Int J Clin Exp Med 2021;14(5):1843-1851
www.ijcem.com /ISSN:1940-5901/IJCEM0122671

Original Article

NF-κB interacting lncRNA expression as a new independent prognostic biomarker for colon adenocarcinoma: a study based on The Cancer Genome Atlas database

Li Shan*, Xiao-Li Zhu*, Yuan Zhang, Cheng-Cheng Xiang, Rong Li, Er-Dong Zuo, Hui-Zhu Qiu, Xu Cheng

*Department of Hematology and Oncology, Soochow University Affiliated Taicang Hospital (The First Peoples Hospital of Taicang), 215400, Jiangsu, China. *Equal contributors.*

Received September 18, 2020; Accepted February 24, 2021; Epub May 15, 2021; Published May 30, 2021

Abstract: Background: Colon carcinoma is one of the most common malignancies of the digestive tract. More than 90% of the colon cancer histological subtypes are colon adenocarcinoma (COAD). This study aimed to identify a new independent prognostic biomarker for COAD. Methods: The gene expressions and relevant clinical data were acquired from TCGA. The relationship between the NKILA levels and the clinicopathological features were estimated using a logistic regression analysis and a Wilcoxon signed-rank test. A Kaplan-Meier analysis was used to elucidate the relationship between the NKILA expression and OS. The effects of the NKILA expression and other clinical features on survival were studied using univariate and multivariate Cox analyses. Based on the estimated coefficients in the multivariate Cox analysis, a regression equation was derived, and the risk scores were obtained. GSEA was used to determine the NKILA-related signaling pathways. Results: The NKILA expression levels were markedly higher in COAD than in the healthy tissues. An overexpression of NKILA in COAD was linked to staging (odds ratio [OR] = 2.12 for IV + III vs I + II), lymph node metastasis (OR = 2.13 for positive vs negative), and distant metastasis (OR = 1.79 for M1 vs M0). A NKILA overexpression in COAD patients was significantly associated with poor patient survival. According to our multivariate analysis, NKILA is an independent risk factor for survival with an HR of 1.15 (CI: 1.01-1.32, $p = 2.00\times10^{-2}$). A nomogram based on the risk score was constructed to predict the 1-, 3-, and 5-year OS of COAD. The areas under the curve for the 1-, 3-, and 5-year OS were 0.72, 0.80, and 0.78, respectively. GSEA indicated that TGF-β signaling, EMT, angiogenesis, apical junction, and hedgehog signaling were differentially enriched in the phenotype with an overexpression of NKILA. Conclusions: NKILA expression may act as a new independent prognostic biomarker for COAD. The TGF-β and EMT signaling pathways may be critical for NKILA regulation in COAD.

Keywords: Colon adenocarcinoma, prognostic biomarkers, NKILA

Introduction

Colon carcinoma is one of the most common digestive tract malignancies worldwide, and is the main cause of cancer-related deaths in both men and women [1, 2]. Despite steady progress in treatment strategies, the survival rate of colon cancer patients is far from satisfactory owing to its late diagnosis, fast development, and ability to metastasize [3, 4]. The tumor, node, metastasis (TNM) staging system has been extensively used to estimate the stages and to forecast patients' cancer prognoses, including colon cancer patients. According to the TNM staging system, colon cancer patients can be divided into staging groups I-IV. Most patients with the same stage have a similar prognosis, but others have different prognoses. Therefore, further research, especially in terms of the tissue-based prognostic indicators, is required to improve the diagnostic and treatment efficiencies of colon cancer and to predict its prognosis.

Nuclear factor-κB (NF-κB), a regulator of inflammatory and immune reactions, is involved in the development of some human diseases [5, 6]. Recently, it has been reported that NF-κB is involved in tumor pathogenesis [7]. The NF-κB signaling pathway has been widely recognized as a regulator of cell proliferation, metastasis, and angiogenesis in many tumors

[8]. Approximately 70% of the human genome can be transcribed into RNA, and it can be divided into long non-coding RNAs (lncRNAs), housekeeping RNAs, and small non-coding RNAs [9-11]. lncRNAs are products of polymerase II, and they execute their functions by interacting with proteins, RNA, or DNA [12]. lncRNAs play a vital role in many diseases, including cancer [13]. NF-κB interacting lncRNA (NKILA) can suppress the progression of cancer by inactivating the NF-κB signaling pathway, and low expression levels of NKILA are associated with poor patient outcomes [14-16].

NKILA inhibits rectal cancer cell proliferation, migration, and invasion through its suppression of NF-κB signaling [17], and a low expression of NKILA is linked to a poor prognosis. Additionally, low expression levels of NKILA are associated with poor outcomes in colorectal cancer patients [18]. Thus, NKILA acts as a biomarker for colorectal cancer. However, to date, no detailed analysis has been conducted to elucidate the relationship between NKILA expression, the TNM stage, and colon cancer patient survival.

