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Original Article

Overexpressed gene signature of EPH receptor A/B family in cancer patients-comprehensive analyses from the public high-throughput database

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Abstract: Although a previous study suggested that erythropoietin-producing hepatoma (EPH) receptors play important roles in tumor progression and the overexpression of EPHs in cancer patients is related to poor prognoses, high-throughput gene expression profiling of EPH family members in different types and subtypes of cancers has so far not been conducted. We herein carried out a series of bioinformatic analyses on expressive profiles of every EPH member across 21 different types of clinical cancers versus matched normal tissues gathered from the Oncomine platform. We validated these results by protein expression study of all EPHs family members by The Human Protein Atlas repository. Our results uncovered the overexpression of most EPH subunits in numerous cancer types, especially the dramatic overexpression of six EPHs members, namely EPHA1, EPHA2, EPHA3, EPHA4 and EPHB1, EPHB2, EPHB3, EPHB4 in bladder, colorectal, esophageal, gastric, and prostate cancers. Furthermore, EPHB2 was specifically highly expressed in cervical cancer, EPHA3 in liver cancer, and EPHB1 in uterine cancer. Collectively, expressive profiles of these EPHs were confirmed and correlated with different cancer subtypes as potential biomarkers. This study provides useful information for further studies on cancer development and clinical treatments.

Keywords: Erythropoietin-producing hepatoma (EPH) receptors, ephrins, erythropoietin-producing hepatocellular type-A (EPHA) receptor, erythropoietin-producing hepatocellular type-B (EPHB) receptor, medical oncology, bioinformatics

Introduction

Erythropoietin-producing hepatoma (EPH) and ephrins have recently become a focal point of research. Mammalian EPH receptors were documented to be the dominant group of tyrosine kinase receptors that are composed of nine A-type EPHs (EPHA1~8, 10), five A-type ephrins (ephrins-A1~5), five B-type EPHs (EPHB1~4, 6), and three B-type ephrins (ephrin-B1~3). The binding complexes of EPHs and ephrins are also known to play important roles in cell-cell communication, as they regulate the actin cytoskeleton, cell structure, and cell motility. Furthermore, other cellular processes, such as cell growth, differentiation, apoptosis, and secretion, are also influenced by these proteins [1, 2].

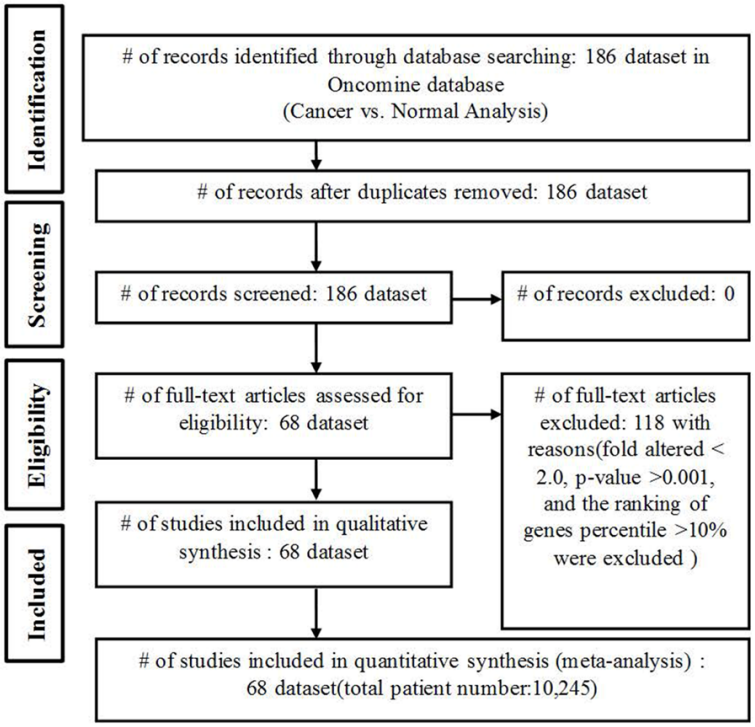


Figure 1. Flow Diagram. Flow chart presenting the identification and collection of studies for the statistical meta-analysis.

EPHs are involved in many important human physiologic activities such as angiogenesis, plasticity and regenerative capacity of the nervous system, glucose and intestinal homeostasis, immune responses, bone formation process, and stem cell flexibility. Besides the physiological activities and effects, the activation and inactivation of the EPH/ephrin system are also involved in many pathophysiological processes such as cancer, diabetes, and Alzheimer's disease [3, 4]. Recently, EPHs garnered attention as potential therapeutic targets in cancer treatment. Numerous studies have revealed correlations between EPH/ephrin levels and tumor angiogenesis. In cancer progression, angiogenesis plays a crucial role in metastasis and invasion. These processes are actualized by the signaling communication between cancer cells and tumor-associated endothelial cells [5, 6]. Toma et al. showed that cancer progression and angiogenesis are correlated with EPHB4 expression levels [7]. Another study reported that EPHA1 was significantly overexpressed in metastatic renal cell carcinoma [8]. Despite these meaningful findings, no comprehensive screening method has been exploited to examine EPH member expressions in various types of cancer. The advantage of a high-throughput screening strategy is the ability to explore and collect data from numerous studies in an unbiased way. It can help predict information about cancer progression.

In this study, we addressed the expression profiles of EPH family members in 21 types of cancer from the Oncomine database. To our knowledge, this is the first comprehensive study of gene expression profiling in tumor samples versus corresponding cancer cell lines for all EPH family members. These data may shed new light on novel biomarkers for EPHA/B gene family for use in cancer research.

Material and methods

Analysis of public clinical datasets and gene set enrichment analysis (GSEA)

A meta-analysis of mRNA expression profiles of EPH family members in clinical cancer and matched normal tissues was conducted obeying the PRISMA guidelines (**Figure 1**) [9]. The Oncomine database (www.oncomine.org) was used to obtain a systematic analysis of different types cancer microarray data [10]. Oncomine has over 700 independent datasets, equivalent to 90,000 microarray experiments. This database covers every major cancer type and many pathological subtypes. Differential expressions of EPHs in cancer versus matched normal tissues were determined by the multiple of change-based standard with linear model correlation. Screening criteria in this study were as follows: a fold change of >2.0, a p value of <0.001, and the percentile ranking of genes of <10%. Oncomine default algorithms (two-tailed Student's t-test and multiple testing corrections) were used to calculate p values and significant differences in EPH expressions between cancerous and control samples. The false discovery rate (FDR) method was used to perform multiple testing corrections. Corrected p values (Q-values) were calculated as $Q = N \cdot P/R$, where $P = p$ value, $N =$ total number of genes, and R is the sorted rank of p values. By comparing mRNA expressions in 21 cancer types with the corresponding nor-

Analysis Type by Cancer	Cancer vs Normal													
	EPHA1	EPHA2	EPHA3	EPHA4	EPHA5	EPHA6	EPHA7	EPHA8	EPHA10	EPHB1	EPHB2	EPHB3	EPHB4	EPHB6
Bladder	2	1		1							1			3
Brain and CNS			2	1						2	2			
Breast	1			1					3					
Cervical											1			
Colorectal	2	1						1			4	8	10	
Esophageal				1					1	3	2		2	
Gastric				1						2	4		1	
Head and Neck				2							2			
Kidney	1		3				2			1				
Leukemia							1							3
Liver			2											
Lung									1	2	2	3		
Lymphoma					1					3	1			1
Ovarian											1	1		
Pancreatic		1	1	3										
Prostate	1									1		1	1	
Renal														
Sarcoma			2				1			1	2	1		
Skin														
Testis														
Uterus														
Others	1	3					1			1	2	1	5	1
Significant Unique Analyses	8	6	10	12	1	4	4	1	5	16	24	15	19	8
Total Unique Analyses	356	357	305	343	343	329	329	166	169	314	346	358	364	337

Figure 2. Expression of erythropoietin-producing hepatoma A/B (EPHA/B) family genes across different cancers. Expressions of EPHA/B family genes in different types of cancers compared to normal patients. Each gene was found in its tissue of origin, and the color gradient correlates with a decreasing gene rank percentile. The search criteria threshold was set to $p<0.001$ with a multiple of change of >2.0 and gene rank percentile of <10% for screening high-throughput datasets of cancer versus normal cases.

mal tissues, genes of the EPH receptor family (EPHA1~8 and EPHA10, and EPHB1~4 and EPHB6) were studied across the range of various cancer types and sorted by their sets of origin as we previously described [11, 12]. Our data encompassed 68 studies and 10,245 samples in total. In Oncomine, the gene summary view mode was displayed during this analysis, and it also presented expression rankings, which were illustrated by color shading. In particular, a gene's expression color in cancer was related to the gene rank percentile, from the above-described threshold analysis.

Analysis of the human protein atlas database

EPH protein expressions were further evaluated using the publicly available Human Protein Atlas database which contains images of tissue microarrays labeled with antibodies against 11,250 human proteins. These tissue microarrays comprise sections from 46 normal human tissues and more than 20 types of human cancers [13].

