.

Resumen(español)

Se ha reportado sobre la sobreexpresión de la citocina proinflamatoria IL-6 en el cáncer de mama. Apuntar. Investigar el papel de la IL-6 en el metabolismo y el cáncer de mama utilizando bases de datos públicas. Analizamos estos datos para la función biológica de IL-6, expresión, mutación somática y correlación en cáncer normal y de mama utilizando habilidades bioinformáticas. Dentro de la base de datos de Oncomine, la IL-6 representó una expresión reducida y no mostró diferencias significativas en la expresión entre el cáncer de mama y los controles normales. Las frecuencias de regulación positiva del ARNm de IL-6 en pacientes con carcinoma lobulillar invasivo de mama fueron mayores (5,41%) que en el carcinoma de mama invasivo (1,82%). Nuestros resultados revelaron que en 1.084 pacientes con cáncer de mama en cBioPortal, las frecuencias de alteración del gen IL-6 mostraron que la IL6 exhibió una frecuencia de alteración más baja (1,1%) y la amplificación del gen representó la mayoría de los cambios. La tasa de mutaciones puntuales en IL6 en cáncer de mama fue de 0,42 en la base

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de datos COSMIC. En conclusión, el ARNm observado y la tasa de mutación de IL6 pueden correlacionarse con la carga tumoral, controlando la metástasis del cáncer de mama y el metabolismo alterado.

Palabrasclave(español)

Interleukina 6, metabolismo, cancer, genetica, cancer de mama.

Introducction

Breast cancer has been the primary cause of cancer globally for many years (1). Despite remarkable improvements in cancer treatment approaches, breast cancer is still the leading cause of cancer-related death in women (2). Research indicates that IL-1beta, IL-6, and IL-10 were associated with breast cancer risk (3), and the expression of IL-6 was positively correlated with tumor growth or ER in breast cancer (4) and leads to chemotherapy resistance (5). IL-6 shows a variety of biological functions in the tissue regeneration process, immune system, and metabolism (6). Several names, such as interferon-β2, BCDF, and HSF, were allocated to this novel protein of 27- kDa (7). Coulie et al. called this cytokine IL-6, which was accepted by the majority of the community (8). It has been established that IL-6 plays a role in breast cancer via different routes. The following studies highlight the role of IL-6 in breast cancer. In a study conducted by Hefler et al. (9), the IL-6 polymorphism was significantly associated with breast cancer. In another study, the high levels of IL-6 were associated with hormone-refractory metastatic breast cancer (10). The IL6 secreted from adipose stromal cells promotes migration and invasion of breast cancer cells (11). Autocrine production of IL-6 causes multidrug resistance in breast cancer cells (12). IL-6 binds to IL-6R and forms a complex associated with the signaling subunit gp130 to induce the intracellular IL6 signaling cascade and thus promotes breast cancer cell proliferation (13). Ahmed et al. (14) demonstrated that the serum level of IL-6 is a valuable prognostic factor in metastatic breast cancer patients. IL-6 is an inducer of an EMT phenotype in breast cancer cells and may promote breast cancer metastasis (15); invasion and staging in breast cancer are generally increasing because of their association with increases in preoperative serum IL-6 levels (16). Furthermore, IL-6 could distinguish between women with breast cancer and healthy controls (17).

In summary, IL-6 has been identified to play a critical role in cancer, focusing on the therapeutic approach and the immune cells that secrete IL-6 in the tumor microenvironment. Since IL-6 in breast cancer show its role in tumor growth, metastasis, and therapeutic resistance. Therefore, targeting IL-6 with other potent anticancer therapies may be one of the promising therapeutic approaches for breast cancer treatment (18). Furthermore, the IL-6 plays a unique role in the differentiation and expansion of tumor cells. Although this gene is still in its infancy, its role in breast cancer thus needs further molecular investigation. In this study, the expression and genetic alterations in the IL-6 gene were investigated by utilizing different bioinformatics-based databases such as HPA, GEPIA, cBioPortal for cancer genomics, COSMIC, and STRING.

Materials y methods

BioRender. Biorender is a tool for producing high-quality figures with pre-designed motifs. The entry version is free for educational and academic use (BioR 2021). We used BioRender for IL-6 figure 1, metabolism and its role in cancer. Login is required and is freely available at BioRender.com. Analysis of the IL-6 gene using cBioPortal

This portal is an open web-based source for exploring cancer data visualization and analysis (19). It contains 10,000 samples from mostly TCGA, ICGC, and 40,000 curated study samples in hundreds of studies from other publically available datasets. cBioPortal lowers the barriers to cancer researchers accessing complex genomic data, promoting rapid, intuitive, and high-quality access to molecular profiles and clinical prognostic correlations from large-scale cancer genomics projects and allowing researchers to translate these rich data sets into biological insights and clinical applications.

