Identification of potential target genes associated with the effect of propranolol on angiosarcoma via microarray analysis

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Abstract. The purpose of the present study was to explore the effect of propranolol on angiosarcoma, and the potential target genes involved in the processes of proliferation and differentiation of angiosarcoma tumor cells. The mRNA expression profile (GSE42534) was downloaded from the Gene Expressed Omnibus database, including three samples without propranolol treatment (control), three samples with propranolol treatment for 4 h and three samples with propranolol treatment for 24 h. The differentially expressed genes (DEGs) in angiosarcoma tumor cells with or without propranolol treatment were obtained via the limma package of R and designated DEGs-4 h and DEGs-24 h. The DEGs-24 h group was divided into two sets. Set 1 contained the DEGs also contained in the DEGs-4 h group. Set 2 contained the remainder of the DEGs. Functional and pathway enrichment analysis of sets 1 and 2 was performed. The protein-protein interaction (PPI) networks of sets 1 and 2 were constructed, termed PPI 1 and PPI 2, and visualized using Cytoscape software. Modules of the two PPI networks were analyzed, and their topological structures were simulated using the tYNA platform. A total of 543 and 2,025 DEGs were identified in angiosarcoma tumor cells treated with propranolol for 4 and 24 h, respectively, compared with the control group. A total of 401 DEGs were involved in DEGs-4 h and DEGs-24 h, including metallothionein 1, heme oxygenase 1, WW domain-binding protein 2 and sequestosome 1. Certain significantly enriched gene ontology (GO) terms and pathways of sets 1 and 2 were identified, containing 28 overlapping GO terms. Furthermore, 121 nodes and 700 associated pairs were involved in PPI 1, whereas 1,324 nodes and 11,839 associated pairs were involved in PPI 2. A total of 45 and 593 potential target genes were obtained according to the node degrees of PPI 1 and PPI 2. The results of the present study indicated that a number of potential target genes, including AXL receptor tyrosine kinase, coatomer subunit alpha, DR1-associated protein 1 and ERBB receptor feedback inhibitor 1 may be involved in the effect of propranolol on angiosarcoma.

Introduction

Angiosarcoma is a rare malignant vascular tumor and is difficult to diagnose and treat (1). It may be characterized by rapidly proliferating and extensively infiltrating anaplastic cells, which are derived from blood vessels, and lining irregular blood-filled spaces (2,3). Angiosarcoma is derived from mesenchymal cells and usually originates from the liver, breast, spleen, bone or heart (2,4-6). Angiosarcoma accounts for between 1 and 2% of all sarcomas, and its overall 5-year survival rate is <20%, owing to the high recurrence and distant metastasis rates (2). In addition, metastasis usually occurs in the liver, lung, bone and lymph nodes (7). Treatment of angiosarcoma is multifaceted and primarily consists of radiotherapy, surgery and chemotherapy (8).

Propranolol is a non-selective β-blocker and may inhibit the growth of angiosarcoma by affecting the proliferation and differentiation of angiosarcoma tumor cells, thus being considered a promising treatment to delay surgery (9-11). However, its underlying molecular mechanisms and pharmacodynamics of the effects on angiosarcoma remain obscure, and the potential target genes involved in the proliferation and differentiation processes of angiosarcoma tumor cells also require investigation.

Gene microarray is widely used as an effective technology to detect the gene expression in cells and tissues at different disease stages of cancer. Thus, it may aid in the identification of novel signaling pathways or molecular mechanisms associated with tumorigenesis.
In the present study, the differentially expressed genes (DEGs) in angiosarcoma tumor cells treated with propranolol compared with the control group were identified via a bioinformatics-based method. Furthermore, enrichment analysis, protein-protein interaction (PPI) network construction and module analysis were performed. These analyses aided in the identification of essential genes associated with angiosarcoma, such as AXL receptor tyrosine kinase (AXL), coamter subunit α, DR1-associated protein 1, ERBB receptor feedback inhibitor 1, family with sequence similarity 195 member A, expressed sequence AA467197, apoptosis-associated tyrosine kinase, ATP-binding cassette subfamily A member 7, acyl-CoA dehydrogenase family member 9 and acyl-CoA-binding domain containing 6. Thus, this may contribute to understanding the molecular mechanism underlying angiosarcoma in order to identify potential gene targets for the diagnosis and treatment of patients with angiosarcoma.

