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STING expression in colorectal cancer: prognostic role and immune microenvironment link via mIHC

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Colorectal cancer (CRC) is a malignant tumor originating in the mucosal epithelium of the colon or rectum and is among the most common cancers of the digestive system. Now it is the fourth deadliest cancer in the world. Stimulator of Interferon Genes (STING) is a dimeric transmembrane protein on the endoplasmic reticulum membrane that induces the secretion of type I interferons and pro-inflammatory cytokines and is triggered by the cell membrane DNA of pathogens and hosts. It is widely expressed in immune cells (such as dendritic cells, macrophages) and some tumor cells, and has been shown to play a crucial role in the development of several tumors. However, issues such as the expression of STING in CRC and patient prognosis remain to be further elucidated. We investigated the expression of STING (in CRC tumor cells) and immune markers (CD3, CD4, CD8, CD56, CD163) in 86 CRC patients by tissue microarray using multicolor immunohistochemistry. Subsequently, the effect of STING on the tumor immune microenvironment was further explored. Finally, we analyzed the clinical significance of STING in CRC patients. We found elevated STING expression in tumor cells from CRC patients, which correlated with overall patient survival. High STING levels were associated with suppression of lymph node metastasis and reduction of CD163 tumor-associated macrophages. In contrast, upregulation of STING promoted infiltration of CD3+ T lymphocytes and CD8 lymphocyte subtype in the tumor microenvironment. Our study demonstrated that changes in STING expression in cancer cells in the tumor immune microenvironment have clinical significance and regulatory roles. STING-related functional mechanisms can be considered as therapeutic targets for CRC, which provides a theoretical basis for the subsequent clinical application of STING agonists.

Key words: STING; multi-color immunohistochemistry; lymphatic metastasis; tumor immune microenvironment; colorectal cancer

Colorectal cancer (CRC) is now the fourth deadliest cancer in the world, causing nearly 900,000 deaths annually [1] and accounting for approximately 10% of diagnosed cancers and cancer-related deaths [2]. Multiple factors contribute to the death of CRC patients. Lymph node metastasis is regarded as an indubitable factor [3]. Pathologic examination of lymph nodes in patients with CRC remains crucial for postoperative treatment and prognosis prediction [4].

Stimulator of interferon genes (STING) is an evolutionarily conserved transmembrane protein [5]. STING is an important signaling molecule in innate immunity, recognizing microbial DNA from the nucleus or mitochondrial DNA via cGAS [6]. STING induces the secretion of type I interferon (IFN) and pro-inflammatory cytokines [7]. Therefore, STING is not only an innate immune system regulator of IFN produced by viral or bacterial infections [8], but has also become a promising target for tumor therapy in recent years [9].

There are two types of STING activation in tumors, spontaneous and non-spontaneous [10, 11]. On the one hand, activation of immune cells in the tumor microenvironment, such as dendritic cells (DCs) and macrophages, STING induces downstream type I IFN transcription and enhances adaptive anti-tumor immunity [12, 13]. STING agonists activate the DC-regulated immune microenvironment in the CT26 colon cancer cell line [14, 15]. On the

other hand, activation of STING in tumor cells mediates the secretion of pro-inflammatory cytokines [16], which can inhibit or promote tumor growth [17]. The expression of STING and its impact on tumors vary among different tumors [18]. Studies have shown that STING expression is significantly elevated in cancer cells from pancreatic and squamous cancer samples, and decreased in malignant melanoma [19]. However, the relationship between STING expression in cancer cells of colon cancer patients and patient prognosis, and with the tumor immune microenvironment, remains to be further elucidated [11]. Therefore, this experiment provides a theoretical basis for the clinical application of STING by multiple immunohistochemical staining.

Activation of the cGAS-STING signaling pathway in tumors can influence tumor development by remodeling the tumor immune microenvironment through interferons and chemokines. It has been shown that in CRC, STING agonists activate DCs in the CRC microenvironment and increase the infiltration of $CD8^+$ T cells. Meanwhile, activation of the STING pathway in tumor-associated macrophages (TAMs) inhibits liver metastasis of colon cancer by regulating natural killer (NK) cells [20]. However, the relationship between STING expression in CRC cells and lymph node metastasis, as well as the effects on infiltrating lymphocytes, TAMs, and NK cells in the immune microenvironment, remain unclear. In this study, we confirmed that STING is clinically significant in patients with CRC and is associated with lymph node metastasis. We also elucidated that STING can regulate the tumor microenvironment. These results provide evidence for understanding the role of STING in CRC.

Patients and methods

Patients and tissue microarrays (TMA) tissue samples. 93 CRC tumor tissues and paraneoplastic control tissues were collected from CRC patients who underwent surgery between June 2007 and April 2008 (44 males and 49 females, aged 43 to 90 years). All patients were also followed up for 7–8 years. The last 86 cases were included in the experiment and statistics because some of the samples had too little or dried cancer tissues (Table 1). Human CRC TMA was prepared by Shanghai Outdo Biotech Company (Shanghai, China; #HCOLA180SU18).

Table 1. Clinicopathologic characteristics of 86 patients with CRC.

Characteristics		Cases
Pathological grade	I	9
	II	63
	III	14
Gender	M	43
	F	43
Clinical Stages	I	4
	II	51
	III	31
Median	Median survival (months)	88 (2–97)
	Median age (years)	68 (43–90)

The study was approved by the Ethics Committee of Shanghai Outdo Biotech Company (Approval No. IRB-2023-334). All participants were recruited after providing signed informed consent.