Construction of protein-protein interaction (PPI) networks and screening of modules

Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database (https://string-db.org) was used to conduct the protein-protein interaction network. Briefly, the EPH protein symbols were keyed into the search box with multiple proteins/identifiers option. All default parameters from STRING database were selected for this analysis [14]. Subsequently, Cytoscape was used to visualize the network with ClueGO and CluePedia [15-17].

Results

EPH/ephrin receptor expressions in cancer

In order to identify expressions of EPH receptors in different cancer subtypes, the web-based high-throughput Oncomine database was

utilized [10]. Expression ratios of cancer versus normal tissues are presented in **Figure 2**, and the stronger intensity of red shows higher overexpression of target genes. The number in each cell reveals the number of analyses that conformed to the selection criteria (a multiple of change of >2.0, a *p* value of <0.001, and a percentile ranking of genes of <10%). The analyses were classified by the original organ, and all cancerous subtypes were included (e.g., gastric mixed adenocarcinoma or gastric intestinal-type adenocarcinoma). Our bioinformatics data demonstrated that mRNAs of most EPH receptors genes increased in diverse types of cancers. EPHA1 had high expression in prostate carcinoma and infiltrating bladder urothelial tumor tissues (**Figure 2**). EPHA2 was overexpressed in bladder, colorectal, pancreatic, and vulvar cancers, and seminomas. Expression of EPHA3 increased in brain tumors, kidney, liver, and pancreatic cancers, and sarcomas (**Figure 2**). Expression of EPHA4 was elevated in bladder, brain, gastric, head and neck, and pancreatic cancers. For EPHB family membranes, 16 of 314 analyses conformed to the selection threshold for EPHB1, 24 of 346 for EPHB2, 15 of 358 for EPHB3, 19 of 364 for EPHB4, and eight of 337 for EPHB6.

EPHA family member expressions in cancer

The current data revealed that EPHA1 was overexpressed in several types of cancer such as bladder, colon, breast, prostate, and renal cancers (**Figure 2**). EPHA1 had multiples of increase in bladder cancer tissues of 5.16~12.17, *p* value changes ranged 2.91E-16~7.24E-24, and EPHA1 ranked in the top 1% in either superficial or infiltrating bladder urothelial carcinoma. The multiples of change of EPHA1 significantly increased in all subtypes of colon, breast, prostate, and renal cancers with gene rankings in the top 9% (**Table 1**).

The current analysis revealed that EPHA2 was overexpressed in pancreas, bladder, colon, and vulvar cancers, and seminomas (**Figure 2**). EPHA2 had a significant multiple of change of >3.6 and a gene ranking within the top 5% in yolk sac tumors. EPHA2 was also overexpressed with maximum multiples of increase of >2-fold compared to normal tissues, and the gene ranked in the top 5% in infiltrating bladder urothelial carcinoma, rectal mucinous adenocarcinomas, and vulvar intraepithelial neoplasia (**Table 1**).

Our data also showed that EPHA3 had high expressions in liver, brain, renal, and pancreas cancers and sarcomas, relative to normal matched tissue types (**Figure 2**). Moreover, it also had significant multiples of increase (>5-fold) in hepatocellular carcinoma and cirrhosis, with the gene ranked in the top 1%. In brain cancer, sarcomas, renal cancer, and pancreas cancer, EPHA3 ranked in top 3%~10% of overexpressed genes with a maximum multiple of change of 9.62 in desmoplastic medulloblastomas (**Table 1**).

The present data revealed that EPHA4 was significantly overexpressed in seven types of cancers and presented in the top 10% of the majority of commonly altered genes (**Figure 2**). In invasive breast carcinoma, EPHA4 was found to be significantly overexpressed with a *p* value of 3.93E-15 and was ranked in the top 6% relative to normal tissues. For infiltrating bladder urothelial carcinoma compared to normal tissues, EPHA4 had a 4.95-fold-increase and was ranked in the top 2%. EPHA4 was overexpressed in pancreas cancer and was ranked within the top 4%~7%. Compared to normal tissues, EPHA4 had gene ranking in the top 3%~10% in head and neck squamous cell carcinomas and floor of the mouth carcinomas. For brain cancer, gastric cancer, myelomas, melanomas, and esophageal cancer, EPHA4 had multiples of change of up to 6-fold with gene ranking in the top 2%~10% (**Table 1**).

Our results showed that EPHA5 had a 2.06-fold increase in diffuse large B-cell lymphomas relative to normal tissues (**Table 1**). We found that EPHA7 was overexpressed in kidney cancer, B-cell acute lymphoblastic leukemia, sarcomas, and parathyroid adenomas (**Figure 2**). EPHA7 had multiples of increase in papillary renal cell carcinoma and clear cell sarcomas of the kidney of 2.489~5.238 (**Table 1**). For parathyroid adenomas compared to normal tissues, EPHA7 had a 3.173-fold increase with a *p* value of 2.09E-5, and the gene was ranked in the top 2% (**Table 1**). We found that EPHA8 had a 2.445-fold increase in rectosigmoid adenocarcinomas with a *p* value of 2.60E-5, and the gene was ranked in the top 4% (**Figure 2**, **Table 1**). We found that EPHA10 not only had

Table 1. Expression of EPHA family members in cancer

Gene	Cancer	Subtype	*N* (case)	*p* value (cancer/normal)	*t*-test (cancer/normal)	Multiple of change (cancer/normal)	% Gene ranking	Database reference
EPHA1	Bladder	Superficial bladder cancer	157	7.24E-24	14.661	12.168	30 (in top 1%)	J Clin Oncol [62]
		Infiltrating bladder urothelial carcinoma	157	2.91E-16	9.620	5.164	97 (in top 1%)	J Clin Oncol [62]
	Colorectal	Colon adenoma	64	5.32E-14	9.912	2.243	437 (in top 3%)	Mol Cancer Res [63]
		Rectal adenoma	64	2.07E-5	7.220	2.464	1334 (in top 7%)	Mol Cancer Res [63]
	Breast	Invasive ductal and lobular carcinoma	593	4.01E-9	6.765	2.040	253 (in top 2%)	Nature [64]
	Seminoma	Yolk sac tumor, NOS	107	8.73E-6	6.916	2.980	750 (in top 5%)	Cancer Res [65]
	Prostate	Prostate carcinoma	34	7.19E-5	4.364	4.740	444 (in top 6%)	Cancer Res [66]
	Renal	Clear cell renal cell carcinoma	67	8.53E-4	3.932	2.602	1746 (in top 9%)	BMC Cancer [67]
EPHA2	Bladder	Infiltrating bladder urothelial carcinoma	157	6.09E-9	6.196	2.848	592 (in top 5%)	J Clin Oncol [62]
	Pancreas	Pancreatic carcinoma	52	9.50E-8	6.523	4.139	307 (in top 2%)	Cancer Cell [68]
	Colorectal	Rectal mucinous adenocarcinoma	105	1.14E-4	8.193	2.615	618 (in top 4%)	Genome Biol [69]
	Seminoma	Yolk sac tumor, NOS	107	1.29E-5	8.319	3.577	843 (in top 5%)	Cancer Res [65]
		Teratoma, NOS	107	8.81E-7	7.929	2.915	1200 (in top 7%)	Cancer Res [65]
	Vulva	Vulvar intraepithelial neoplasia	19	2.32E-4	4.353	2.597	869 (in top 5%)	Int J Cancer [70]
EPHA3	Liver	Hepatocellular carcinoma	115	5.73E-14	9.844	5.891	54 (in top 1%)	Mol Med [71]
		Cirrhosis	75	4.84E-7	6.863	5.143	82 (in top 1%)	Hepatology [72]
	Brain	Classic medulloblastoma	85	2.15E-8	6.567	9.620	138 (in top 3%)	Nature [73]
		Desmoplastic medulloblastoma	85	6.28E-4	4.011	8.838	190 (in top 4%)	Nature [73]
	Sarcoma	Dedifferentiated liposarcoma	158	3.78E-9	6.954	3.850	415 (in top 4%)	Nat Genet [74]
		Round cell liposarcoma	54	9.79E-4	3.809	3.791	709 (in top 6%)	Cancer Res [75]
	Renal	Hereditary clear cell renal cell carcinoma	70	3.04E-9	7.518	2.733	515 (in top 5%)	Cancer Res [76]
		Non-hereditary clear cell renal cell carcinoma	70	3.27E-7	6.231	2.350	642 (in top 6%)	Cancer Res[76]
		Clear cell renal cell carcinoma	20	2.39E-4	4.254	5.148	1192(in top 10%)	Clin Cancer Res [77]
	Pancreas	Pancreatic ductal adenocarcinoma	78	2.01E-10	7.208	4.834	681 (in top 4%)	Hepatogastroenterology [78]
EPHA4	Breast	Invasive breast carcinoma stroma	59	3.93E-15	13.162	3.137	962 (in top 6%)	Nat Med [79]
	Bladder	Infiltrating bladder urothelial carcinoma	157	5.46E-15	9.099	4.959	133 (in top 2%)	J Clin Oncol [62]
	Pancreas	Pancreatic ductal adenocarcinoma	78	1.89E-10	7.196	2.884	674 (in top 4%)	Hepatogastroenterology [78]
		Pancreatic carcinoma	52	6.24E-6	4.859	2.147	833 (in top 5%)	Cancer Cell [68]
		Pancreatic adenocarcinoma	27	4.28E-4	6.646	121.141	334 (in top 7%)	Cancer Res [80]
	Head-Neck	Head and neck squamous cell carcinoma	54	5.79E-10	7.635	4.288	359 (in top 3%)	Cancer Res [81]
		Floor of the mouth carcinoma	84	8.39E-4	4.223	2.557	1934 (in top 10%)	Cancer Res [82]
	Brain	Glioblastoma	101	1.30E-6	7.380	2.781	421 (in top 3%)	Cancer Cell [83]
	Gastric	Gastric mixed adenocarcinoma	69	1.32E-6	7.196	3.984	264 (in top 2%)	Eur J Cancer [84]
	Myeloma	Monoclonal gammopathy of undetermined significance	78	3.90E-5	4.263	2.034	1885 (in top 10%)	Blood [85]
	Melanoma	Benign melanocytic skin nevus	70	8.41E-5	5.143	6.083	493 (in top 4%)	Clin Cancer Res [86]
	Esophagus	Esophageal adenocarcinoma	48	4.63E-4	3.752	2.481	1137 (in top 8%)	Gastroenterology [87]
EPHA5	Lymphoma	Diffuse large B-cell lymphoma	102	9.70E-4	3.714	2.064	317 (in top 8%)	J Exp Med [88]