More than 90% of the colon cancer histological subtypes are colon adenocarcinoma (COAD). Therefore, this study was conducted on COAD patients to determine patient prognosis and its relationship between the TNM stage and NKILA and to elucidate the mechanism of NKILA in the development of COAD.

Materials and methods

Data profile

The gene expression data of 398 COAD patients and 39 healthy controls were obtained from the official website of The Cancer Genome Atlas (TCGA, April 2020). Among these cases, 380 contained relevant clinical information.

Gene set enrichment analysis (GSEA)

To evaluate the distribution of the predefined genomes within the gene list ordered by phenotypic relevance and to identify the contributions of the individual genes to the phenotype, a GSEA was conducted. In this study, GSEA 4.0.3 and the "h.all.v7.1.symbols.gmt" gene set were used, and the NKILA expression level was considered to be a tag of the phenotype. A total of 1,000 replications were evaluated to obtain nominal *p*-values and normalized enrichment scores (NESs), which were used to evaluate the enrichment pathways of the different phenotypes.

Construction and assessment of the risk score model

Using the estimated coefficients in a multivariate Cox analysis, a regression equation was derived, and a risk score was obtained. According to the mean expression levels of the risk scores, the COAD patients were divided into low- and high-risk groups. A Kaplan-Meier analysis was conducted to investigate the difference in overall survival (OS) between the two groups. A nomogram was constructed to predict the 1-, 3- and 5-year OS of COAD patients using the risk score model. Finally, the prognostic value of the risk score model was assessed using receiver operating characteristic (ROC) curves. The nomogram plots were generated using the rms package, and the ROC curves were plotted using the survival ROC package of R.

Statistical analysis

R (v.3.6.2) was used to analyze the experimental data, and Beeswarm was employed to determine the NKILA mRNA expression levels. To assess the relationship between the NKILA mRNA levels and the clinicopathological features, Wilcoxon signed-rank tests and logistic regression analyses were performed. The mean expression level of NKILA was used as the cut-off value. Kaplan-Meier analyses were used to define the association between the NKILA expressions and OS. The effect of the NKILA expressions and the other clinical features on survival were studied using univariate and multivariate Cox analyses. Data visualization plots were constructed using R plugin ggplot2.

Results

Patient characteristics

The clinical features of 380 COAD patients from the TCGA dataset are shown in **Table 1**. The complete clinical information of all the patients was not present, and no pathological grading system was employed. The median

Table 1. Characteristics of The Cancer Genome Atlas colon adenocarcinoma patients

Clinical characteristic		Total (380)	%
Age at diagnosis (y)		68 (31-90)	
Gender	Male	202	53.16
	Female	178	46.84
Stage	I	65	17.57
	II	150	40.54
	III	102	27.57
	IV	53	14.32
Tumor	T1	9	2.37
	T2	67	17.68
	T3	259	68.34
	T4	44	11.61
Lymph nodes	N0	228	60.00
	N1	87	22.89
	N2	65	17.11
Distant metastasis	Negative	319	85.75
	Positive	53	14.25

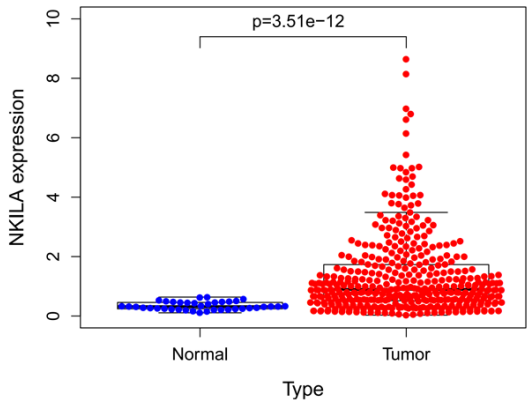

Figure 1. The NF-κB interacting lncRNA (NKILA) expressions in tumors vs the normal samples.

metastasis time for the living patients was 518 days (range 0-4270 days) at the last follow-up.

The NKILA expression and its relationship with the clinical features

The NKILA expression levels (**Figure 1**) in COAD were higher than they were in the normal tissues ($P = 3.51\times10^{-12}$). Elevated expression levels of NKILA were markedly associated with lymph node metastasis ($P = 2.33\times10^{-7}$), clinical staging ($P = 4.24\times10^{-6}$), and distant metastasis ($P = 0.02$) but not with T-rating ($P = 0.73$, **Figure 2**). Our logistic regression analyses (**Table 2**) revealed that an overexpression of NKILA in COAD was markedly associated with staging (odds ratio [OR] = 2.12 for stage IV + III vs II + I), lymph node metastasis (OR = 2.13 for positive vs negative), and distant metastasis (OR = 1.79 for M1 vs M0), but it was not associated with T-grading (OR = 1.13 for stage T4 + 3 vs stage T2 + 1), age (OR = 0.65), and sex (OR = 1.09).