TMA and multi-color immunohistochemistry (mIHC). The mIHC was performed using Opal staining. First, CRC TMA paraffin sections were prepared. Next, they were rehydrated by a series of xylene-ethanol reactions and washed with distilled water. Subsequently, the slides were immersed in antigen recovery buffer (citrate buffer, pH 6) and processed by microwave heating. Finally, the primary antibody (diluted with blocking buffer) was incubated to optimize antibody concentration and incubation time for the detection of Opal.

Information on the antibodies used is as follows: anti-STING (1:4000 dilution, #ab239074, Abcam, Cambridge), anti-CD3 (1:200 dilution, #abs16669, anti-CD163 (1:1000 dilution, #ab74604, Abcam, Cambridge), anti-CD56 (1:500 dilution, #99746T, CST, USA), anti-CD8 (1:3000 dilution, #ab237710, Abcam, Cambridge), anti-CD4 (1:1000 dilution, #ab133616, Abcam, Cambridge), anti-PD1 (1:1000 dilution, #ab237728, Abcam, Cambridge) and anti-CK (ready to use, #GM302, Gene Tech, China).

The slide was incubated with the polymer HRP-conjugated secondary antibody and Opal Fluorophore Solution (Opal 7-color fluorescent IHC kit, #NEL811001KT, PerkinElmer, USA). The antibodies were removed by microwave heat treatment, and the process was repeated until the desired amount of antibody was used. Finally, tissues were nuclear stained and mounted with 4,6-diamidino-2-phenylindole (DAPI) (Thermofisher, USA).

Imaging analysis. Stained slides were scanned in their entirety using the Vectra Polaris Automated Quantitative Pathology Imaging System, which captures images at 20× magnification in the spectral range of 520 nm to 690 nm and collects the full spectrum of the image at each pixel location. After collecting the full image spectrum at each pixel location, the Inform (Akoya Biosciences) software analyzes the tissue images. First, each multispectral signal was unmixed to identify and separate weak overlapping signals from background autofluorescence. Second, artificial intelligence algorithms are trained to automatically detect and segment specific tissue types. After training, the software will automatically locate and analyze specific regions within or between images. Subsequently, machine learning algorithms are used to isolate cellular phenotypes in the tissue sections. Finally, positive thresholds are set based on quantification of staining intensity and calculated H-scores, as well as batch processing, reviewing, and merging a large number of images or sections to speed up image analysis and increase efficiency.

Correlation of STING expression with CRC. The Human Protein Atlas (HPA, https://www.proteinatlas.org/) provides data such as STING expression in tumors and prognostic

relevance [21]. UALCAN (http://ualcan.path.uab.edu/) is an interactive portal for in-depth analysis of TCGA gene expression data [22]. This study used UALCAN to investigate the level of STING in the colon adenocarcinoma (COAD). Since STING is also known as TMEM173, we use TMEM173 instead of STING in UALCAN searches [23]. Survival analysis was performed with default parameters (log-rank test, p-value <0.05).

Statistical analysis. All statistical analyses and visualizations were performed using R software (R version 3.6.3, R Project for Statistical Computing, RRID:SCR_001905) and GraphPad Prism 9.0 (GraphPad software). The Wilcoxon rank-sum test (for comparisons of two groups) or Kruskal-Wallis' test (for comparisons of more than two groups) was used to compare disease-related factors in patients with low and high expression in different cell populations. The Kaplan-Meier method was applied to estimate survival probabilities. Log-rank survival analysis was used to predict patients' postoperative overall survival (OS). Optimal cutoff values for survival analysis were determined by maximally selected rank statistics wrapped in the R package "survminer". The Cox model was used to assess the prognostic value of different parameters involving the expression of in different cell populations. For multiple comparisons, the Benjamini and Hochberg (BH) method was used to adjust the p-value; $p<0.05$ was considered to indicate statistical significance. The significance of all statistical tests is shown in the figures as not significant (NS), *$p<0.05$, **$p<0.01$.

Results

STING expression in tumor cells positively correlates with survival in CRC. First, we observed the expression of STING in CRC. We used IHC to detect STING expression in CRC tumor TMAs (Figure 1A). The results showed that STING was expressed in the cytoplasm of CRC cells. However, the intensity of STING expression in CRC cells varied from patient to patient, with negative (no expression), weak, moderately strong, and strong expression (Figure 1A). To clarify the correlation between STING expression and the prognosis of CRC patients, we analyzed the relationship between STING expression and survival time of CRC