The Human Protein Atlas (HPA) database. We used this platform to analyze the breast cancer tissue histology, mutation types, frequencies, and expression of IL-6. IL-6 gene analysis using Human Protein Atlas (HPA) This database (http://www.proteinatlas.org) maps all the human body proteins by applying various omics technologies (20). It consists of ten individual sections, including tissue, brain, single cell type, tissue cell type, pathology, immune cell, blood protein, subcellular, cell line, and a metabolic section showing

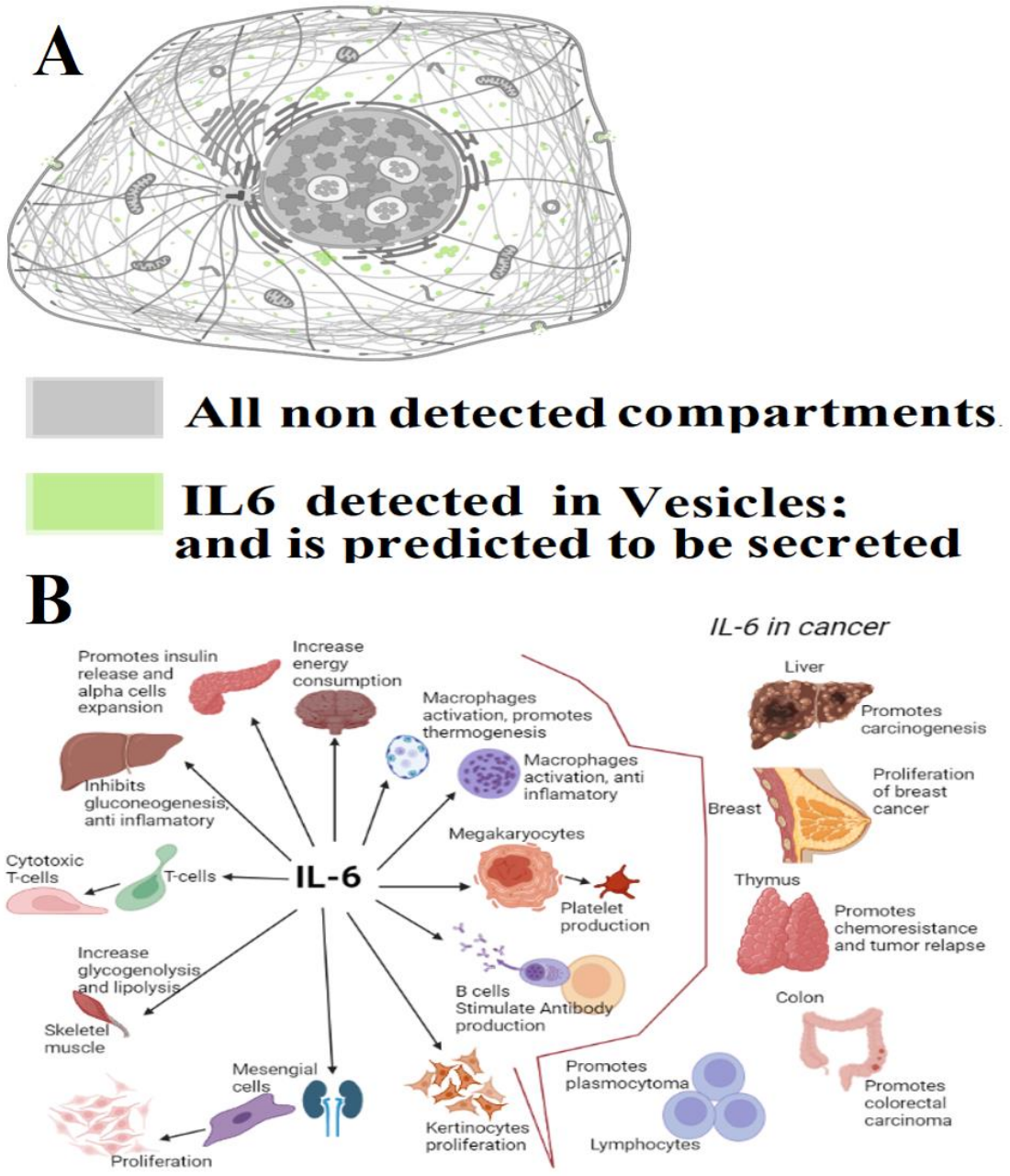


Figure 1. A) Subcellular localization of IL-6. **B)** IL-6 in metabolism and cancer.

the specific material upon selection. All the data is freely available to allow researchers in academia and industry to access the data to explore the human proteome freely. We used this platform to analyze the subcellular localization.