The correlation between the NKILA expression and survival

Our Kaplan-Meier survival analysis revealed that a NKILA overexpression in COAD patients was significantly associated with a shorter survival period (**Figure 3**, $P = 0.02$). According to our univariate analysis (**Table 3**), the patients with COAD had a significantly poor OS with high levels of NKILA (hazard ratio (HR): 1.20, 95% confidence interval (CI): 1.06-1.37, $P = 5.70\times10^{-3}$), and the other prognostic indicators included lymph node metastasis, various levels of staging, the T-classification, distant metastasis, and age. According to our multivariate analysis, NKILA was an independent risk factor for survival with an HR of 1.15 (CI: 1.01-1.32, $P = 0.02$) together with distant metastasis and age (**Table 3**; **Figure 4**).

Construction of the risk score model

Based on the multivariate analysis results, we constructed the following risk score model: risk score = 0.81 * age (> 70 = 1, ≤ 70 = 0) + 1.03 * M (M1 = 1, M0 = 0) + 0.21 * NKILA.

The prognostic value of the risk score

According to the risk score model, the high-risk groups showed poor prognoses (**Figure 5**, $P = 1.76e-07$). The nomogram based on the risk scores, which can predict the 1-, 3-, and 5-year OS of COAD, is shown in **Figure 6**. The areas under the curve (AUC) of the 1-, 3-, and 5-year OS were 0.75, 0.80, and 0.78, respectively (**Figure 7**).

The NKILA-related signaling pathways

GSEA was used to determine the signal transduction pathway associated with the changing levels of NKILA. The findings revealed a significant difference in the MSigDB set enrichment (false discovery rate (FDR) < 0.25, nominal (NOM) $P < 0.05$). According to NES, the most predominant pathways for signal transduction

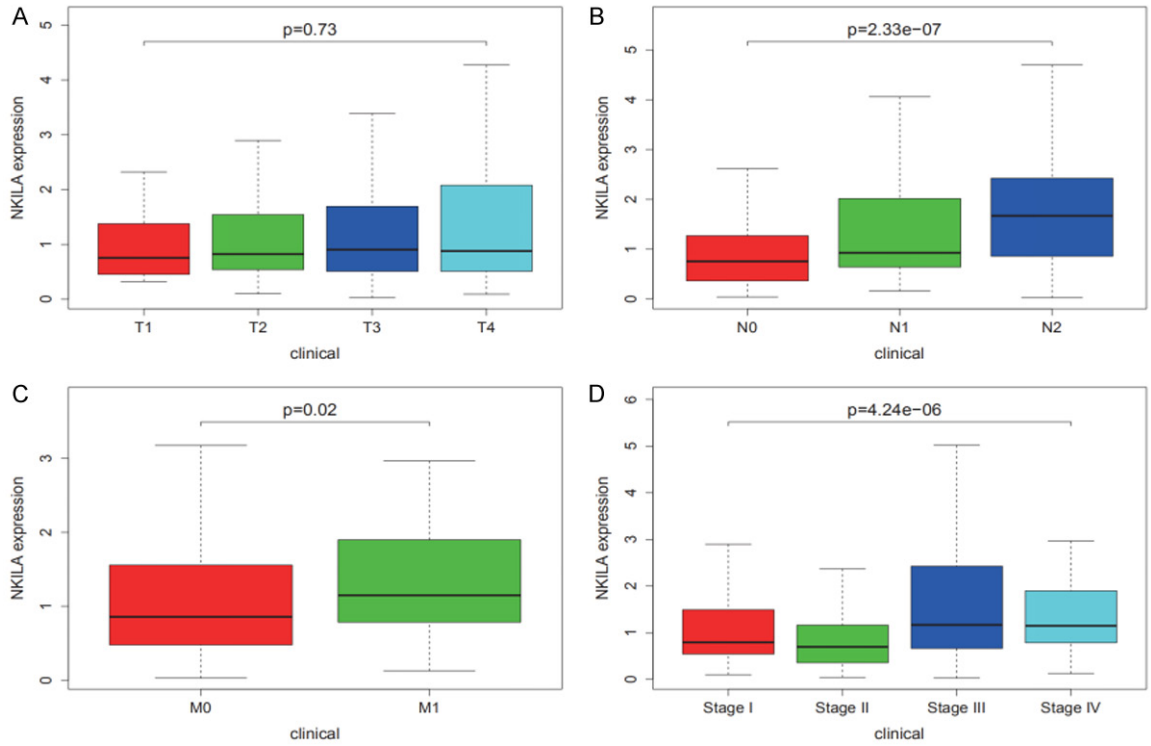

Figure 2. The relationship between the NF-κB interacting lncRNA (NKILA) expression and the clinicopathological characteristics: (A) T classification, (B) N classification, (C) distant metastasis, and (D) clinical stage.