EPHA7	Leukemia	B-Cell acute lymphoblastic leukemia	2096	1.07E-24	12.237	2.468	1058 (in top 6%)	J Clin Oncol [89]
	Renal	Papillary renal cell carcinoma	92	3.79E-9	14.352	5.238	571 (in top 5%)	Clin Cancer Res [90]
		Clear cell sarcoma of the kidney	35	5.92E-4	6.479	2.489	498 (in top 4%)	Clin Cancer Res [91]
	Parathyroid	Parathyroid gland adenoma	61	2.09E-5	4.855	3.173	251 (in top 2%)	Am J Pathol [92]
EPHA8	Colorectal	Rectosigmoid adenocarcinoma	237	2.60E-5	5.202	2.445	706 (in top 4%)	Nature [93]
EPHA10	Breast	Invasive breast carcinoma stroma	59	1.95E-15	13.532	2.230	909 (in top 5%)	Nat Med [79]
		Male breast carcinoma	593	5.94E-8	9.165	3.480	319 (in top 2%)	Nature [64]
		Mixed lobular and ductal breast carcinoma	593	3.07E-4	5.030	3.417	1229 (in top 7%)	Nature [64]
	Lung	Lung adenocarcinoma	246	5.65E-10	9.846	4.732	1378 (in top 8%)	Cancer Res [94]
	Esophagus	Barrett's esophagus	48	2.93E-5	4.684	3.784	400 (in top 3%)	Gastroenterology [87]
	Prostate	Prostate carcinoma	122	3.33E-5	4.527	1.970	1068 (in top 6%)	Nature [95]
		Prostate carcinoma	21	1.26E-4	4.694	1.980	158 (in top 1%)	Clin Cancer Res [96]

NOS: not otherwise specified.

high expression in breast cancer but also in lung, esophageal, and prostate cancers (**Figure 2**, **Table 1**). EPHA10 was overexpressed in invasive breast carcinoma, male breast carcinoma, and mixed lobular and ductal subtypes (**Table 1**).

EPHB family members expression in cancer

EPHB1 was reported to involve in colorectal cancer [18] and overexpression of EPHB1 was found in patients with gastric cancers [19]. The current data revealed that EPHB1 was overexpressed in brain, esophageal, gastric, kidney, lung, and prostate cancers, lymphomas, sarcomas, and melanomas (**Figure 2**). EPHB1 was overexpressed in oligodendrogliomas and anaplastic oligodendrogliomas of the brain, in uterus corpus leiomyomas, in diffuse and intestinal subtypes of gastric adenocarcinomas, in Barrett's esophagitis and esophageal adenocarcinomas, in subtypes of lymphoma (including follicular lymphomas and diffuse large B-cell lymphomas), in benign melanocytic skin nevi, in adenocarcinomas and squamous cell carcinoma of the lungs, in intraepithelial neoplasia of the prostate, and also in clear cell carcinoma of the kidneys (**Table 2**). Overall, EPHB1 was suggested to be a potential oncogene in cancer development.

We found that EPHB2 had higher expressions not only in colon and cervix tumors but also in head-neck, ovarian, bladder, lung, gastric, brain, esophagus, brain, and salivary-gland cancers, lymphomas, sarcomas, mesotheliomas, and seminomas (**Figure 2**). EPHB2 was overexpressed in adenomas and carcinoma of the colon, in squamous cell carcinoma of the tongue, head, and neck, in ovarian carcinoma, in infiltrating uroepithelial carcinoma of the bladder, in adenocarcinoma of the lungs, in squamous carcinoma of the cervix, in centroblastic lymphomas, in intestinal or mixed subtypes of gastric adenocarcinomas, in subtypes of sarcomas (myxofibrosarcomas and round cell liposarcomas), in glioblastomas and meningiomas, in Barrett's esophagitis and esophageal adenocarcinomas, in yolk sac tumors, and in pleural malignant mesotheliomas (**Table 2**). All of the increases of cancer/normal multiples of change were significant.

We also found that EPHB3 not only had high expression in lung and prostate cancers but also in a variety of cancer subtypes, such as ovarian cancer, sarcomas, and testicular cancer. EPHB3 was present in both colorectal and testicular cancers with gene ranks within the top 1% of upregulated genes (**Figure 2**). EPHB3 was overexpressed in adenomas, adenocarcinomas, and mucinous carcinoma of the colon and rectum, in serous cystadenocarcinomas of the ovaries, in squamous cell carcinoma of the lungs, in synovial sarcomas, in testicular seminomas, and in prostate adenocarcinomas (**Table 2**). EPHB3 exhibited the top ranking of expression in all these cancers.

We found that EPHB4 had high expressions in prostate, colorectal, testicular, gastric, and esophageal cancers seminomas, and melanomas (**Figure 2**). EPHB4 was overexpressed in adenomas, adenocarcinomas, mucinous carcinoma of the colon and rectum, in seminomas, mixed germ cell tumors, and yolk sac tumors of the testes, in the intestinal subtype of gastric adenocarcinomas, in squamous cell carcinoma of the esophagus, in basal cell carcinoma of the skin, and in prostate carcinoma (**Table 2**). Increased expression of EPHB6 was detected in bladder cancer, leukemia, lymphomas, and pleural malignant mesotheliomas (**Figure 2**). EPHB6 was mostly overexpressed in T-cell leukemia and superficial bladder cancer (**Table 2**).

Validation of EPH family member expressions with protein expressions

To further confirm our bioinformatics results analyzed on the Oncomine platform, we used the Human Protein Atlas database to verify EPH receptor members' protein expressions in a variety of cancer cell lines. Pathology data of clinical human cancer tissues in the Human Protein Atlas collection were analyzed. These data revealed similar protein expression patterns of target genes in different cancer patients. Expressions of EPHA and EPHB family members in various types of cancer, namely colorectal cancer, breast cancer, lung cancer, gliomas, and prostate cancers, were examined by immunohistochemistry (**Figures 3**, **4**). In particular, EPHA1, EPHA6, EPH7, EPHB2, and EPHB3 had strong high expressions throughout many cancer cell lines. These data from the Human Protein Atlas were used to confirm the expressions of EPHA/B proteins from clinical patient tissues. Results of the Human Protein Atlas analysis were consistent with findings fr-