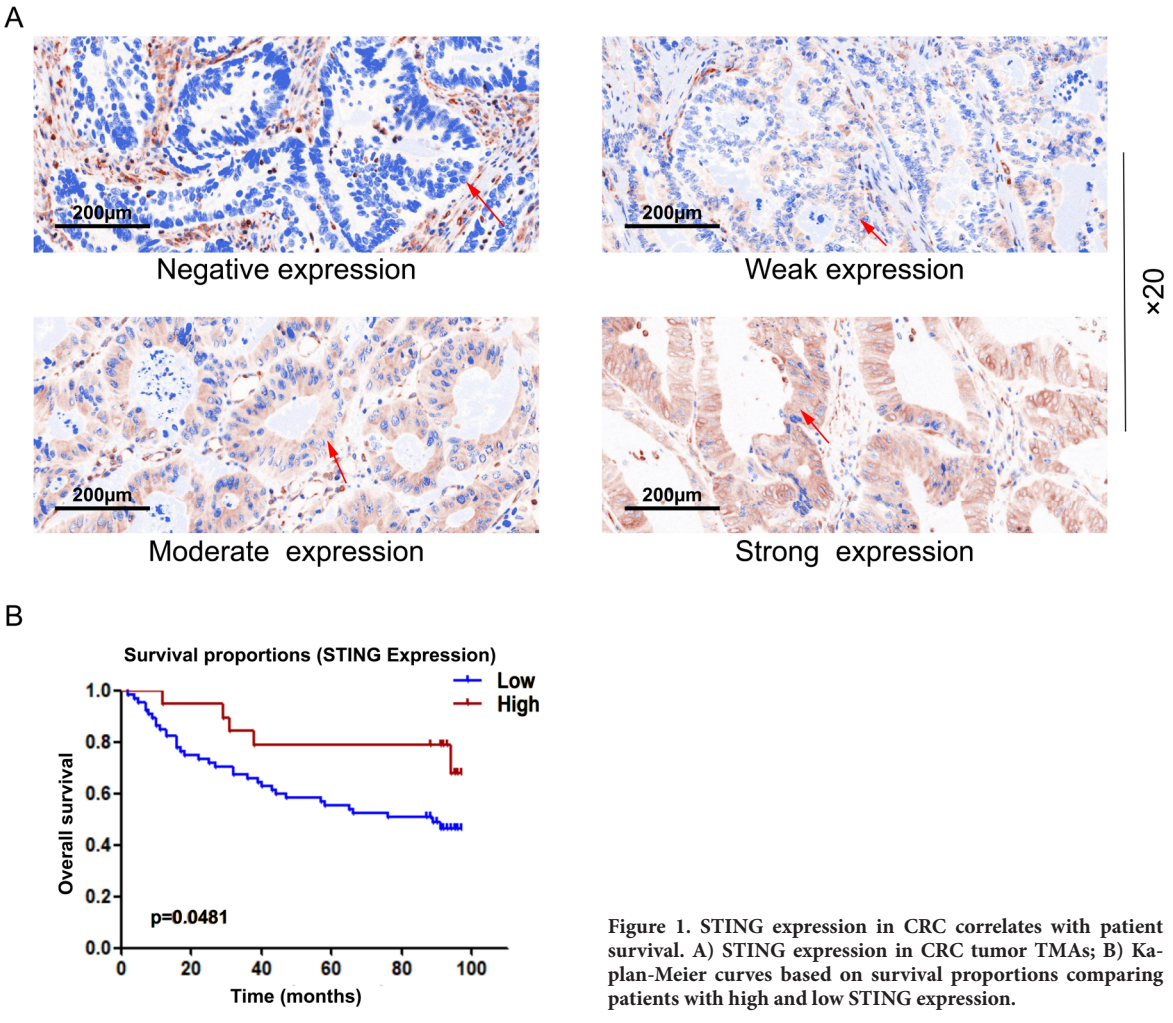

Figure 1. STING expression in CRC correlates with patient survival. A) STING expression in CRC tumor TMAs; B) Kaplan-Meier curves based on survival proportions comparing patients with high and low STING expression.

patients using Kaplan-Meier curves. The results showed that patients with high STING expression had a significantly higher survival rate than those with low STING expression (p=0.0481; Figure 1B). Therefore, STING expression in CRC may be associated with patient survival.

The analysis of HPA revealed that STING had the highest incidence in CRC, ovarian cancer, and pancreatic cancer, with 83.33%, 58.33%, and 50%, respectively (Supplementary Figure S1). From the data, it is clear that STING is highly expressed in CRC cells. The relationship between STING (TMEM173) expression and COAD prognosis was further verified by UALCAN. 279 COAD patients from TCGA database were studied. The results showed that high STING expression was positively associated with patient prognosis (Supplementary Figure S2). The above results are consistent with the positive correlation between high STING expression and patient prognosis in the 89 CRC patients we analyzed. The difference in our p-values was more significant, which is thought to be possibly related to differences in the selected clinical samples.

STING expression in tumor cells is associated with CRC lymph node metastasis. The clinical TNM staging of 86 CRC patients was as follows: tumor size was classified as T1, T2, and T3, with 5 patients with T1, 14 patients with T2, and 67 patients with T3. Lymph node metastases were categorized as non-metastatic N0 and N1 metastases, of which 31 were N1 patients and 55 were N0 patients. No hematogenous metastases were detected in the patients (M=0).

We found that STING expression was higher in N0 and lower in N1 of CRC patients, which were statistically different (p=0.0046; Figure 2A). Thus, high STING expression was negatively correlated with lymph node metastasis in CRC patients (Figure 2A). Furthermore, statistical results showed no statistically significant association between STING expression and tumor size: T1and T2, p=0.9096, and T1 and T3, p=0.9481. Thus, STING expression did not correlate with tumor size in CRC patients (Figure 2B).

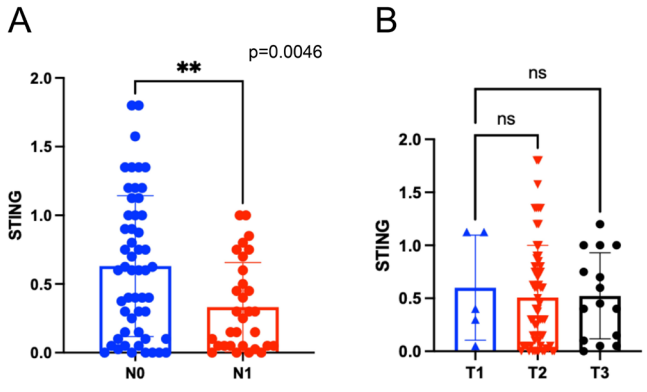

Figure 2. Analysis of the correlation between STING and adverse clinical features of CRC. A and B. The statistical significance computed by the Wilcoxon test is annotated by the number of stars (*p < 0.05; **p < 0.01).

