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*Retrospective Study*

**Reduced serum HDL-C levels and aberrantly expressed cholesterol metabolism genes in colorectal cancer**

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**Abstract**

BACKGROUND

Colorectal cancer (CRC) is a common malignant tumor of the gastrointestinal tract. Lipid metabolism, as an important part of material and energy circulation, is well known to play a crucial role in CRC.

AIM

To explore the relationship between serum lipids and colorectal cancer (CRC) development and identify aberrantly expressed cholesterol metabolism genes in CRC.

METHODS

We retrospectively collected 843 patients who had confirmed CRC and received surgical resection from 2015 to 2017 at the Cancer Hospital of the Chinese Academy of Medical Sciences as our research subjects. The levels of serum total cholesterol (TC), triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), LDL-C/HDL-C and clinical features were collected and statistically analyzed by SPSS. Then, we used the data from Oncomine to screen the differentially expressed genes (DEGs) of the cholesterol metabolism pathway in CRC

and used GEPIA to confirm the candidate DEGs. PrognScan was used to analyze the prognostic value of the DEGs, and STRING was used to construct the PPI network of DEGs.

## RESULTS

The serum HDL-C level in CRC patients was significantly correlated with tumor size, and patients whose tumor size was more than 5 cm had a lower serum HDL-C level ( $1.18 \pm 0.41$  mmol/L vs.  $1.25 \pm 0.35$  mmol/L,  $P < 0.01$ ) than their counterparts. In addition, TC/HDL ( $4.19 \pm 1.33$  vs.  $3.93 \pm 1.26$ ,  $P < 0.01$ ) and LDL-C/HDL-C ( $2.83 \pm 1.10$  vs.  $2.61 \pm 0.96$ ,  $P < 0.01$ ) were higher in patients with larger tumors. The levels of HDL-C ( $P < 0.05$ ), TC/HDL-C ( $P < 0.01$ ) and LDL-C/HDL-C ( $P < 0.05$ ) varied in different stages of CRC patients, and the differences were significant. We screened 14 differentially expressed genes (DEGs) of the cholesterol metabolism pathway in CRC and confirmed that LRP8, PCSK9, LDLR, MBTPS2 and FDXR are upregulated, while ABCA1 and OSBPL1A are downregulated in cancer tissue. Higher expression of LDLR (HR = 3.12, 95%CI: 1.77-5.49,  $P < 0.001$ ), ABCA1 (HR = 1.66, 95%CI: 1.11-2.48,  $P = 0.012$ ) and OSBPL1A (HR = 1.38, 95%CI: 1.01-1.89,  $P = 0.041$ ) all yielded significantly poorer DFS outcomes. Higher expression of FDXR (HR = 0.7, 95%CI: 0.47-1.05,  $P = 0.002$ ) was correlated with longer DFS. LDLR, ABCA1, OSBPL1A and FDXR were involved in many important cellular function pathways.

## CONCLUSION

Serum HDL-C levels are associated with tumor size and stage in CRC patients. LRP8, PCSK9, LDLR, MBTPS2 and FDXR are upregulated, while ABCA1 and OSBPL1A are downregulated in CRC. Among them, LDLR, ABCA1, OSBPL1A and FDXR were valuable prognostic factors of DFS and were involved in important cellular function pathways.

**Key Words:** colorectal cancer; HDL-C; cholesterol metabolism; prognosis

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**Core Tip:** Cholesterol metabolism is closely related to colorectal cancer. In this study, we explored the association between serum HDL-C and tumor characteristics in patients with CRC, identified differentially expressed genes in the cholesterol metabolism pathway and analyzed the prognostic value of these DEGs in CRC. These findings provide clues for further research on cholesterol metabolism and CRC.

## **INTRODUCTION**

Colorectal cancer (CRC) is a common malignant tumor of the gastrointestinal tract. It ranks third in the incidence of male malignant tumors in the world and second in female malignant tumors<sup>[1]</sup>. The occurrence and development of colorectal cancer involve multiple dysregulated genes and complicated physiological processes. Lipid metabolism, as an important part of material and energy circulation, is well known to play a crucial role in CRC.

Numerous studies have found that lipid abnormalities are closely related to CRC. <sup>5</sup> There have been a number of reports in the literature regarding the relationship <sup>12</sup> between abnormal serum lipid levels, including total cholesterol (TC), triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), and CRC<sup>[2, 3]</sup>, but there is no consistent conclusion at present. Most of these studies focus on the different lipid levels between healthy people and patients with CRC, but it is difficult to clarify the specific causal relationship between lipid alterations and cancer. Additionally, research on the underlying mechanism is relatively scarce.

Many studies have shown that some key enzymes and transporters in metabolic pathways play very important roles in various cancers<sup>[4]</sup>. Dysregulation of these genes causes altered metabolic phenotypes that influence the nutrient, energy and signal transduction balance in cells. However, only a few metabolic genes are presently known to be directly implicated in CRC, especially in the cholesterol metabolism pathway, and there is still much more to learn about the causal role of metabolic genes in cancer.

