



Original Article

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Meta-Analysis of Transcriptomic Responses to Tamoxifen Therapy in Breast Cancer

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Abstract

Tamoxifen (Tam) is an effective hormone therapy in order to reduce the risk of cancer recurrence. Investigation of the effect of Tam on transcriptome features by meta-analysis can help us to understand the effect of Tam on biological pathways and expression of key genes. Here, whole-transcriptome (RNA-seq) datasets (19 samples) were derived from European Bioinformatics Institute (EBI). The process of differential gene expression analysis was carried out through CLC Genomics Workbench (12). The total reads of differential expressed genes were analyzed by Meta-seq package in order to identification of common up and down-regulated genes. The outcomes of meta-analysis indicated that several candidate genes contribute to tumor suppression process. As an example, XIAP-associated factor 1 was reported as an up-regulated gene under Tam therapy. It is a tumor suppressor that contributes to the apoptosis and tumor growth inhibition along with *TP53*. Estrogen-based growth regulation in breast cancer 1 (*GREB1*) as another up-regulated gene is an ESR1 (estrogen receptor 1) that could mediate the estrogen action. The results showed that *PROM1*, *KLHL14* and *FBN2* were highly down-regulated. Our findings suggested that Tam usage in MCF7 cell line could be associated with apoptosis, proteolysis, and tumor suppression. In addition, Tam may decrease the expression of candidate genes involved in tumor progression, invasion, and metastasis.

Keywords

Tamoxifen, Breast cancer, Meta-analysis, RNA-seq

Introduction

According to the last World Health Organization (WHO) report in 2020, there were 2.3 million women diagnosed with breast cancer and 685,000 deaths globally (<https://www.who.int/>). Usually, treatment process for breast cancer depends on the subtype of cancer and metastasis stage. Surgery, radiation therapy, chemotherapy and hormonal therapies are the main strategies for breast cancer treatment [1,2]. Tamoxifen (Tam) is a non-steroidal compound and commonly used as an adjuvant hormonal therapy for patients with breast cancer. [3], which inhibits the estrogen activity through binding to the estrogen receptor (ER) competitively [4]. Its beneficial effects in reducing metastasis, tamoxifen can also lower the risk of death from breast cancer [5]. It has been demonstrated that 10 years of Tam in ER-positive disease produces substantial reductions in rates of recurrence and in breast cancer mortality during the first decade [6]. There are several investigations carried out to describe the hormonal therapy effects and drug response mechanism [7-9]. The appropriate drug response is a complex interdependent procedure that is highly dependent upon several factors including the genetic variants background, lifestyle, climate, smoking, and alcohol consumption [10]. Moreover, consumption of Tam can have side effects that may affect the purpose of the treatment [11]. It is shown that Tam induces DNA damages in human

endometrial cells and increases the incidence of endometrial tumors [12]. Therefore, investigating the effect of Tam on transcriptome features by meta-analysis can allow us to reduce the side effects and explain the role of key genes under Tam therapy.

Gene expression analysis at transcriptome level is a reliable tool that can show the effects of hormone therapy on genes expression profiles. It has been shown through several studies that there is a close association between transcriptome response and therapeutic drug consumption [13-16]. It was found from one of the main investigations that carried out a comprehensive transcriptomic analysis on Tam resistance that lncRNAs profiling breast cancer cells would provide a new light on the identification of novel endocrine resistance biomarkers [17]. Lanceta, et al. (2020)

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carried out RNA sequencing (RNA-seq) and pathway analysis in ER+ MCF7, and reported 2183 up-regulated and 1548 down-regulated transcripts that contributed to cell cycle, DNA replication, and DNA repair and autophagy [18]. It was indicated that the effects of Tam on the breast cancer MCF-7 cell line are mediated by the activation of important signaling pathways including Tp53 and Mitogen-Activated Protein Kinase (MAPKs) to induce apoptosis [19]. Meta-analysis of integrated Chip-seq and transcriptome data demonstrated that many transcription factors such as *POU5F1B*, *ZNF662*, *ZNF442* affected by ER were up-regulated [20]. Interestingly, the meta-analysis investigations showed that that circRNAs could be considered as a good potential clinical biomarkers in breast cancer patients [21,22].

