Differences in potential key genes and pathways between primary and radiation-associated angiosarcoma of the breast

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ABSTRACT

Background: Angiosarcoma of the breast is a high-grade malignant soft tissue tumor, it can be divided into primary and radiation-associated angiosarcoma (secondary). However, the differences between primary and secondary angiosarcomas in terms of pathogenesis, clinical behavior, early diagnosis biomarkers, genetic abnormalities, and therapeutic targets remain to be fully elucidated. At the same time, due to its rarity, most of current information relating to angiosarcoma is provided by case reports. Therefore, exploring the mechanisms of primary and secondary breast angiosarcoma have important value for the discovery of new biomarkers and research into potential therapeutic targets.

Methods: The differentially expressed genes (DEGs) between 36 cases of primary angiosarcoma and 54 cases of secondary breast angiosarcoma were screened. Then, the DEGs were used to gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. Then, a protein-protein interaction (PPI) network was constructed using the STRING database.

Results: A total of 18 DEGs were identified, of which 13 were upregulated and 5 were downregulated in secondary breast angiosarcoma. The GO enrichment analysis showed that the DEGs were most enriched in metabolism, energy pathways, and protein metabolism in biological processes. The enriched signaling pathways of DEGs were the transforming growth factor-β (TGF-β), Wnt, Hippo and PI3K-Akt signaling pathways. Then, the PPI network was conducted and hub genes were identified and they were involved in thyroid hormone, Hippo and other signaling pathways.

Conclusion: This study lay the foundation for the discovery of effective and reliable molecular biomarkers and essential therapeutic targets for these malignancies.

Background

Angiosarcoma is a high-grade malignant soft tissue tumor, originating from lymphatic or vascular endothelial cells, which exhibit rapid proliferation and invasion capacity that is associated with a poor prognosis [1,2]. Angiosarcoma may arise in any location of the body, such as bone, liver, heart or breast; it occurs most frequently in the skin and soft tissues [3]. When it occurs in the breast of younger women with no previous cancer history or any associated factor that is called primary breast angiosarcoma. It is most frequent in women between age 20 to 50 and usually present as a lump that appears in the parenchymal tissue of the breast without any changes in the skin [4]. Although the mechanisms underlying angiosarcoma remain to be fully clarified, recent studies have highlighted some definite risk factors, including UV irradiation, chronic lymphoedema, occupational exposure to vinyl chloride, and certain familial syndromes [5], as well as a history of radiotherapy, which is one of the most important factors. Breast cancer is one of most common malignancies and the second leading cause of cancer-related death in women [6,7]. With the rapid improvement of medical and health care, most breast cancer patients are diagnosed at an early stage. In the last few decades, breast conserving surgery combined with whole-breast radiotherapy (WBRT) has become the gold standard treatment for breast cancer [8-12]. However, radiation-associated angiosarcoma of the breast (secondary breast angiosarcoma) is a very serious complication of radiation exposure and occurs mainly in elderly women after a median period of 4–8 years post-radiotherapy [13]. Secondary breast angiosarcoma often occurs in the irradiated area after breast-conserving treatment [14]. It is an extremely rare malignant...
tumor, and its incidence is less than 1% of all soft tissue sarcomas [15]. Like primary breast angiosarcoma, secondary breast angiosarcoma also has a worse prognosis than breast cancer.

Although primary and secondary breast angiosarcomas share some similarities, such as the first symptom is the appearance of lumps in the breast [16,17], and have similar morphology [18], these entities are clinically and histologically different. Primary breast angiosarcoma is also very rare, accounting for 0.04% of malignant breast cancers and 8% of breast sarcomas. It usually occurs in the parenchyma of unirradiated breast and may or may not spread to the skin and subcutaneous tissue. It is manifested as a painless diffuse enlargement of the mass or no mass, and the median age of onset is approximately 40 years old [19]. In contrast, secondary breast angiosarcoma usually originates from the dermis and subcutaneous tissue of the irradiated breast and presents with ecchymosis, erythema, pruritus, skin thickening, or some combination of these features. Because secondary breast angiosarcoma is manifested clinically as ecchymosis or an area of thickened skin, features that are very similar to bruises, this malignancy is difficult to distinguish and the diagnosis is usually delayed [20,21]. Moreover, some studies have revealed differences in the pathogenesis and mechanism of development between primary and secondary angiosarcomas.

