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 immunoprecipitation (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 the NF-κB signaling pathway in the progression of CRC and indicates that the SAFB–TAK1–NF-κB axis is a potential target for early therapeutic intervention in CRC progression. Clin Cancer Res; 23(22); 7108–18. ©2017 AACR.

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...
Scaffold attachment factor B (SAFB) has recently been implicated in the carcinogenesis and metastasis of prostate cancer and breast cancer. However, the biological functions and underlying mechanisms of SAFB in the regulation of the progression of colorectal cancer (CRC) are largely unknown. Our results showed that SAFB was downregulated in CRC tissues. Low expression of SAFB was significantly associated with poorer survival of patients with CRC. In addition, the downregulation of SAFB enhanced the activity of the NF-κB signaling pathway by relieving the transcriptional repression of transforming growth factor-β-activated kinase 1 (TAK1). Exogenous expression of SAFB inhibited the aggressive features and metastases of CRC cells both in vitro and in vivo. Moreover, the overexpression of TAK1 in cells that overexpressed SAFB restored the emergence of aggressive cellular features. Taken together, we highlight a novel mechanism of the SAFB–TAK1–NF-κB axis in the regulation of CRC progression, and our work may help promote the development of new therapeutic strategies for CRC.

**Translational Relevance**

Scaffold attachment factor B (SAFB) has recently been implicated in the carcinogenesis and metastasis of prostate cancer and breast cancer. However, the biological functions and underlying mechanisms of SAFB in the regulation of the progression of colorectal cancer (CRC) are largely unknown. Our results showed that SAFB was downregulated in CRC tissues. Low expression of SAFB was significantly associated with poorer survival of patients with CRC. In addition, the downregulation of SAFB enhanced the activity of the NF-κB signaling pathway by relieving the transcriptional repression of transforming growth factor-β-activated kinase 1 (TAK1). Exogenous expression of SAFB inhibited the aggressive features and metastases of CRC cells both in vitro and in vivo. Moreover, the overexpression of TAK1 in cells that overexpressed SAFB restored the emergence of aggressive cellular features. Taken together, we highlight a novel mechanism of the SAFB–TAK1–NF-κB axis in the regulation of CRC progression, and our work may help promote 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 blotting (WB) and IHC, were conducted according to previously described methods (20). Further details are provided in the Supplementary Materials and Methods section.

**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 ultrasonication 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 × 10⁶ 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...
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.

**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 Ouilier 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, GSE17358, 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 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 IκBα (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 downregulation 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. S3A). Thus, we concluded that TAK1 might be a key target of SAFB. To verify this hypothesis, we first determined the expression of TAK1 from information in the public database. The results showed that the expression of TAK1 in colorectal cancer was significantly higher than that in normal intestinal mucosa (Supplementary Fig. S3B and S3C). Next, we verified this hypothesis through reexpression of TAK1 in SAFB-overexpressing cells and by the knockdown or inhibition of TAK1 in SAFB-silenced cells. NF-κB luciferase reporter assays revealed that the reexpression of TAK1 rescued the activation of NF-κB signaling (Fig. 3C). Conversely, the knockdown of TAK1 or the treatment of cells with the TAK1 inhibitor 5Z-7-oxozeaenol (5Z-7-OXO) significantly inhibited the NF-κB signaling pathway (Fig. 3D). Chromatin immunoprecipitation (ChIP) assays revealed that endogenous SAFB protein was bound to the first E-box (P1) region of the TAK1 promoter (Fig. 3E). Moreover, SAFB inhibition activated the wild-type TAK1 promoter but did not affect the mutant promoter (Fig. 3F).

**Downregulation of SAFB promoted the aggressiveness of CRC cells through the SAFB–TAK1–NF-κB axis**

To analyze the functional relationship between SAFB and TAK1, we overexpressed TAK1 in SAFB-overexpressing cells,
Downregulation of SAFB Promotes CRC Progression

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-κB pathway signaling. A, GSEA plot showed that low expression of SAFB was positively correlated with the NF-κB pathway (BIOCARTA_NFKB_PATHWAY, GILMORE_NFKB_PATHWAY, SCHOOEN_NFKB_SIGNALING) in published CRC patient gene expression profiles (NCBI/GEO/GSE13294, n = 155, and GSE35896, 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-κB 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-IKKα, total IKKα, p-IKKβ, and total IKKβ expression in the indicated cells. LaminB1 was used as a loading control. E, WB for nuclear p65 and cytoplasmic p65 in the indicated cells. α-Tubulin was used as a loading control, and α-tubulin was used as a cytoplasmic loading control. F, RT-PCR analyses indicated an apparent overlap between NF-κB-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 SAFB-depleted CRC cells (Fig. 4B and D, top).
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