Current study investigates the effect of Tam on the gene expression profile at transcriptome level. Meta-analysis of genes expression studies could be useful to understand the drug response mechanism; also, it would provide a new insight to the increase of the chance of survival, decrease the side effects, and select an appropriate strategy for the therapy period.

Materials and Methods

Data collection

In current study, the whole-transcriptome (RNA-seq) dataset of four investigations were derived from EBI (<https://www.ebi.ac.uk/>). More details of collected datasets were provided in Table 1.

Quality control and trimming

Various parameters were applied in CLC Genomic Workbench (12) in order to determine the quality for each sample including length distribution, GC content, ambiguous base content, Phred score, nucleotide contribution, enrich 5 mers, and duplicate sequences [23]. Due to the fact that the adaptor sequences were cleaned in the achieved datasets, the adaptor trimming was not achieved.

RNA-seq analysis, meta-analysis and gene ontology enrichment analysis

The reference genome (hg38) and all of the annotations were downloaded from Ensembl database (www.ensembl.org). Also, the process of differential expressed genes (DEGs) analysis was carried out through CLC Genomics Workbench (12) on the basis of following parameters including mismatch cost = 2, insertion cost = 3, deletion cost = 3, length fraction = 0.7, similarity fraction = 0.8, expression value = total reads,

calculate RPKM for genes without transcripts = Yes [24]. The total reads of DEGs were analyzed by Meta-seq package in order to identification of common up and down-regulated genes among experiments [25]. The outputs of meta-analysis were used in gene ontology enrichment analysis ($P \leq 0.01$) by gene ontology consortium (<http://geneontology.org>). Heat map and volcano plot were implemented to visualize the Meta-analysis results.