Materials and methods

mRNA expression microarray data. The standardized mRNA expression profile GSE42534 (9) was downloaded from the Gene Expression Omnibus (www.ncbi.nlm.nih.gov/geo/) database, including 3 samples without propranolol treatment (the control group), 3 samples with propranolol treatment for 4 h and 3 samples with propranolol treatment for 24 h.

Identification and grouping of differentially expressed genes. The DEGs in angiosarcoma tumor cells of the propranolol treatment groups compared with the control group were obtained using the limma package of R (http://bioconductor.org/packages/release/bioc/html/l limma.html) (12). They were designated DEGs-4 h and DEGs-24 h. The DEGs-24 h were divided into 2 sets. Set 1 contained those DEGs also contained in the DEGs-4 h group. Set 2 contained the remainder of the DEGs. For the sake of accuracy, all DEGs were identified according to the following criteria: P<0.001; llog_{2} (fold-change) ≥1.

Gene ontology (GO) and pathway enrichment analysis. In order to explore the potential biological processes that were altered, GO and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were performed using the Database for Annotation, Visualization and Integrated Discovery (DAVID; david.abcc.ncifcrf.gov/) (13). The GO terms and the KEGG pathways were identified with the criterion P<0.05.

Construction of protein-protein interaction (PPI) networks. The two PPI networks for sets 1 and 2 were constructed using the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) (14) database, termed PPI 1 and PPI 2, respectively, and visualized using Cytoscape software (version 3.4.0; http://www.cytoscape.org/) (15). STRING, which manipulates the interactions between genes or proteins from multiple sources, was used to identify the interactions of DEGs. A combined score (a representation of reliability of interactions) >0.4 was used as the threshold for the selection of interaction pairs. Modules of the two PPI networks were analyzed using the Multi Contrast Delayed Enhancement plug-in of Cytoscape (16). When the combined score was >1.5, function enrichment analysis of all enrolled DEGs was performed using DAVID, and the GO terms and the KEGG pathways with P<0.05 were identified. Topological structures of the two PPI networks were analyzed using TynA (tyna.gersteinlab.org/tyna) (17), and potential target genes, whereby the degree of node attributes was ≥10, were identified. Degree represents the number of direct interactions a node has with with other nodes.

Results

Identification of DEGs. A total of 543 DEGs (242 up- and 301 downregulated) and 2,025 DEGs (1,107 up- and 918 downregulated) were identified in angiosarcoma tumor cells treated with propranolol (DEGs-4 h and DEGs-24 h, respectively) compared with the control group. A total of 401 DEGs (set 1) were involved in DEGs-4 h and DEGs-24 h, including metallothionein 1, heme oxygenase 1, WW domain-binding protein 2 and sequestosome 1. Among set 1, 179 DEGs in the DEGs-4 h group were upregulated, of which 170 DEGs were upregulated and 9 DEGs (2410011G03Rik, 2810417H13Rik, ATPase inhibitory factor 1, G2 and S-phase expressed 1, LSM5 homolog U6 small nuclear RNA and mRNA degradation associated, non-SMS condensing I complex subunit H, Rp127, ubiquitin-40A ribosomal protein S27a precursor and zinc finger CCHC-type-containing 8) were downregulated in the DEGs-24 h group. Similarly, 222 DEGs of the DEGs-4 h group were downregulated, of which 196 DEGs were downregulated and 26 DEGs (D730049H07Rik, desert hedgehog, dual-specificity phosphatase 7, endothelin 1, ETS proto-oncogene 1, general receptor for phosphoinositides, mitogen-associated protein kinase 6, midnolin, myeloid-associated differentiation marker, lysophosphatidic acid receptor 6, platelet-derived growth factor subunit A, PDZ and LIM domain (Pdlim) 1, Pdlim7, plexin A2, phosphatidic acid phosphatase type 2B, Ppm1f, regulator of G-protein signaling 16, ras homolog family member B, roundabout guidance receptor 4, sterile α motif domain-containing 4, solute carrier family 2 member 1, solute carrier family 9 isoform A3 regulatory factor 2, tissue inhibitor of metalloproteinase 3, tumor necrosis factor-α-induced protein 2, trophoblast glycoprotein and WNT1-inducible signaling pathway protein 1) were upregulated in the DEGs-24 h group.

Functional and pathway enrichment analysis of sets 1 and 2. The top 20 most significantly enriched GO terms of sets 1 and 2 are presented in Table IIA and B, respectively. Among them, 28 terms were coincident (Table IIA). The enriched KEGG pathways were presented in Table II A and B.