STING expression in tumor cells positively correlates with CRC immune microenvironment lymphocyte expression, negatively correlates with tumor-associated M2 macrophages, and does not correlate with NK cells. To investigate the correlation of STING expression with CRC immune microenvironment lymphocytes, tumor-associated M2 macrophages, and NK cells. We used multiplex immunofluorescence to detect the expression of tumor cells STING, CD3, CD163, and CD56 in CRC TMAs and quantified the statistical differences between STING and CD3, CD163, and CD56 (Figure 3A). STING expression in CRC tumor cells was positively correlated with CD3 expression (p=0.0021; Figure 3B). In contrast, STING expression was negatively correlated with CD163 expression (p=0.2740; Figure 3C). However, there was no statistical significance between STING and CD56 expression (p=0.5027; Figure 3D).

Tumor cell STING expression positively correlates with CD8 lymphocyte expression in the CRC immune microenvironment and does not correlate with CD4 lymphocytes. Further, we clarified the correlation between tumor cell STING expression and CRC immune microenvironment lymphocyte CD4 and CD8 subtypes. We used multiplex immunofluorescence to detect the expression of STING, CD4, and CD8 in consecutive CRC TMA tumor cells and quantified the statistical differences between STING and CD4 and CD8 lymphocytes (Figure 4A). The results showed that STING was positively correlated with CD8 lymphocytes (p=0.0020; Figure 4B) and not correlated with CD4 (p=0.2939; Figure 4C).

Discussion

Tumor cells are mostly characterized by abnormalities such as genomic instability, oncogene mutations or deletions, and oxidative stress [24–26], which allows leakage of nuclear and mitochondrial DNA into the cytoplasm [27–29]. Subsequently, it is recognized by cGAS and activates the downstream effector molecule STING [30–32]. The role of STING expression within different tumors varies with respect to the tumor [33, 34]. Existing studies have shown that STING expression in breast [35], pancreatic [36], squamous, and malignant melanomas correlates with disease prognosis [37, 38]. However, for CRC, a March 2025 study identified four key genes in the cGAS-STING signaling pathway: NLRC3, CASP1, CXCL10, and AIM2 (this work had already been published at the time of this manuscript's review) [39].

Liang et al. found that the upregulation of PD-L1 expression mediated by a first-line chemotherapy regimen for the treatment of CRC (FOLFOX: consisting of 5-FU, oxaliplatin, and leucovorin) was dependent on tumor cell-intrinsic cGAS/STING signaling [40]. Combination therapies targeting STING signaling [41], especially in combination with immune checkpoint blockade or cytotoxic therapies, have shown enhanced anti-tumor efficacy. Deng et al. designed the STING agonist prodrug GB2 to activate