Results

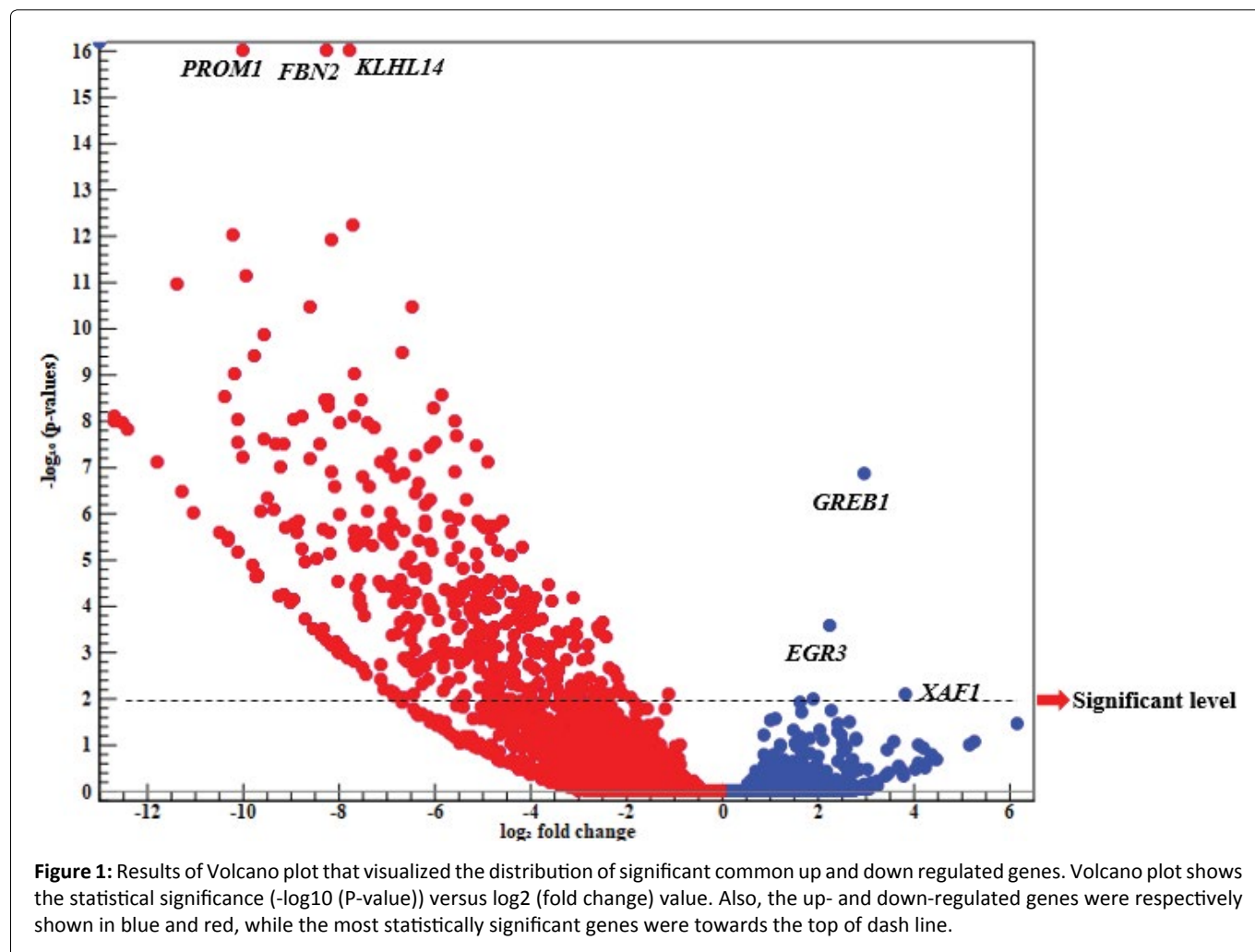
Meta-analysis outcomes

Volcano plot: Results of the meta-analysis showed that there were 21515 common up and down-regulated genes, while findings of Volcano plot indicated that most of DEGs were classified as the down-regulated genes. At significant levels ($P < 0.01$, $-\text{Log}_{10}(P\text{-value}) > 2$), there were 910 and 3 candidate genes reported as the significant down- and up-regulated ones (Figure 1).

Results of Volcano plot showed that three candidate genes including *GREB1*, *EGR3*, and *XAF1* were clustered as the up-regulated genes. It was also found that the estrogen-based growth regulation in breast cancer 1 (*GREB1*) was an early estrogen-responsive gene, and there was a close association between *GREB1* expression and estrogen levels in breast cancer patients. In fact, *GREB1* was an ESR1 (estrogen receptor 1) that could mediate the estrogen action. It was reported that the optimal level of *GREB1* expression was required for breast cancer cells proliferation [26]. However, *GREB1* knockdown could prevent the breast cancer cell lines proliferation; therefore, it was found that targeting *GREB1* could provide a possible treatment strategy through inhibiting the tumor-promoting pathways [27]. Early growth response (*EGR*) is a family of transcription factors that contributes to various biological pathways [28]. It was reported that *EGR3* could be induced by estrogen in breast cancer *MCF-7* cells and consequently, become involved in the estrogen-signaling pathway [29]. Moreover, *EGR3* levels were significantly higher within tissue samples derived from patients with recurrent breast cancer compared to those with primary tumors [30]. XIAP-associated factor 1 (*XAF1*) is a tumor suppressor observed in the multiple human neoplasm's [31]. It was shown that *XAF1* loss expression would be resulted from tumor staging and its dysfunction was associated with tumor progression. Moreover, its appropriate expression could play a critical role in the apoptosis inductions and tumor growth inhibition in the gastric cancer [32]. Pinto, et al. (2020) reported that *XAF1* may be considered as a *TP53* function modifier through increasing the transcriptional

Table 1: More details of RNA-seq datasets to discover the genetic variants and gene expression analysis.

Accession number	Control samples	Treatment samples	Drug type	Cell line
E-MTAB-822	1	2	Tamoxifen	MCF7
E-GEOD-59536	1	1	Tamoxifen	MCF7
E-GEOD-62613	1	1	Tamoxifen	MCF7
E-GEOD-78199	6	6	Tamoxifen	MCF7
Total	9	10	----	----



activity of hypo orphic *TP53* variants [33]. *TP53* is one of the most significant tumor suppressor genes, which is commonly mutated in various cancers such as breast cancer [34].

