Overexpression of CCDC34 in colorectal cancer and its involvement in tumor growth, apoptosis and invasion

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Abstract. It has been previously reported that increased expression of coiled-coil domain containing 34 (CCDC34), a member of the CCDCs family, may promote the proliferation and invasion of bladder cancer cells. However, its role in colorectal cancer (CRC) remains unclear. The present study investigated CCDC34 expression in CRC tissues and determined the association between CCDC34 expression and biological characteristics in patients with CRC. Additionally, the variation of cell activity, apoptosis, invasion and associated mechanisms were evaluated following CCDC34 inhibition in SW620 cells with small interfering RNA (siRNA). The role of CCDC34 in CRC growth, apoptosis and invasion was investigated. In the current study, immunohistochemistry revealed an overexpression of CCDC34 in CRC tissues compared with para-cancerous tissue (\( \chi^2 = 29.810, P < 0.001 \)). Furthermore, CCDC34 expression was revealed to be associated with tumor invasion depth and lymphatic metastasis (\( \chi^2 = 4.343, P = 0.037 \); \( \chi^2 = 7.915, P = 0.005 \)). Additionally, the inhibition of CCDC34 expression in SW620 cells led to reduced tumor cell activity, increased apoptosis rate and reduced invasion ability, and expression of apoptosis and invasion-associated genes varied simultaneously which demonstrated that B cell leukemia/lymphoma 2, survivin, N-cadherin, and MMP-9 were decreased, whereas E-cadherin increased significantly in cells of CCDC34-siRNA group compared with the control group (P < 0.05). Therefore, CCDC34 may contribute to CRC development by inhibiting apoptosis of cancer cells and promoting invasion.

Introduction

Colorectal cancer (CRC) is one of the most common malignant cancers worldwide (1), with considerable medical cost to society and suffering of patients with CRC (2,3). As CRC is characterized by rapid progression, majority of patients are diagnosed with advanced stage at the first hospital visit and cannot undergo operation to remove tumor (4). Patients that have had the tumor removed surgically, still have high risk of recurrence and metastasis postoperatively (5,6) due to rapid growth (7), resistance to apoptosis (8) and invasion of CRC tumor cells (9). Thus, it is important to identify the genes relevant to regulation of apoptosis and invasion of CRC cells to improve the diagnosis and comprehensive treatments for CRC.

Coiled-coil domain containing (CCDC) proteins, one family of protein with coiled-coil structures, possess a wide range of physiological functions (10), and the potential associations between some members of CCDC family and cancers have been previously reported. Previous studies have confirmed that CCDC67, CCDC6 and CCDC134 were associated with apoptosis and invasion of thyroid, lung and stomach cancer cells (11-14). CCDC34 is also a member of CCDC family, and has been reported to contribute to apoptosis and invasion of bladder cancer cells (15); however, it is currently uncertain whether CCDC34 can exacerbate this process in CRC cells. In the current study, the expression of CCDC34 protein in paraffin-embedded tissue samples was detected and clinical pathological data of patients with CRC was also collected. The association between CCDC34 expression and the biological characteristics of patients with CRC was analyzed. Additionally, endogenous CCDC34 expression in SW620 cells was suppressed with small interfering RNA (siRNA) and the changes of cell metabolic activity, apoptosis and invasion ability were detected following the siRNA transfection. Subsequently, reverse-transcription quantitative polymerase chain reaction (RT-qPCR) and western blotting was used to detect the expression levels of apoptosis and invasion-associated genes, including B cell leukemia/lymphoma 2 (Bcl-2), survivin, E-cadherin, N-cadherin and matrix metalloproteinase-9 (MMP-9) after endogenous CCDC34 in CRC cells was inhibited. The current findings suggested that the detection of CCDC34 may be valuable for the evaluation of patients with CRC and provided evidence for the investigation of its role in invasion and metastasis of CRC.

Materials and methods

Patients and tissue specimens. In the current study, a total of 85 paraffin specimens of tumor tissues were obtained from

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patients with CRC diagnosed and received surgical treatment at Hebei General Hospital (Shijiazhuang, China) between January 2015 and June 2016. In addition, 60 paraffin specimens of paracancerous tissues were selected as controls, which were >3 cm from edge of cancer and no cancer cells were observed with microscopic examination. In total, 59 male patients and 26 female patients were recruited, and the patients aged from 41-76 (mean age, 57.29±7.49). All enrolled patients did not suffer from other cancers and were pathologically confirmed as adenocarcinoma with no preoperative treatments such as radiotherapy, chemotherapy or targeted therapy. The current study has been approved by the Medical Ethics Committee of Hebei General Hospital and informed consent was obtained from all participants.