The progression of primary angiosarcoma may be related to mesenchymal stem cells or progenitor cells and can therefore occur anywhere in the body. In contrast, secondary angiosarcoma develops due to external damage, and is mainly limited to the damaged area [22]. Furthermore, molecular studies have shown that MYC and KDR were significantly upregulated in secondary angiosarcomas compared to primary angiosarcomas [23]. However, the exact differences between primary and secondary angiosarcomas in terms of pathogenesis, clinical behavior, early diagnosis biomarkers, genetic abnormalities, and therapeutic targets remain to be fully elucidated. Due to its rarity, most of the current information relating to angiosarcoma is provided by case reports and single-institution retrospective cohort studies and the research with large-scale genomic studies published to date are very limited. Meanwhile, a growing number of studies found that a variety of signaling pathways were involved in the development of angiosarcoma. However, few studies have addressed the differences among the signaling pathways involved in primary and secondary angiosarcomas, which have limited the diagnosis and treatment of these two types of angiosarcoma. Therefore, identification of new biomarkers and therapeutic targets is important for improving the diagnosis and treatment of primary and secondary breast angiosarcomas.

In this study, we aimed to identify novel biomarkers, pathways, and potential therapeutic targets for primary and secondary breast angiosarcomas to facilitate future research. We downloaded the GSE52664 and GSE49790 datasets from the gene expression omnibus (GEO) database and identified the differentially expressed genes (DEGs) between primary and second breast angiosarcomas. Then, other approaches including gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis, and protein-protein interaction (PPI) network construction were performed to predict the potential regulatory mechanisms.

Materials and methods

Data collection

Two datasets (GSE52664 and GSE49790) were retrieved from the GEO database (http://www.ncbi.nlm.nih.gov/geo/). The GSE52664 dataset consisted of 26 primary breast angiosarcomas and 29 secondary breast angiosarcomas, all of which developed following radiotherapy for primary breast cancer. The GSE49790 dataset consisted of 10 primary breast angiosarcomas and 25 secondary breast angiosarcomas. The two datasets have the same characteristics.

Data processing and DEG analysis

We screened the DEGs between primary and secondary breast angiosarcomas based on the following criteria: In the GSE49790 database, the criteria for DEGs were fold change (FC) > 2.0 and the P-value < 0.05. In the GSE52664 database, a false discovery rate (FDR) of 0% and a fold change (FC) of minimum 2.0 were considered statistically significant. VENN (Version 2.1.0) was used to identify the overlapping DEGs in the two datasets.

Functional enrichment analyses

To analyze the function, the overlapping DEGs were subjected to GO and KEGG pathway analysis using the Functional Enrichment analysis tool (FunRich3.1.3) [24] and KEGG Orthology Based Annotation System (KOBAS) 3.0 (kobas.cbi.pku.edu.cn/) [25], respectively. P < 0.05 was considered to indicate statistical significance. The top GO and KEGG pathway terms were depicted using the ggplot2 (version 3.1.1) package in R.

PPI network construction

The PPI network was predicted by the STRING database (version 11.0; http://www.string-db.org/) to explore the functions of the overlapping DEGs. No more than 20 interactions were shown and the minimum required interaction score was 0.4 (medium confidence). The disconnected nodes in the identified network were hidden.
Table 2
The up-/down-regulated differentially-expressed genes (DEGs) between secondary and primary AS in GSE49790 datasets.