Analysis of IL.6 gene using ONCOMINE. It is the world's most extensive collection of curated cancer genomics data storing information on 1800 genes (21). These data come from different resources like microarray technologies, targeted assays, and next-generation sequencing analysis. We used this database to analyze the expression of the IL-6 gene in breast cancer. As the primary filter, we have chosen 'Cancer vs. Normal Analysis' and the type of cancer as breast cancer. The top 10% gene was set as the threshold with a 2.0-fold change and 0.05 p-value. COSMIC database Is the world's largest source of expert manually curated somatic mutation information relating to human cancers (22). It stores information on over 37,000 genomes, including peer-reviewed large-scale genome

screening data and other databases such as ICGC and TCGA.

COSMIC analysis. We used the COSMIC database for mutation information related to our gene of interest. The database is publically available at https://cancer. Sanger. ac.UK/cosmic. LinkedOmics analysis Is the latest portal for analyzing clinical and multi-omics data from The Cancer Genome Atlas (TCGA) (23). We utilized LinkedOmics to analyze the specific genes via heat map and volcano plot correlating negative and positive IL-6. The Spearman test was applied for statistical analysis. LinkedOmics is freely

Results

Subcellular localization and role of IL6 in metabolism

Gene function assumes a key model of how specific gene products act to attain biological aims. The subcellular localization of the protein is important for profiling the protein expression data. Localization of IL6 is displayed in (Fig 1A). IL6 comprises a wide variety of biological functions in immunity, tissue regeneration, and metabolism (Fig. 1B).

The expression profile of the IL-6 gene in normal and breast cancer

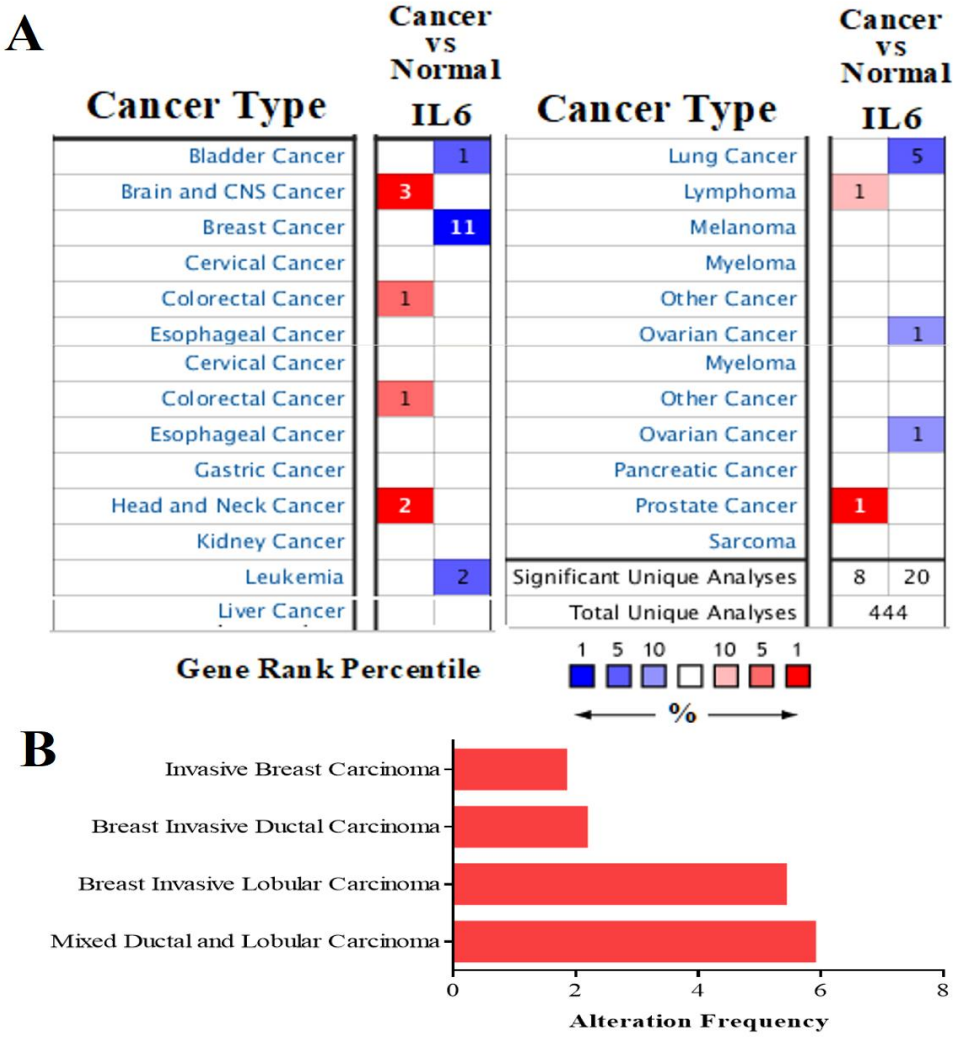
We next focused on the expression level of this pleiotropic cytokine, which was analyzed using the ONCOMINE and cBioPortal. We first obtained the expression levels of IL-6 in 21 different types of cancers and compared the expression levels to those in standard samples. In cancers such as brain, colorectal, head/neck, and prostate, IL-6 showed significantly increased expression (Figure 2a). However, according to Nikolsky and TCGA, the mRNA expression of the IL-6 gene in breast cancer was not significant (Table 1). Therefore, we also assessed whether alterations in IL-6 gene mRNA are associated with a specific invasive type of breast cancer (Figure 2b). To address this possibility, we utilized the cBioPortal In the TCGA PanCancer Atlas (Liu J et al., 2018), with 51 samples of breast mixed ductal and lobular carcinoma, 37 samples of breast invasive lobular carcinoma, 278 cases of breast invasive ductal carcinoma and 55 cases invasive breast carcinoma with the mRNA expression z-score ±2.0 as the threshold. Our analysis revealed that the IL-6 mRNA upregulation frequencies in breast mixed ductal and lobular carcinoma was 5.88%, which was lower than breast invasive lobular carcinoma recorded at 5.41%.