Table 2. Expressions of EPHB family members in cancer

Gene	Cancer	Subtype	*N* (case)	*p* value (cancer/normal)	*t*-test (cancer/normal)	Multiple of change (cancer/normal)	% Gene ranking	Database reference
EPHB1	Brain	Oligodendroglioma	180	7.90E-10	6.947	4.531	501 (in top 3%)	Cancer Cell [97]
		anaplastic oligodendroglioma	33	3.39E-7	6.559	2.201	379 (in top 2%)	Cancer Res [98]
	Uterus	Uterine corpus leiomyoma	77	4.90E-7	5.366	2.903	318 (in top 2%)	Cancer Res [99]
	Gastric	Diffuse gastric adenocarcinoma	90	4.87E-6	5.109	2.050	473 (in top 3%)	Clin Cancer Res [100]
		Gastric intestinal type adenocarcinoma	90	7.86E-5	4.540	2.178	467 (in top 3%)	Clin Cancer Res [100]
	Esophagus	Barrett's esophagus	118	7.23E-6	6.398	2.369	1230 (in top 7%)	PLoS One [101]
		Esophageal adenocarcinoma	48	2.68E-5	7.013	10.052	436 (in top 3%)	Gastroenterology [87]
		Barrett's esophagus	48	4.32E-4	3.870	2.827	783 (in top 6%)	Gastroenterology [87]
	Lymphoma	Follicular lymphoma	120	1.25E-5	5.106	2.613	39 (in top 2%)	Nature [102]
		Diffuse large B-cell lymphoma	120	3.04E-4	5.286	3.006	52 (in top 2%)	Nature [102]
		Follicular lymphoma	102	1.10E-4	4.555	2.088	40 (in top 1%)	J Exp Med [88]
	Melanoma	Benign melanocytic skin nevus	70	2.21E-5	5.241	2.185	328 (in top 3%)	Clin Cancer Res [86]
	Lung	Lung adenocarcinoma	73	1.01E-4	5.192	2.608	303 (in top 3%)	Proc Natl Acad Sci U S A [103]
		Squamous cell lung carcinoma	73	1.35E-4	4.645	3.360	337 (in top 4%)	Proc Natl Acad Sci U S A [103]
	Prostate	Prostatic intraepithelial neoplasia	101	3.44E-4	3.899	2.616	465 (in top 5%)	Nat Genet [104]
	Renal	Clear cell sarcoma of the kidney	35	3.79E-4	19.043	8.371	48 (in top 4%)	Clin Cancer Res [91]
EPHB2	Colorectal	Colon adenoma	64	1.14E-18	14.090	2.901	72 (in top 1%)	Mol Cancer Res [63]
		Colorectal carcinoma	82	4.91E-15	11.319	2.266	184 (in top 1%)	Clin Exp Metastasis [105]
		Colon adenoma	40	2.96E-8	11.028	3.221	222 (in top 2%)	PLoS One [106]
		Colon carcinoma	40	9.04E-8	10.042	2.765	990 (in top 6%)	PLoS One [106]
	Head-Neck	Tongue squamous cell carcinoma	58	7.10E-13	9.363	3.708	33 (in top 1%)	BMC Cancer [107]
		Head and neck squamous cell carcinoma	38	4.79E-5	8.795	2.652	142 (in top 2%)	Oncogene [108]
	Ovarian	Ovarian carcinoma	195	4.75E-12	15.823	2.250	328 (in top 3%)	Cancer Res [109]
	Bladder	Infiltrating bladder urothelial carcinoma	157	7.49E-12	7.678	3.380	295 (in top 3%)	J Clin Oncol [62]
	Lung	Lung adenocarcinoma	246	1.02E-10	9.515	2.400	1122 (in top 6%)	Cancer Res [94]
		Lung adenocarcinoma	66	7.60E-7	5.548	2.958	264 (in top 3%)	BMC Genomics [110]
	Cervix	Cervical squamous cell carcinoma	66	4.73E-10	7.630	4.561	128 (in top 2%)	Genes Chromosomes Cancer [111]
	Lymphoma	Centroblastic lymphoma	336	7.80E-10	7.767	4.212	416 (in top 5%)	Nat Genet [112]
	Gastric	Gastric intestinal type adenocarcinoma	69	4.82E-9	6.762	4.236	956 (in top 5%)	Eur J Cancer [84]
		Gastric intestinal type adenocarcinoma	90	1.42E-7	7.171	2.155	46 (in top 1%)	Clin Cancer Res [100]
		Gastric mixed adenocarcinoma	90	6.08E-5	6.158	2.177	313 (in top 2%)	Clin Cancer Res [100]
		Gastric cancer	27	1.42E-4	4.220	3.812	360 (in top 2%)	Med Oncol [113]
	Sarcoma	Myxofibrosarcoma	158	2.82E-7	6.033	2.155	1084 (in top 9%)	Nat Genet [74]
		Round cell liposarcoma	54	8.21E-4	3.742	2.288	665 (in top 6%)	Cancer Res [75]
	Brain	Glioblastoma	54	6.63E-6	5.413	2.239	743 (in top 6%)	Cancer Res [114]
		Meningioma	18	8.07E-4	4.871	4.265	37 (in top 3%)	Am J Pathol [115]
	Esophagus	Barrett's esophagus	24	3.81E-5	5.544	6.303	27 (in top 1%)	Cancer Res [116]
		Esophageal adenocarcinoma	24	2.20E-4	4.856	7.833	164 (in top 2%)	Cancer Res [116]
	Seminoma	Yolk sac tumor, NOS	107	6.91E-5	5.585	2.350	1350 (in top 8%)	Cancer Res [65]
	Mesothelioma	Pleural malignant mesothelioma	54	4.38E-4	4.421	2.444	938 (in top 8%)	Am J Pathol [117]

EPHB3	Colorectal	Colorectal adenocarcinoma	105	3.71E-18	12.557	3.833	65 (in top 1%)	PLoS One [106]
		Colon adenoma	64	7.26E-16	11.608	2.321	218 (in top 2%)	Mol Cancer Res [63]
		Colon adenocarcinoma	105	8.52E-12	9.012	2.106	206 (in top 2%)	Genome Biol [69]
		Colon mucinous carcinoma	105	8.05E-6	6.513	2.106	947 (in top 5%)	Genome Biol [69]
		Colon adenoma	40	5.62E-11	19.664	6.410	27 (in top 1%)	PLoS One [106]
		Colon adenoma	40	7.05E-11	18.096	4.881	30 (in top 1%)	PLoS One [106]
		Colon adenocarcinoma	123	2.68E-9	6.525	2.171	627 (in top 7%)	Int J Cancer [63]
		Rectal mucinous carcinoma	237	1.61E-4	6.917	3.393	1364 (in top 7%)	Nature [93]
	Ovarian	Ovarian serous Cystadenocarcinoma	594	3.43E-10	15.427	2.306	63 (in top 1%)	Nature [118]
	Lung	Squamous cell lung carcinoma	156	5.56E-10	8.577	2.130	964 (in top 5%)	PLoS One [119]
		Squamous cell lung carcinoma	73	7.31E-5	4.961	4.747	272 (in top 3%)	Proc Natl Acad Sci U S A [103]
		Squamous cell lung carcinoma	203	6.27E-4	3.502	5.147	389 (in top 5%)	Proc Natl Acad Sci U S A [103]
	Sarcoma	Synovial sarcoma	54	8.17E-7	7.323	7.234	77 (in top 1%)	Cancer Res [75]
	Testicular	Testicular seminoma	74	8.38E-7	6.034	2.418	475 (in top 5%)	Proc Natl Acad Sci U S A [120]
	Prostate	Prostate adenocarcinoma	89	1.66E-4	4.303	3.914	226 (in top 2%)	Cancer Res [121]
EPHB4	Colorectal	Colorectal adenocarcinoma	105	1.21E-23	15.254	2.122	20 (in top 1%)	PLoS One [106]
		Colon adenoma	64	8.31E-22	16.394	2.589	20 (in top 1%)	Mol Cancer Res [63]
		Rectal adenoma	64	4.41E-6	10.091	2.758	831 (in top 5%)	Mol Cancer Res [63]
		Colon adenocarcinoma	237	8.13E-16	12.139	2.265	962 (in top 5%)	Nature [93]
		Cecum adenocarcinoma	237	4.04E-13	10.517	2.729	317 (in top 2%)	Nature [93]
		Rectal adenocarcinoma	237	6.18E-13	8.617	2.091	1483 (in top 8%)	Nature [93]
		Colon mucinous carcinoma	237	1.07E-11	9.348	2.444	408 (in top 2%)	Nature [93]
		Colorectal carcinoma	82	3.99E-12	11.872	2.525	476 (in top 3%)	Clin Exp Metastasis [105]
		Colon carcinoma	40	2.92E-10	16.846	3.071	218 (in top 2%)	PLoS One [106]
		Colon adenoma	40	1.45E-7	13.443	3.056	355 (in top 2%)	PLoS One [106]
	Testicular	Testicular seminoma	74	1.39E-11	9.097	3.313	31 (in top 1%)	Proc Natl Acad Sci U S A [120]
		Mixed germ cell tumor, NOS	107	3.43E-9	7.921	2.246	1007 (in top 6%)	Cancer Res [65]
		Seminoma, NOS	107	1.28E-8	10.424	3.845	393 (in top 3%)	Cancer Res [65]
		Yolk sac tumor, NOS	107	9.63E-5	5.59;2	2.345	1476 (in top 9%)	Cancer Res [65]
	Gastric	Gastric intestinal type Adenocarcinoma	69	8.77E-9	7.324	2.367	1057 (in top 6%)	Eur J Cancer [84]
	Esophagus	Esophageal squamous cell carcinoma	34	2.90E-6	6.257	2.054	555 (in top 5%)	BMC Genomics [122]
		Barrett's esophagus	48	7.42E-4	3.516	2.623	917 (in top 7%)	Gastroenterology [87]
	Melanoma	Skin basal cell carcinoma	87	8.72E-6	8.478	2.458	360 (in top 2%)	BMC Med Genomics [123]
	Prostate	Prostate carcinoma	101	2.58E-5	4.437	2.363	305 (in top 3%)	Nat Genet [104]
EPHB6	Leukemia	T-cell acute lymphoblastic leukemia	2096	3.83E-55	21.261	3.924	71 (in top 1%)	J Clin Oncol [89]
		T-cell childhood acute lymphoblastic leukemia	288	1.62E-7	10.033	4.216	173 (in top 2%)	Blood [124]
		T-cell acute lymphoblastic leukemia	127	1.13E-6	8.926	7.396	655 (in top 7%)	Leukemia [125]
	Bladder	Superficial bladder cancer	157	3.90E-13	10.463	5.740	786 (in top 7%)	J Clin Oncol [62]
		Superficial bladder cancer	60	2.86E-7	6.025	2.224	477 (in top 4%)	Cancer Res [126]
		Superficial bladder cancer	54	1.16E-6	10.625	3.650	15 (in top 2%)	Clin Cancer Res [127]
	Lymphoma	Mantle cell lymphoma	336	3.65E-6	5.395	5.250	193 (in top 3%)	Nat Genet [112]
	Mesothelioma	Pleural malignant mesothelioma	54	1.85E-5	5.509	2.033	354 (in top 3%)	Am J Pathol [117]

om mRNA expressions in the Oncomine analysis.