| DEGs | gene symbol |
|------|-------------|
| Up-regulated genes | PROX1 GPR1 PTX3 CTLA4 EYA1 |
| | CLDN10 SCN3A IQCA1 MFNG GNG4 |
| | SCN3B UCHL1 CAAXDPR3 MYC GNP2 |
| | FAP6 DISP CDK12 RF3BP1 ECLN |
| | POTEI DGCH2 GPR1 RPTX3 PPRC9 |
| | PRSS21 ROPN1L SNGH8 GAL IL12BR2 |
| | CHRNA1 SL7A1 ALPK3 SEMA3A SLC17A9 |
| | WASF3 Cbcrf1-41 Icos SEMA3D SHPRK2 |
| | POTEF ZSWIM5 PCID1 GRAP PLK1 |
| | YHDC MAST1 CENPF GETP TSTA3 |
| | SXN1 POLR3G BCA1 DNAJC12 PMG5 ODG1 |
| | C1QBP SLC19A1 KIAA409 CBS SMDY2 PVT1 |
| | C1orfl0 SFN19A1 KIAA0435 MLT1A |
| | C2K2 PRKAA2 MRH17IG LOX MYO7A |
| | CDC47L1 HIST1H28O SLC2A4 RBBP3 |
| | HIST1H2AJ HIST1H4D TERC HIST1H4C TAF4B |
| | HIST1H2AE CCNB1 PRMD8 TOP2A FAM83D UHRF1 |
| | HIST1H2BM PRI11 GRAPL FSD1 ABC4C |
| | HIC2 HIST1H2AL CCNA2 CLDN5 GPR97 |
| | LEP3 NT3DC3 NPI6 NLSM1 HIST1H11B2 |
| | KHK TSPAN11 NOV SGM1 SLC7A5 SCLM2 |
| | TRIB3 LOXHD1 BIRC5 RPSK8A KRT18 |
| | CMLB TTLL12 S100A4 UBEC2 ABCA3 |
| | FLNC HP5 TRN | |
| | DEGs | gene symbol |
| Down-regulated genes | LXN APLNR R2L12 TMEM115C |
| | TNFAIP6 SNORD114 Chor4 CHIC1 IGFBP3 |
| | LRRC17 TRO PXB1 NRXN3 C3 |
| | NCOA2 GPX8 GYU1K33 NOSTRIN ANO1 |
| | APOD SEMAD6 SVEP1 TSC2D3 EDL3 |
| | ECM2 EBP2 ILR1 SGP20 FBXN |
| | FPK2 PLD2C XH | |
| | PCDH85 ADAMTS9 HMGAM1 CDC20 |
| | GLI3 RUNXI SPAG16 P90X1 POTEF |
| | BEX4 KCNE4 PCDH17 CTGF PTGIS |
| | GLIPR1 MAMDC2 TMG2 TSP513 |
| | ERRF1 MEI1SP1 KCNM4 CYRF1 |
| | FAM184A SGCO DCC VGL3 |
| | HOXB2 SRD SSF P60D3 |
| | NR4A2 BABM1 SMARCA1 SPPX1 |
| | PLEXHA5 ANXA1 SLC16A4 COL1DA |
| | ZNF334 MAFB ZNF347 FAS |
| | TRX5 PI3 JAM2 GUCY1A3 SPP2 |
| | CYR1 Y ASPN LDHB STEAP4 MXRA5 |
| | CDC80 CTSO ISLKR HMCN1 EGR2 |
| | OLFLM1 BEND7 FORB OLFML3 |
| | EGR1 CX3CR1 ZNF382 DAOH1 PAMPD |
| | PALLD OLFM2 LRN5 ZNF462 LOXL2 |
| | RERG EFHD1 CYBD1 SPON1 COL5A2 |
| | NEO1 LAMA2 PRICKLE1 SNX7 ACTA2 |
| | CRISPLD1 ZNF320 GALNT1 PDE7B ZNF528 NRP4 |
| | ZNF660 Cbcrf4-43 MYF22 |
| | HEYL sulfi NOTCH3 CHD2 |
| | ZC412 H C7orf58 PRICKLE2 KCN2 JIA15986 |
| | EPS52L4A EMCN SPCAR1 P2Y14R14 FST1L |
| | FG77 FG77 ADAMTS1 ATL1 MEET7A CD44 |
| | SGC7 JUN LARP6 DPT DCBLD2 |
| | TEM30B FAM66C FAM13C PCX2L2 |
| | THBD PTI2R FBLN7 TSWG1 CDC7 |
| | DCN CDH11 OGN DACH1 SERNINE2 |
| | GSTM5 NTRK2 MEG3 GATA6 CPH |
| | TSH3 E3 PARM1 BMRP1 A SVM |
| | SEDN3 IGFBP3 DACT1 |
| | SRPR3 CO1L1A2 EMG1 EFN1 CDK14 |
| | CLMN LOX1L SYT2 PCDH1 FM01 |
| | VSG21 LPAR4 ZNF238 ORO2B GUCY1A2 |
| | MAGED2 JPH1 GSTM1 MGP PDGFRB |
| | (continued on next page) |