It is noteworthy that *PROM1*, *FBN2*, and *KLHL14* were highly down-regulated (Figure 1). Prominin 1 (*PROM1* or *CD133*) is known as a biomarker of cancer stem cells; however, its biological role is not illustrated perfectly [35]. Findings showed that there was an association between *PROM1* levels and malignancy properties stages including initiation, progression, and metastasis. Moreover, it was reported that *PROM1* would contribute to the cell motility and invasion, and may affect the malignancy of breast tumors. Also, *PROM1* genes were highly expressed in TNBC cell lines [36,37]. Fibrillin-2 (*FBN2*) is an extracellular calcium-binding micro fibril that contributes to several biological pathways including the bone mineralization, osteoblast maturation, and calcium binding (UniProtKB: P35556). *FBN2* is considered as a biomarker of cancers early diagnosis. For example, Promotor hypermethylation of *FBN2* is associated with colorectal cancer as an early event. In fact, Methylation may lead to *FBN2* down-regulation in primary tumors [38], while Kelch-like protein 14 (*KLHL14*) belongs to Kelch family genes and interacts with torsin-1A (UniProtKB: Q9P2G3). It was shown that *KLHL14* was significantly over-expressed in breast cancer compared to normal breast tissues, and had a positive relationship with tumor aggressiveness [39]. Moreover,

findings indicated the vital role of *KLHL14* in the development of various cancers including ovarian cancer [40].

Heat map analysis: The visualization of meta-analysis results derived from control and treated samples were shown in a heat map (Figure 2).

It was also shown that mitochondrial respiratory genes were expressed at lower levels within treated samples compared to control ones. In current study, it was reported that *MT-CO1*, *MT-CO3*, *MT-ND2*, *MT-ND4*, *MT-ND5*, *MT-ND6*, and *MT-ATP6* were the mitochondrion respiratory genes. *MT-ND* genes provide NADH dehydrogenise. This protein is a part of a large enzyme complex encoded by the mitochondrial genome. Moreover, the dysfunction of *MT-ND* proteins would lead to the electron transport chain disruption and ATP production. *MT-CO* genes encode Cytochrome C Oxidase subunits within mitochondria. It is found that they were the last enzyme in the mitochondrial electron transport chain for ATP synthesis [23]. Findings derived from heat map analysis suggested that several candidate genes including *ALDOA*, *RPL13*, *HSPB1*, *GATA3*, *KRT18*, *IGFBP4*, and *SULF2* were associated with the lowest gene expression level in treated samples. Aldolase (*ALDOA*) is known as an oncogene, which is a glycolytic enzyme that promotes the metastatic progression of cancers [41,42]. It was shown that there was an association between *ALDOA* knock down and proliferation reduction of