Scoring of genetic associations based on ClueGo and CluePedia

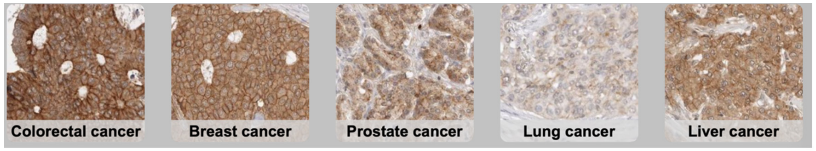
We used the ClueGO and CluePedia databases to query genetic interaction networks associated with EPHA and EPHB family genes. The ClueGO and CluePedia databases incorporate gene-gene interactions from various databases, including Gene Ontology, KEGG, CORUM, and WikiPathways. The various sources of associated data are standardized in the ClueGo and CluePedia databases. A combined score was obtained by computing both known and predicted associations. A higher combined score represents a more-reliable association from more than one type of information. Based on these combined scores, a graphical network of gene-gene interactions was generated for some of the EPHA and EPHB family genes (**Figure 5**). Strong evidence for interactions among these EPHA and EPHB family genes was supported by STRING, and other networks were validated in previous reports (**Figures 6**, **7**). Hence, our interacting network presents a novel tool for screening potential biomarkers in the EPHA/B gene family.

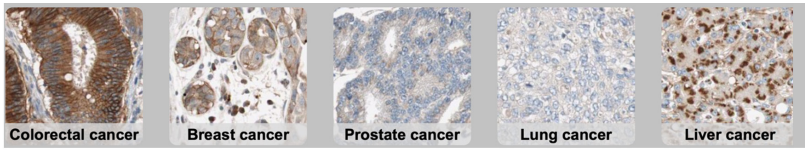
Discussion

It is obvious that the EPH and ephrin binding complex functions in the development and progression of different types of tumors. These genes control the proliferation of stem cells and progenitor cells, invasion, and angiogenesis. Functions of EPH/ephrin receptors are distinct; however, all these genes play vital roles in cancer metastasis. Therefore, EPHs and ephrins are proposed to be potential therapeutic targets for cancer treatment [20]. The present study analyzed expression levels of EPHA/B genes in diverse clinical samples and cell lines of various cancers. By determining novel targets of EPHA/B in various types of cancer using high-throughput technology, the present data selected potential targets for future cancer treatment. According to our bioinformatics data, many EPHA/B family genes participate in diverse types of cancer. For instance, colorectal cancer exhibited significant upregulation in EPHA1, EPHA2, EPHA8, EPHB2, EPHB3, and EPHB4. Likewise, EPHA1, EPHA2, EPHA4, EPHB2, and EPHB6 were shown to be highly expressed in bladder tumors. Also, esophageal cancer showed dramatic upregulation of EPHA4, EPHA10, EPHB1, EPHB2, and EPHB4. Gastric cancer showed dramatic upregulation of EPHA4, EPHB1, EPHB2, EPHB3, and EPHB4. Prostate cancer showed dramatic upregulation of EPHA1, EPHA10, EPHB1, EPHB1, EPHB3, and EPHB4. Our study suggested that the high expression of EPHB2 was associated with cervical cancer. EPHA3 and EPHB1 were only respectively upregulated in liver cancer and uterine cancer. Many microarray and RNA-Seq datasets were analyzed for expression patterns of EPHA/B through multiple types of cancer. The present study targeted candidates for carcinogenesis of specific cancers, and further studies should be conducted according to these findings.

EPHA/B and their ephrin ligands are known to be involved in tissue boundary formation, vascular development, and axon control [21, 22]. EPHs and ephrins are membrane proteins which allow bidirectional signaling between adjacent cells. EPH-ephrin binding can regulate the actin cytoskeleton by affecting G-protein and Rho GTPase signaling to regulate cell morphology, adhesion, and migration [23]. In various cell types, cell motility is controlled by crucial processes, such as microtubular dynamics, polymerization dynamics, and polarization of the cytoskeleton. Expressions of EPH receptors are upregulated in the course of tumor development. Overexpression of EPHA receptors is associated with a poor prognosis of cancer patients [24]. EPHB receptors interact with surrounding stromal cells to promote migration and invasion of cancer cells [25]. However, there are no systematic approaches to examine the functions of EPHA/B receptor family genes in diverse types of cancer.

Previous research showed that positive EPHA1 protein staining was significantly linked to more-aggressive renal cell carcinoma [8]. Increased expression in EPHA1 was also detected in prostate cancers [26]. EPHA2 is expressed by most epithelial cells [27]. The independence of EPHA2 with its ephrin ligand suggests its potency with that type of cancer cell development [28]. The EPHA2 staining intensity was dramatically elevated in advanced stages of urothelial carcinoma relative to the normal uro-


Colorectal cancer
Breast cancer
Prostate cancer
Lung cancer
Liver cancer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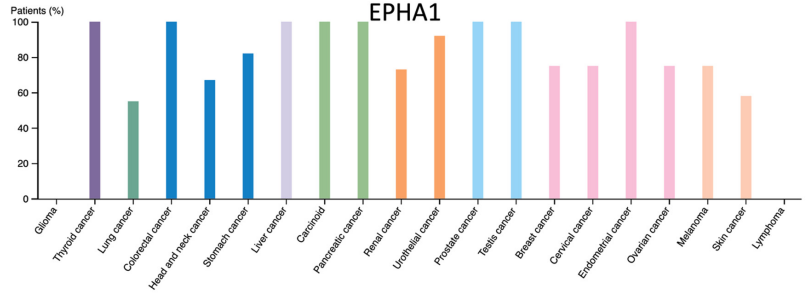
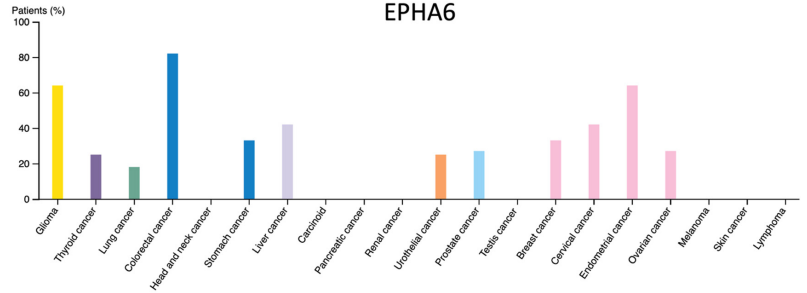
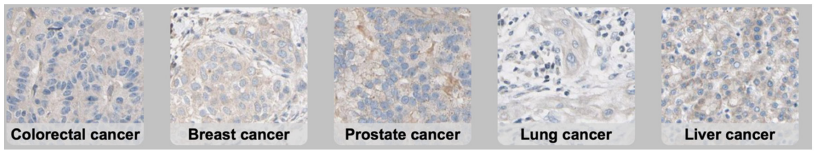
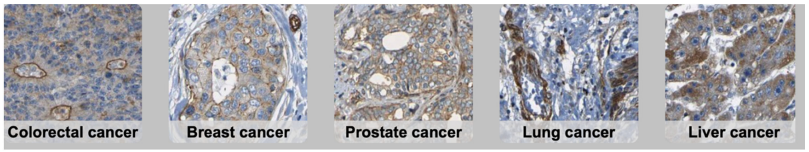
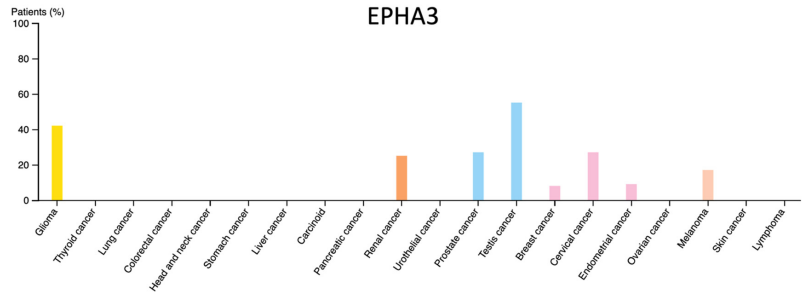
Lung cancer
Liver cancer

