Identification of Significant Genes and Pathways Associated with Tenascin-C in Cancer Progression by Bioinformatics Analysis

Abstract

Background: Tenascin-C (TNC) is a large glycoprotein of the extracellular matrix which associated with poor clinical outcomes in several malignancies. TNC over-expression is repeatedly observed in several cancer tissues and promotes several processes in tumor progression. Until quite recently, more needs to be known about the potential mechanisms of TNC as a key player in cancer progression and metastasis. **Materials and Methods:** In the present study, we performed a bioinformatics analysis of breast and colorectal cancer expression microarray data to survey TNC role and function with holistic view. Gene expression profiles were analyzed to identify differentially expressed genes (DEGs) between normal samples and cancer biopsy samples. The protein-protein interaction (PPI) networks of the DEGs with CluePedia plugin of Cytoscape software were constructed. Furthermore, after PPI network construction, gene-regulatory networks analysis was performed to predict long noncoding RNAs and microRNAs associated with TNC and cluster analysis was performed. Using the Clue gene ontology (GO) plugin of Cytoscape software, the GO and pathway enrichment analysis were performed. **Results:** PPI and DEGs-miRNA-lncRNA regulatory networks showed TNC is a significant node in a huge network, and one of the main gene with high centrality parameters. Furthermore, from the regulatory level perspective, TNC could be significantly impressed by miR-335-5p. GO analysis results showed that TNC was significantly enriched in cancer-related biological processes. **Conclusions:** It is important to identify the TNC underlying molecular mechanisms in cancer progression, which may be clinically useful for tumor-targeting strategies. Bioinformatics analysis provides an insight into the significant roles that TNC plays in cancer progression scenarios.

Keywords: *Gene regulatory network, microarray analysis, protein interaction maps, Tenascin-C*

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Introduction

The tumor microenvironment is highly heterogeneous meshwork, encompassing immune cells, fibroblasts, adipocytes, and endothelial cells, and a complex network termed the extracellular matrix (ECM).[1] The ECM's composition and organization are highly regulated and control cell behavior, but the evidence is increasing on the crucial role of the altered ECM components in providing oncogenic signals that promote cancer cell proliferation, invasion, new angiogenesis, and metastasis. Growing evidence showed that the composition and organization of ECM are underlying numerous changes in cancer when compared to normal tissue.[2,3]

Tenascin-C (TNC) is a large hexameric glycoprotein that is located primarily in the ECM and interacts with cell surface receptors and other ECM proteins. TNC is a highly conserved ECM protein, without noticeable mutational hotspots, reflecting its importance for the maintenance of tissue homeostasis. TNC expression is tightly regulated, and TNC presents in stem cell niche regions and at sites of epithelial-mesenchymal interaction in adults and is frequently up-regulated in a variety of pathological conditions including chronic inflammation and cancer.[2,4,5] Its expression in several cancer tissues of breast, lung, colon, glioblastoma, liver, prostate, gastric cancer, pancreatic cancer, and gastrointestinal tract have been well documented in previous studies.[6,7]

TNC expression in tumors is significantly higher than in normal tissue and correlated with distant metastasis and invasiveness, and tumor metastases can also express TNC.[7] Because of the abundance of TNC in tumor stroma and its association with cancer progression, invasion, angiogenesis, and metastasis, identification

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Access this article online

Website: www.advbiores.net

DOI: 10.4103/abr.abr_201_20

Quick Response Code:

How to cite this article: Rahimmanesh I, Fatehi R, Khanahmad H. Identification of significant genes and pathways associated with tenascin-C in cancer progression by bioinformatics analysis. Adv Biomed Res 2022;11:17.

of the TNC-related pathways may be clinically useful for representing the cancer progression process and tumor-targeting.

Systems biology approaches have a holistic view of the cancer molecular mechanisms and in the present study, to identify TNC-related pathways in cancer, we performed a bioinformatics analysis on breast and colorectal cancer expression microarray data.