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Subsequently, Cytoscape software (version 3.7.1) was used to visualize the PPI network. The Molecular Complex Detection (MCODE) application in Cytoscape was employed to select significant modules using the default parameters. CytoHubba was used to calculate the degree of each protein node and the top 10 genes were described as hub genes. Then, FunRich3.1.3 and KOBAS were used to conduct functional enrichment analyses of the hub genes in the modules.

**Results**

**Identification of DEGs in the expression profiles**

Compared to primary angiosarcoma, we screened 103 DEGs in secondary angiosarcoma, including 54 up-regulated and 49 down-regulated genes in the GSE52664 dataset (Table 1). For the GSE49790 dataset, a total of 794 DEGs were identified (192 upregulated and 602 downregulated) in secondary breast angiosarcomas compared to the primary breast angiosarcomas (Table 2). As shown in the Venn diagram (Fig. 1), 18 overlapping DEGs (5 downregulated and 13 upregulated) were identified among the two datasets (Table 3).

**GO and KEGG pathway analysis of the overlapping DEGs**

GO and KEGG pathway analysis were performed to gain a more in-depth understanding of the overlapping DEGs. Metabolism, energy pathways, and protein metabolism were dramatically enriched in secondary angiosarcoma, including 54 up-regulated and 49 down-regulated genes in the GSE52664 dataset (Table 1). For the GSE49790 dataset, a total of 794 DEGs were identified (192 upregulated and 602 downregulated) in secondary breast angiosarcomas compared to the primary breast angiosarcomas (Table 2). As shown in the Venn diagram (Fig. 1), 18 overlapping DEGs (5 downregulated and 13 upregulated) were identified among the two datasets (Table 3).
biological processes (BP) (Fig. 2). Perinuclear region of the cytoplasm, nucleolus and exosomes were mainly enriched in cellular component (CC) (Fig. 3). Transcription factor activity, serine-type peptidase activity and cytoskeletal protein binding were mainly enriched in molecular function (MF) (Fig. 4). In addition, the most enriched KEGG pathways were the TGF-β, T cell receptor, Wnt, Hippo and PI3K-Akt signaling pathways (Fig. 5).

**PPI network and sub-modules analysis**

STRING was used to construct the PPI network to further explore the underlying associations between the DEGs (Fig. 6A). The top two modules were identified with the MCODE application (Fig. 6B,C). Module 1 consisted of 15 nodes and 36 edges, with a score of 5.143. Module 2 consisted of four nodes and six edges. CytoHubba was used to screen out the top 10 genes as hub genes (Fig. 6D,E). MYC was identified as the most outstanding gene. Details of the top 10 hub genes are shown in Table 4. GO and KEGG pathway enrichment analysis were then conducted to investigate the functional associations of the top 10 hub genes. The hub genes were mainly related to protein metabolism and cell proliferation and differentiation, adhesion, transcription factor activity, serine-type peptidase activity and cytoskeletal protein binding, as well as known transcription factors (Table 5).

**Discussion**

Angiosarcoma is a highly malignant soft tissue sarcoma that originates from vascular or lymphatic endothelial cells, accounting for about 1%-2% of soft tissue sarcomas. It occurs mainly in the head, face, neck and other parts, and its occurrence is related to chronic lymphedema and radiation [26,27]. Patients diagnosed with angiosarcoma lesions have poor survival, with 5-year disease-free survival and 5-year survival rates of <50% and <35%, respectively [28]. Studies have shown that more than half of patients with angiosarcoma have high prevalence of recurrence and distant metastases, and eventually die of the malignant tumor [29].