Moreover, the mRNA expression for normal and cancer tissue and cell lines was assessed by GEPIA. The non-invasive Hs 742. T breast cancer cells were observed with the highest expression of IL-6. The mRNA expression score of BRCA was lower than LUSC (9.01 TPM). The regular breast tissue expression of IL-6 was higher (11.68 TPM) than the breast tumor (1.39 TPM) (Supplementary figure 1).

IL6 gene mutations in breast cancer

The IL-6 gene mutations in breast cancer were assessed by cBioPortal (29). In our analysis, we found that IL-6 genetic mutations in breast invasive (TCGA; https://tcga-data.nci.nih.gov) were not higher compared with those in esophageal adenocarcinoma, urothelial bladder carcinoma, uterine corpus endometrial carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, sarcoma, cutaneous skin melanoma, prostate adenocarcinoma, and ovarian serous cystadenocarcinoma TCGA, PanCancer Atlas studies (34) but were present in 1.11% of the 1084 cases. This analysis was done across 32 cancer studies of genetic mutations (Figure 3a). Herein, we have analyzed the IL-6 gene mutation frequencies and types in 6786 samples from 20 breast cancer studies (Figure 3b). The gene amplification accounted for most changes for the IL-6 gene and exhibited higher mutation frequencies (2%). Concerning invasive breast cancer, we here show the correlation between mRNA expression and CNVs of IL-6. IL-6 mRNA was increased in the breast cancer tissues in which IL-6 was amplified. In Pan-Cancer Atlas, the somatic mutations for BRCA analysis show that it has only two mutations (Figure 3c). These mutations were also derived with the IL-6 3D structure using the cBioPortal (Figure 3d). The PPI network of the IL6 gene appeared with a number of nodes11, a number of edges: 51, average node degree: 9.27, avg. local clustering coefficient: 0.941 expected number of edges: 22 and PPI enrichment p-value: 1.09e-07 (Figure 3e). We also assessed the mutation rates of the IL-6 gene from the COSMIC database, a comprehensive resource for exploring somatic mutations in human cancer (25). The genetic point mutations of IL-6 in breast cancer was 0.42% exhibited 2.06% (CNV) (Table 2). The prognostic information on the IL-6 gene in breast cancer is freely available at KM Plotter (http://kmplot.com/analysis) (Gayorrfy et al., 2013). However, there were no significant associations between IL-6 (HR 0.92 (0.75– 1.15); P=0.48) and expression levels with the OS, DSF, and PPS of breast cancer patients (Supplementary fig 2).

Enrichment of co-expressed genes related to IL-6 In breast cancer



Summary for Breast Mixed Ductal and Lobular Carcinoma **Gene altered in 5.88% of 51 cases**	
Alteration	Alteration
mRNA High	5.88% (3 cases)

Summary for Breast Invasive Lobular Carcinoma **Gene altered in 5.41% of 37 cases**	
Alteration	Alteration
mRNA High	5.41% (2 cases)

Summary for Breast Invasive Ductal Carcinoma **Gene altered in 2.16% of 278**	
Alteration	Alteration
mRNA High	2.16% (6 cases)

Summary for Invasive Breast Carcinoma **Gene altered in 1.82% of 55 cases**	
Alteration	Alteration
mRNA High	1.82% (1 case)

Figure 2. continued..