The differentially expressed genes (DEGs) in these datasets were analyzed and their interaction with TNC was investigated by protein-protein interaction (PPI) network analysis. In addition, TNC gene regulatory networks (GRN) were constructed to identify possible regulatory mechanisms at the transcriptional level. Moreover, possible functions of TNC and its related protein were evaluated by gene and pathway enrichment analyses. Therefore, we anticipated that the findings of the present study may provide further insight into TNC-related pathways in cancer pathogenesis and development at the molecular level.

Materials and Methods

Acquisition of microarray data

Gene expression profiles GSE37364, which was composed of 104 breast tumor samples and 17 normal breast tissue samples and GSE42568 included 36 samples from normal colonic biopsy and 55 samples related to different stages of colorectal cancer, were downloaded from the NCBI gene expression omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo/). Both datasets were based on the Affymetrix GPL570 platform (Affymetrix Human Genome U133 Plus 2.0 Array). The reason for choosing these gene expression profiles was the appropriate number of cancers and control of human samples, also based on previous studies which represent the role of TNC in breast and colorectal cancer.

Data processing and DE genes determination

The quality control assessment of these datasets was assigned using prcomp function and "ggplot2" package[8] of R software.[9] The GEO2R, (http://www.ncbi.nlm.nih.gov/geo/geo2r/), the web tool of GEO, was used to identify genes that are differentially expressed across experimental conditions. The adjusted *P* values (adj. p) were applied to correct the false-positive results by default Benjamini-Hochberg false discovery rate method. The adjusted $P \leq 0.05$ was considered as the cutoff value.

Protein-protein interaction network analysis

The PPI networks were constructed with CluePedia plugin V1.5.4[10] of Cytoscape software V3.6.2.[11] STRING v11 database (https://string-db.org) was used for retrieving interactions. The topological properties of the networks were calculated by the Network Analyzer tool based on undirected interactions.

Gene-regulatory networks and clustering analysis

The Enrichr database (http://amp.pharm.mssm. edu/Enrichr/) was used to predict long noncoding RNAs (lncRNAs) associated with DEGs. The lncHUB lncRNA Co-Expression based on Recount2 library was used. With the Network Analyst database,[12] experimentally validated miRNA-gene interactions were obtained from Tar Base and miRTarBase databases. The Cytoscape was utilized to build and visualize the GRN. Cytoscape merge tool was used for the construction of comprehensive intercoms gene regulators and genes obtained from PPI network analysis. Furthermore, the plug-in of molecular complex detection (MCODE) (Bader and Hogue, 2003) in Cytoscape software was applied to explore the significant modules in GRN networks and, with a graph-theoretic clustering algorithm, identifies densely connected regions and interconnected clusters in the networks. The advanced options set as degree cutoff = 2, K-Core = 2, and Node Score Cutoff = 0.2. Moreover, the function and pathway enrichment analysis was performed for genes in the modules.

Gene ontology and functional analysis

Function and pathway enrichment analysis was performed for DEGs in the modules using Clue gene ontology (GO) plugin V2.5.4,[13] a Cytoscape plug-in. For exploring functions and pathways related to DEGs, Kyoto Encyclopedia of Genes and Genomes (KEGG) and GO databases were used to identify their biological meaning. Enriched terms with >3 genes and adjusted $P \leq 0.05$ was considered to be statistically significant.

Results

Identification of differentially expressed genes

Gene expression datasets GSE42568 and GSE37364 were downloaded from GEO datasets. DEGs were identified between normal tissue and cancerous samples based on the GEO2R analysis, using the adjusted $P \leq 0.05$ and | logFC| ≥1 as the cutoff criteria.

A total of 9341 and 12240 DEGs were identified from GSE42568 and GSE37364 datasets, respectively, and Venn diagram results indicate that intersection included 6609 genes and TNC is common in both datasets [Figure 1a and Supplementary Table 1 available on the website].

In the quality assay step, the samples were segregated based on their states, indicate the acceptable quality of these datasets [Figure 1b].

Protein-protein interaction network construction and analysis

Cytoscape was applied to evaluate the primary assay of the PPI interactions, protein interactome was investigated based on the STRING database. Activation, expression, inhibition, posttranslation modification, and binding interactions were retrieved.