Table 2. A logistic regression analysis of NF-κB interacting lncRNA (NKILA) expression related to the clinicopathological features

Clinical characteristic	Total (N)	Odds ratio in NKILA expression	*p*-value
Stage (IV + III vs I + II)	370	2.12 (1.40-3.25)	4.61E-03
T (4 + 3 VS 1 + 2)	379	1.13 (0.69-1.88)	6.26E-01
Lymph (positive vs negative)	380	2.13 (1.40-3.25)	4.06E-04
Distant metastasis (M1 vs ≤ M0)	372	1.79 (0.99-3.20)	4.60E-02
Age (> 70 vs ≤ 70)	380	0.65 (0.41-1.01)	5.59E-02
Gender	380	1.09 (0.73-1.63)	6.81E-01

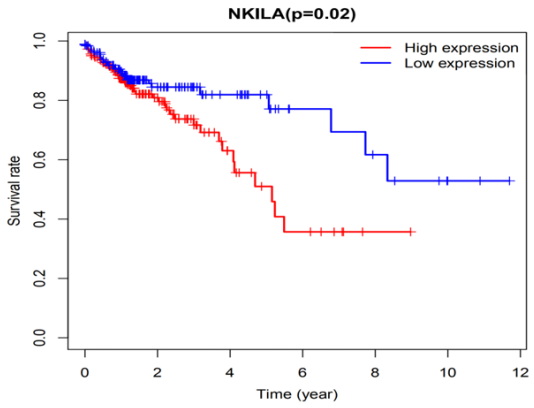

Figure 3. The correlation between the NF-κB interacting lncRNA (NKILA) expression and overall survival (OS) using a Kaplan-Meier analysis.

are shown in **Figure 8** and **Table 4**. The results indicated that tumor growth factor beta (TGF-β) signaling, epithelial mesenchymal transition (EMT), angiogenesis, apical junction, and hedgehog (HH) signaling were differentially enriched in the phenotype with a high expression of NKILA.

Discussion

Colon cancer is one of the most common malignant tumors worldwide, and its treatment and prognosis are complicated. Additionally, the pathogenesis of colon cancer is complex and includes constant accumulation and changes in multiple genes and pathways. Although

Table 3. Univariate and multivariate Cox regression analyses in relation to overall survival

Parameter	Univariate analysis			Multivariate analysis			
	HR	95% CI	*p*-value	Coef	HR	95% CI	*p*-value
Age	1.03	1.01-1.05	1.18E-02	0.81	2.35	1.34-4.12	2.75E-03
Gender	1.28	0.78-2.09	3.27E-01	-	1.10	0.66-1.84	7.15E-01
Stage	2.17	1.64-2.87	5.35E-08	-	0.97	0.44-2.14	9.45E-01
T	2.34	1.44-3.81	6.00E-04	-	1.41	0.77-2.57	2.69E-01
M	4.63	2.78-7.71	3.80E-09	1.03	3.56	1.19-10.64	2.28E-02
N	1.96	1.47-2.60	3.33E-06	-	1.46	0.88-2.41	1.30E-01
NKILA	1.20	1.06-1.37	5.70E-03	0.21	1.15	1.01-1.32	2.00E-02

Abbreviations: HR, hazard ratio; CI, confidence interval; Coef, coefficient; T, tumor; N, node; M, metastasis; NKILA, NF-κB interacting lncRNA.

