Downregulation of SAFB Sustains the NF-κB Pathway by Targeting TAK1 during the Progression of Colorectal Cancer

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Abstract

Purpose: To investigate the role and the underlying mechanism of scaffold attachment factor B (SAFB) in the progression of colorectal cancer (CRC).

Experimental Design: SAFB expression was analyzed in the Cancer Outlier Profile Analysis of Oncomine and in 175 paraffin-embedded archived CRC tissues. Gene Ontology analyses were performed to explore the mechanism of SAFB in CRC progression. Western blot, RT-PCR, luciferase assay, and chromatin immuno-precipitation (ChIP) were used to detect the regulation of transforming growth factor-β-activated kinase 1 (TAK1) and NF-κB signaling by SAFB. The role of SAFB in invasion, metastasis, and angiogenesis was investigated using in vitro and in vivo assays. The relationship between SAFB and TAK1 was analyzed in CRC tissues.

Results: SAFB was downregulated in CRC tissues, and low expression of SAFB was significantly associated with an aggressive phenotype and poorer survival of CRC patients. The downregulation of SAFB activated NF-κB signaling by targeting the TAK1 promoter. Ectopic expression of SAFB inhibited the development of aggressive features and metastasis of CRC cells both in vitro and in vivo. The overexpression of TAK1 could rescue the aggressive features in SAFB-overexpressed cells. Furthermore, the expression of SAFB in CRC tissues was negatively correlated with the expression of TAK1- and NF-κB-related genes.

Conclusions: Our results show that SAFB regulated the activity of NF-κB signaling in CRC by targeting TAK1. This novel mechanism provides a comprehensive understanding of both SAFB and NF-κB-related genes.

Introduction

Colorectal cancer (CRC), one of the most common malignancies worldwide, is associated with high morbidity and mortality rates (1). Metastasis and recurrence, which increase the incidence of complications and treatment failure, are the major causes of CRC-related death (2). Therefore, an early diagnosis of CRC and effective interventions are of vital importance. However, early diagnosis is infrequent, and the prognosis is often difficult to determine despite advances in clinical management, histopathologic findings, and molecular markers (3). Thus, further studies of molecular markers that are able to assist with early diagnosis and treatment of metastatic CRC are urgently needed (4).

Scaffold attachment factor B (SAFB) is a nuclear matrix protein that binds to the scaffold or the matrix attachment regions of DNA elements (5). SAFB was initially found to inhibit the activity of the heat shock protein 27 (HSP27) promoter by binding to its TATA box in human breast cancer cells (6). Structurally, SAFB contains a DNA binding region in the SAF box at its N-terminus, an RNA recognition motif, a nuclear localization signal at its center, and Glu/Arg-, Ser/Lys-, and Gly-rich protein interaction regions at its C-terminus (7). Functionally, SAFB is localized within the nucleus where it participates primarily in transcriptional repression by preventing the assembly of transcriptional complexes (7, 8). Genetic deletion of SAFB in embryonic fibroblasts causes upregulation of T-box 2 and downregulation of p19ARF, suggesting that SAFB is important in the processes of cellular immortalization and transformation (9). Additionally, SAFB has been reported to repress the...
human xanthine oxidoreductase gene (hXOR; ref. 10), which is involved in inflammation and tumorigenesis and is a source of reactive oxygen species (11, 12). Low expression of SAFB is related to the metastasis of prostate cancer and poorer outcomes in patients with breast cancer, which is partly due to the unrestrained activities of the androgen receptor and estrogen receptor α, respectively (13, 14). Our preliminary work and a published microarray analysis found that SAFB expression was downregulated in CRC. However, the underlying mechanisms by which SAFB regulates the progression of CRC are largely unknown.

The NF-κB signaling pathway has been shown to promote the progression of different cancers, including breast cancer, prostate cancer, pancreatic cancer, and CRC (15–18). In CRC, cross-talk occurs between NF-κB and many other important signaling pathways, such as the RAS, AKT, and WNT signaling pathways. Together, these pathways form a complex network that regulates the progression of CRC (15, 19). Our preliminary work and a published microarray analysis showed that the downregulation of SAFB expression increased the activation of NF-κB signaling in CRC, but the molecular mechanisms by which SAFB regulates the activation of NF-κB signaling are unclear.