Network topology was measured based on the graph theory concepts such as degree, betweenness, and closeness centrality. It is remarkable, TNC is one-fourth of the genes with high centrality. DEGs interacted directly with TNC in PPI networks are listed in Table 1.

Identification of Tenascin-C related regulatory network

After enrichment of genes at regulatory levels, GRNs were constructed and analyzed. Cluster analysis to determine significant modules was performed. Modules consider as protein complexes which are highly interconnected subnetworks. The results of module detection showed, In the GSE42568 dataset, TNC is clustered in MCODE Cluster 9 (score: 10.824) and in GSE37364 in MCODE Cluster 10 (score: 11.157). They are important clusters of the networks. Furthermore, the analytic results from lncRNAs and miRNAs prediction and DEGs-miRNA-lncRNA regulatory network construction indicated that TNC could be potentially modulated by hsa-mir-335-5p also by LINC01326, LINC00603, and TENM3-AS1 [Figure 2a and b].

Biological classification and pathway enrichment analysis

Aiming to evaluate the functions of identified DEGs, we uploaded DEGs clustered in modules to Clue GO plugin V2.5.4 to find significant GO categories and KEGG pathways. GO analysis and KEGG pathway analysis indicated that the TNC was significantly enriched in biological process, including cellular response to stress, focal adhesion, extracellular structure organization, PI3K-Akt signaling pathway, positive regulation of cell population proliferation, and regulation of cell adhesion [Table 2].
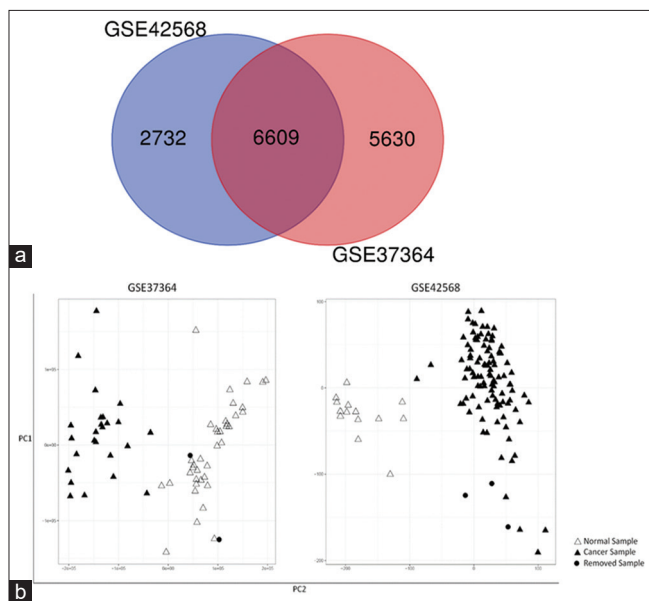
Discussion

Previously data demonstrated that TNC promotes several procedures in tumor progression and involved in a wide range of cellular processes including cell proliferation, migration, invasiveness, angiogenesis, and immunomodulation.[7,14] TNC is one of the most highly expressed proteins in the tumor ECM which has poor prognostic value for patient survival in a variety of malignant tumors.

Despite advances in current molecular methods, the potential mechanism of TNC as a major player in cancer progression and metastasis was not well known.[1,2] Therefore, it's meaningful to explore the TNC-related underlying molecular mechanisms in cancer progression procedure.

In the present study, we downloaded gene expression profiles from GEO to identify DEGs associated with breast cancer and colorectal cancer.

To explore the TNC protein interaction in these cancers, the PPI and GRN networks were constructed, and central parameters analyzed. The MCODE was applied to explore the significant modules in GRNs and TNC included in the main modules that were selected for further analysis.