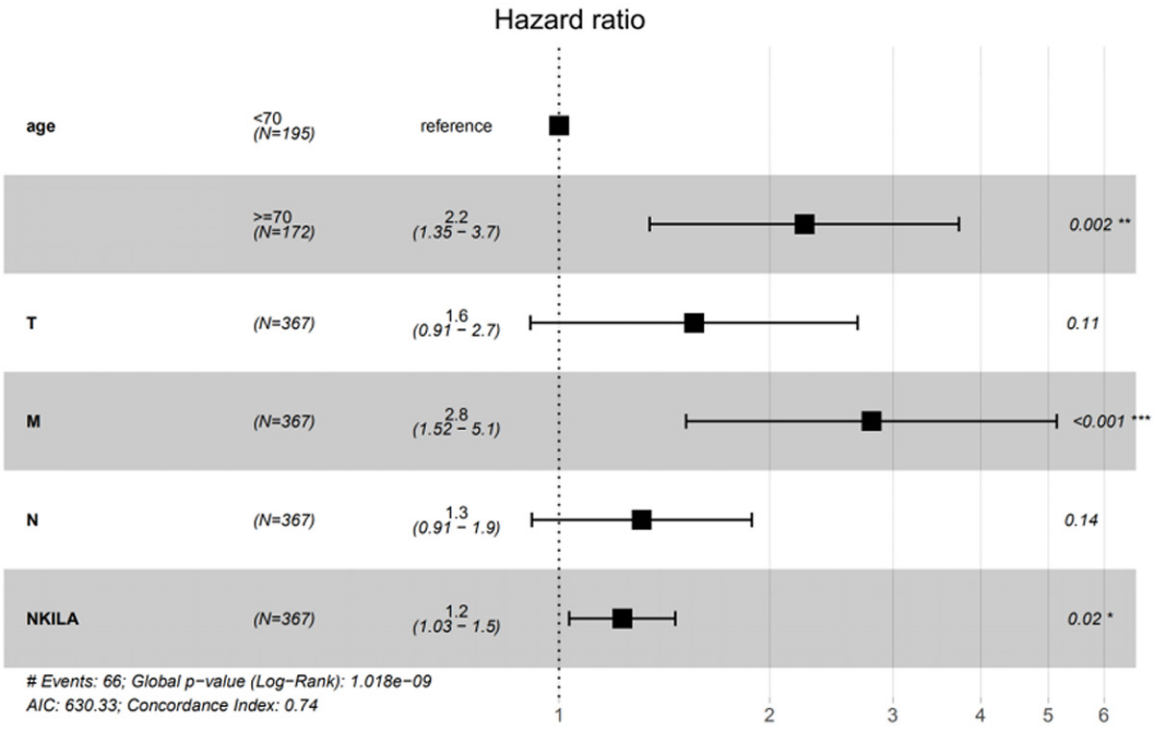

Figure 4. A Forest map of the multivariate Cox regression analysis. Abbreviations: T, tumor; N, node; M, metastasis; NKILA, NF-κB interacting lncRNA.

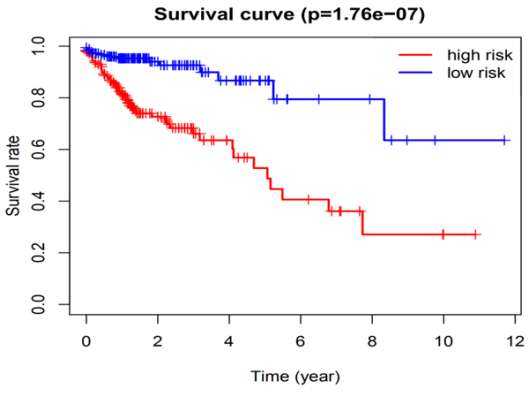

Figure 5. The correlation between the risk score and overall survival (OS) using a Kaplan-Meier analysis.

many genes have been associated with colon cancer, additional pathogenic and prognostic information is needed to guide patient management.

NKILA, a type of lncRNA, plays an essential role in inhibiting the NF-κB signaling pathway [19]. NKILA can inhibit NF-κB-mediated metastasis in many malignant tumors [20]. There-

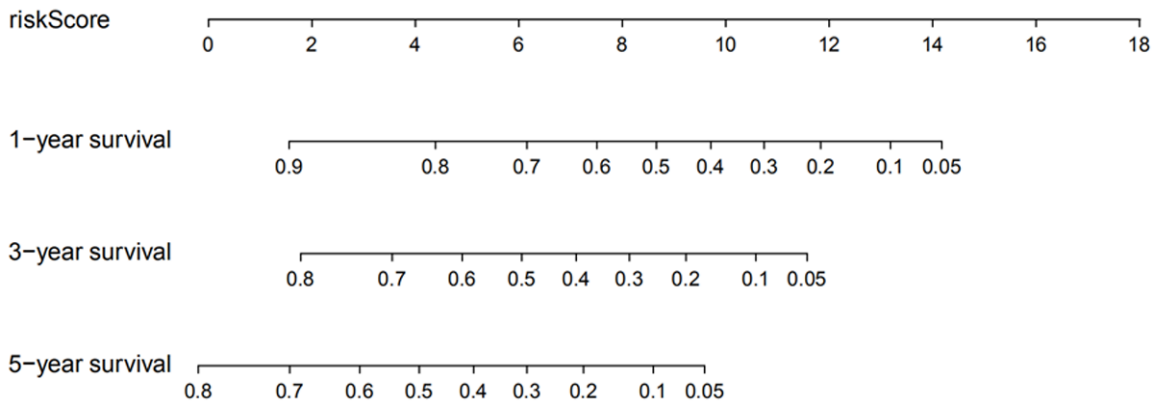

Figure 6. A nomogram based on the risk score to predict the 1-, 3-, and 5-year overall survival (OS) of colon adenocarcinoma (COAD) patients.