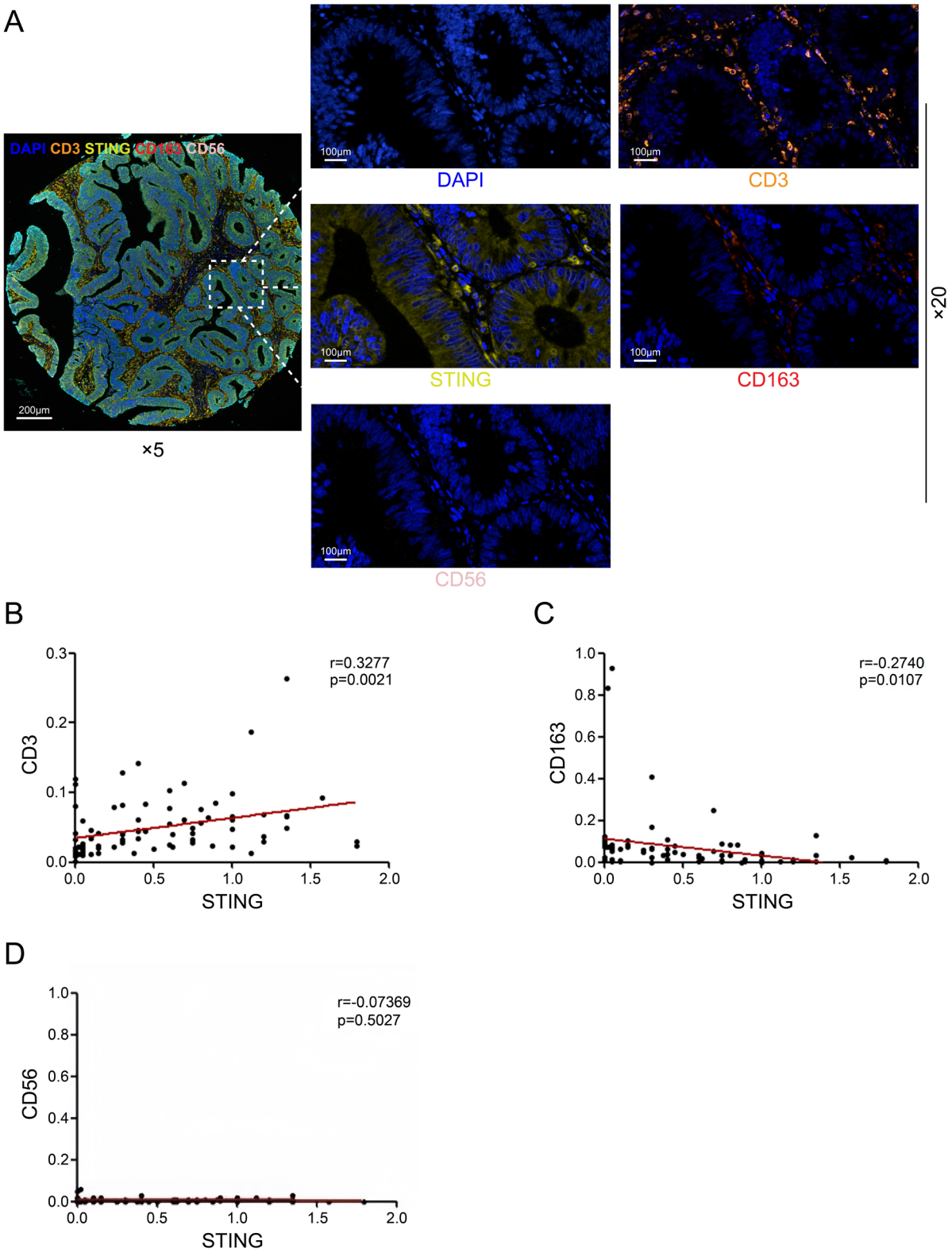

Figure 3. The relationship between STING and the CRC immune microenvironment. A) Multiplex immunofluorescence detection of STING, CD3, CD163, CD56 expression in CRC TMAs; B) Relationship between STING expression in CRC tumor cells and infiltrating CD3 within the immune microenvironment; C) Relationship between STING expression and CD163 in M2 macrophages infiltrating the tumor microenvironment; D) Relationship between the expression of STING and the expression of CD56 on NK cells infiltrated within the tumor.

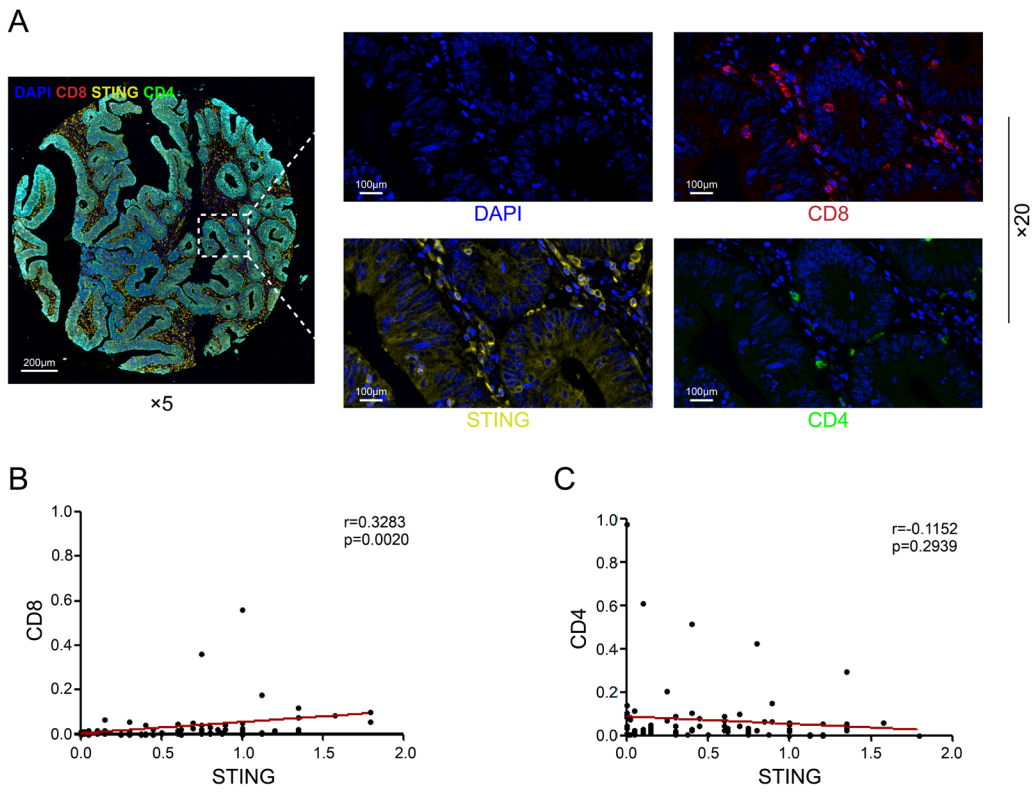

Figure 4. The relationship between STING and the CRC immune microenvironment. A) Multiplex immunofluorescence was used to detect the expression of STING, CD4, and CD8 in consecutive CRC TMA tumor cells; B) Relationship between STING expression in CRC tumor cells and CD8 infiltrated by lymphocytes within the tumor; C) Relationship between STING expression in CRC tumor cells and CD4 in lymphocytes infiltrated within the tumor.

the STING signaling pathway in TAM by targeting CRC patients, triggering receptor expressed on myeloid cells 2, showing excellent antitumor efficacy and immune activation [42]. These findings define STING as a promising prognostic biomarker and therapeutic target. However, systematic studies are needed to determine its environment-dependent mechanisms in tumorigenesis, especially its paradoxical role in immune activation and primary tumor signaling cascades under different microenvironmental conditions.

We examined STING levels in the tumor tissues of 86 patients with CRC and explored their clinical significance in CRC. Our findings confirm that increased STING expression in CRC is associated with improved patient survival and that high STING expression is an independent poor prognostic factor. Clinical characterization revealed that STING expression levels were significantly correlated with TNM stage and lymphatic metastasis. Among them, STING expression was negatively correlated with lymph node metastasis, but not with tumor size (no patient showed hematogenous metastasis). Therefore, it is initially hypothesized that STING in CRC improves patient survival by suppressing lymph node metastasis.

Whether the inhibitory effect of STING on CRC lymph node metastasis might be related to the effect of STING on the tumor immune microenvironment remains to be clarified. In this study, we observed the relationship between STING expression and the regulation of lymphocytes, tumor-associated M2 macrophages, and NK cells in the CRC tumor microenvironment. The results showed that STING activation in CRC cells was negatively correlated with CD163 expression and positively correlated with CD3 expression, but not with NK cells. Further analysis of the correlation between STING expression and CD3, CD4, and CD8 subtypes in CRC cells showed that STING could promote the infiltration of CD8 lymphocytes.