Construction of the PPI networks for sets 1 and 2 and analysis of modules. The PPI networks of PPI 1 and PPI 2 are presented in Figs. 1 and 2. A total of 121 nodes and 700 associated pairs were involved in PPI 1, whereas 1,324 nodes and 11,839 associated pairs were involved in PPI 2. Fig. 3 and Table III A present the module information of PPI 1. Fig. 4 and Table III B present the module information of PPI 2.
Table I. Significantly enriched and coincident GO terms in sets 1 and 2.

A. Top 20 most significantly enriched GO terms in set 1

| GO ID       | GO name                              | Gene number | P-value       |
|-------------|--------------------------------------|-------------|---------------|
| GO:0005730  | Nucleolus                            | 23          | 0.000000006   |
| GO:0016126  | Sterol biosynthetic process          | 8           | 0.000000580   |
| GO:0031974  | Membrane-enclosed lumen              | 43          | 0.000000604   |
| GO:0001525  | Angiogenesis                         | 12          | 0.00017900    |
| GO:0070013  | Intracellular organelle lumen        | 38          | 0.00025500    |
| GO:0043233  | Organelle lumen                      | 38          | 0.00027000    |
| GO:0006694  | Steroid biosynthetic process         | 9           | 0.00027800    |
| GO:006695   | Cholesterol biosynthetic process     | 6           | 0.00037100    |
| GO:0048514  | Blood vessel morphogenesis           | 14          | 0.00037200    |
| GO:0016125  | Sterol metabolic process             | 9           | 0.00050400    |
| GO:0001568  | Blood vessel development             | 15          | 0.00081700    |
| GO:0031981  | Nuclear lumen                        | 31          | 0.00082000    |
| GO:0001944  | Vasculature development              | 15          | 0.00106000    |
| GO:0005773  | Vacuole                              | 13          | 0.00118000    |
| GO:0008610  | Lipid biosynthetic process           | 16          | 0.00120000    |
| GO:0005764  | Lysosome                             | 12          | 0.00148000    |
| GO:0000323  | Lytic vacuole                        | 12          | 0.00156000    |
| GO:0043232  | Intracellular non-membrane-bounded organelle | 51  | 0.00034000 |
| GO:0043228  | Non-membrane-bounded organelle       | 51          | 0.00034000    |
| GO:0042127  | Regulation of cell proliferation      | 22          | 0.00038700    |

B. Top 20 most significantly enriched GO terms in set 2

| GO ID       | GO name                              | Gene number | P-value       |
|-------------|--------------------------------------|-------------|---------------|
| GO:0030529  | Ribonucleoprotein complex            | 100         | 0.000000000   |
| GO:0005739  | Mitochondrion                        | 178         | 0.000000000   |
| GO:0005840  | Ribosome                             | 52          | 0.000000000   |
| GO:0044429  | Mitochondrial part                   | 84          | 0.000000000   |
| GO:0003735  | Structural constituent of ribosome   | 39          | 0.000000000   |
| GO:0043233  | Organelle lumen                      | 142         | 0.000000000   |
| GO:0031974  | Membrane-enclosed lumen              | 145         | 0.000000000   |
| GO:0070013  | Intracellular organelle lumen        | 141         | 0.000000000   |
| GO:0043228  | Non-membrane-bounded organelle       | 208         | 0.000000000   |
| GO:0043232  | Intracellular non-membrane-bounded organelle | 208  | 0.000000000 |
| GO:0006412  | Translation                           | 58          | 0.00000000047 |
| GO:0031090  | Organelle membrane                   | 108         | 0.00000000050 |
| GO:0005681  | Splicosome                            | 33          | 0.00000000056 |
| GO:0006396  | RNA processing                        | 70          | 0.000000000140|
| GO:0008380  | RNA splicing                          | 42          | 0.000000000438|
| GO:0031967  | Organelle envelope                   | 79          | 0.000000000456|
| GO:0031975  | Envelope                             | 79          | 0.000000000543|
| GO:0019866  | Organelle inner membrane             | 54          | 0.000000001140|
| GO:0006397  | mRNA processing                       | 48          | 0.000000002120|
| GO:0016071  | mRNA metabolic process                | 51          | 0.000000010600|

C. Coincident enriched GO terms in sets 1 and 2

| GO ID       | GO name                              | GO ID       | GO name             |
|-------------|--------------------------------------|-------------|---------------------|
| GO:0000166  | Nucleotide binding                   | GO:0031981  | Nuclear lumen       |
Table I. Continued.