Here, we sought to investigate the potential role of SAFB in the tumorigenesis, invasion and metastasis of CRC and to discover new molecular mechanisms of how SAFB regulates the activation of NF-κB signaling. Our work may help to increase our understanding of the precise role of SAFB in the progression of CRC, which may assist in the development of new therapeutic strategies for CRC.

Materials and Methods

Patients and tissue specimens

This study was conducted on 175 paraffin-embedded colorectal cancer samples, which were histopathologically and clinically diagnosed at Nanfang Hospital, Southern Medical University. Prior patient consent and approval were obtained from the Institutional Research Ethics Committee. Clinical information regarding the samples is summarized in Supplementary Table S1 and in the Supplementary Materials and Methods. Ten CRC specimens and matched adjacent noncancerous mucosa tissues were frozen and stored in liquid nitrogen until further use.

Cell culture

The human CRC cell lines SW480, Colo205, Ls174t, HT29, HCT116, LoVo, HCT15, and SW620 were purchased from American Type Culture Collection. SW620 and HT29 cells were cultured in DMEM medium (Gibco) with 10% FBS (Gibco) at 37°C with 5% CO₂. SW480, Colo205, Ls174t, HCT116, LoVo, and HCT15 cells were cultured in RPMI 1640 medium (Gibco) with 10% FBS (Gibco) at 37°C with 5% CO₂.

Real-time quantitative PCR, Western blot, and IHC

The real-time quantitative PCR (RT-PCR), Western bloting (WB) and IHC, were conducted according to previously described methods (20). Further details are provided in the Supplementary Materials and Methods section.

Transwell and luciferase assays

The Transwell and luciferase assays were performed according to previously described methods (21). Further details are provided in the Supplementary Materials and Methods section.

Chicken chorioallantoic membrane assay

A chicken chorioallantoic membrane (CAM) assay was performed on the sixth day of development of fertilized chicken eggs (22). Further details are provided in the Supplementary Materials and Methods section.

Human umbilical vein endothelial cell formation assay

First, 200 μl Matrigel was pipetted into each well of 24-well plates and was allowed to polymerize for 30 minutes at 37°C. Human umbilical vein endothelial cells (HUVEC; 5 × 10⁴) in 200 μl of conditioned medium were added to each well and incubated at 37°C in 5% CO₂ for 8 hours. Images were obtained under a 100 × bright-field microscope and the capillary tubes were quantified by counting length.

Chromatin immunoprecipitation

Cells (2 × 10⁶) in a 10-cm culture dish were treated with 1% formaldehyde to cross-link proteins to DNA. The cell lysates were subjected to ultrasound to shear the DNA into fragments between 200 and 1,000 bps. Equal aliquots of chromatin supernatants were respectively incubated with 1 μg of anti-SAFB antibody (Abcam) and anti-IgG antibody (Millipore) overnight at 4°C with rotation. After the cross-links of the protein/DNA complexes were reversed to free the DNA, RT-PCR was performed. Further details are provided in the Supplementary Materials and Methods section.

Orthotopic mouse metastatic model

A surgical orthotopic implantation mouse model of CRC was established as previously described (23). Cells (2 × 10⁴ per mouse) were subcutaneously injected into the right dorsal flank of female BALB/c athymic nude mice (4–6 weeks of age, 18–20 g), which were obtained from the Animal Center of Nanfang Hospital, Southern Medical University.
Southern Medical University, Guangzhou, China. Two weeks later, the animals were sacrificed, and the tumors were excised. A portion of the tumor was fixed in 10% formaldehyde and paraffin-embedded, and then 5-μm sections were cut and subjected to IHC using an anti-CD31 antibody (Dako); other sections were stained with hematoxylin and eosin (H&E). The micro-vessel density (MVD) was quantified by counting the proportion of CD31-positive cells. Another portion of tumor was divided into small pieces approximately 1 mm in diameter. Surgical orthotopic implantation of the CRC tumor fragments onto the mesentery of the cecum was performed in nude mice after anesthesia was administered. The mice were euthanized 70 days after surgery, the individual organs were excised, and metastases were observed by histological analysis.