This study is based on the analysis of TMA tissue samples and, therefore, may be biased compared to online databases. To verify the generalizability of the results, we analyzed the expression of STING in several cancer types by HPA (https://www.proteinatlas.org/). STING was highly positive in CRC. Subsequently, the UALCAN database (http://ualcan.path.uab.edu/) further showed that patients with high STING expression had a favorable prognosis. These findings are consistent with our TMA results, suggesting that patients

with high STING expression may have a better prognosis. However, the difference in our p-values was more significant and considered to be related to the differences in the selected clinical samples.

In summary, the expression and localization of STING in CRC are closely related to the prognosis of patients. Highly expressed STING improved survival and inhibited lymph node metastasis in CRC patients, but was not related to tumor size. In addition, STING may participate in the CRC immune microenvironment by affecting CD3, CD163, and CD8. We hypothesized that STING expression changes in CRC cells could be one of the promising targets for the clinical prognosis of CRC patients. These results provide a theoretical basis for the clinical application of STING agonists or inhibitors.

Supplementary information is available in the online version of the paper.

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References

[1] DEKKER E, TANIS PJ, VLEUGELS JLA, KASI PM, WALLACE MB. Colorectal cancer. Lancet 2019; 394: 1467–1480. https://doi.org/10.1016/S0140-6736(19)32319-0

[2] BRAY F, FERLAY J, SOERJOMATARAM I, SIEGEL RL, TORRE LA et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394–424. https://doi.org/10.3322/caac.21492

[3] KANG J, CHOI YJ, KIM IK, LEE HS, KIM H et al. LASSO-Based Machine Learning Algorithm for Prediction of Lymph Node Metastasis in T1 Colorectal Cancer. Cancer Res Treat 2021; 53: 773–783. https://doi.org/10.4143/crt.2020.974

[4] XIONG X, WANG C, CAO J, GAO Z, YE Y. Lymph node metastasis in T1-2 colorectal cancer: a population-based study. Int J Colorectal Dis 2023; 38: 94. https://doi.org/10.1007/s00384-023-04386-w

[5] HAAG SM, GULEN MF, REYMOND L, GIBELIN A, ABRAMI L et al. Targeting STING with covalent small-molecule inhibitors. Nature 2018; 559: 269–273. https://doi.org/10.1038/s41586-018-0287-8

[6] GUI X, YANG H, LI T, TAN X, SHI P et al. Autophagy induction via STING trafficking is a primordial function of the cGAS pathway. Nature 2019; 567: 262–266. https://doi.org/10.1038/s41586-019-1006-9

[7] ZHANG H, YOU QD, XU XL. Targeting Stimulator of Interferon Genes (STING): A Medicinal Chemistry Perspective. J Med Chem 2020; 63: 3785–816. https://doi.org/10.1021/acs.jmedchem.9b01039

[8] LIU N, PANG X, ZHANG H, JI P. The cGAS-STING Pathway in Bacterial Infection and Bacterial Immunity. Front Immunol 2022; 12: 814709. https://doi.org/10.3389/fimmu.2021.814709

[9] SAMSON N, ABLASSER A. The cGAS-STING pathway and cancer. Nat Cancer 2022; 3: 1452–1463. https://doi.org/10.1038/s43018-022-00468-w

[10] CORRALES L, GAJEWSKI TF. Molecular Pathways: Targeting the Stimulator of Interferon Genes (STING) in the Immunotherapy of Cancer. Clin Cancer Res 2015; 21: 4774–4779. https://doi.org/10.1158/1078-0432.CCR-15-1362

[11] FLOOD BA, HIGGS EF, LI S, LUKE JJ, GAJEWSKI TF. STING pathway agonism as a cancer therapeutic. Immunol Rev 2019; 290: 24–38. https://doi.org/10.1111/imr.12765

[12] IVASHKIV LB. IFNγ: signalling, epigenetics and roles in immunity, metabolism, disease and cancer immunotherapy. Nat Rev Immunol 2018; 18: 545–558. https://doi.org/10.1038/s41577-018-0029-z

[13] CHIN EN, SULPIZIO A, LAIRSON LL. Targeting STING to promote antitumor immunity. Trends Cell Biol 2023; 33: 189–203. https://doi.org/10.1016/j.tcb.2022.06.010

[14] LI T, CHENG H, YUAN H, XU Q, SHU C et al. Antitumor Activity of cGAMP via Stimulation of cGAS-cGAMP-STING-IRF3 Mediated Innate Immune Response. Sci Rep 2016; 6: 19049. https://doi.org/10.1038/srep19049

[15] MCLAUGHLIN M, PATIN EC, PEDERSEN M, WILKINS A, DILLON MT et al. Inflammatory microenvironment remodelling by tumour cells after radiotherapy. Nat Rev Cancer 2020; 20: 203–217. https://doi.org/10.1038/s41568-020-0246-1

[16] ZHOU Q, ZHOU Y, LI T, GE Z. Nanoparticle-Mediated STING Agonist Delivery for Enhanced Cancer Immunotherapy. Macromol Biosci 2021; 21: e2100133. https://doi.org/10.1002/mabi.202100133

[17] SALAROGLIO IC, AVILES P, KOPECKA J, MERLINI A, NAPOLI F et al. Ecteinascidin synthetic analogues: a new class of selective inhibitors of transcription, exerting immunogenic cell death in refractory malignant pleural mesothelioma. J Exp Clin Cancer Res 2024; 43: 327. https://doi.org/10.1186/s13046-024-03253-y

[18] HAO F. An overview of the crosstalk between YAP and cGAS-STING signaling in non-small cell lung cancer: it takes two to tango. Clin Transl Oncol 2022; 24: 1661–1672. https://doi.org/10.1007/s12094-022-02826-7