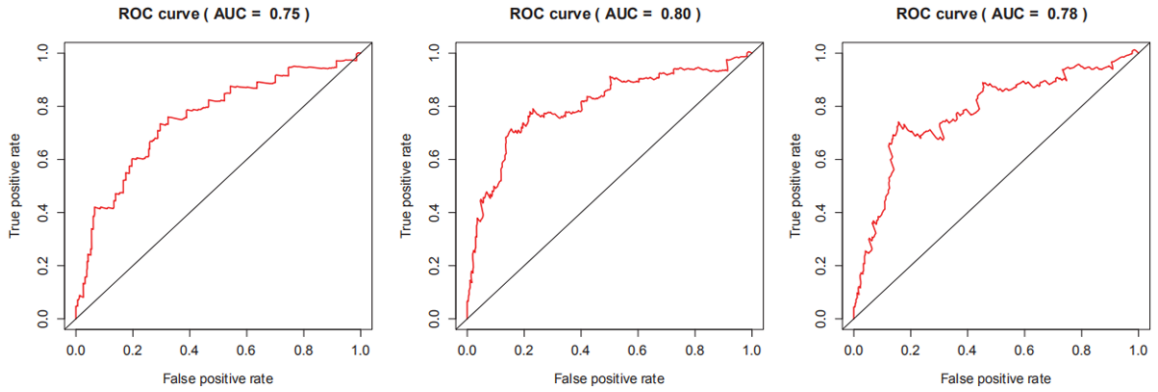

Figure 7. The receiver operating characteristics (ROC) of the 1-, 3-, and 5-year overall survival (OS) based on the risk scores. Abbreviation: AUC, area under the curve.

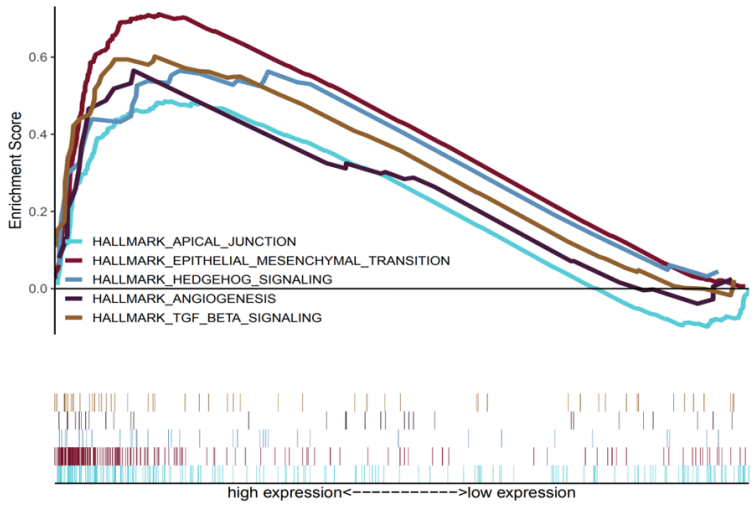

Figure 8. The NF-κB interacting lncRNA (NKILA)-related signaling pathways using a gene set enrichment analysis.

fore, NKILA usually functions as a tumor suppressor, and high NKILA expression levels are always linked with excellent clinical outcomes.

Two studies on colorectal and rectal cancers have reported the tumor-suppressive role of NKILA [17, 18]. However, contrary to these results, our study demonstrated that the NKILA expression levels are higher in COAD patients than in normal tissues, and they correlate with the lymph node metastasis, the clinical staging, and the distant metastasis. The same results were obtained using a logistic regression analysis. Our findings indicate that the overexpression of the NKILA gene may be linked to metastasis, and it may lead to a poor prognosis.

Table 4. Phenotypically high genome enrichment

MSigDB collection	Gene set name	NES	NOM p-val	FDR q-val
c2.h.all.v7.1.symbols.gmt	HALLMARK_TGF_BETA_signalling	2.055	0.000	0.026
	HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION	2.004	0.012	0.029
	HALLMARK_ANGIOGENESIS	1.846	0.006	0.076
	HALLMARK_APICAL_JUNCTION	1.741	0.038	0.096
	HALLMARK_HEDGEHOG_signalling	1.719	0.029	0.093

Abbreviations: NES, normalized enrichment score; NOM, nominal; FDR, false discovery rate. Gene sets with NOM p-val < 0.05 and FDR q-val < 0.25 are considered as statistically significant.

According to our Kaplan-Meier survival analysis, an overexpression of NKILA in COAD patients is significantly associated with a short survival. Our multivariate analysis revealed that an elevated expression of NKILA is an independent risk predictor for survival, along with distant metastasis and age. Therefore, NKILA can serve as a promising biological prognostic indicator in COAD. Based on the three independent risk predictors, we constructed a risk score model and nomogram to predict the 1-, 3-, and 5-year OS of COAD. The AUC values for the 1-, 3-, and 5-year OS were 0.752, 0.803, and 0.777, respectively. Therefore, the nomogram is considered to accurately predict the prognosis of COAD in patients, especially the 3-year OS.