Previous data reported that TNC induces epithelial-mesenchymal transition (EMT) in cancer

Figure 1: (a) The intersection of the differentially expressed genes from GSE37364 and GSE42568 datasets. The intersection included 6609 genes. (b) The principle component analysis results indicate the acceptable quality of the GSE37364 and GSE42568 datasets
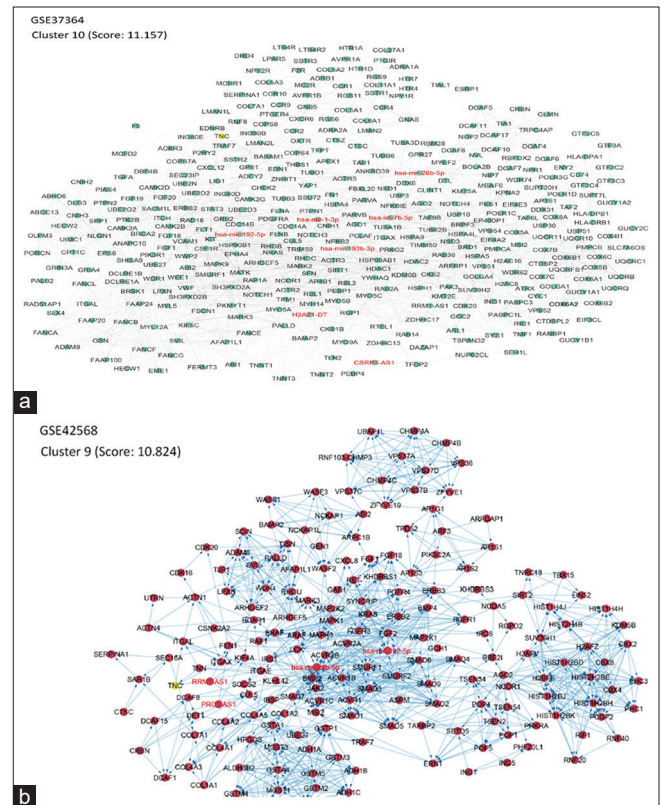

Figure 2: Gene regulatory networks. Tenascin-C is a component of key modules from GSE42568 (a) and GSE37364 (b) datasets gene regulatory networks analysis, respectively

Table 1: Protein-protein interaction networks analysis. Tenascin-C included the main node in protein-protein interaction networks, with high centrality parameters. GSE42568 and GSE37364 datasets, respectively

GSE37364			
Gene	Degree	CC	Eccentricity
EDN1	201	0.39	6
FN1	113	0.37	6
TNC	58	0.35	6
ITGAX	31	0.32	6
NOTCH1	304	0.42	6
VWF	61	0.35	6
COL2A1	60	0.34	6
EDNRA	62	0.34	6
ITGA11	74	0.33	6
ITGA6	113	0.36	6
ITGA1	152	0.36	6
ITGA2	109	0.35	6
ITGA2B	130	0.36	6
ITGA3	94	0.34	6
ITGA4	98	0.35	6
ITGA5	108	0.34	6
ITGA7	84	0.34	6
ITGAV	146	0.37	6
ITGB1	265	0.38	6
ITGB3	178	0.37	6
ITGB5	162	0.36	6
ITGB7	137	0.35	6
ITGB8	115	0.35	6
PTK2	299	0.39	6
ITGA8	86	0.34	6
IL1A	57	0.35	6
MMP9	222	0.40	6
VEGFA	539	0.43	5
FHL2	64	0.38	6
EGFR	594	0.44	6
MAPK1	1195	0.44	5
MMP2	142	0.39	5
SAT1	17	0.31	6
MMP1	88	0.36	6
CDH1	341	0.41	5
WNT7B	85	0.32	6
IL6	463	0.42	5
JUN	484	0.43	6
CAV1	215	0.41	5
PTPRZ1	99	0.35	6
ITGA10	71	0.33	6
FGF2	260	0.40	5
KHDRBS1	56	0.35	6
VCAN	18	0.33	6
ACAN	23	0.32	6
F3	54	0.35	5
NOTCH2	139	0.37	6
PRRX1	4	0.27	7

Contd...

Table 1: Contd...