[19] CHAMMA H, VILA IK, TAFFONI C, TURTOI A, LAGUETTE N. Activation of STING in the pancreatic tumor microenvironment: A novel therapeutic opportunity. Cancer Lett 2022; 538: 215694. https://doi.org/10.1016/j.canlet.2022.215694

[20] SUN Y, HU H, LIU Z, XU J, GAO Y et al. Macrophage STING signaling promotes NK cell to suppress colorectal cancer liver metastasis via 4-1BBL/4-1BB co-stimulation. J Immunother Cancer 2023; 11: e006481. https://doi.org/10.1136/jitc-2022-006481

[21] UHLÉN M, FAGERBERG L, HALLSTRÖM BM, LINDSKOG C, OKSVOLD P et al. Proteomics. Tissue-based map of the human proteome. Science 2015; 347: 1260419. https://doi.org/10.1126/science.1260419

[22] CHANDRASHEKAR DS, BASHEL B, BALASUBRAMANYA SAH, CREIGHTON CJ, PONCE-RODRIGUEZ I et al. UALCAN: A Portal for Facilitating Tumor Subgroup Gene Expression and Survival Analyses. Neoplasia 2017; 19: 649–658. https://doi.org/10.1016/j.neo.2017.05.002

[23] ZHANG R, KANG R, TANG D. The STING1 network regulates autophagy and cell death. Signal Transduct Target Ther 2021; 6: 208. https://doi.org/10.1038/s41392-021-00613-4

[24] SLADE D. PARP and PARG inhibitors in cancer treatment. Genes Dev 2020; 34: 360–394. https://doi.org/10.1101/gad.334516.119

[25] SOSA V, MOLINE T, SOMOZA R, PACIUCCI R, KONDOH H et al. Oxidative stress and cancer: an overview. Ageing Res Rev 2013; 12: 376–390. https://doi.org/10.1016/j.arr.2012.10.004

[26] MARTINEZ-OUTSCHOORN UE, PEIRIS-PAGES M, PESTELL RG, SOTGIA F, LISANTI MP. Cancer metabolism: a therapeutic perspective. Nat Rev Clin Oncol 2017; 14: 11–31. https://doi.org/10.1038/nrclinonc.2017.1

[27] DE MATTOS-ARRUDA L, CORTES J, SANTARPIA L, VIVANCOS A, TABERNERO J et al. Circulating tumour cells and cell-free DNA as tools for managing breast cancer. Nat Rev Clin Oncol 2013; 10: 377–389. https://doi.org/10.1038/nrclinonc.2013.80

[28] KOPINSKI PK, SINGH LN, ZHANG S, LOTT MT, WALLACE DC. Mitochondrial DNA variation and cancer. Nat Rev Cancer 2021; 21: 431–445. https://doi.org/10.1038/s41568-021-00358-w

[29] ZONG WX, RABINOWITZ JD, WHITE E. Mitochondria and Cancer. Mol Cell 2016; 61: 667–676. https://doi.org/10.1016/j.molcel.2016.02.011

[30] ZHANG X, BAI XC, CHEN ZJ. Structures and Mechanisms in the cGAS-STING Innate Immunity Pathway. Immunity 2020; 53: 43–53. https://doi.org/10.1016/j.immuni.2020.05.013

[31] DING C, SONG Z, SHEN A, CHEN T, ZHANG A. Small molecules targeting the innate immune cGAS-STING-TBK1 signaling pathway. Acta Pharm Sin B 2020; 10: 2272–2298. https://doi.org/10.1016/j.apsb.2020.03.001

[32] DU H, XU T, CUI M. cGAS-STING signaling in cancer immunity and immunotherapy. Biomed Pharmacother 2021; 133: 110972. https://doi.org/10.1016/j.biopha.2020.110972

[33] MAXWELL MB, HOM-TEDLA MS, YI J, LI S, RIVERA SA et al. ARID1A suppresses R-loop-mediated STING-type I interferon pathway activation of anti-tumor immunity. Cell 2024; 187: 3390–3408. https://doi.org/10.1016/j.cell.2024.04.025

[34] LI S, MIRLEKAR B, JOHNSON BM, BRICKEY WJ, WROBEL JA et al. STING-induced regulatory B cells compromise NK function in cancer immunity. Nature 2022; 610: 373–380. https://doi.org/10.1038/s41586-022-05254-3

[35] DUAN Y, HU Z, HAN P, LEI B, WANG S et al. ADSL-generated fumarate binds and inhibits STING to promote tumour immune evasion. Nat Cell Biol 2025; 27: 668–682. https://doi.org/10.1038/s41556-025-01627-8

[36] KABASHIMA A, MATSUO Y, ITO S, AKIYAMA Y, ISHII T et al. cGAS-STING signaling encourages immune cell overcoming of fibroblast barricades in pancreatic cancer. Sci Rep 2022; 12: 10466. https://doi.org/10.1038/s41598-022-14297-5

[37] BIESAGA B, SMOLARCZYK R, MUCHA-MAŁECKA A, CZAPLA J, RYŚ J et al. Prognostic Significance of STING Immunoexpression in Relation to HPV16 Infection in Patients with Squamous Cell Carcinomas of Oral Cavity and Oropharynx. Biomedicines 2022; 10: 2538. https://doi.org/10.3390/biomedicines10102538

[38] WANG M, HUANG Y, CHEN M, WANG W, WU F et al. Inhibition of tumor intrinsic BANF1 activates antitumor immune responses via cGAS-STING and enhances the efficacy of PD-1 blockade. J Immunother Cancer 2023; 11: e007035. https://doi.org/10.1136/jitc-2023-007035