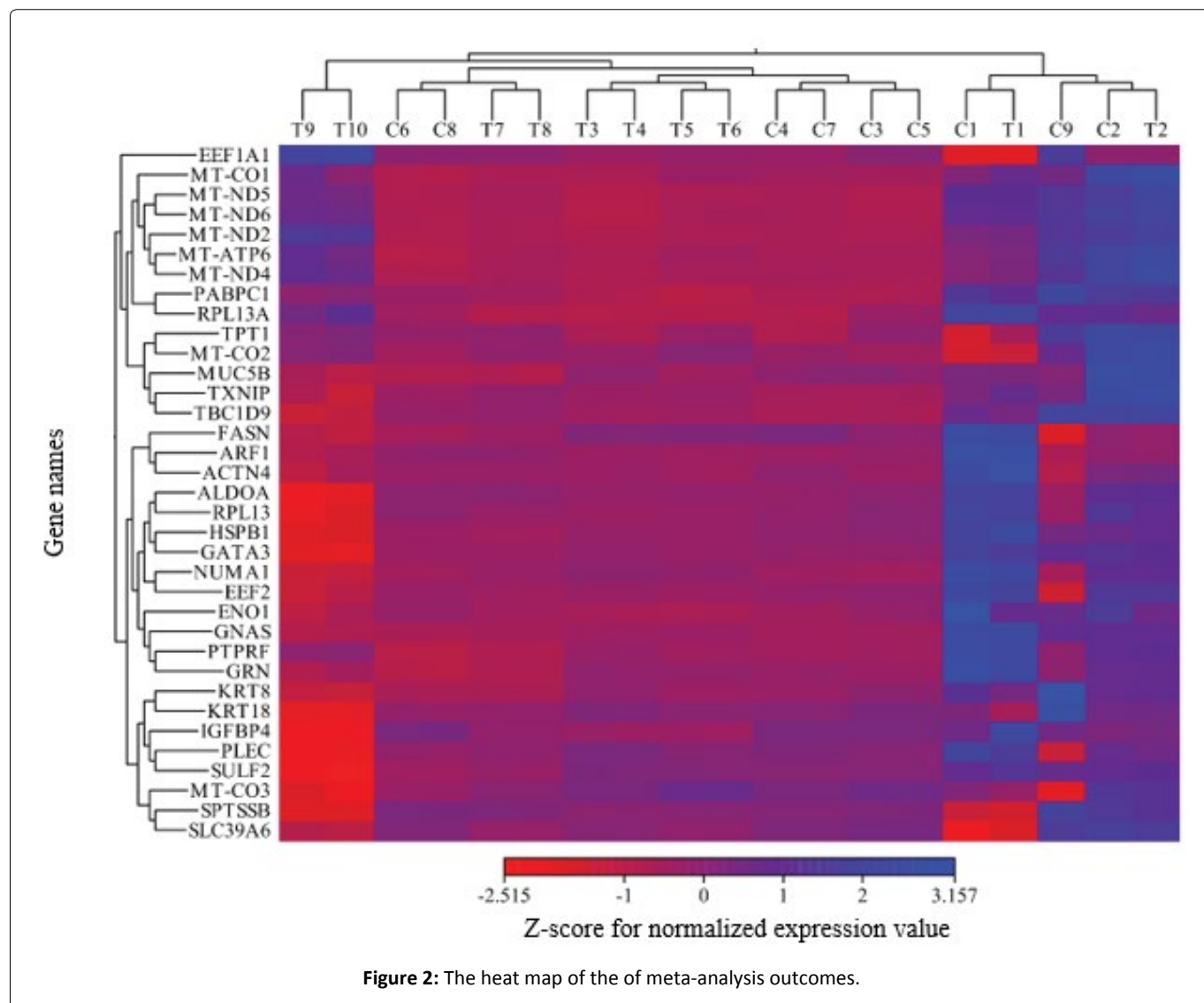


Figure 2: The heat map of the of meta-analysis outcomes.

breast cancer cells [43]. *RPL13* encodes a ribosomal protein, which is a component of 60S subunit. Ribosomal proteins (RP) expression patterns were implemented as a diagnostic strategy in human cancers. Reports of several cancers indicated the deregulation of RP expression (e.g. *RPL13*) [44]; therefore, it could be said that *RPL13* would be expressed at significantly higher levels in benign breast lesions compared to that of breast carcinomas (Gene Cards: GC16P089674). *HSPB1* is a member of heat shock proteins, which are considered as a large family of proteins with breast cancer behavior [45]. It was reported that the down-regulation of *HSPB1* protein may induce the expression of phosphatase and tensin homologue (PTEN) as a tumor suppressor gene. In other words, PTEN stabilization depends upon *HSPB1* low-level expression [46]. *GATA* binding protein 3 (*GATA3*) is a highly conserved transcription factor that belongs to *GATA* family and leads to the expression of a large number of important genes [47]. Furthermore, it contributes to the human growth and differentiation cells including the mammary tissue. Lower levels of *GATA3* expression in breast tumors are associated with larger tumors. Therefore, *GATA3* is considered as an important gene in breast cancer development; however, its exact role as an oncogene or tumor suppressor is unclear

[48,49]. Keratin 18 (*KRT18*) is a member of the intermediate filament family of cytoskeleton protein that is involved in the tissue integrity, and its over-expression has been reported in many cancers [50]. It was also re-reported that *KT18* was over-expressed in breast cancer and played a vital role in the breast tumorigenesis and tumor dedifferentiation [51]. Insulin-like growth factor binding proteins (*IGFBPs*) would regulate many cellular processes such as cell proliferation. *IGFBPs* act as binding proteins for insulin-like growth factor (IGF); furthermore, it is evidenced that they play a critical role in the cancer progression, especially in breast cancer [52]. However, there are various reports regarding their activities as oncogene or tumor suppressors. *IGFBP5* may be considered as an oncogene due to its contribution to metastasis, proliferation, and limited responses to endocrine treatment; also, it acts as a tumor suppressor because of its apoptotic role, anti-metastatic function, and anti-migratory effects [53]. Sulphates family, which includes sulfatase1 (*SULF1*) and sulphates 2 (*SULF2*), plays an important role in the multiple biological pathways through regulating the sulfation status [54]. It was confirmed that *SULF2* would promote the breast cancer progression and regulate the tumor-related genes expression in breast cancer [55].