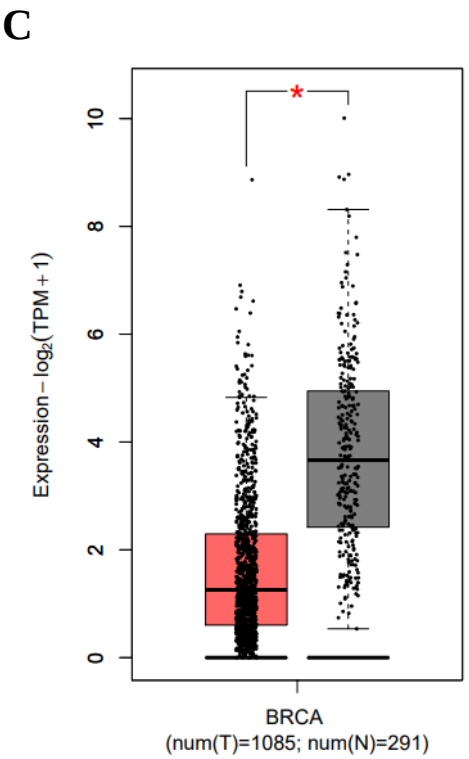


Figure 2. mRNA expression of IL6 in cancer. (A) IL-6 gene expression status in different types of cancers with the threshold of P≤0.05, fold change ≥2, and gene rank ≥top 10%, by ONCOMINE database. The numbers in the cells represent the number of datasets that met the threshold settings. The colour indicates the gene expression trend: red represents significant overexpression and blue represents reduced expression. The depth of the color indicates the degree of overexpression or under expression. **(B)** IL-6 gene mRNA alterations in 04 type of breast cancer and. Dysregulation of IL-6 gene mRNA levels in 51 cases with breast mixed ductal and lobular carcinoma, 37 cases with breast invasive lobular carcinoma, 278 with breast invasive ductal carcinoma and 55 with invasive breast carcinoma. mRNA upregulation indicated with red bars and while gray bars indicates no alterations were excluded. **(C)** The mRNA expression of IL6 gene in breast tumors and normal tissues in GEPIA. mRNA expression profile; red: tumor and green color represents normal tissue; *P<0.05 and |Log2 (fold-change)| cutof=1. level.

to IL-6 in breast cancer, we utilized LinkedOmics to analyze the mRNA sequencing data. For instance, the volcano plot (Figure 4a) shows that 7550 genes (dark red dots) are significantly positively correlated with IL-6, whereas 12605 genes (dark green dots) show significant negative correlations (false discovery rate [FDR] <0.01). The top 50 genes significantly negatively and positively correlated with IL-6 are shown in the heat map (Figure 4b, c). We also show the cancer type enrichment analysis on the IL-6 gene by utilizing ToppGene (Supplementary Table 1). The analysis yielded enrichment on IL-6 in Node-positive breast cancer was at the top compared with the other BRCA (p-value; 2.07E-03, q-value Bonferroni;1.00E+00). In Premenopausal breast cancer p-value; 2.63E-03, q-value Bonferroni; 1.00E+00, Advanced breast cancer p-value; 7.80E-03, q-value Bonferroni; 1.00E+00, HER2-negative breast cancer p-value; 8.26E-03, q-value Bonferroni; 1.00E+00, Estrogen receptor-negative breast cancer p-value; 1.84E-02, q-value Bonferroni; 1.00E+00. The enrichment analysis output can display a selected amount of diseases which can then be filtered, sorted, and navigated by pages. Chosen diseases are associated with the corresponding Medical Subject Headings thesaurus entries.