Figure 4.
Downregulation of SAFB contributed to the aggressive features of CRC cells through the SAFB-TAK1-NF-κB axis. A, WB for nuclear p65 and total p65 expression in the indicated cells. LaminB1 was used as the nuclear loading control. B, WB for nuclear p65 and total p65 expression in the indicated cells with different treatments. LaminB1 served as a nuclear loading control whereas α-tubulin served as a cytoplasmic loading control. C, The numbers of migrating CRC cells were evaluated by the Matrigel-coated Boyden chamber invasion assay. D, HUVEC tube formation after stimulation with conditioned media from the indicated cells. E, Representative images of the blood vessels formed in the CAM assay after stimulation with conditioned media from the indicated cells; **, P < 0.01.
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.
related and oncogenic genes (31). Our study revealed that SAFB, the nuclear translocation of p65, and regulated invasion, 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 both (6, 10). In the current study, through both in vitro and in vivo experiments, we showed that SAFB targeted the first E-box of the 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.

Discussion

CRC progression is a multistep process that requires the accumulation of a driver mutation and abnormal expression of many markers that are involved in signal transduction pathways (25). This study revealed that decreased expression of SAFB was significantly associated with aggressive cellular characteristics of CRC (e.g., poor cellular differentiation, advanced Dukes stage, advanced TNM stage) and with a poorer outcome of patients, suggesting that SAFB might be a tumor suppressor and a prognostic marker of CRC progression. Consistent with our results, the downregulation of SAFB has been reported to be responsible for the metastasis of prostate cancer and poorer outcomes in patients with breast cancer (13, 14).

As a nuclear matrix protein with multiple domains, SAFB serves as a transcription factor that regulates the expression of target genes and the activity of many signaling pathways that play important roles in various cellular processes (7, 8, 26). Interestingly, we discovered that the downregulation of SAFB was correlated with the activation of the NF-κB signaling pathway. NF-κB plays a pivotal role in the stroma formation of colon adenomatous polyps as well as the carcinogenesis (27, 28) and metastasis of CRC (29). The NF-κB family contains p65 (RelA), RelB, c-Rel, p50/p105 (NF-κB1), and p52/p100 (NF-κB2), while NF-κB itself consists of p65 and one of the other homodimers or heterodimers (30). In its silent state, the NF-κB dimers are retained in the cytoplasm where they bind to inhibitory IkBs (1kB), whereas in its stimulated state, IkBs induce proteasomal degradation after they are phosphorylated by activated IkB kinases (IKKα/β; ref. 31). The NF-κB dimers are activated by various other modifications and ultimately translocate into the nucleus where they regulate the expression of inflammation-related and oncogenic genes (31). Our study revealed that SAFB decreased the levels of phosphorylated p65 and IkBκBα, decreased the nuclear translocation of p65, and regulated invasion, metastasis and angiogenesis in CRC both in vitro and in vivo. These results further indicate that the downregulation of SAFB promotes the progression of CRC via the regulation of NF-κB signaling pathway activity.

In this study, the downregulation of SAFB enhanced the activity of the NF-κB pathway, but the specific molecular mechanisms by which SAFB regulates the activation of NF-κB signaling require further discussion. Notably, TAK1 is a key regulator of the canonical NF-κB signaling pathway (32), as the successful activation of signals induced by stimuli that bind to receptors largely depends on TAK1 (33, 34). TAK1 has also been reported to activate 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).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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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 (U11021226), the National Natural Science Foundation of China (81402277, 81472313, 81712055, 81472710 and 81402375), the Postdoctoral Science Foundation of China (2016M592511), the Guangdong Provincial Natural Science Foundation of China (S2012100009643, 2014A030113283, 2016A030103283, 2016A0301030095, 2016A0301030932), the Science and Technology Innovation Foundation of Guangdong Higher Education (CZXD1016), the Key

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Clin Cancer Res; 23(22) November 15, 2017 7117

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Published OnlineFirst September 14, 2017; DOI: 10.1158/1078-0432.CCR-17-0747

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Program of the National Natural Science Foundation of Guangdong (2018A0301500012), and the Guangzhou Science & Technology Plan Project (201300000056).

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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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