GSE37364			
Gene	Degree	CC	Eccentricity
BCAN	6	0.31	7
SDC4	70	0.35	6
GSE42568			
Gene	Degree	CC	Eccentricity
ITGAE	38	0.32	7
ITGAX	35	0.31	7
TNC	38	0.29	7
ITGAL	43	0.32	7
TNN	34	0.29	7
ITGA2	100	0.34	6
ITGA3	92	0.33	7
ITGA7	82	0.32	7
ITGA9	81	0.32	7
ITGB4	103	0.35	7
ITGB8	77	0.33	7
ITGA8	91	0.33	7
ITGA1	133	0.35	6
ITGB1	196	0.36	6
PTK2	244	0.37	6
SDC1	65	0.33	7
ITGB5	107	0.34	7
SDC4	58	0.34	6
VCAN	13	0.31	7
F12	15	0.29	7
GPLD1	16	0.29	7
CD209	15	0.31	7
MASP1	10	0.27	7
SVEP1	10	0.30	7
FRAS1	9	0.32	7
ADAMTS3	5	0.29	7

TNC: Tenascin-C

tissues at the initial steps of cancer cell invasion, during which carcinoma cells lose their epithelial polarity and intercellular connections, which leads to cancer cell escape from the surrounding epithelium.[4-6] Data extracted from previous studies showed that binding of avb6 and avb1 integrins to TNC as their essential ligand induces EMT.[15] In addition, via bioinformatics analysis, we show some other integrin's family members are co-express with TNC, which included ITGA7, ITGB8, ITGAV, ITGBL1, ITGA5, and ITGA6. The co-expression of these integrins with TNC can involve in some biological processes such as ECM organization, extracellular structure organization, cell-matrix adhesion, blood vessel development, cell adhesion molecule binding, blood vessel morphogenesis, angiogenesis, integrin-mediated signaling pathway, and cell-cell adhesion. These pathways are significantly related to cancer metastasis, invasion, and angiogenesis.[7,16,17]

The versican (VCAN) a large aggregating chondroitin sulfate proteoglycan, is an important ECM component and associated with cell survival, growth, migration, invasion, angiogenesis, and metastasis in several cancers.[18] The PPI