[39] LI Y, JIANG X, CAO H, WU X, ZHANG H et al. The cGAS-STING-related signature affects the prognosis of colorectal cancer through its regulation of multiple immune cells. IUBMB Life 2025; 77: e70009. https://doi.org/10.1002/iub.70009

[40] LIANG B, XING X, STORTS H, YE Z, CLAYBON H et al. Antagonistic roles of cGAS/STING signaling in colorectal cancer chemotherapy. Front Oncol 2024; 14: 1441935. https://doi.org/10.3389/fonc.2024.1441935

[41] HAO Y, MA S, GU Z, HAGHPARAST A, SCHOMANN T et al. Combination of photodynamic therapy and stimulator of interferon genes (STING) agonist inhibits colorectal tumor growth and recurrence. Cancer Commun (Lond) 2023; 43: 513–518. https://doi.org/10.1002/cac2.12405

[42] DENG A, FAN R, HAI Y, ZHUANG J, ZHANG B et al. A STING agonist prodrug reprograms tumor-associated macrophage to boost colorectal cancer immunotherapy. Theranostics 2025; 15: 277–299. https://doi.org/10.7150/thno.101001

https://doi.org/10.4149/neo_2025_250307N108

STING expression in colorectal cancer: prognostic role and immune microenvironment link via mIHC

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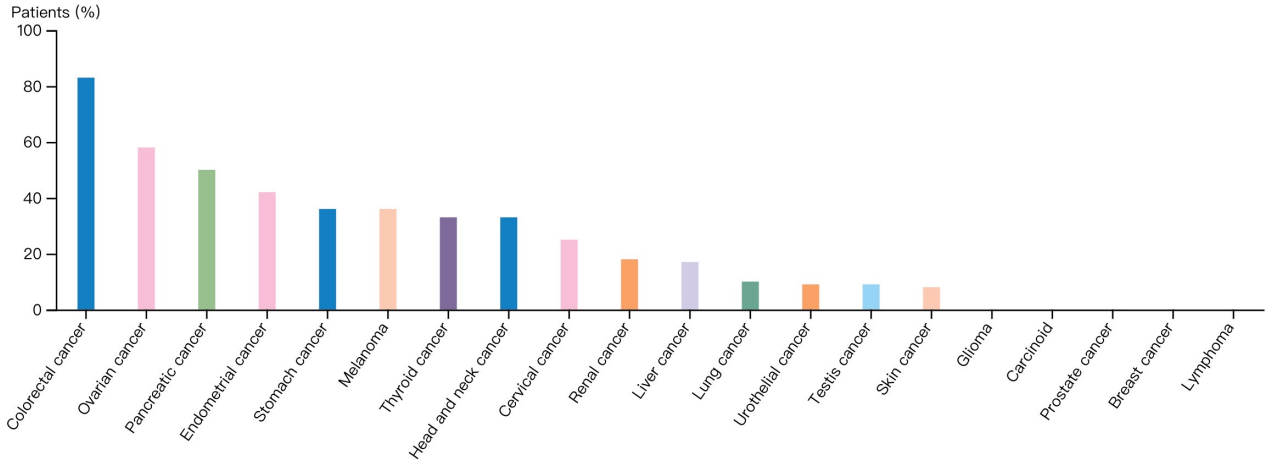
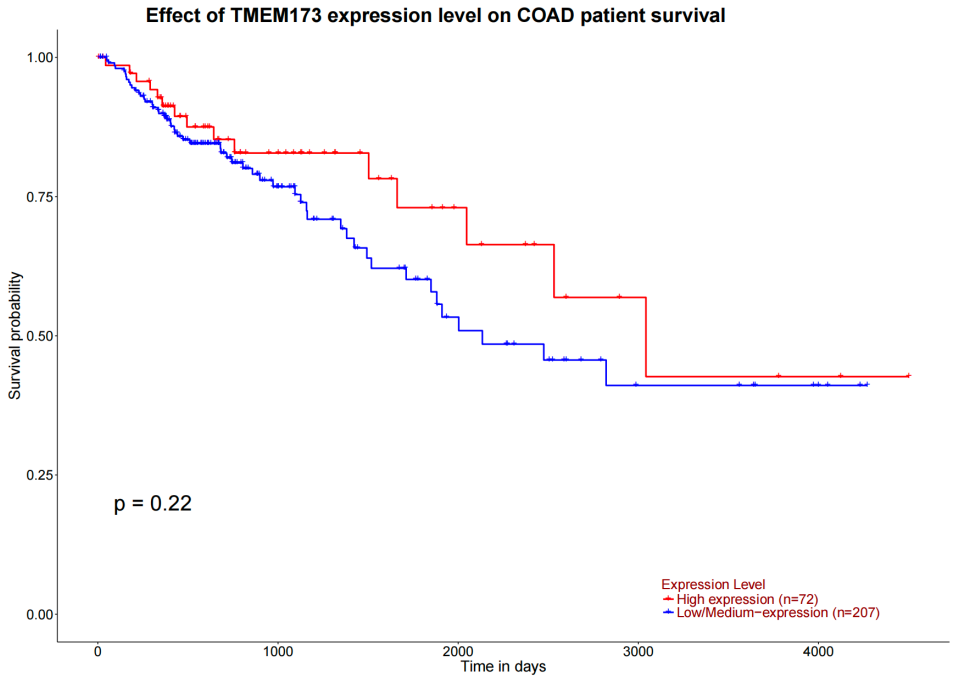
Supplementary Information



Supplementary Figure S1. STING expression in several cancer types. Expression data of STING in tumor tissues (HPA, https://www.proteinatlas.org).



Supplementary Figure S2. Survival analysis of TMEM173 (STING) in patients with COAD.