**5Z-7-OXO inhibitor treatment**

We treated SW480 cells with a TAK1 inhibitor (5Z-7-oxozeaenol, Tocris Cookson Ltd.) at a concentration of 0.5 μmol/L. For in vivo treatment, mice received a daily oral dose of 100 mg/kg of 5Z-7-OXO after the orthotopic implantation surgery.

**Statistical analysis**

All statistical analyses were performed using SPSS22.0 for Windows. Statistical tests included the Fisher exact test, log-rank test, χ² test, and Student t test. Bivariate correlations between study variables were calculated by the Spearman rank correlation coefficients. Survival curves were plotted by the Kaplan–Meier method and were compared by the log-rank test. Data represent the mean ± SD. P < 0.05 was considered statistically significant.

**Results**

The downregulation of SAFB was correlated with advanced progression and poorer prognosis of CRC

To investigate the role of SAFB in CRC progression, we first examined the expression of SAFB in the public database Oncomine (www.oncomine.com), which provides a Cancer Outlier Profile Analysis (COPA) for 20 different types of cancer (Supplementary Fig. S1A, left). Among 176 unique analyses of statistical significance, 124 data sets showed low expression of SAFB (Supplementary Fig. S1A, left), which was also demonstrated in 8 (72%) of 11 CRC data sets (Supplementary Fig. S1A, right). Gene set enrichment analysis (GSEA; ref. 24) using expression data from the primary colorectal cancers GSE13294 and GSE35896 suggested that low expression of SAFB was associated with the upregulation of CRC-related gene sets (Supplementary Fig. S1B). We measured the expression levels of SAFB protein and mRNA in 10 pairs of primary CRC tissues and matched adjacent normal tissues. Consistent with these results, a relatively lower expression of SAFB was found in CRC tissues compared with the matched adjacent normal mucosa (Fig. 1A and B). Furthermore, the expression of SAFB was measured in 175 paraffin-embedded CRC tissues by IHC. Analyses of the results indicated that a lower expression of SAFB was significantly correlated with poorer differentiation, more advanced Duke’s stage, increased TNM stage, and poorer survival of patients (Fig. 1C and D; Supplementary Table S1). Kaplan–Meier survival analyses of five published CRC data sets (GSE39582, GSE17538, GSE14333, GSE17536, and GSE17537) revealed the same relationship (Fig. 1D; Supplementary Fig. S1C). Taken together, these results suggest that SAFB may be a prognostic biomarker for CRC.

Downregulation of SAFB enhanced the activity of NF-κB pathway signaling

Analyses of SAFB-regulated gene signatures via GSEA and GO analyses revealed that lower expression of SAFB was positively correlated with an enrichment of NF-κB signaling pathway gene signatures (GSE13294, GSE35896, and GSE15548; Fig. 2A; Supplementary Fig. S2A). Genes upregulated by SAFB-silencing showed enrichment for the GO terms "double-stranded DNA binding," "transcription factor binding," and "NF-κB binding" (Supplementary Fig. S2B). These results suggested that SAFB contributes to the activation of NF-κB signaling through DNA binding. To further validate these results, we established stable SAFB-overexpressing and SAFB-knockdown CRC cell lines (Fig. 2B; Supplementary Fig. S2C–S2E). As shown in Fig. 2C, the overexpression of SAFB significantly reduced NF-κB luciferase activity, but the knockdown of SAFB enhanced NF-κB luciferase activity. The same trend was observed for phosphorylated levels of IKKβ, p65 (Ser 536), and NF-κB DNA binding (Fig. 2D). In addition, the nuclear translocation of p65 was inhibited by SAFB overexpression (Fig. 2E; Supplementary Fig. S2F and S2G). Furthermore, an analysis of a number of NF-κB downstream genes revealed that the silencing of SAFB significantly upregulated the expression of NF-κB downstream genes (Fig. 2F). These results indicate that down-regulation of SAFB enhances the activity of NF-κB signaling.