C, Coincident enriched GO terms in sets 1 and 2

| GO ID       | GO name                  | GO ID       | GO name                                      |
|-------------|--------------------------|-------------|----------------------------------------------|
| GO:0005730  | Nucleolus                | GO:0032553  | Ribonucleotide binding                       |
| GO:0005773  | Vacuole                  | GO:0032555  | Purine ribonucleotide binding                |
| GO:0005783  | Endoplasmic reticulum    | GO:0034404  | Nucleobase, nucleoside and nucleotide biosynthetic process |
| GO:0005829  | Cytosol                  | GO:0034654  | Nucleobase, nucleoside, nucleotide and nucleic acid biosynthetic process |
| GO:0006334  | Nucleosome assembly       | GO:0034728  | Nucleosome organization                      |
| GO:0006364  | rRNA processing          | GO:0042254  | Ribosome biogenesis                          |
| GO:0006396  | RNA processing            | GO:0043228  | Non-membrane-bounded organelle               |
| GO:0009165  | Nucleotide biosynthetic process | GO:0043232 | Intracellular non-membrane-bounded organelle |
| GO:0016072  | rRNA metabolic process    | GO:0043233  | Organelle lumen                              |
| GO:0017076  | Purine nucleotide binding | GO:0044271  | Nitrogen compound biosynthetic process       |
| GO:0022613  | Ribonucleoprotein complex biogenesis | GO:0046907 | Intracellular transport                      |
| GO:0030529  | Ribonucleoprotein complex | GO:0051726  | Regulation of cell cycle                     |
| GO:0031974  | Membrane-enclosed lumen  | GO:0070013  | Intracellular organelle lumen                |

GO, gene ontology; set 1, coincident differentially expressed genes in angiosarcoma tumor cells treated with propranolol for 4 h and treated with propranolol for 4 h compared with treated without propranolol; set 2, differentially expressed genes in angiosarcoma tumor cells treated with propranolol for 24 h compared with treated without propranolol, but not in angiosarcoma tumor cells treated with propranolol for 4 h compared with treated without propranolol.

Table II. Enriched KEGG pathways in sets 1 and 2.

A, Enriched KEGG pathways in set 1

| Term                                   | Count | P-value  |
|----------------------------------------|-------|----------|
| mmu04115: p53 signaling pathway        | 9     | 0.000105 |
| mnu00100: Steroid biosynthesis         | 5     | 0.000398 |
| mnu00900: Terpenoid backbone biosynthesis | 4     | 0.003012 |
| mnu04142: Lysosome                     | 9     | 0.004013 |
| mnu00600: Sphingolipid metabolism      | 5     | 0.012340 |
| mnu00240: Pyrimidine metabolism        | 7     | 0.017197 |
| mnu00270: Cysteine and methionine metabolism | 4     | 0.033547 |
| mnu00650: Butanoate metabolism         | 4     | 0.044913 |
| mnu05214: Glioma                       | 5     | 0.048883 |

B, Enriched KEGG pathways in set 2

| Term                                   | Count | P-value  |
|----------------------------------------|-------|----------|
| mnu03040: Spliceosome                  | 37    | 0.000000 |
| mnu00190: Oxidative phosphorylation    | 31    | 0.000001 |
| mnu03010: Ribosome                     | 22    | 0.000026 |
| mnu04142: Lysosome                     | 24    | 0.000291 |
| mnu05211: Renal cell carcinoma         | 17    | 0.000350 |
| mnu00480: Glutathione metabolism       | 13    | 0.001727 |
| mnu05016: Huntington's disease         | 28    | 0.006229 |
| mnu05012: Parkinson's disease          | 22    | 0.007000 |
| mnu05222: Small cell lung cancer       | 16    | 0.007770 |
| mnu03030: DNA replication              | 9     | 0.010537 |
Extent of enriched function and topological structure analysis of the PPI networks.

There were 20 GO terms (including...