Discussion

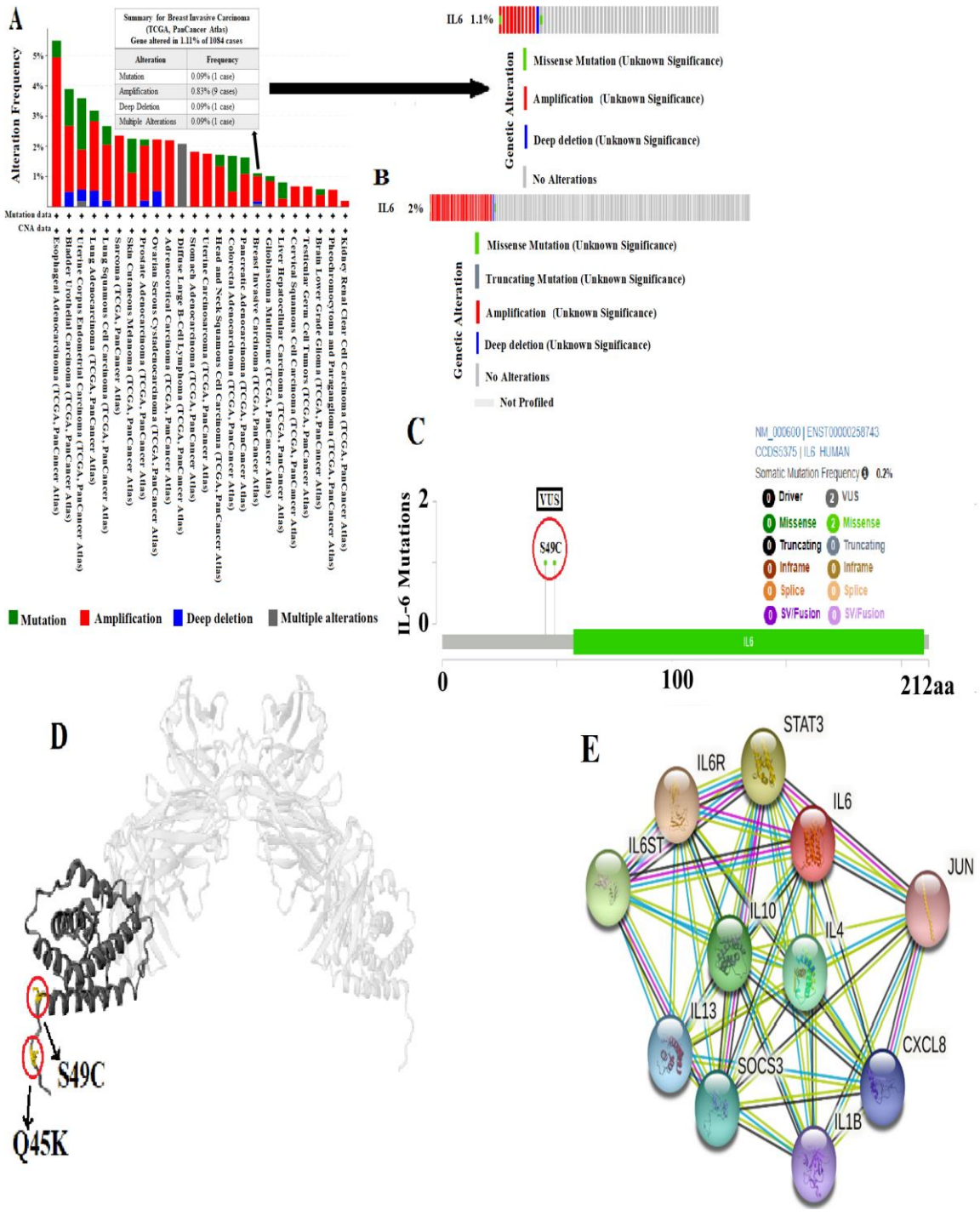


Figure 3. Analysis of IL-6 gene mutations and PPI network. (A) Gene mutation frequencies of IL-6 gene in different cancer types. The red color represent gene amplifications, blue (homozygous deletions), green (non synonymous mutations) and gray (multiple alterations)**. (B)** The IL-6 mutation frequencies and types in 6,786 breast cancer samples. Red color represent gene amplifications, blue (deep deletions), green (missense mutations) and gray color (truncating mutations). **(C)** The protein level mutation of IL-6 in invasive breast carcinoma with 994 samples showing 02 missense mutations**. (D)** 3D Structure for IL-6 alongside with the observed amino acid mutations. (E) Network analysis of IL-6 gene derived from STRING. In a biological network, the node is any molecule (biological), and an edge specifies the interaction between 02 nodes.