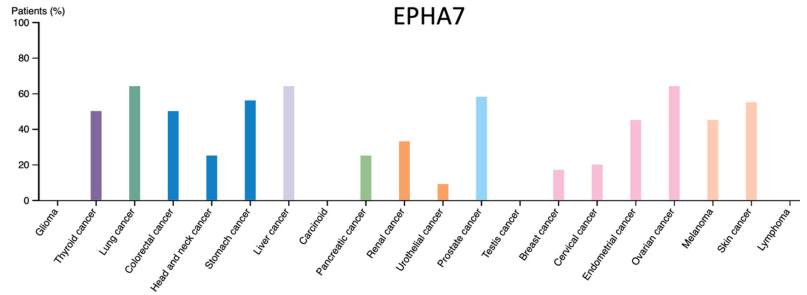

EPHA1
Patients (%)
100
80
60
40
20
0
Glioma
Thyroid cancer
Lung cancer
Colorectal cancer
Head and neck cancer
Stomach cancer
Liver cancer
Carcinoid
Pancreatic cancer
Renal cancer
Urothelial cancer
Prostate cancer
Testis cancer
Breast cancer
Cervical cancer
Endometrial cancer
Ovarian cancer
Melanoma
Skin cancer
Lymphoma

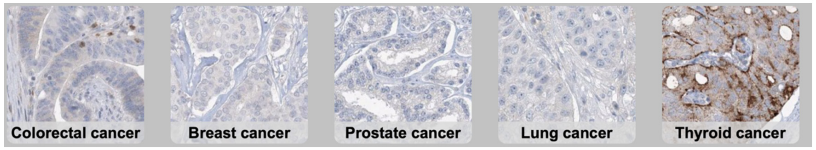

EPHA6
Patients (%)
100
80
60
40
20
0
Glioma
Thyroid cancer
Lung cancer
Colorectal cancer
Head and neck cancer
Stomach cancer
Liver cancer
Carcinoid
Pancreatic cancer
Renal cancer
Urothelial cancer
Prostate cancer
Testis cancer
Breast cancer
Cervical cancer
Endometrial cancer
Ovarian cancer
Melanoma
Skin cancer
Lymphoma

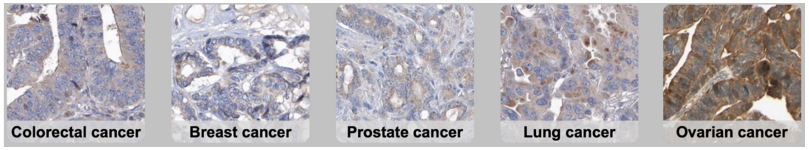

Colorectal cancer
Breast cancer
Prostate cancer
Lung cancer
Liver cancer


Colorectal cancer
Breast cancer
Prostate cancer
Lung cancer
Liver cancer


EPHA3
Patients (%)
100
80
60
40
20
0
Glioma
Thyroid cancer
Lung cancer
Colorectal cancer
Head and neck cancer
Stomach cancer
Liver cancer
Carcinoid
Pancreatic cancer
Renal cancer
Urothelial cancer
Prostate cancer
Testis cancer
Breast cancer
Cervical cancer
Endometrial cancer
Ovarian cancer
Melanoma
Skin cancer
Lymphoma


EPHA7
Patients (%)
100
80
60
40
20
0
Glioma
Thyroid cancer
Lung cancer
Colorectal cancer
Head and neck cancer
Stomach cancer
Liver cancer
Carcinoid
Pancreatic cancer
Renal cancer
Urothelial cancer
Prostate cancer
Testis cancer
Breast cancer
Cervical cancer
Endometrial cancer
Ovarian cancer
Melanoma
Skin cancer
Lymphoma


Colorectal cancer
Breast cancer
Prostate cancer
Lung cancer
Thyroid cancer


Colorectal cancer
Breast cancer
Prostate cancer
Lung cancer
Ovarian cancer

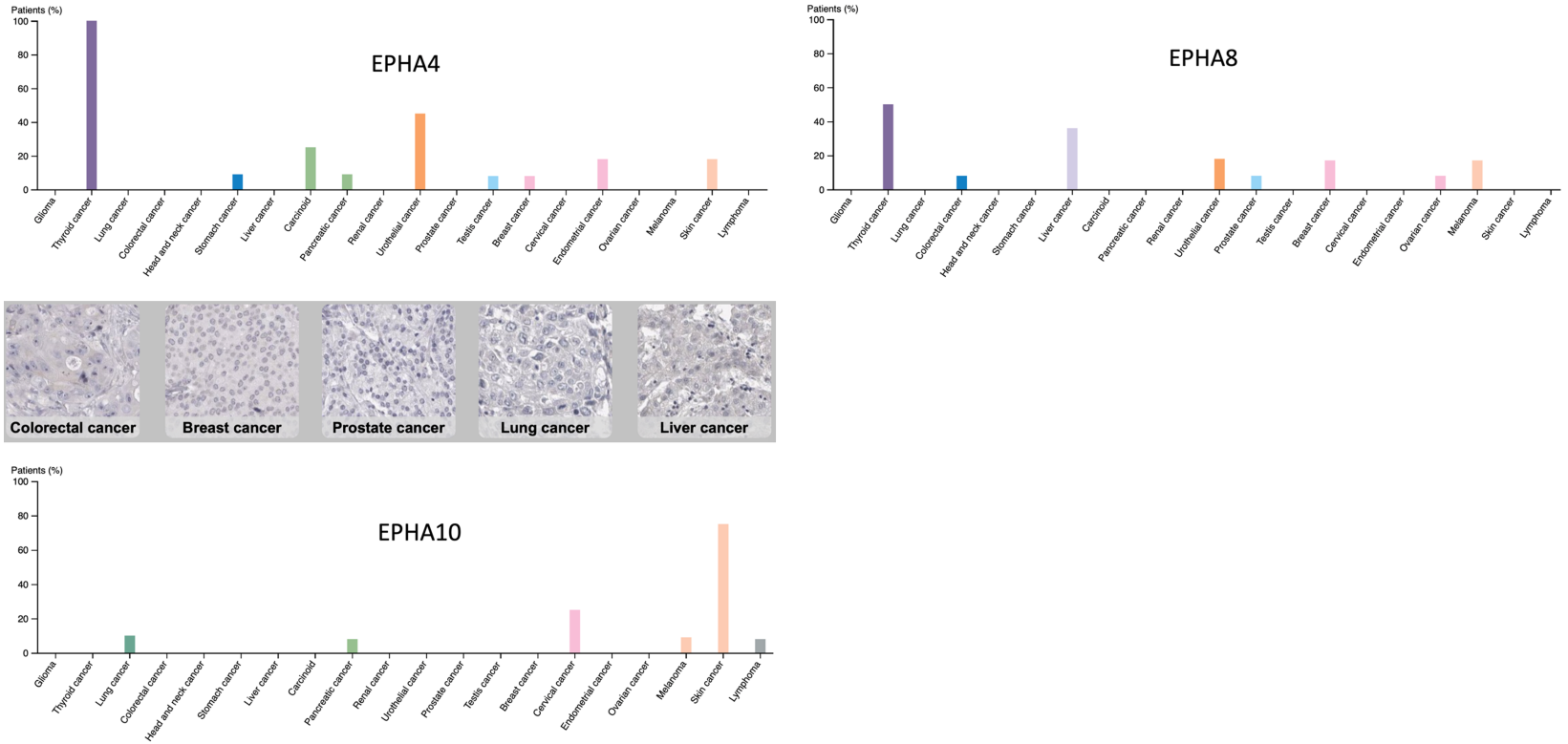


Figure 3. Protein expressions of erythropoietin-producing hepatoma A (EPHA) family members in human tumor samples. Protein expression data of EPHA family members were acquired from the Human Protein Atlas. Representative pathology images of immunohistochemical staining for the top four cancers are indicated in the left panel, and the overall protein expression is indicated in the right panel.