The reason for the inconsistency between our results and those of previous studies is unclear. However, the following factors could be responsible: 1. Canonical NF-κB is a Fas transcription activator, and a reduction in NF-κB expression caused by NKILA may impair the Fas-mediated apoptosis and influence the host immune cell-mediated tumor suppression [21, 22]. 2. A high expression level of NKILA has been linked to adverse outcomes in glioma patients [23], and NKILA can stimulate angiogenesis both *in vivo* and *in vitro*. Additionally, angiogenesis is an essential pathogenic pathway in colon cancer. 3. The small number of cases in both studies conducted on colorectal and rectal cancers may cause a bias, which leads to different conclusions.

To explore the signaling pathway linked to the changing NKILA levels, a GSEA enrichment analysis was performed. The results indicated that TGF-β signaling, EMT, angiogenesis, apical junction, and hedgehog signaling were enriched to varying degrees in the phenotype with a high expression of NKILA. TGF-β signaling plays an important role in the development of colon cancer, especially in the process of metastasis [24]. The TGF-β signaling pathway induces NKILA expression and indicates a good prognosis in esophageal squamous cell carcinoma and non-small cell lung cancer [25, 26]. To date, no study has investigated the relationship between NKILA and the TGF-β signaling pathway in colon cancer. During EMT, epithelial cells change their shapes by being stripped off their epithelial markers and gain a more aggressive phenotype. EMT is involved in the pathogenesis of various tumors, including colon cancer [27, 28]. The activation of the EMT pathway often indicates a poor prognosis in colon cancer patients, which is consistent with our findings in patients with high NKILA expressions. Therefore, the relationship between a high expression of NKILA and the EMT pathway in colon cancer patients requires further investigation. Angiogenesis plays an important role in the development of colon cancer, but the relevance of the relationship between NKILA and angiogenesis has not been investigated yet. The apical junction proteins are the key factor involved in maintaining the epithelial barrier function, and its abnormal expression is related to inflammatory bowel diseases and colon cancer [29]. The relationship among NKILA, the apical junction, and HH has not been explored either. Therefore, further studies are warranted to estimate the regulatory mechanism of these signaling pathways in colon cancer.

Our study has some limitations. First, although TCGA is the most commonly-used bioinformatics analysis database, it does not represent all colon cancer patients, especially Asian patients. Second, the mechanism that causes the poor prognosis in colon cancer patients with high expressions of NKILA has not been determined. Thus, extensive studies, especial-

ly in Asian patients, are required to confirm our findings and to explore the mechanism of NKILA in colon cancer.

In conclusion, NKILA may act as a new biomarker, which is an independent prognostic marker for COAD, and the TGF-β and EMT signaling pathways have a potential role as key modulators of NKILA in COAD. Further studies are required to define the biological mechanism of NKILA.

Acknowledgements

This work was supported by the Science and Technology Development Plan of Taicang in Jiangsu Province P.R.C. (No. TC2017SFYL01).

Disclosure of conflict of interest

None.

Address correspondence to: Xu Cheng, Department of Hematology and Oncology, Soochow University Affiliated Taicang Hospital (The First Peoples Hospital of Taicang), 215400, Jiangsu, China. Tel: +86-18915768366; E-mail: chx1029@163.com

References

[1] Hu T, Li Z, Gao CY and Cho CH. Mechanisms of drug resistance in colon cancer and its therapeutic strategies. World J Gastroenterol 2016; 22: 6876-6889.

[2] Aarons CB, Shanmugan S and Bleier JI. Management of malignant colon polyps: current status and controversies. World J Gastroenterol 2014; 20: 16178-16183.

[3] Compton CC. Colorectal carcinoma: diagnostic, prognostic, and molecular features. Mod Pathol 2003; 16: 376-388.

[4] Sun Y, Yang B, Lin M, Yu H, Chen H and Zhang Z. Identification of serum miR-30a-5p as a diagnostic and prognostic biomarker in colorectal cancer. Cancer Biomark 2019; 24: 299-305.

[5] Zhang Q, Lenardo MJ and Baltimore D. 30 years of NF-κB: a blossoming of relevance to human pathobiology. Cell 2017; 168: 37-57.

[6] Mitchell S, Vargas J and Hoffmann A. Signaling via the NF-κB system. Wiley Interdiscip Rev Syst Biol Med 2016; 8: 227-241.

[7] Viatour P, Merville MP, Bours V and Chariot A. Phosphorylation of NF-κB and IκB proteins: implications in cancer and inflammation. Trends Biochem Sci 2005; 30: 43-52.

[8] Karin M, Cao Y, Greten FR and Li ZW. NF-κB in cancer: from innocent bystander to major culprit. Nat Rev Cancer 2002; 2: 301-310.

[9] Mattick JS and Rinn JL. Discovery and annotation of long noncoding RNAs. Nat Struct Mol Biol 2015; 22: 5-7.

[10] Costa FF. Non-coding RNAs: meet thy masters. Bioessays 2010; 32: 599-608.

[11] Gutschner T and Diederichs S. The hallmarks of cancer: a long non-coding RNA point of view. RNA Biol 2012; 9: 703-719.