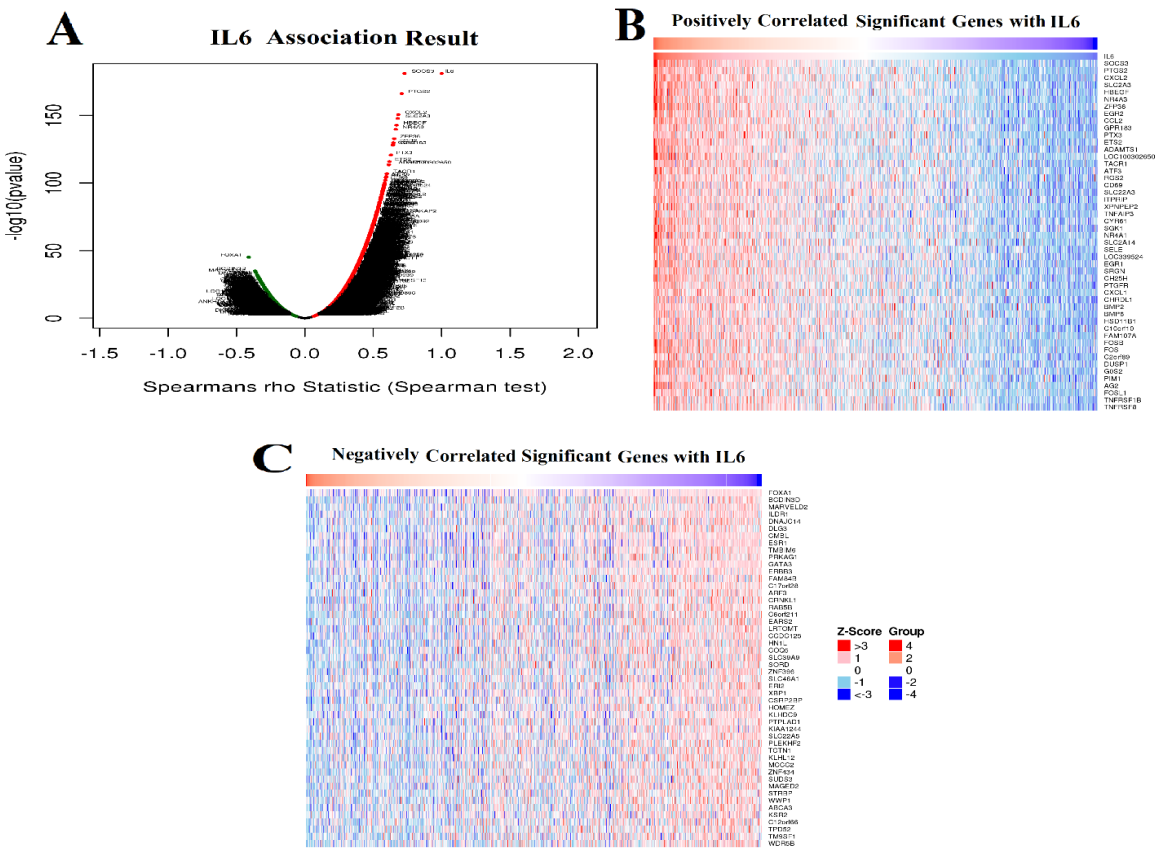


Figure 4. Genes differentially expressed in correlation with IL-6 in breast cancer (LinkedOmics). (A) Spearman test was used to analyze correlations between IL-6 and genes differentially expressed in breast cancer**. (B, C)** Heat maps showing the top 50 genes significantly negatively and positively correlated with IL-6 in breast cancer. Blue represents negatively associated genes with IL-6 and Red represents positively associated genes with IL-6.

databases is a novel platform that can be used to analyze tissue-specific histology, protein localization, expression, gene mutations, and correlation profiles in a high throughput fashion. The last review to describe the biological role of IL-6 in metabolism and cancer was published by Mauer et al. (26). We update this status by including some new data from the literature (Fig 1). The subcellular protein localization of a protein is important for profiling PTM patterns and protein expression. Further, its importance cannot be ignored for a better understanding of the biological function, network, interaction, and activation state of the specific protein (27). In our study, we made possible this approach by utilizing the HPA platform. The IL-6 was detected in vesicles and was predicted to be secreted; these sentences are in line with an earlier published article (28), in which they demonstrated the amount of IL-6 molecules released per secretory vesicle. Over the past

Table 1. Expression status of IL-6 gene at the transcriptional levels in different breast cancer by Oncomine database.

Gene	Types of breast cancer	Fold change	P-value	Sample	t-test	(Refs.)
IL-6	Ductal Breast Carcinoma in Situ	1.029	0.010	191	2.525	Nikolsky et al., 2008
	Ductal Breast Carcinoma	1.045	0.217	138	0.807	Nikolsky et al., 2008
	Invasive Ductal and Lobular Carcinoma	1.116	0.000	14	3.924	Nikolsky et al., 2008

Table 2. Genetic alterations from COSMIC database.

Genetic alteration	Mutated (%)	Tested
Point Mutations	0.42	1440
Copy Number gain	0.97	1136
Copy number loss	1.09	1104

The genetic point mutations of IL6 gene were accessed in 1440 breast cancer patients. The CNV of IL6 gene was accessed in 1136 and CNL in 1104 breast cancer patients.