Cell lines and reagents. HCT8, HCT116, SW620, SW480, LS-174T, HT29 human colon cancer cell lines were purchased from the Cell Resource Centre of Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences (Shanghai, China), and passed and preserved in Hebei General Hospital. Cells after 5-8 passages were used and stored in -80 °C. The cells were used at logarithmic growth phase were used for the subsequent experiments. This procedure was repeated three times.

Cell culture. HCT8, HCT116, SW620, SW480, LS-174T, HT29 human colon cancer cell lines which were cultured in DMEM containing 10% FBS and incubated at 37°C supplemented with 5% CO₂. Cells were passaged every 2-3 days. The cells at logarithmic growth phase were used for the subsequent experiments.

Cell apoptosis assay. The cells of all groups transfected for 48 h were collected by trypsinization after rinsed with PBS and the cell density was adjusted to 5x10⁴ cells/ml. Then, 500 µl binding buffer was added to suspend cells and 10 µl Annexin V-FITC or PI was added and mixed respectively. The cells were counted by FACS flow cytometry after incubation in dark for 15 min and subjected to calculate percentage of apoptotic cells.

Cell invasion ability assay. SW620 cells were seeded in 24-well plates with 10⁴ cells/well and treated as the different groups, which were transfected with CCDC34-siRNA or NS-siRNA. Transwell chambers were coated with 100 µl Matrigel was treated with ultraviolet radiation. SW620 cells from each group were seeded in 200 µl in the upper chamber with serum free DMEM, and DMEM medium containing 20% FBS was added to the lower chamber. After 24 h, Matrigel glue and extra SW620 cells in the upper chamber were wiped with cotton swabs. Methanol was utilized to fix the membranes for 10 min. The cells penetrating to the lower membrane were counted following crystal violet staining. Each experiment was repeated 3 times.
The absorbance values at the 405 nm wavelength of 405 nm were obtained from a microplate reader. The caspase activity was presented as caspase enzyme units in per unit cell protein.

### Statistical analysis

Statistical analyses were performed with SPSS software version 19.0 (IBM Corp., Armonk, NY, USA). Chi-squared test, Mann-Whitney rank sum test, Spearman correlation, one-way analysis of variance and Dunnett’s test were used for data analysis. P<0.05 was considered to indicate a statistically significant difference.

### Results

**CCDC34 protein expression in CRC tissues and adjacent normal mucosa.** The IHC results illustrated the CCDC34-positive rate in the 85 CRC tissues was 74.12% (63/85) and 28.33% (28/60) in paracancerous tissues. As presented in Fig. 1, the expression of CCDC34 was increased in CRC tissues compared with adjacent tissues (χ²=29.810, P<0.001).

**Association between CCDC34 protein expression and CRC clinical pathology parameters.** Findings are presented in Table II and revealed that the protein expression of CCDC34 was related to invasion depth of the tumor, differentiation and metastasis in the lymph node. CCDC34-positive CRC tissues were characterized with deeper infiltrating of the tumor and higher positive rate of lymphatic metastasis (P<0.05). No significant association was identified between CCDC34 protein expression and the remaining biological characteristics (P>0.05).

**Alteration of CCDC34 protein expression in SW620 cells post CCDC34-siRNA treatment.** The protein expression levels of CCDC34 in SW620 cells transfected with CCDC34-siRNA for 48 h was detected with western blotting. As demonstrated in Fig. 2, CCDC34 protein expression in the CCDC34-siRNA transfected group was significantly lower than the negative control and blank control groups (P<0.05), whereas there was no obvious difference between the NS-siRNA group and the blank control groups (P>0.05).