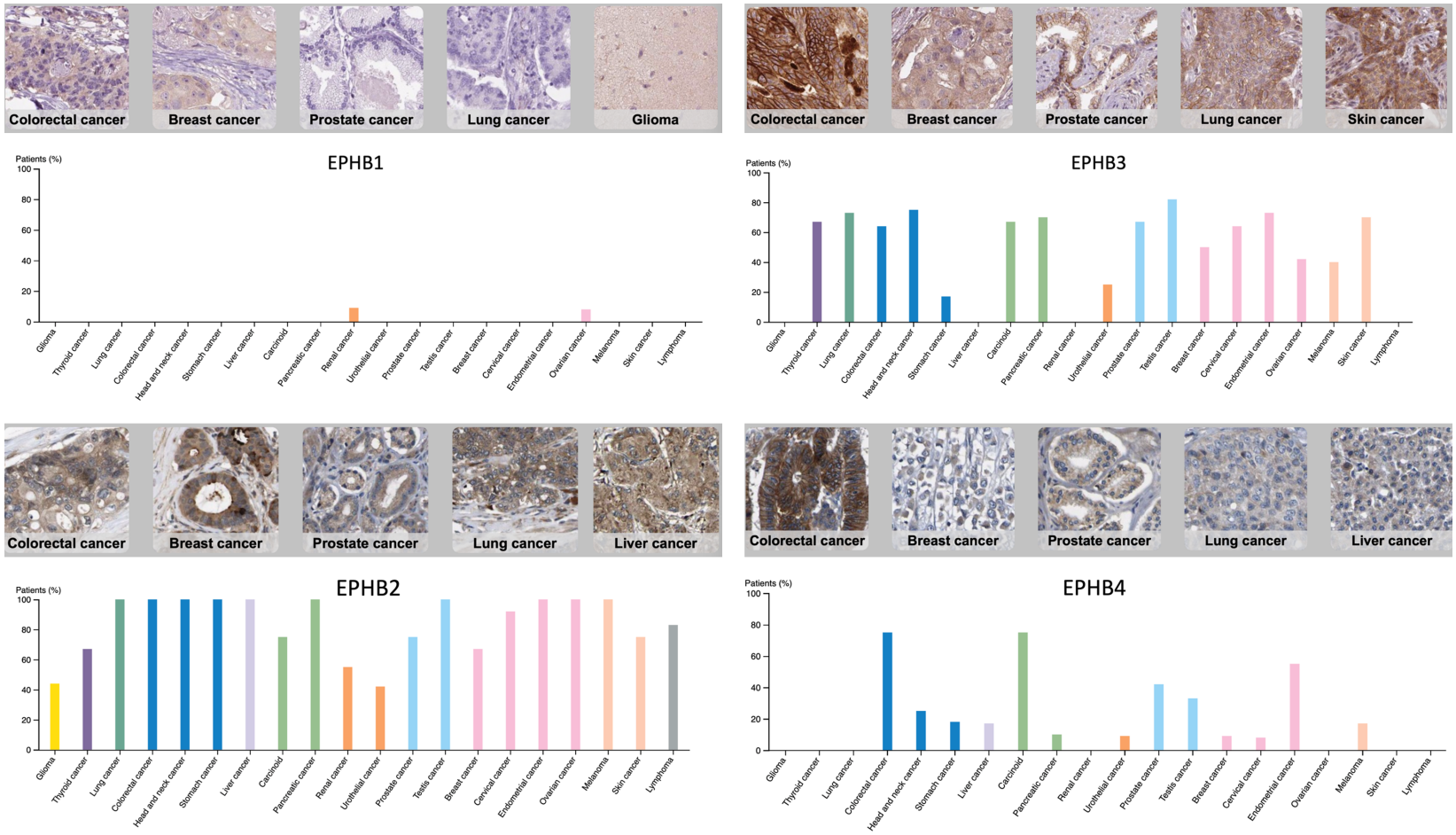


Figure 4. Protein expressions of erythropoietin-producing hepatoma B (EPHB) family members in human tumor samples. Protein expression data of EPHB family members were acquired from the Human Protein Atlas. Representative pathology images of immunohistochemical staining for the top four cancers are indicated in the left panel, and the overall protein expression is indicated in the right panel.

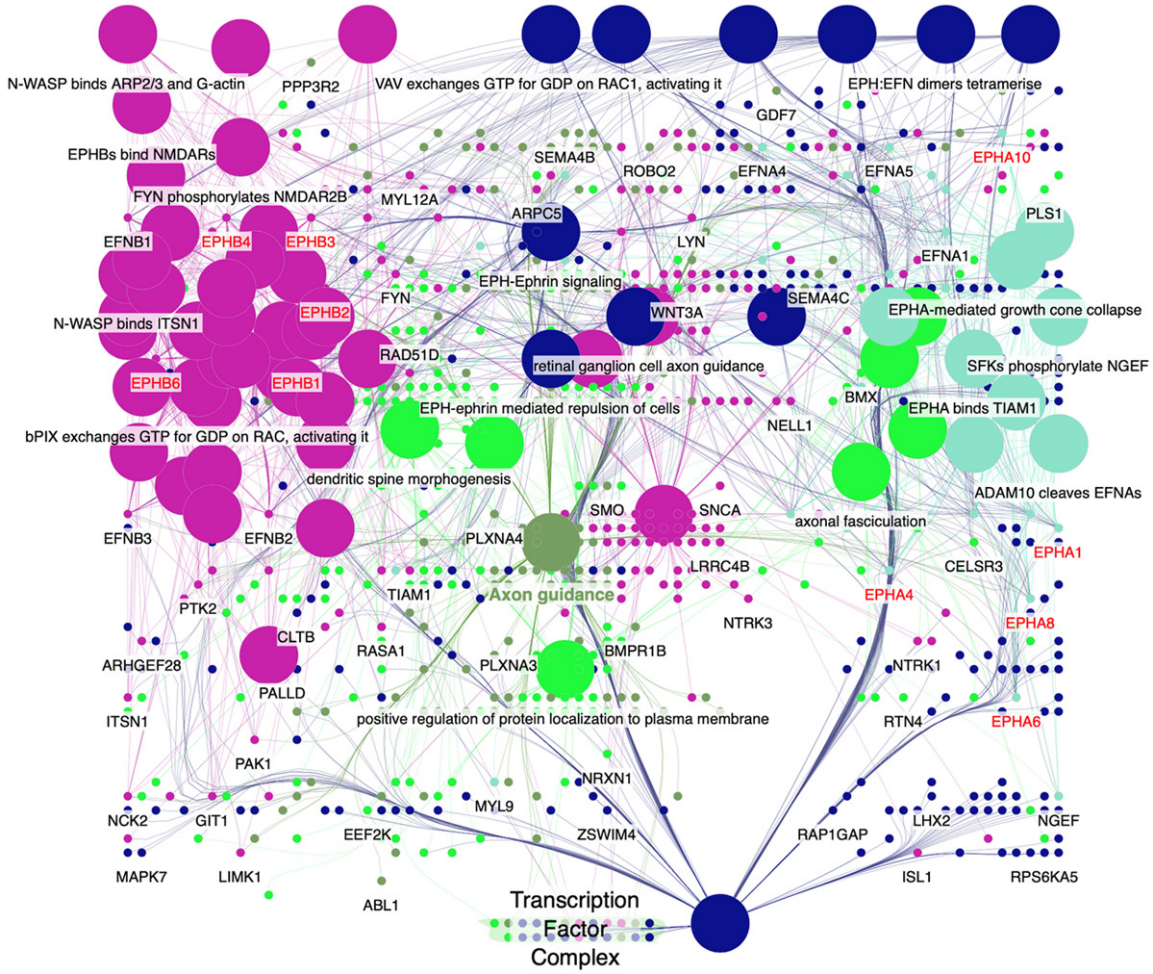


Figure 5. Erythropoietin-producing hepatoma (EPH) member's interaction network via ClueGo and CluePedia. The interaction network among EPHA and EPHB family members were analyzed with ClueGo and CluePedia with gene ontology. Nodes represent genes and lines represent gene-gene interactions. The network modules were established based on the network structure and biological functions of uploaded EPHA and EPHB member genes.

thelium [29]. EPHA2 was suggested to play essential roles in stages I and II of colon carcinogenesis [30]. EPHA3 is well known to play oncogenic roles in carcinogenesis, migration, invasion, angiogenesis, and cancer progression [31]. Expression of EPHA3 was correlated with poor survival of liver cancer patients [32]. EPHA4 is known to be dominantly expressed in the nervous system and inhibit axon regeneration [33, 34]. In certain types of cancer, inhibition of EPHA4 impedes the progression and invasion of cancer cells [35]. Higher expression of EPHA4 was associated with cancer metastasis [36, 37]. EPHA5 is mostly recognized for its critical role in axonal guidance during embryonic development [38]; however, its involvement in cancer is still largely unknown. The expression of EPHA6 was reported to be controlled by HOXA13 in the genital tubercle and its vasculature [39]. Although the biological function of EPHA6 is still largely unknown, EPHA6 was not selected for further examination because its expression data did not satisfy the selection criteria of the present study. Throughout vertebrates and humans, EPHA7 is highly conserved. EPHA7 is also highly present in embryonic tissues, particularly in the central nervous system in the developing stage [40]. But little is known about the role of EPHA7 in cancer development. Recent genetic studies suggested that EPHA8 is involved in regulating cell adhesion and apoptosis [41]. Some findings suggested that the EPHA8 receptor induces axonal projections through regulation of the