Angiosarcoma of the breast can be divided into primary and secondary malignancies. Primary angiosarcoma of the breast is a rare malignant tumor that occurs without a history of cancer or identifiable risk factors and usually occurs in women between the ages of 30 and 50 years [30]. Recently, multiple reports highlighted the increasing incidence in secondary breast angiosarcoma with the rise in the number of women with breast cancer treated with breast conservation therapy (BCT) and postoperative radiotherapy [22,30,31]. However, most current studies on primary and secondary angiosarcomas are case reports and little is known about the genetic abnormalities due to the lack of large-scale genomic studies, which seriously hinders the progress of diagnosis and treatment of angiosarcoma. Therefore, there is an urgent need to find effective biomarkers and therapeutic targets for early diagnosis and treatment of primary and secondary angiosarcomas.

In this study, we downloaded two datasets from the GEO database, which together contain 36 cases of primary angiosarcoma and 54 cases of secondary angiosarcoma. A total of 18 DEGs were identified, of which 13 were upregulated (UNC5A, CTLA4, ISLR2, MYC, ICOS, CMBL, IQCA1, GCOM1, WASF3, RELN, PGM5, CDC24L, CETP) and five were downregulated (TGM2, BNC2, LXN, SERPINE1 and BAMBI) in secondary angiosarcoma compared to primary breast angiosarcoma. We then built the related PPI networks of these DEGs and identified hub genes, which showed that MYC, FOXP3 and SERPINE1 were the most outstanding genes.

MYC is a proto-oncogene that plays a key role in a variety of oncogenic pathways, such as cell proliferation and differentiation, adhesion, invasion and apoptosis [32]. Lae et al. reported that MYC amplification was detected in all 32 cases of breast radiation-induced angiosarcomas, but only one out of 15 cases of primary angiosarcoma [33]. Styring et al. found that MYC was upregulated in secondary angiosarcoma [34]. Thariat et al. demonstrated that C-myc overexpression can be used to identify radiation-induced angiosarcoma [35]. Mito et al. revealed that MYC overexpression is common among radiation-induced angiosarcomas compared with other angiosarcomas [36]. Requena et al. [37]...
detected MYC amplification by fluorescence in-situ hybridization (FISH) in six cases, all of which were secondary angiosarcoma. Furthermore, among 15 cases analyzed, MYC overexpression was detected in eight cases, consisting of seven cases of secondary angiosarcoma and one case of idiopathic angiosarcoma. Overall, MYC amplification and MYC overexpression were almost always detected in secondary angiosarcoma [37]. Among 37 patients with secondary angiosarcoma, Fraga–Guedes found that 20 patients had high levels of MYC amplification and MYC overexpression, while this pattern was not detected in any cases of primary angiosarcoma or atypical angiopathy [38]. Using the DISH and FISH detection techniques, Ko et al. reported MYC amplification in all 11 cases of secondary angiosarcoma [39]. Shon et al. identified high levels of MYC gene amplification and MYC overexpression in secondary angiosarcoma, but not in primary angiosarcoma. These results are consistent with the current research; however, some conflicting studies have also been reported. Verbeke et al. detected MYC amplification in both primary angiosarcoma and secondary angiosarcomas [40]. Therefore, further well-designed studies with a larger sample size are needed to verify our results.