**Metabolic activity of SW620 cells following CCDC34-siRNA treatment.** In Fig. 3, metabolic activity of SW620 cells transfected...
Table II. Relationship between coiled-coil domain containing 34 protein expression and clinicopathological characteristics of patients with colorectal cancer.

| Clinicopathological parameters       | Positive (63) | Negative (22) | Total | \( \chi^2 \) | P   |
|-------------------------------------|--------------|--------------|-------|--------------|-----|
| Sex                                 |              |              |       |              |     |
| Male                                | 45           | 14           | 59    | 0.466        | 0.495|
| Female                              | 18           | 8            | 26    |              |     |
| Age (years)                         |              |              |       |              |     |
| ≥60                                 | 18           | 9            | 27    | 1.145        | 0.285|
| <60                                 | 45           | 13           | 58    |              |     |
| Tumor differentiation              |              |              |       |              |     |
| Well-differentiated                 | 45           | 17           | 62    | 0.282        | 0.595|
| Poorly differentiated               | 18           | 5            | 23    |              |     |
| Depth of invasion                   |              |              |       |              |     |
| Serosal infiltration                | 49           | 12           | 61    | 4.343        | 0.037|
| No serosal infiltration             | 14           | 10           | 24    |              |     |
| Lymphatic metastasis                |              |              |       |              |     |
| Positive                            | 51           | 11           | 62    | 7.915        | 0.005|
| Negative                            | 12           | 11           | 23    |              |     |
| TNM stages                          |              |              |       |              |     |
| I                                   | 5            | 4            | 9     | 2.012        | 0.570|
| II                                  | 10           | 4            | 14    |              |     |
| III                                 | 43           | 12           | 55    |              |     |
| IV                                  | 5            | 2            | 7     |              |     |
| Distant metastasis                  |              |              |       |              |     |
| Positive                            | 5            | 2            | 7     | 0.029        | 0.865|
| Negative                            | 58           | 20           | 78    |              |     |

TNM, tumor-node-metastasis.

Figure 1. Expression of CCDC34 protein in CRC and adjacent normal mucosa tissues. A total of 85 paraffin tissues from patients with CRC were collected to determine CCDC34 protein expression using immunohistochemistry. Positive staining for CCDC34 protein was located in cell membrane and/or cytoplasm. Expression level of CCDC34 protein in (A) CRC tissues and (B) adjacent normal mucosa tissues. CCDC34, coiled-coil domain containing 34; CRC, colorectal cancer.

with CCDC34-siRNA for 48 h was 0.232±0.031, and was significantly lower compared with the NS-siRNA group (0.283±0.029) and the blank group (0.306±0.041; P<0.05), whereas there was no difference observed between con-siRNA group and the blank control group (P>0.05).

*Apoptosis rate of SW620 cells post CCDC34-siRNA treatment.* In Fig. 4, the apoptotic rate of SW620 cells transfected with CCDC34-siRNA was 28.62±4.57% compared with 12.65±3.05% in the NS-siRNA group and 11.26±2.26% in the blank group. This indicated that the
apoptotic rate of the CCDC34-siRNA group was evidently elevated when compared with the two other groups (P<0.01). Cell invasion ability of SW620 cells following CCDC34-siRNA treatment. As presented in Fig. 5, Transwell assay results highlighted the lower number of SW620 cells crossing the Transwell chamber membrane in the CCDC34-siRNA group (50.17±6.15) compared with the NS-siRNA group (83.50±6.47) and the blank group (85.67±5.05; P<0.05), whereas there was no obvious difference between the NS-siRNA group and the blank group (P>0.05). Additionally, the activity of caspase-3 and -8 in cells of CCDC34-siRNA group was higher compared with the control groups (P<0.05), whereas there was no obvious difference between the NS-siRNA and blank groups (P>0.05; Fig. 6D).

Alteration of the expression of invasion-associated genes in SW620 cells following CCDC34-siRNA treatment. As presented in Fig. 7, western blotting and RT-qPCR revealed mRNA and protein expression of E-cadherin was significantly increased in cells of the CCDC34-siRNA group compared with the control groups (P<0.05), whereas that of N-cadherin and MMP-9 were significantly reduced (P<0.05). No obvious difference between the NS-siRNA group and the blank group was identified (P>0.05).

