

Table S15. Hub genes whose connection score was ≥ 50 and average TPM of control samples ≤ 10 among all non-redundant genes over the three stages.

#	GS ¹	Normal		Tumor		FC ⁴	Cnx ⁵	GC3	Isochore	References
		AV ²	SD ³	AV	SD					
1	BRCA1	2.4	1.0	10.2	6.3	4.3	170	35.9	L	(Fu et al., 2022)
2	CDC6	1.6	1.1	29.7	19.0	18.4	52	44.2	L, H1	(Borlado and Méndez, 2008)
3	CDH1	102.9	30.5	233.0	130.5	2.3	164	57.1	H1	(Ye et al., 2020)
4	CENPQ	9.6	3.5	23.0	13.3	2.4	58	35.7	L	(Wang et al., 2023)
5	CLNS1A	32.2	6.7	76.7	55.4	2.4	56	40.8	L	(Noblejas-López et al., 2021)
6	DTX2	12.2	3.5	28.9	17.2	2.4	180	77.5	H3	(Liu et al., 2024)
7	EIPR1	11.0	2.0	23.5	9.9	2.1	76	69.6	H2	(Topalidou et al., 2020)
8	EXOSC5	21.4	5.1	76.6	42.0	3.6	154	73.7	H2, H3	(Pan et al., 2019)
9	FSCN1	66.0	51.3	412.4	308.8	6.25	88	92.1	H3	(Liang et al., 2022)
10	IGF2BP2	10.7	3.7	71.2	69.0	6.7	56	62.3	H1, H2	(Li et al., 2024)
11	KIF22	10.6	2.6	42.2	21.3	4.0	88	65.0	H2	(Yu et al., 2014)
12	MAPK6	20.6	6.4	64.5	34.3	3.1	732	36.6	L	(Cai et al., 2021)
13	MCM2	5.9	3.0	62.4	46.8	10.6	164	77.2	H3	(Sun et al., 2022)
14	MLF2	133.8	17.0	306.9	139.0	2.3	56	68.3	H2	(Dave et al., 2014)
15	NDC80	1.5	1.3	22.9	15.7	14.8	140	36.4	L	(Wang et al., 2024)
16	NOTCH3	54.3	27.7	156.7	123.1	2.9	100	74.0	H2, H3	(Bodas et al., 2022)
17	PFKP	17.7	8.7	62.3	37.6	3.5	66	75.2	H2, H3	(Peng et al., 2023; Shen et al., 2020)
18	POLD1	11.8	3.2	27.4	16.7	2.3	98	84.9	H3	(Shimizu et al., 2024)
19	RNF126	22.1	5.6	45.9	20.1	2.1	56	79.5	H3	(Sun et al., 2021)
20	RPLP0	745.4	234.6	1560.9	724.1	2.1	88	63.2	H1, H2	(Xu et al., 2024)
21	SPAG5	2.4	1.4	28.7	18.8	12.1	128	53.2	H1	(He et al., 2020)
22	TACC3	7.5	3.1	31.8	24.8	4.2	114	64.5	H2	(Bai et al., 2025)
23	TFAP2C	8.8	3.0	47.4	34.2	5.4	152	69.0	H2	(Szmajda-Krygier et al., 2023)
24	TMEM132A	6.4	2.9	62.1	41.9	9.6	74	74.9	H2, H3	(Zhang et al., 2024)
25	TNC	56.4	44.7	226.2	300.3	4.0	58	62.8	H2	(Donovan et al., 2023)
26	TNK2	11.4	4.3	28.0	21.8	2.5	80	81.7	H3	(Qi and Ding, 2018)
27	TRAF4	26.4	8.1	59.6	34.0	2.3	168	70.7	H2, H3	(He et al., 2022)
28	UFD1	11.1	2.2	23.9	10.8	2.2	54	58.4	H1, H2	(Huiting et al., 2018)
29	XPO1	14.3	4.2	34.1	15.2	2.4	118	32.9	L	(Quintanal-Villalonga et al., 2022)

¹ GS: Gene symbol. ² AV: Average. ³ SD: Standard deviation. ⁴ FC: Fold change. ⁵ Cnx, Connection score.