Downregulation of SAFB enhanced the activity of the NF-κB signaling pathway by relieving transcriptional repression of TAK1

To further test the mechanism of how SAFB inhibits NF-κB signaling, we quantified the levels of phosphorylated and total protein involved in this pathway. It was found that SAFB regulated the phosphorylation of IKKβ and p65, but it did not affect the total expression levels of these proteins (Fig. 2E). We then tested how SAFB affected proteins upstream of the NF-κB signaling pathway, including TAK1, RIP, FLOT, and CYLD. RT-PCR results showed that TAK1, RIP, and FLOT were affected by SAFB downregulation (Fig. 3B; Supplementary Fig. S2H). These results suggested that TAK1, RIP, and FLOT were affected by SAFB downregulation (Fig. 3B; Supplementary Fig. S2H). Furthermore, an analysis of a number of NF-κB downstream genes revealed that the silencing of SAFB significantly upregulated the expression of NF-κB downstream genes (Fig. 2F). These results indicate that down-regulation of SAFB enhances the activity of NF-κB signaling.
Figure 1.
Downregulation of SAFB was correlated with advanced progression and poor prognosis in CRC. A, WB for SAFB expression in 10 human CRC tissues (T) and matched adjacent normal tissues (N) from the same patient. α-Tubulin was used as a loading control. Expression levels were normalized to those of α-tubulin (left). Ratio (N/T) of SAFB mRNA expression in 10 primary CRC tissues and adjacent normal tissues from the same patient, as determined by RT-PCR (right). Expression levels were normalized to those of GAPDH (right). Error bars represent the mean ± SD calculated from 3 parallel experiments.

B, IHC staining indicated that SAFB protein expression was reduced in human CRC (well to poorly differentiated) compared with normal intestinal epithelium.

C, Statistical analyses of the average MOD of SAFB staining between normal intestinal tissues and CRC specimens with different degrees of differentiation, T classification, N classification, and M classification.

D, Kaplan–Meier analyses of the outcome of CRC patients with low versus high expression of SAFB according to our data (left), the GSE39582 data sets (middle), and the GSE17538 data sets (right) (P < 0.05, log-rank test).

**, P < 0.01.
Figure 2.
Downregulation of SAFB enhanced the activity of NF-kB pathway signaling. A, GSEA plot showed that low expression of SAFB was positively correlated with the NF-kB pathway (BIOCARTA_NFKB_PATHWAY, GILMORE_NFKB_PATHWAY, SCHOEN_NFKB_SIGNALING) in published CRC patient gene expression profiles (NCBI/GEO/GSE13294, n = 155, and GSE5896, n = 62) and in published gene expression profiles of MCF-7 breast cancer cells (GSE15548, n = 6). B, Ectopic expression of SAFB mRNA in HCT116, SW620, SW480, and HCT15 CRC cell lines as detected by RT-PCR. The mRNA expression levels were normalized to those of GAPDH. Error bars represent the mean ± SD calculated from 3 parallel experiments. **, P < 0.01. C, NF-kB luciferase reporter activity was analyzed in the indicated cells. Error bars represent the mean ± SD of 3 independent experiments, ** P < 0.01. D, WB analyses of p-p65, total p65, p-IκBα, total IκBα, p-IKKβ, and total IKKα/β expression in the indicated cells. α-Tubulin was used as a loading control. E, WB for nuclear p65 and cytoplasmic p65 in the indicated cells. LaminB1 was used as a nuclear loading control, and α-tubulin was used as a cytoplasmic loading control. F, RT-PCR analyses indicated an apparent overlap between NF-kB-dependent gene expression and SAFB-regulated gene expression. The pseudo colors represent the intensity scale for SAFB-shRNA versus the scrambled vector, generated by a log2 transformation.
knocked down TAK1 using two TAK1 shRNAs, and suppressed TAK1 using a TAK1 inhibitor (5Z-7-OXO). We found that overexpression of TAK1 in SAFB-overexpressing cells significantly rescued NF-κB signaling activity as well as the invasive and metastatic phenotypes of the cells (Fig. 4A and C, top; Supplementary Fig. S4A). Conversely, inhibition of TAK1 by shRNAs or the inhibitor 5Z-7-OXO attenuated NF-κB signaling activity as well as the invasive and metastatic phenotypes of