Table II. Continued.

| Term                                      | Count | P-value     |
|-------------------------------------------|-------|-------------|
| mmu04666: Fc gamma R-mediated phagocytosis | 17    | 0.012796    |
| mmu04114: Oocyte meiosis                  | 19    | 0.013122    |
| mmu03018: RNA degradation                 | 12    | 0.016095    |
| mmu04110: Cell cycle                      | 20    | 0.018766    |
| mmu05200: Pathways in cancer              | 41    | 0.020303    |
| mmu04662: B cell receptor signaling pathway| 14    | 0.024365    |
| mmu05212: Pancreatic cancer               | 13    | 0.024948    |
| mmu00600: Sphingolipid metabolism         | 9     | 0.030444    |
| mmu00980: Metabolism of xenobiotics by cytochrome P450 | 12 | 0.031062 |
| mmu00330: Arginine and proline metabolism | 10    | 0.043757    |
| mmu00860: Porphyrin and chlorophyll metabolism | 7  | 0.046693    |
| mmu00511: Other glycan degradation         | 5     | 0.048603    |
| mmu04062: Chemokine signaling pathway     | 24    | 0.056122    |
| mmu05010: Alzheimer's disease             | 24    | 0.056122    |
| mmu05215: Prostate cancer                 | 14    | 0.056323    |
| mmu04620: Toll-like receptor signaling pathway | 15 | 0.056726 |
| mmu03410: Base excision repair            | 8     | 0.061961    |
| mmu00230: Purine metabolism               | 21    | 0.066837    |
| mmu00982: Drug metabolism                 | 12    | 0.068874    |
| mmu04920: Adipocytokine signaling pathway | 11    | 0.073182    |
| mmu04810: Regulation of actin cytoskeleton | 27 | 0.075019 |

KEGG, Kyoto Encyclopedia of Genes and Genomes; set 1, coincident differentially expressed genes in angiosarcoma tumor cells treated with propranolol for 4 h and treated with propranolol for 4 h compared with treated without propranolol; set 2, differentially expressed genes in angiosarcoma tumor cells treated with propranolol for 24 h compared with treated without propranolol, but not in angiosarcoma tumor cells treated with propranolol for 4 h compared with treated without propranolol; DEGs, differentially expressed genes.

Figure 1. Protein-protein interaction network of set 1.

Figure 2. Protein-protein interaction network of set 2.

Extent of enriched function and topological structure analysis of the PPI networks. There were 20 GO terms (including...
nucleolus, intracellular organelle lumen, membrane-enclosed lumen, ribosome biogenesis and RNA processing) and no KEGG pathways enriched in module 1 of PPI 1. The numbers of the enriched module functions of PPI 2 are presented in Table IV. The results identified that no enriched KEGG pathways appeared in modules 1 and 9 of PPI 2. A total of 45 and 593 potential target genes were obtained according to the node degrees of PPI 1 and PPI 2, and the top 10 nodes (potential target genes) which were associated with the other nodes in the PPI networks for sets 1 and 2 are presented in Table VA and VB, respectively.

Discussion

Numerous studies have demonstrated the selective cytotoxicity and relative safety of propranolol on vascular tumors, and laid the groundwork for the notable efficacy and the suppressive ability of propranolol on angiosarcoma (9-11,18-20). In the present study, it was found that the number of DEGs-24 h was higher compared with the number of DEGs-4 h. In addition, nearly all of the DEGs-4 h overlapped with and were contained in the DEGs-24 h group. Furthermore, differential expression (upregulated or downregulated) of DEGs-24 h was more evident compared with DEGs-4 h. This indicated that the 401 overlapping DEGs in set 1 were important in the effects of propranolol on angiosarcoma tumor cells. Notably, 9 upregulated DEGs of the DEGs-4 h group were downregulated in the DEGs-24 h group, whereas 26 downregulated DEGs of the DEGs-4 h group were upregulated in the DEGs-24 h group. It was possible that these genes perform multiple roles in the effect of propranolol on angiosarcoma; however, this conjecture requires additional experimental verification.

The enriched GO terms of set 1 primarily contained ‘angiogenesis, blood vessel morphogenesis, vasculature development’, ‘sterol biosynthetic process, cholesterol biosynthetic process, lipid biosynthetic process’, ‘lysosome, lytic vacuole, vacuole’, and ‘nucleolus, intracellular non-membrane-bounded organelle, regulation of cell proliferation’. It is well known that lipid metabolism may affect the development of blood vessels (21-23) and various organelles involved in various biological processes (23,24). Cell proliferation is an essential process in the development of blood vessels (25). According to Table IA, the majority of enriched GO terms of set 1 were associated with the biological processes of blood vessels, whereas the enriched GO terms of set 2 were primarily associated with energy metabolism (including ribosome, structural constituent of ribosome), protein transfer (including ribonucleoprotein complex, ribosome, membrane-enclosed lumen) and compounds biosynthesis (including RNA processing, mRNA metabolic process and envelope). The overlapping enriched GO terms of sets 1 and 2 were primarily involved in nucleic acid metabolism, nucleotide biosynthesis and nucleic
Acid binding. Therefore, it was concluded that propranolol affected angiosarcoma primarily by influencing the biological processes of blood vessels in the early stage and by effecting the biological metabolism and transfer processes in the later stage.