Table 2: Pathway enrichment analysis

GSE37364

GO term	Associated genes found
Cellular response to stress	ABI2, ACKR3, ACTR2, ACTR5, ADAM8, APEX1, ARFRP1, ARHGEF5, ATRX, AVPR1A, BABAM1, BRCA2, BRSK1, CAMK2A, CAMK2B, CAMK2D, CAMK2G, CCR4, CD74, CDC14B, CHEK2, COPS4, COPS7A, COPS8, CTDSP2, CXCL12, DCLRE1A, DCLRE1B, DDX6, DTL, EDN1, EIF4A2, EME1, EPHA4, FAAP100, FAAP20, FAAP24, FANCA, FANCB, FANCE, FANCF, FANCG, FANCL, FGF1, FGF19, FSCN1, GPS1, GRB2, GUCY1B1, HDAC2, HSP90AB1, HSP90B1, HSPA5, HSPA9, HSPH 1, INO80B, INO80D, INO80E, ITCH, KDM6B, KMT5A, LIG1, MAPK9, MYEF2, NCOR1, NOTCH1, PAK3, PALB2, PCLAF, PDGFRA, PEBP1, PIAS4, PIK3R1, PMPCB, PTGER4, PTK2B, PTPN1, PTPN2, RAD18, RAD51AP1, RAP1A, RBL1, RBL2, RHOB, RNF8, RTEL1, SEH1L, SFN, SIRT1, SLX4, SMURF1, SPP1, SUV39H2, TAB1, TAF9B, TFDP2, TFPT, THBS1, TNC, TPM1, UBE2D3, UBE2G2, UBE2N, UBE2T, UIMC1, UQCRFS1, USP10, USP3, USP51, VPS51, VPS52, WDR1, YAP1
Focal adhesion	ERBB2, FLNA, FLNB, FLT1, FN1, GRB2, MAPK9, MYL12A, MYL5, PAK3, PARVA, PARVB, PDGFRA, PIK3R1, RAP1A, SPP1, THBS1, TLN2, TNC, VWF
PI3K-Akt signaling pathway	CSF1R, ERBB2, F2R, FGF1, FGF18, FGF19, FGF20, FLT1, FN1, GNB5, GRB2, HSP90AB1, HSP90B1, KIT, LPAR5, NRAS, PDGFRA, PIK3R1, RBL2, SPP1, TGFA, THBS1, TNC, VWF, YWHAQ
Extracellular structure organization	ABI2, ADAM8, COL11A1, COL27A1, COL5A1, COL5A2, COL5A3, COL7A1, COL8A1, FN1, FSCN1, GLMN, ITGAL, ITGAX, NFKB2, NOTCH1, PDGFRA, PMPCA, SH3PXD2A, SH3PXD2B, SPP1, THBS1, TNC, VCAM1, VWF, WDR1
Extracellular matrix organization	ADAM8, COL11A1, COL27A1, COL5A1, COL5A2, COL5A3, COL7A1, COL8A1, FN1, FSCN1, GLMN, ITGAL, ITGAX, NFKB2, NOTCH1, PDGFRA, SH3PXD2A, SH3PXD2B, SPP1, THBS1, TNC, VCAM1, VWF
Response to wounding	ADRA2A, CCR1, CCR2, COL5A1, EDN1, EPHA4, ERBB2, F2R, F5, FERMT3, FLNA, FN1, GLMN, GNAS, GSN, HDAC1, HDAC2, MCFD2, MYL12A, NOTCH1, NOTCH4, PDGFRA, PEBP1, PIK3R1, PMPCA, RHOC, SERPINA1, SPP1, TGFA, THBS1, TNC, TPM1, TSPAN32, VPS52, VWF, YAP1
Response to antibiotic	ACTR2, ADCY2, APEX1, ARHGEF5, CCR4, DRD4, EDN1, EPS8, GRIN3A, GSN, GUCY2C, HDAC2, HSPA5, KDM6B, PEBP1, PTK2B, RANBP1, RHOB, SIRT1, STAT3, TNC, UQCRFS1, VCAM1
Response to fibroblast growth factor	ESRP1, FGF1, FGF18, FGF19, FGF20, GRB2, GUCY2C, RAB14, RBFOX2, THBS1, TIA1, TIAL1, TNC
Response to ketone	ADCY2, AVPR1A, EDN1, EIF4A2, GNAS, GPS1, GUCY2C, OXTR, PEBP1, PTGER4, PTK2B, SIRT1, SPP1, THBS1, TNC, YAP1
Wound healing	ADRA2A, COL5A1, EDN1, ERBB2, F2R, F5, FERMT3, FLNA, FN1, GLMN, GNAS, GSN, HDAC1, HDAC2, MCFD2, MYL12A, NOTCH1, NOTCH4, PDGFRA, PIK3R1, PMPCA, RHOC, SERPINA1, TGFA, THBS1, TNC, TPM1, TSPAN32, VWF, YAP1

GSE42568

GO term	Associated genes found
PI3K-Akt signaling pathway	COL1A1, COL1A2, COL4A1, COL4A2, COL4A3, COL4A5, ERBB2, ERBB3, FGF1, FGF18, FGF2, FGFR1, FGFR3, FGFR4, IBSP, IRS1, JAK2, KRAS, MAP2K1, MAP2K2, MAPK1, MAPK3, RAF1, TNC, TNN
Focal adhesion	ACTN1, ACTN4, BCAR1, BRAF, COL1A1, COL1A2, COL4A1, COL4A2, COL4A3, COL4A5, ERBB2, IBSP, MAP2K1, MAPK1, MAPK3, RAF1, TNC, TNN
Response to fibroblast growth factor	COL1A1, CXCL8, FGF1, FGF18, FGF2, FGFR1, FGFR3, FGFR4, KDM5B, MAPK1, MAPK3, TNC, WASF1
Osteoblast differentiation	ACVR1, ACVR2A, ACVR2B, BMP2, BMP4, COL1A1, IBSP, SMAD1, SMAD3, SMAD5, SMAD6, SMAD9, SYNCRIP, TNC, TNN
ECM-receptor interaction	COL1A1, COL1A2, COL4A1, COL4A2, COL4A3, COL4A5, IBSP, TNC, TNN
Morphogenesis of a branching epithelium	ACVR1, ARHGEF5, BMP2, BMP4, COL4A1, FGF1, FGF2, FGFR1, KDM5B, KRAS, SMAD4, TNC
MicroRNAs in cancer	ERBB2, ERBB3, FGFR3, IRS1, KRAS, MAP2K1, MAP2K2, MAPK1, RAF1, TNC, TNN, UBE2I