Table 2: Results of GO enrichment analysis of common up and down regulated genes.

GO Term	Reference genes in category	Description	DGEs count	Gene names
0051248	20	Negative regulation of protein metabolic process	8	<i>CTSZ, GPX1, GSTP1, IGFBP3, ITM2C, MAGEA2, MAGEA3, MECOM</i>
0010941	30	Regulation of cell death	10	<i>CTSZ, GPX1, GSTP1, IGFBP3, MAGEA3, MALT1, MECOM, MSX1, PAX8, TRIM2</i>
0030162	6	Regulation of proteolysis	4	<i>CTSZ, GPX1, MAGEA3, MALT1</i>
0032269	17	Negative regulation of cellular protein metabolic process	7	<i>CTSZ, GPX1, GSTP1, IGFBP3, MAGEA2, MAGEA3, MECOM</i>
0043281	4	Regulation of cysteine-type endopeptidase activity involved in apoptotic process	7	<i>GPX1, MAGEA3, MALT1</i>
0045861	4	Negative regulation of proteolysis	3	<i>CTSZ, GPX1, MAGEA3</i>
0052548	4	Regulation of endopeptidase activity	3	<i>GPX1, MAGEA3, MALT1</i>
2000116	4	Regulation of cysteine-type endopeptidase activity	3	<i>GPX1, MAGEA3, MALT1</i>
0043067	29	Regulation of programmed cell death	9	<i>GPX1, GSTP1, IGFBP3, MAGEA3, MALT1, MECOM, MSX1, PAX8, TRIM2</i>
0019904	12	Protein domain specific binding	5	<i>CCN1, CXADR, GPX1, SCNN1A, TCEAL9</i>
0004602	2	Glutathione peroxidase activity	2	<i>GPX1, GSTP1</i>
0070062	49	Extracellular exosome	14	<i>ACSL4, AKR1B1, CRISPLD1, CTSZ, FSTL1, GREB1, GSTP1, IGFBP7, ITM2C, LDHB, MSN, PSAT1, RAB34, SCNN1A</i>
0043230	50	Extracellular organelle	14	<i>ACSL4, AKR1B1, CRISPLD1, CTSZ, FSTL1, GREB1, GSTP1, IGFBP7, ITM2C, LDHB, MSN, PSAT1, RAB34, SCNN1A</i>
1903561	50	Extracellular vesicle	14	<i>ACSL4, AKR1B1, CRISPLD1, CTSZ, FSTL1, GREB1, GSTP1, IGFBP7, ITM2C, LDHB, MSN, PSAT1, RAB34, SCNN1A</i>
0044432	28	Endoplasmic reticulum part	9	<i>ACSL4, COL9A2, CTSZ, FADS2, FSTL1, GJA1, IGFBP3, IGFBP7, RCN1</i>

Gene ontology enrichment analysis: Results derived from GO enrichment analysis of DEGs showed that most of DEGs were enriched in the regulations of apoptosis and cell death pathways (Table 2). Cell cycle damage is considered as the main cause of cancer incidence; therefore, the balance between proliferation and cell death is disrupted in cancers. It was shown that apoptosis inactivation would play a vital role in the process of cancer development [56]. Therefore, it could be said that significant GO term of apoptosis pathways could contribute to cancerous cell death under Tamoxifen therapy. Proteolysis is a hydrolysis reaction that occurs when peptide bonds and proteins are broken down into smaller polypeptides or amino acids. There is an association between the metastasis of malignancy tumor and overexpression of proteolytic enzyme. More importantly, proteolysis inactivation in cancerous tissue plays a critical role in the inhibition of tumor invasion, angiogenesis, and migration [57]. Interestingly, our findings suggested that negative proteolysis regulation and consequent regulations of proteolytic pathways could be regarded as considerable GO terms that control the cancer under Tamoxifen treatment (Table 2).