Contextualization of Table S15 information

To make Table S15 more informative, we compiled and briefly summarized the quotations from its publication references as presented below.

In lung cancer, patients with elevated breast cancer susceptibility gene 1 (BRCA1) expression were reported to have markedly worse overall survival and progression-free survival compared to those with reduced BRCA1 levels (Guo et al., 2023). Cell division cycle 6 (CDC6) play a role in regulating the cell cycle and promoting tumor staging. Downregulating CDC6 expression was shown to significantly inhibit tumor cell migration, invasion and proliferation. Moreover, *in vivo* experiments demonstrated that

downregulating CDC6 expression significantly reduced the burden and metastasis of *in situ* lung tumors in mice (Lou et al., 2024) [2]. Cadherin 1 (Cdh1) has been reported as a potential target in a broad spectrum of human cancers including lung adenocarcinoma (LUAD). Experimentally, CDH1 was shown to promote the self-renewal of lung cancer stem cells, consistent with its function in embryonic and normal stem cells. This process occurs through an intricate cross-talk between oncogenic and stem cell pathways involving PI3K and MAPK (Ye et al., 2020). Centromere proteins (CENPs) form a family of 16 proteins that are positioned at the centromere throughout the cell cycle. The overexpression of CENPs is common in many cancers and predicts a poor prognosis. These proteins were reported as potential targets in LUAD (Wang et al., 2023). CLNS1A is involved in both the assembly of spliceosomal snRNPs and the methylation of Sm proteins and cooperates with the protein PRMT5. It functions as an epigenetic activator of androgen receptor transcription in prostate cancer that continues to grow and spread despite treatments that lower testosterone levels (castration resistance prostate cancer) (Noblejas-López et al., 2021). Human Deltex 2 (DTX2) is a ubiquitin E3 ligase that functions as an oncogene and has been shown to participate in many human cancers. Silencing of DTX2 suppressed glioma cell viability, colony formation, and migration and induced cell apoptosis, which suggests that it could serve as a prognostic or therapeutic marker (Liu et al., 2024). EIPR1 interact with EARP for controlling levels of dense-core vesicles cargoes, which package and release neuropeptides, biogenic amines, and peptide hormones in neurons and endocrine cells. The role of EIPR1 was described in insulinoma cells (Topalidou et al., 2020). Exosome component 5 (EXOSC5) is a novel cancer-related gene that is aberrantly expressed in various malignancies. It promotes colorectal cancer growth partly through activation of ERK and Akt signaling pathways. EXOSC5 was also found in 10–33% of patients with lung cancer, melanoma, and prostate cancer (Pan et al., 2019). Fscin actin-bundling protein 1 (FSCN1) has been identified as a hub immune gene in LUSC where it contributes to the proliferation, anti-apoptotic effect, migration and invasion of the LUSC cells and may act as a potential therapeutic target (Liang et al., 2022). IGF2BP2, as a reader of m6A methylation, plays a pivotal role in the post-transcriptional regulation of RNA through the methylation of m6A sites. It not only contributes to cancer initiation and progression but also plays a key role in tumor drug resistance. It has been suggested that its targeting may improve patients' benefit (Li et al., 2024). KIF22 is a microtubule-dependent molecular motor protein with DNA-binding capacity that plays a critical role in cell mitosis. The inhibition of KIF22 significantly led to accumulation of cells in the G₂/M phases, resulting in suppression of cancer cell proliferation (Yu et al., 2014). Mitogen-activated protein kinase 6 (MAPK6) interacted with AKT; its overexpression is associated with decreased overall survival and the survival of patients with lung adenocarcinoma. Thus, MAPK6 can promote cancer by activating AKT and its inhibition may be effective in cancers (Cai et al., 2021). Minichromosome Maintenance Complex Component 2 (MCM2) is a vital regulator in DNA replication. The overexpression of MCM2 was detected in multiple types of cancers, and the dysfunction of MCM2 was correlated with the progression and poor prognoses of malignant tumors. The anti-tumor effect induced by MCM2 inhibition implies the potential of MCM2 to be a novel therapeutic target for cancer treatment (Sun et al., 2022). Myeloid leukemia factor 2 (MLF2) is one of the top candidates to affect cancer stem cells self-renewal. Targeting MLF2 reduces tumor initiation and metastasis in breast cancer by inhibiting nitric oxide synthase signaling (Dave et al., 2014). The NDC80 complex is a conserved spindle microtubule-binding component of the kinetochore that is associated with prognosis in LUAD, when overexpressed (Wang et al., 2024). The NOTCH signalling pathway plays an important role in lung development, differentiation and regeneration. Dysregulation of the NOTCH pathway has been