Figure 3.
Downregulation of SAFB enhanced the activity of the NF-κB signaling pathway by relieving transcriptional repression of TAK1. A, Expression of TAK1 mRNA in the indicated cells. Expression levels were normalized to those of GAPDH. B, WB analyses of TAK1 and p-p65 in the indicated cells. α-Tubulin was used as a loading control. C and D, NF-κB luciferase reporter activity was analyzed (top), and WB was used to detect TAK1 expression in the indicated cells (bottom). α-Tubulin was used as a loading control. E, Schematic depiction of the TAK1 promoter with several SAFB binding sites (blue rectangles), as indicated, and the SAFB binding motif in the P1 proximal promoter and its mutant containing altered nucleotides in P1 (top). ChIP analysis of SAFB binding to the TAK1 promoter in SW480 cells. Primers against the −524 to −438 base pairs in the promoter region (P1) showed significant enrichment after normalization to the GAPDH control (bottom). RT-PCR experiments were performed. F, Relative expression of a WT TAK1 promoter–driven luciferase reporter in vector control or SAFB-knockdown CRC cells (left) and the relative expression of WT or MUT TAK1 promoter–driven luciferase reporters in SAFB-knockdown CRC cells (right). Error bars represent the mean ± SD of 3 independent experiments; *, P < 0.05; **, P < 0.01.
SAFB-silenced CRC cells (Fig. 4B and C, bottom; Supplementary Fig. S4B). The tubule formation and chicken CAM assays revealed that overexpression of SAFB strongly inhibited the formation of tubules by HUVECs and inhibited angiogenesis in CAM; both of these effects were increased after SAFB was silenced (Fig. 4D and E; Supplementary Fig. S4C–S4F). Additionally, TAK1 reversed the effects of SAFB on tubule formation and angiogenesis (Fig. 4D and E; Supplementary Fig. S4C–S4F), suggesting that SAFB modulates angiogenesis through the regulation of TAK1 in CRC. Taken together, TAK1 and SAFB are involved in the regulation of NF-κB signaling and the development of aggressive cellular features of CRC.

SAFB-silenced CRC cells (Fig. 4B and C, bottom; Supplementary Fig. S4B).

The tubule formation and chicken CAM assays revealed that overexpression of SAFB strongly inhibited the formation of tubules by HUVECs and inhibited angiogenesis in CAM; both of these effects were increased after SAFB was silenced (Fig. 4D and E; Supplementary Fig. S4C–S4F). Additionally, TAK1 reversed the effects of SAFB on tubule formation and angiogenesis (Fig. 4D and E; Supplementary Fig. S4C–S4F), suggesting that SAFB modulates angiogenesis through the regulation of TAK1 in CRC. Taken together, TAK1 and SAFB are involved in the regulation of NF-κB signaling and the development of aggressive cellular features of CRC.

Upregulation of SAFB inhibited metastasis and angiogenesis in CRC through the SAFB–TAK1–NF-κB axis

Next, exogenous SAFB was overexpressed in cells to test the effects of SAFB upregulation on metastasis and angiogenesis in CRC through the SAFB–TAK1–NF-κB axis. The overexpression of SAFB in HCT116 cells decreased the number of tumors along the intestines and the frequency of liver metastasis (Fig. 5A and C, left; Supplementary Fig. S5A). SAFB
overexpression also extended the overall survival time of nude mice injected with the CRC cell lines (Fig. 5C, right). In contrast, the overexpression of TAK1 significantly increased the frequency of liver metastases (Fig. 5A and C, left; Supplementary Fig. S5A) and shortened the overall survival time of the nude mice (Fig. 5C, right). Conversely, inhibition of TAK1 by shRNAs or the inhibitor 5Z-7-OXO attenuated the metastatic potential of SAFB-silenced SW480 cells (Fig. 5B and D, left; Supplementary Fig. S5B), while the overall survival of the mice was extended (Fig. 5D, right). Additionally, SAFB-overexpressing tumors had a higher micro-vascular density (indicated by CD31-positive cells) than control tumors, while SAFB-silenced tumors had a lower micro-vascular density compared with controls. Micro-vascular density was increased by the reexpression of TAK1 and was decreased by TAK1 knockdown (Fig. 5E and F; Supplementary Fig. S5C and S5D).