few years, with the expansion of the biochemical approach and bandwidth sequencing technology, identifying the various functions of IL-6 RNA modification has become possible. However, the complete genetic profile and expression of IL-6 in breast cancer are still unknown. In this study, we therefore thoroughly analyzed the molecular alterations and biological networks of IL-6 in breast cancer. These Cancers are associated with local peak or abnormal systemic IL-6 involving different organs, including lungs, pancreas, prostate, kidney, colon, and breast (29). Among cytokines, the expression and biological function of IL-6 has been studied in breast cancer (Figure 1). Initial studies have shown that increased expression of IL-6 in cancer tissue and serum was associated with poor outcomes in patients with breast cancer (30). Increased levels of IL-6 can promote tumor growth, angiogenesis (31), and metastasis (32). Other studies have observed that high levels of IL6 expression may indicate a good prognosis in hepatocellular carcinoma (33), and similar results have been obtained in colorectal carcinoma (34). These earlier reports with small cohorts had limited clinical and statistical approaches. The available online sources such as Oncomine and TCGA platforms provide large samples and datasets. Through the combination and analysis of enormous bioinformatics data, we can increase the credibility of the research results by avoiding the errors associated with small sample experimental research. In the present study, mRNA expression levels, gene mutations, network analysis, correlation, and prognostic values of the IL-6 gene were investigated, aiming to pave the way for further investigation and potential therapeutic targets in breast cancer. A number of studies have reported that the IL-6 gene is associated with an increased risk of cancer. It was demonstrated that the IL-6 gene was associated with an increased risk of breast cancer (15), gastric cancer (35), and colorectal cancer (Turano et al., 2021). The relationships between the massive-based genetic studies of the IL-6 gene and breast cancer susceptibility are not fully understood. In our study, the types of alterations and frequencies of the IL-6 gene were analyzed through the cBioPortal and COSMIC databases. The present results revealed that IL-6 family gene mutation rates were, in general, low, and amplification and deep deletion were the main mutation type. In the ONCOMINE database, our results revealed that eleven datasets showed significantly decreased IL-6 expression in breast cancer. On the basis of invasive type, the current analysis revealed that IL-6 gene mRNA expression was high in breast invasive lobular carcinoma (5.41%) compared to breast invasive and invasive ductal carcinoma. The incidence of CNG was found to be higher than that of point mutations and CNL. IL-6, which had the highest CNV in breast cancer, represents a promising potential oncogene in breast cancer that warrants further experimental and clinical research studies in the future. Analysis of the mRNA expression in 03 types of breast cancer revealed that the breast invasive ductal carcinoma has accounted for more alteration (1.64%) in which IL-6 was amplified. The earlier data have shown that the IL-6 signaling cascade plays a crucial role in endothelial cell dysfunction (36). In our study, the normal breast tissue accounted for high IL-6 mRNA expression than breast cancer tissue (Supplementary figure 1). Breast histological studies have demonstrated that, as compared to normal tissue, expression of IL-6 in human breast tissue is significantly reduced in invasive ductal carcinoma (37). These findings were also supported by In vitro studies, which demonstrated that the IL-6 expression was significantly reduced in cultures derived from ductal carcinoma. The idea comes from these reports suggesting that genetic alterations in IL-6 pathways are a frequent event in breast cancer (38). In regard to the different breast invasive and non-invasive cancer cell lines, the Hs 742. T non-invasive breast cancer cells were observed with the highest expression of IL-6 (Supplementary figure 1). The observation in the current study that the mRNA expression score of IL-6 in BRCA was lower than LUSC was recently reported by Antczak lab (39). However, the prognostic information indicated that IL-6 showed no effect on the OS, DFS, and PPS of patients with breast cancer (Supplementary fig 2). Our study also revealed significant enrichment of six breast cancer studies on IL-6 (Supplementary Table 1). A study from the Coppola lab shows that IL-6 has been proposed as profiling markers for HER2 negative breast cancer, especially triple-negative breast cancer (TNBC), while having no significant correlation with HER2 positive breast cancer (40). We found that differentially expressed genes with IL-6 in the same functional

category had highly correlated expression patterns. Moreover, the expression of some genes had a highly positive correlation. There were some exceptions to this observation between LinkedOmics and the cBioportal. Further, we found a very low expression of IL-6 in these breast cancer cells, which may be in the negligible range. In this regard, the results from a specific type of cells could change the IL-6 value in breast cancer. There is a need for further molecular and cellular investigation of other breast cancer cells and normal breast cells to clarify the expression and impact of IL-6 on the signaling pathway. The aforementioned information suggests that the relationship between the IL-6 gene and the breast cancer immune microenvironment should be studied in-depth by conducting more molecular-based studies. Based on our results, we can conclude that IL-6 gene mutation rates were, in general, low and that amplification and deep deletion were the key mutation type. These findings can provide a reference for further experimental studies to identify the molecular mechanism of IL-6 in breast cancer progression.

In conclusion, the current study has systematically analyzed the biological function, expression, and molecular alterations of IL-6 in breast cancer. We ultimately determined that the IL-6 gene had, in general, low genetic alterations, and the expression levels of these alterations may be associated with the invasiveness of breast cancer. Instead, we found a rich biological network in breast cancer, which would lead to dysregulation of gene expression and significant dysfunction. Moreover, IL-6 was not associated with the prognosis of breast cancer patients. We believe that our results contribute to guiding further studies of IL-6 RNA modification in breast cancer and will provide new therapeutic strategies for breast cancer.

Conflict of interest

None to declare.

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