associated with lung cancer (Bodas et al., 2022). Phosphofructokinase (PFK) expression is a major feature of malignant tumors. PFKP may serve as a prognostic biomarker of lung cancer where it is highly expressed, regulates the level of glycolysis, and associated with tumor size and cell proliferation (Shen et al., 2020; Peng et al., 2023). The catalytic subunit of DNA polymerase delta 1 (POLD1) has been proposed as a novel therapeutic as a result of the loss-of-function or amplification of Pol δ subunits that has been implicated in various types of cancers (Shimizu et al., 2024). The Ring Finger Protein 126 (RNF126) was found to be highly expressed and a poor prognosis for LUAD patients. RNF126 knockdown suppressed proliferation of LUAD cells and xenografts, which make it a potential therapeutic target (Sun et al., 2021). In LUAD, ribosomal proteins RPLP0, RPLP1 or RPLP2 have worse clinical outcomes in terms of overall survival (OS), first progression (FP) and post-progression survival (PPS), indicating poor prognosis (Xu et al., 2024). Sperm-associated antigen 5 (SPAG5) is involved in the tumorigenesis of multiple cancer types. In LUAD malignant tissues, its expression was found to be up-regulated and its high expression was associated with unfavorable prognosis (Huang et al., 2020). Transforming acidic coiled-coil protein-3 (*TACC3*) has been identified as a critical factor in tumor progression and immune infiltration across cancers, including NSCLC, enabling significant patient prognosis (Bai et al., 2025). Transcription factor-activating enhancer-binding protein 2C (TFAP2C) overexpression has been positively correlated with poor prognosis in patients with certain types of cancer. TFAP2C promoted tumor progression by upregulation of TGFBR1 and consequent activation of PAK1 signaling (Yuanhua et al., 2019; Szmajda-Krygier et al., 2023). TMEM132A expression levels are higher in the majority of tumors compared to non-tumor tissues. In addition, high TMEM132A expression may have a higher prognostic value in some cancers for response to specific immunotherapies. This target plays a very important role in UCEC, LUAD and LIHC (Zhang et al., 2024). Tenascin C (TNC) is a multifunctional large extracellular matrix protein involved in numerous cellular processes in embryonic development. TNC expression is increased during lung development in biopsy cells, endothelial cells, mesenchymal cells, and epithelial cells. It has been proposed that targeting TNC may provide a novel therapeutic target for lung diseases (Donovan et al., 2023). TNK2 is a tyrosine kinase that binds Cdc42Hs and that was considered as a potential drug target in the treatment of metastatic colorectal cancer (Qi and Ding, 2018). Tumor necrosis factor receptor-associated factor 4 (TRAF4) is overexpressed in a variety of carcinomas. TRAF4 overexpression is associated with increased activity of extracellular signal-regulated kinase 5 (ERK5) in NSCLC tissues. As a result, the EGFR-TRAF4-MEKK3-ERK5 axis promotes the proliferation of tumor cells, and it may be a potential target for therapeutic intervention of NSCLC (He et al., 2022). The protein ubiquitin fusion degradation 1 (UFD1) contributes to MYC-mediated aggressiveness with implications for MYC-driven cancers (Huiting et al., 2018). Exportin 1 (XPO1) regulates the export of proteins from the nucleus; its inhibition decreases the growth of tumors and increases their chemosensitivity, which suggests that XPO1 could be a promising therapeutic target in lung cancer (Quintanal-Villalong et al., 2022).

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