Expression of SAFB in CRC tissue was negatively correlated with that of TAK1 and NF-κB – related genes

Finally, we examined whether activation of the SAFB–TAK1–NF-κB axis identified in our CRC cell models is also evident in clinical CRC tissues. As shown in Supplementary Fig. S6A, correlation studies using the public database revealed a negative correlation between SAFB and TAK1 in the GSE17538 dataset.
Figure 6.
Expression of SAFB in CRC tissue was negatively correlated with that of TAK1 and NF-κB–related genes. A, The SAFB expression level was negatively associated with TAK1 expression in 78 CRC and 2 normal intestinal epithelium tissue arrays. Three representative cases are shown. Original magnification, ×200. Correlation analysis of the average MOD of SAFB and TAK1 staining in 80 specimens. B, Kaplan-Meier analysis of the prognostic significance of the expression of TAK1 in patients with CRC from the published gene expression profile GSE17538 (log-rank test, P < 0.05). C, SAFB and TAK1, MMP9, IL6, VEGF, and IL8 mRNA expression in 10 fresh human CRC samples. Correlation analysis of the mRNA expression of SAFB and TAK1 (D), and MMP9, IL6, VEGF, and IL8 (E) in 10 fresh human CRC samples. Error bars represent the mean ± SD of 3 parallel experiments. F, Model: SAFB downregulation induces TAK1 expression and activates the NF-κB signaling pathway, ultimately leading to an aggressive CRC phenotype.
Decreased the levels of phosphorylated p65 and IKK related and oncogenic genes (31). Our study revealed that SAFB, the nuclear translocation of p65, and regulated invasion, metastasis of CRC (29). The NF-κB plays a pivotal role in the stroma formation of colonic adenocarcinoma (27) and the suppression of the NF-κB signaling pathway during CRC progression is mediated by the transcriptional repressor SAFB (31). The NF-κB-inducing kinase that is responsible for the activation of the noncanonical NF-κB signaling pathway (35). Moreover, TAK1 plays critical roles in the metastasis of breast cancer and CRC to the lungs (36, 37). With respect to the regulation of TAK1, previous studies were focused on posttranslational modifications, including phosphorylation, ubiquitination, methylation, and acetylation (38–40). However, little is known about the transcriptional regulation of TAK1 in CRC. As a transcriptional repressor, SAFB was discovered to target the TATA box of the HSP27 promoter and the E-box of the hXOR promoter, inhibiting the expression of TAK1 promoter and inhibited its activity, which led to the suppression of the NF-κB signaling pathway during CRC invasion, metastasis, and angiogenesis. Overall, we highlight a novel mechanism of regulation by the TAK1–NF-κB axis, which is mediated by the transcriptional repressor SAFB during CRC progression.

In summary, this study demonstrates that SAFB regulates the activity of the NF-κB signaling pathway in CRC via the targeting of TAK1. Together, these data implicate the SAFB–TAK1–NF-κB axis as a potential target for early therapeutic intervention to decrease the progression of CRC.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Authors’ Contributions**

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**Grant Support**

This work was supported by the National Basic Research Program of China (973 program, 2015CB554002), Project of the National Natural Science Foundation of China supported by the NSFC-Guangdong Joint Fund (U11201226), the National Natural Science Foundation of China (81402277, 81402277, 81727318, 81727310, and 81403275), the Postdoctoral Science Foundation of China (2016M592531), the Guangdong Provincial Natural Science Foundation of China (2014A0301009643, 2014A030103283, 2016A030310395, 2016A030310392), the Science and Technology Innovation Foundation of Guangdong Higher Education (CXZ1D1016), the Key...
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Received March 22, 2017; revised July 17, 2017; accepted September 7, 2017; published OnlineFirst September 14, 2017.

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