Discussion

Generally, breast cancer tumors are hormone receptor-positive with highly estrogen- and progesterone-dependent growth rates. Tamoxifen is a type of hormonal therapy implemented with the purpose of treating the estrogen receptor-positive breast cancer; also, it can decrease the risk of invasive cancer development. However, it is able to affect the gene expression profile at transcriptome level [58]. Results achieved from RNA-seq analysis in MCF7 cell line under Tamoxifen therapy revealed that there were several candidate genes and biological pathways that could result in the tumor suppression and consequently, effective treatments. XIAP-associated factor 1 (*XAF1*) can be up-regulated under Tamoxifen therapy; also, it is a tumor suppressor that plays a critical role in the apoptosis induction and tumor growth inhibition in gastric cancer [32]. Interestingly, it was reported that the combination of *XAF1* with *TP53* would act as a modifier. *TP53* is a key tumor suppressor gene, which is generally mutated in various cancers such as breast cancer [33,34]. It was found in current study that *PROM1* and *KLHL14* were down-regulated under

hormone therapy; also, an association was observed between *PROM1* levels and malignancy features including initiation, progression, and metastasis. Results showed that *PROM1* led to the cell motility and invasion and may impact on the breast tumors malignancy [36,37]. It was observed that there was a high level of *KLHL14* expression in breast cancer compared to the normal breast tissues, which was associated with considerable tumor aggressiveness. *KLHL14* also played a vital role in the development of various cancers such as ovarian cancer [40], and results derived from GO enrichment analysis of DGEs indicated that most of DGEs could considerably result in the cell death, apoptosis, and negative regulation of proteolysis process. Generally, apoptosis has a critical role in the inhibition of cancerous cell growth. Proteolysis activation in cancerous tissues would result in the tumor invasion [56,57]. All of the above-mentioned findings were in accordance with those of Rouhimoghadam, et al. (2018) who showed that tamoxifen treatment on the breast cancer MCF-7 cell line could lead to the apoptosis induction through activating the apoptotic signaling pathways including Tp53 and MAPKs [59]. Comparable results reported that Tamoxifen induced the apoptosis through inhibiting the cancerous inhibitor of protein phosphatase 2A (CIP2A) and phospho-Akt (p-Akt) in ER-negative breast cancer cell lines [60]. Frasor, et al. (2006) also reported that Tamoxifen could regulate the gene expression in breast cancer cells and indicated several Tamoxifen-regulated candidate genes including SOCS1 and *IEX-1*, which was in accordance with our findings. Cytokine Signaling 1 (SOCS1) suppressor is considered as a tumor suppressor that plays a negative regulatory role for cytokine action through JAK/STAT pathway and suppresses the growth of hepatocellular carcinomas. *IEX-1*, which is an immediate early response gene that can widely be expressed in various tissues, is over expressed in breast cancer cells and has an inhibitory effect on breast cancer cell proliferation [61]. Generally, it could be concluded that Tamoxifen implementation in the treatment procedures could be beneficial at the transcriptome level; however, it may induce the oncogene expression in rodent uterine [62].

Conclusion

Results of current study that was carried out at transcriptome level showed that Tamoxifen consumption in MCF7 cell line could be associated with candidate genes and biological pathways that contribute to the apoptosis, proteolysis, and tumor suppression. Moreover, Tamoxifen could decrease the expression of candidate genes involved in tumor progression, invasion, and metastasis.

Ethics Approval and Consent to Participate

This investigation is in accordance with relevant guidelines and regulations of Shiraz University of Medical Science (permit number: IR.SUMS.REC.1399.1276).

Author Contributions

HKK and STH conceived the study. HKK contributed to data analysis and prepared the primary draft of manuscript. STH and KBL revised the manuscript. All authors read and approve the manuscript.

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Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

The datasets which were analyzed during the current study are available in the European Bioinformatics Institution (EBI) repository (Table 1).

Acknowledgments

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

Preprint Repository

The most parts of the manuscript have been published previously in Research Square website (<https://doi.org/10.21203/rs.3.rs-783422/v1>).

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