The enriched KEGG pathways of set 1 were tumor-associated biological processes, including the p53 signaling pathway and cysteine and methionine metabolism. In the later stage, the enriched KEGG pathways were more extensive, including the ribosome signaling pathway, lysosome signaling pathway, Huntington's disease, and Parkinson's disease.

According to the topological structure analysis of the PPI networks, certain potential biomarkers were identified:

Table V. Top 10 nodes most significantly associated with other nodes in the protein-protein interaction network of sets 1 and 2.

| Gene symbol | Degree | Clustering coefficient | Eccentricity | Betweenness centrality |
|-------------|--------|------------------------|--------------|------------------------|
| AXL         | 45     | 0                      | 6            | 0                      |
| COPA        | 44     | 0                      | 7            | 0                      |
| DRAP1       | 44     | 0                      | 2            | 0                      |
| ERRFI1      | 41     | 0                      | 2            | 0                      |
| FAM195A     | 38     | 0                      | 8            | 0                      |
| FAM98A      | 36     | 0                      | 8            | 0                      |
| FASTKD5     | 36     | 0                      | 8            | 0                      |
| FEZ2        | 33     | 0                      | 2            | 0                      |
| FST         | 33     | 0                      | 6            | 0                      |
| GADD45G     | 33     | 0                      | 7            | 0                      |

Set 1, coincident differentially expressed genes in angiosarcoma tumor cells treated with propranolol for 4 h and treated with propranolol for 4 h compared with treated without propranolol; set 2, differentially expressed genes in angiosarcoma tumor cells treated with propranolol for 24 h compared with treated without propranolol, but not in angiosarcoma tumor cells treated with propranolol for 4 h compared with treated without propranolol.

Table IV. Enriched function numbers of modules of the protein-protein interaction network of set 2.

| Modules | Enriched GO term numbers | Enriched KEGG pathway number |
|---------|--------------------------|-----------------------------|
| Module 1 | 0                        | 0                           |
| Module 2 | 47                       | 1                           |
| Module 3 | 10                       | 1                           |
| Module 4 | 122                      | 6                           |
| Module 5 | 62                       | 5                           |
| Module 6 | 90                       | 11                          |
| Module 7 | 105                      | 15                          |
| Module 8 | 12                       | 1                           |
| Module 9 | 154                      | 0                           |
| Module 10| 22                       | 6                           |

Set 2, differentially expressed genes in angiosarcoma tumor cells treated with propranolol for 24 h compared with treated without propranolol, but not in angiosarcoma tumor cells treated with propranolol for 4 h compared with treated without propranolol; GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.
including AXL, coatamer subunit α, DR1-associated protein 1, ERBB receptor feedback inhibitor 1, family with sequence similarity 195 member A, expressed sequence AA467197, apoptosis-associated tyrosine kinase, ATP-binding cassette subfamily A member 7, acyl-CoA dehydrogenase family member 9 and acyl-CoA-binding domain containing 6. According to Table VA, AXL was the most significantly meaningful gene in the early stage. AXL is a member of the tyrosine kinase receptor family and is associated with cell adhesion and recognition, cell proliferation, apoptosis, blood coagulation and inflammation (26). It performs important roles in the occurrence and development of various tumors, including the inhibition of tumor cell apoptosis, the involvement in tumor angiogenesis and cellular invasion (27-30). Following its original identification, the upregulation of Axl has been reported in a variety of hematopoietic tumors, including leukemia and melanoma (31-35). Furthermore, previous studies have demonstrated that Axl may also perform a role in a number of chemotherapy-resistant cancers (36,37). In the present study, it was proposed that Axl may be a potential target in the early stage of angiosarcoma treated with propranolol. This discovery may indicate an important direction for future studies. Similarly, AA467197 may be a potential biomarker in the late stage of angiosarcoma treated with propranolol. It is a key point of the effects of propranolol on angiosarcoma to identify and develop small-molecule drugs with the potential to selectively inhibit Axl and AA467197 expression and their signaling pathways.

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