SERPINE1 acts as a vital inhibitor of serine proteases that play
important roles in signal transduction, cell adhesion, and cell migration in many tumors [41,42]. Hung et al. identified SERPINE1 as a useful biomarker to distinguish pseudomyogenic hemangioendothelioma from histologic mimics [43]. Bridge et al. revealed that pseudomyogenic hemangioendothelioma often harbors a rearrangement of the FOSB gene with SERPINE1. The absence or dysfunction FOXP3, which is a master switch gene for regulatory T (Treg) cells, may cause qualitative or functional deficiency of this cell type [44,45]. Gambichler et al. found that CD4 and FOXP3 expression was significantly higher in cutaneous angiosarcoma and associated with disease relapse [46]. Fujii et al. found significantly increased proportions of CD4+ FOXP3+ T cells in the peripheral blood of patients with angiosarcoma [47]. These results are consistent with our study, indicating that these hub genes play an important role in the progression of angiosarcoma. However, the roles of UNC5A, CTLA4, ISLR2, MYC, ICOS, CMBL, IQCA1, GCOM1, WASF3, RELN, PGMS, CDCA7L, CETP and other hub genes in the occurrence and development of primary and secondary angiosarcoma remain to be clarified. Thus, verification of these results is required and our findings provide an important basis for further research.

GO and KEGG pathway enrichment analysis were conducted to gain
Fig. 6. PPI network, module analysis, and hub genes identification. (A) PPI network of DEGs was constructed in STRING database. (B,C) Top two modules screened using MCODE in Cytoscape software. (D) top10 hub genes with neighbors and expanded genes. (E) top 10 hub genes selected by the CytoHubba.
However, NVP-BEZ235 was not suitable for patient treatment due to canine angiosarcoma [48]. Wada et al. showed that the PI3K/mTOR signaling pathway is hyperactivated in human or canine angiosarcoma [52]. Wang et al. revealed that activation of the MAPK and PI3K/Akt pathways was closely related to the progression of angiosarcoma [53]. Meanwhile, there were a number of studies dedicated to HTT. For example, Yakhni M has performed some initial preclinical studies on leukemia, which was one of the best translation inhibitors available.

The results discussed here suggest that miRNAs in cancer, the PI3K/AKT, Notch, p53 signaling pathways as well as other important signaling pathways may interact to promote the occurrence and development of angiosarcoma. However, there are some limitations in our study. Firstly, angiosarcoma is rare malignancies and most of the current information relating to angiosarcoma is provided by case reports and single-institution retrospective cohort, the further well-designed studies and a multi-center clinical study with a larger sample size need to be implemented to validate our results. Secondly, due to lack of samples, we have only conducted bioinformatics analysis and more experiments are required to validate in future.

**Conclusion**

The DEGs between primary and secondary breast angiosarcoma may have the potential to serve as therapeutic targets as well new biomarkers for the diagnosis and prognosis of primary and secondary angiosarcomas. Moreover, further basic research and a well-designed multi-center clinical study with a larger sample size are warranted to verify our results.

### Table 4

| Gene symbol | Description | Chromosome | Map location |
|-------------|-------------|------------|--------------|
| MYC | v-myc avian myelocytomatosis viral oncogene homolog | 8 | 8q24.21 |
| SERPINE1 | serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1 | 7 | 7q22.1 |
| CTLA4 | cytotoxic T-lymphocyte-associated protein 4 | 2 | 2p33 |
| PLAU | plasminogen activator, urokinase type | 10 | 10q22.2 |
| FOXP3 | forkhead box P3 | 17 | Xp11.23 |
| KAT2A | K(linyl) acetyltransferase 2A | 17 | 17q21 |
| SUP3H | suppressor of Ty 3 homolog (S. cerevisiae) | 6 | 6p21.1-22.2 |
| CD80 | CD80 molecule | 3 | 3q13.3-13.4 |
| PLG | plasminogen | 6 | 6q26 |
| MED1 | mediator complex subunit 1 | 17 | 17q12 |

![Fig. 7. GO enrichment analysis of the top 10 hub genes.](image-url)
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Ethics approval and consent to participate

Not applicable.

Availability of data and materials

All data is available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Yuanfeng Wei: Conceptualization, Methodology, Software, Validation, Resources, Writing – original draft. Xi Yang: Conceptualization, Methodology, Validation. Limin Gao: Validation. Yong Xu: Conceptualization, Methodology, Validation. Cheng Yi: Conceptualization, Methodology, Validation.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Fig. 8. KEGG pathway enrichment analysis of the top 10 hub genes.
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