Discussion

CRC is one of the most common cancers globally (17). Although the treatments have improved in terms of surgical technique (18), radiotherapy (19), chemotherapeutics and targeted drugs for patients CRC (20,21), the overall therapeutic efficacy is unsatisfactory with a high mortality rate, which leads to suffering patients and also a considerable burden to society (22). Therefore, investigating the pathogenesis and developing novel therapies have been hotspots in CRC research. Recurrence and metastasis are primary causes of death for CRC patients; therefore, methods blocking this process may potentially improve CRC treatment. Previous studies have reported that CRC cells which have high anti-apoptotic and invasion abilities are prone to rapid progression and metastasis (23,24). The anti-apoptosis and invasion of CRC cells may be due to the combined effects of multiple genes, and considering that, it is important to identify the key genes relevant to this process. Some genes have been previously identified associated with
anti-apoptosis and invasion of CRC cells; however, specific mechanisms remain to be elucidated. CCDC, a protein with a coiled-coil structure, has the functions of metabolism regulation, cell membrane channel and molecular chaperone (25,26). The association between some members of the CCDC family and cancers has been investigated previously. Gong et al (15) revealed that abnormal high expression of CCDC34, a member of CCDC family, was detected in bladder cancer cells, and suppression of CCDC34 contributed to the reduced proliferation and invasion and increased apoptosis of cancer cells. The present study observed high expression of CCDC34 in CRC tissues, particularly in tissues with deep tumor invasion and lymphatic metastasis. This infers that CCDC34 contributed to CRC progression and metastasis, and detection of CCDC34 in CRC tissues may provide information to evaluate patients' condition. Anti-apoptosis, invasion and metastasis of cancer cells have important roles in progression of CRC. As CRC cells have anti-apoptotic ability, previous studies regarding CRC treatment are focused on how to suppress anti-apoptotic ability of CRC cells (27,28). In addition, considering CRC cells have strong invasive and metastatic ability, suppression of these abilities may control tumor development (29,30). In the in vitro experiments in the present study, reduced cell metabolic activity, increased apoptotic rate and decreased invasion were observed following the suppression of the expression of CCDC34 in the SW620 cell line, which may indicate that CCDC34 may have the ability to regulate cell apoptosis and invasion. In order to determine the role of CCDC34 in apoptosis and invasion of CRC cells, the expression levels of apoptosis and invasion-associated genes in CRC cells were detected following the suppression of CCDC34 expression and the role of CCDC34 in CRC was investigated.

Bcl-2 is an important gene that regulates apoptosis through the mitochondrial pathway and it is able to suppress cell apoptosis in various ways (31,32). Survivin, a member of inhibitor of apoptosis proteins family, is able to suppress apoptosis by suppressing caspase-3 and -8 activity which are apoptosis promoting molecules (33,34). In the current study, reduced expression of Bcl-2 and survivin was detected in the SW620 cell line following CCDC34 inhibition, whereas the activity of caspase-3 and -8 was increased. This suggested that CCDC34
increased apoptosis resistance by activating Bcl-2 and survivin and suppressing caspase-3 and caspase-8.

Epithelial-mesenchymal transition (EMT) has been identified to participate in cancer invasion and metastasis (35).
In the current study, the changes of EMT-associated genes in SW620 cell line following suppression of CCDC34 was also detected. E-cadherin, a transmembrane glycoprotein in epithelial cells, is essential for cell junction and integrity of structure (36,37). Previous studies have revealed that the downregulation of E-cadherin expression may trigger the invasion and expansion of basement membrane, which may lead to tumor invasion and metastasis (38,39). N-cadherin is one of the important mesenchymal markers and its upregulated expression is the hallmark of EMT, as well as an indicator of tumor invasion and metastasis (40,41). MMP-9, one of the important members of the MMPs family is involved in the degradation of extracellular matrix and contribution to metastasis in tumors (7,8,42,43) and regulated by E-cadherin (44). The present study determined that E-cadherin expression was significantly increased following the inhibition of the endogenous CCDC34 expression by RNA interference, whereas expression of N-cadherin and MMP-9 was decreased. This indicates that CCDC34 is involved in CRC EMT, which may lead to cancer invasion and metastasis by suppressing E-cadherin and promoting N-cadherin and MMP-9. However, the corresponding molecular mechanisms should be further clarified by future studies.

In conclusion, the present study demonstrated increased expression of CCDC34 protein in CRC tissues was associated with reduced apoptosis and increased metastasis in CRC cell line. CCDC34 may promote anti-apoptosis and invasion by regulating Bel-2, survivin, E-cadherin, N-cadherin and MMP-9. However, the sample size in the present study was limited and the in vitro experiments are insufficient. Despite the limitations, it may be concluded that CCDC34 had an important role in CRC invasion and metastasis. Further investigation of the functions of CCDC34 may be beneficial to CRC evaluation and CCDC34 may also be regarded as the target gene for controlling CRC progression and metastasis.

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