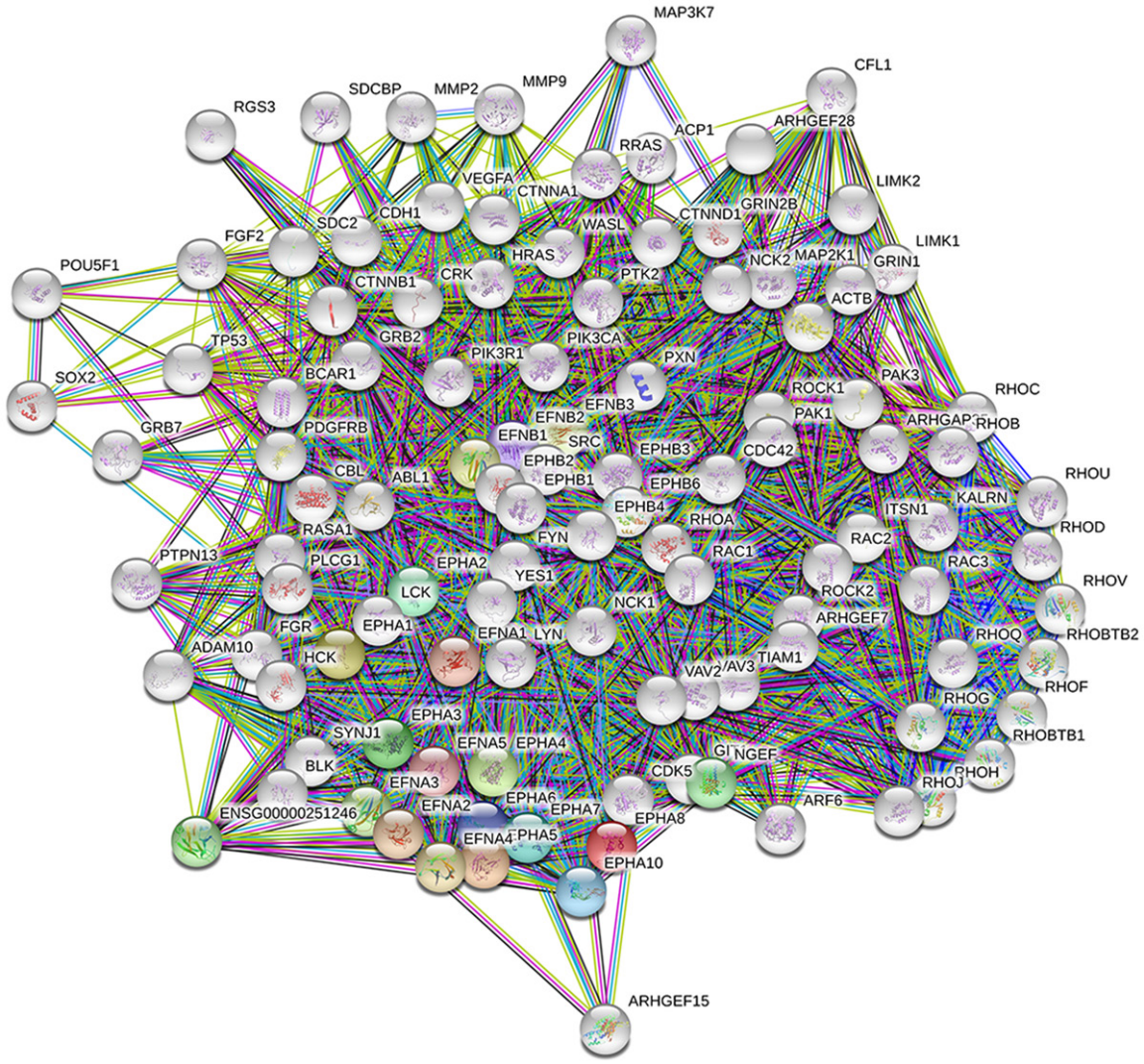


Figure 6. Erythropoietin-producing hepatoma A (EPHA) member's interaction network via the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database. Protein-protein interactions were constructed with the STRING database. The thickness of the line indicates the strength of data support for protein-protein interactions. Colored nodes represent EPHA member proteins and the first shell of interactors; white nodes represent the second shell of interactors.

mitogen-activated protein kinase (MAPK) signaling pathway [42]. A previous study showed that EPHA10 is only expressed in breast cancer but not in normal tissues [43]. Moreover, EPHA10 was also examined for its potential as a therapeutic target [44]. Our data in **Figures 2** and **3** and **Table 1** further confirmed the significance of EPHA family receptors in various types of cancer.

Overexpression of EPHB1 was found in patients with gastric cancer [19]. EPHB2 overexpression is well documented in various types of human cancers. EPHB2 is known to be involved in the onset of colon cancer [45], cervical cancer and cholangiocarcinoma metastasis [46, 47]. EPHB3 was found to engage with the loss of metameric migratory patterns and disorganization of mobility of neural crest cells [48]. Overexpression of EPHB3 improved survival and migration of non-small cell lung cancer cells [49]. EPHB4 is known for playing a vital role in cell signaling and modulates integrin activity to modify the actin skeleton [50]. Upregulation of EPHB4 is associated with the onset and progression of prostate cancer [51, 52]. Overexpression of EPHB3 and EPHB4 was detected in prostate cancer and was associat-

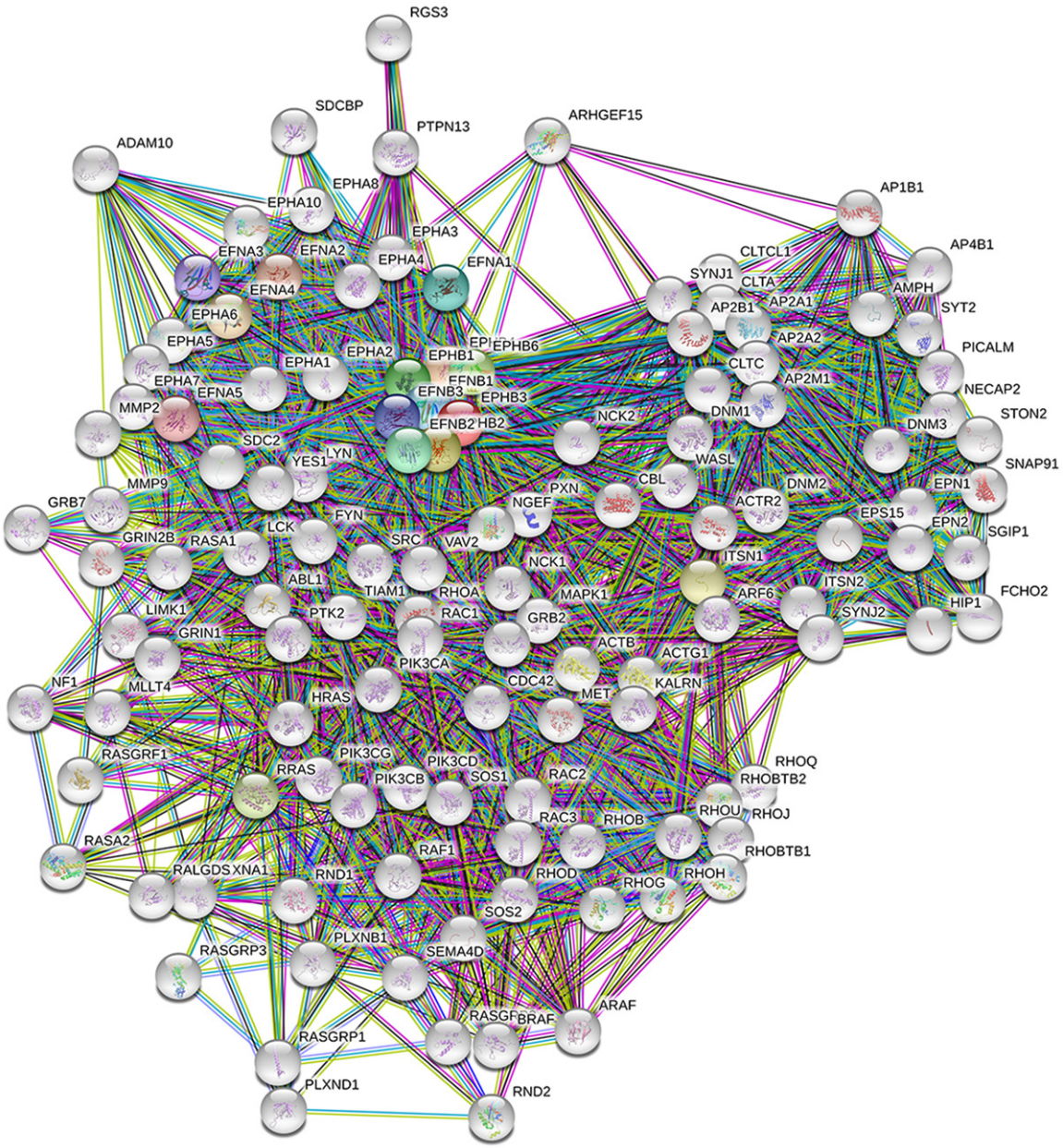


Figure 7. Erythropoietin-producing hepatoma B (EPHB) member's interaction network via the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database. Protein-protein interactions were constructed with the STRING database. The thickness of the line indicates the strength of data support for protein-protein interactions. Colored nodes represent EPHB member proteins and the first shell of interactors; white nodes represent the second shell of interactors.

ed with regional invasion and metastasis [25]. The present study proved the function of EPHB receptors in those cancers (**Figure 2**, **Table 2**).

Meanwhile, ClueGo and CluePedia used different types of data and text mining tools to determine relationships between genes. In the literature, the network of SEMA3C, WNT3A, SEMA4B, and ADAM10 was in an intermediate position between EPHB and EPHA family members [53-61]. Our results showed that EPHA and EPHB family genes interacted with SEMA3C, WNT3A, SEMA4B, and ADAM10. The STRING software contains thousands of organisms and genes with millions of gene-gene interactions. Our present data revealed that

these relationships might play a crucial role as the genetic backbone of cancer development. In conclusion, our study proved associations between upregulation of EPH receptor family genes in public databases from clinical samples and cancer cell lines. The overexpression of many subunits of the EPHA/B confirmed their function in cancer. The overexpression of EPHA1, EPHA4, EPHB1, EPHB2, EPHB3, and EPHB4 in cancers is a novel feature of this study. Partial inhibition of EPHA1, EPHA4, EPHB1, EPHB2, EPHB3, or EPHB4 may suppress cancer development. Therefore, these EPH receptors may serve as potential therapeutic targets for treating and regulating cancer development.

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Disclosure of conflict of interest

None.

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