[12] Ulitsky I and Bartel DP. lincRNAs: genomics, evolution, and mechanisms. Cell 2013; 154: 26-46.

[13] Liu B, Sun L, Liu Q, Gong C, Yao Y, Lv X, Lin L, Yao H, Su F, Li D and Zeng M. A cytoplasmic NF-κB interacting long noncoding RNA blocks IκB phosphorylation and suppresses breast cancer metastasis. Cancer Cell 2015; 27: 370-381.

[14] Yu X, Tang W, Yang Y, Tang L, Dai R, Pu B, Feng C and Xia J. Long noncoding RNA NKILA enhances the anti-cancer effects of baicalein in hepatocellular carcinoma via the regulation of NF-κB signaling. Chem Biol Interact 2018; 285: 48-58.

[15] Bian D, Gao C, Bao K and Song G. The long non-coding RNA NKILA inhibits the invasion-metastasis cascade of malignant melanoma via the regulation of NF-κB. Am J Cancer Res 2017; 7: 28-40.

[16] Tao F, Xu Y, Yang D, Tian B, Jia Y, Hou J and Dong M. lncRNAA NKILA correlates with the malignant status and serves as a tumor-suppressive role in rectal cancer. J Cell Biochem 2018; 119: 9809-9816.

[17] Jiang P, Han X, Zheng Y, Sui J and Bi W. Long non-coding RNA NKILA serves as a biomarker in the early diagnosis and prognosis of patients with colorectal cancer. Oncol Lett 2019; 18: 2109-2117.

[18] Weidle UH, Birzele F, Kollmorgen G and Rueger R. Long non-coding RNAs and their role in metastasis. Cancer Genomics Proteomics 2017; 14: 143-160.

[19] Gupta SC, Awasthee N, Rai V, Chava S, Gunda V and Challagundla KB. Long non-coding RNAs and nuclear factor-κB crosstalk in cancer and other human diseases. Biochim Biophys Acta Rev Cancer 2020; 1873: 188316.

[20] Chien Y, Scuoppo C, Wang X, Fang X, Balgley B, Bolden JE, Premsrirut P, Luo W, Chicas A, Lee CS and Kogan SC. Control of the senescence-associated secretory phenotype by NF-κB promotes senescence and enhances chemosensitivity. Genes Dev 2011; 25: 2125-2136.

[21] Fu B, Xu Y, Wang Y, Chen H, Huang Z, Hu Y, Zhang L, Wu G, Liu J, Deng Y and Mou Y. Prog-

nostic value of NF-κB interacting long non-coding RNA expression in lung adenocarcinoma and lung squamous cell cancer: a study based on the cancer genome atlas datasets. Transl Cancer Res 2018; 7: 109-120.
[22] Chen Z, Li S, Shen L, Wei X, Zhu H, Wang X, Yang M and Zheng X. NF-kappa B interacting long noncoding RNA enhances the Warburg effect and angiogenesis and is associated with decreased survival of patients with gliomas. Cell Death Dis 2020; 11: 323.
[23] Villalba M, Evans SR, Vidal-Vanaclocha F and Calvo A. Role of TGF-β in metastatic colon cancer: it is finally time for targeted therapy. Cell Tissue Res 2017; 370: 29-39.
[24] Lu Z, Chen Z, Li Y, Wang J, Zhang Z, Che Y, Huang J, Sun S, Mao S, Lei Y and Gao Y. TGF-β-induced NKILA inhibits ESCC cell migration and invasion through NF-κB/MMP14 signaling. J Mol Med (Berl) 2018; 96: 301-313.
[25] Lu Z, Li Y, Wang J, Che Y, Sun S, Huang J, Chen Z and He J. Long non-coding RNA NKILA inhibits migration and invasion of non-small cell lung cancer via NF-κB/snail pathway. J Exp Clin Cancer Res 2017; 36: 54.
[26] Hou H, Yu X, Cong P, Zhou Y, Xu Y and Jiang Y. Six2 promotes non-small cell lung cancer cell stemness via transcriptionally and epigenetically regulating E-cadherin. Cell Prolif 2019; 52: e12617.
[27] Matějka VM, Finek J and Králíčková M. Epithelial-mesenchymal transition in tumor tissue and its role for metastatic spread of cancer. Klin Onkol 2017; 30: 20-27.
[28] Landy J, Ronde E, English N, Clark SK, Hart AL, Knight SC, Ciclitira PJ and Al-Hassi HO. Tight junctions in inflammatory bowel diseases and inflammatory bowel disease associated colorectal cancer. World J Gastroenterol 2016; 22: 3117-3126.
[29] Wils LJ and Bijlsma MF. Epigenetic regulation of the hedgehog and Wnt pathways in cancer. Crit Rev Oncol Hematol 2018; 121: 23-44.