ECM: Extracellular matrix, GO: Gene ontology, TNC: Tenascin-C

networks indicate the co-expression of TNC and VCAN both in breast and colorectal cancer.

ADAMTS, which known as adamalysins, is a matrix zinc-dependent metalloproteinases and plays an important role in the cell phenotype regulation and ECM remodeling through its role in cell adhesion and migration. ADAMTS can cleave TNC and generates TNC splice variants.[19]

As same as TNC, E-cadherin is a major contributor to cell-cell adhesion. TNC expression leads to the cytoplasmic delocalization of E-cadherin and β-catenin by Src-mediated focal adhesion kinase (FAK) signaling in combination with αvβ1 and αvβ6 integrins and promotes migratory behavior.[20]

The role of Neuropilin-1 (NRP-1), a multifunctional transmembrane protein that interacts with some of signaling

receptors, in initiating tumorigenic pathways has been shown in several cancer types, including breast cancer.[21] TNC is associated with NRP-1-triggered cell migration and activation of the FAK/Akt signaling pathway. Upregulation of NRP-1 and *TNC* was also related to considerably increased Vimentin expression and downregulation of E-cadherin (mature form) and β-catenin that leads to EMT.[22,23]

In addition, TNC stimulates endothelin receptor type A (EDNRA) expression, and EDNRA supports cell rounding by TNC through concomitant repression of RhoA and tumor suppressor-like molecule tropomyosin-1.[24]

TNC inhibits the interaction between fibronectin and syndecan-4, a transmembrane heparan sulfate proteoglycan, and as a result, activation of Rho family GTPases leads to the induction of actin-rich filopodia and stimulates cell invasion.[25]

The GO analysis results indicated that TNC was shown to be mostly involved in biological processes, including cellular response to stress, focal adhesion, extracellular structure organization, PI3K-Akt signaling pathway, positive regulation of cell population proliferation, and regulation of cell adhesion.

Therefore, studying these signaling pathways could facilitate the prediction of TNC-related cancer progression mechanisms.

The result from this study indicates that TNC can be regulated via some miRNA and lncRNA at the expression level. DEGs-miRNA-lncRNA regulatory network construction also showed that TNC could be significantly impressed by miR-335-5p. Previous data report that miR-335-5p playing a key role in TGF-β1-induced EMT, and its over-expression can negatively regulate cell migration and invasion in nonsmall-cell lung cancer.[26] In addition, a recent study showed that miR-335 could inhibit proliferation, invasion, and migration of the cancer cells, and arrest the cells in S phase.[27,28] This notion is supported by a study which demonstrates that miR-335 suppresses breast cancer cell migration by negatively regulating the HGF/c-Met pathway.[29] Our bioinformatics analysis shows that miR-335 regulates TNC, and this interaction may have a key role in TNC-related EMT and TNC-induced cancer cell proliferation and invasion. Further analysis and comprehensive functional characterization of the TNC-related regulatory network can provide valuable insights into the molecular events which control TNC expression in tumor cells.

Obviously, this study has some limitations to consider. More gene expression profiles of most common cancer types must be included, and in addition, the experimental analysis must be conducted to ensure the accuracy and precision of the results obtained from this study. The evaluated level of TNC reported in previous studies in most

cancer types, but the co-expression of TNC with different DEGs should be assessed.

Conclusion

In summary, based on the gene expression profile analysis, these screened genes and pathways contribute to the molecular mechanisms underlying the TNC-related cancer progression. These data may offer new clues for the identification of the potential targets, therapeutic agents, and biological mechanisms of breast and colorectal cancer after confirmation by further preclinical and clinical studies.

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

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