In this study, we conducted a retrospective analysis of the relationship between serum TC, TG, HDL-C, LDL-C and clinical characteristics in patients with CRC and explored potential CRC-associated cholesterol metabolic genes using a series of bioinformatics databases and tools. We aimed to provide more evidence on the alterations in cholesterol metabolism and identify potential cancer-associated metabolic genes in CRC.

## **MATERIALS AND METHODS**

### ***Ethics statement***

The current research was approved by the Institutional Review Board. Informed consent was obtained from all participants for the use of the clinical information in this research.

### ***Patient characteristics***

This retrospective study enrolled a total of 843 patients with CRC who underwent surgical resection between January 2013 and December 2015 at the Cancer Hospital of the Chinese Academy of Medical Sciences (Beijing, China). The average patient age at surgery was 59 years, 498 were male, 345 were female, 348 cases were colon cancer, and 495 cases were rectal cancer. Tumor staging conformed to the eighth edition of the American Joint Committee on Cancer/Union International Control Center (AJCC/UICC) TNM staging manual (2017). A total of 151, 296, 340 and 56 cases were found to be stages I, II, III and IV, respectively. Patients with diabetes or hyperlipidemia were excluded. The serum lipid information (TC, TG, HDL-C, and LDL-C), body mass index (BMI (weight/height<sup>2</sup> and kg/m<sup>2</sup>)), tumor size (<5 cm/≥5 cm), and smoking and drinking history (yes/no) of these patients were collected.

### ***Statistical analysis***

The levels of TC, TG, HDL-C, LDL-C, TC/LDL-C, TC/HDL-C and LDL-C/HDL-C are presented as the mean±standard deviation and were compared using the independent sample *t* test between different groups of tumor size (<5 cm/≥5 cm). An analysis of variance (ANOVA) was used to compare the differences among stages. A covariance analysis was used to compare multiple variables. Differences between groups with *P* < 0.05 were regarded as statistically significant.

### ***Oncomine database analysis***

The Oncomine database (<https://www.oncomine.org>), an online database consisting of previously published and open-access microarray data<sup>[5]</sup>, was used to identify the transcription level of cholesterol metabolism pathway genes in colorectal cancer. The

analysis type selected was “Cancer vs. Normal Analysis”, the cancer type as “Colorectal cancer”, the data type was “mRNA”, and the GO concept was "Cholesterol metabolism" in the analysis of differentially expressed genes in the cholesterol metabolic pathway in colorectal cancer compared with normal tissues.

#### ***Candidate DEG validation***

The expression of DEGs in CRC was analyzed using Gene Expression Profiling Interactive Analysis (GEPIA). GEPIA is an interactive web server for estimating the mRNA expression data in The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) dataset projects<sup>[6]</sup>.

#### ***Prognostic value analysis***

Prognoscan (<http://www.prognoscan.org/>) is a comprehensive online platform for assessing potential tumor biomarkers and therapeutic targets<sup>[7]</sup>. To analyze the prognostic values of specific DEGs in CRC, the Prognoscan platform was used to display disease-free survival (DFS). The HRs and log-rank *P* values are presented on the webpage.

#### ***Protein-protein interaction network generation***

We built a protein-protein interaction (PPI) network for LDLR, FDXR, ABCA1 and OSBPL1A using STRING (<sup>11</sup> Search Tool for the Retrieval of Interacting Genes/Proteins, <http://string-db.org/>), an online resource search tool for the retrieval of interacting genes, which include physical and functional associations<sup>[8]</sup>.

## **RESULTS**

#### ***Factors related to serum lipid levels in CRC patients***

Several well-known factors are associated with serum lipid levels, such as sex, age, BMI and history of smoking and drinking. We considered all of these factors and found that serum HDL-C level, TC/HDL-C and LDL-C/HDL-C were significantly correlated with tumor size and stage in patients with CRC (Table 1).

#### ***Comparison of serum lipid levels in CRC patients with different tumor sizes***

We defined tumor size as a tumor single diameter more or no more than 5 cm according to some previous studies in CRC. The results showed that the serum HDL-C ( $1.18 \pm 0.41$  mmol/L vs.  $1.25 \pm 0.35$  mmol/L,  $P < 0.01$ ) levels were lower in patients with a larger tumor, while TC/HDL-C ( $4.19 \pm 1.33$  vs.  $3.93 \pm 1.26$ ,  $P < 0.01$ ) and LDL-C/HDL-C ( $2.83 \pm 1.10$  vs.  $2.61 \pm 0.96$ ,  $P < 0.01$ ) were higher, as shown in Table 2.

#### ***Comparison of the serum lipid levels in patients with CRC at different stages***

The analysis of variance regarding serum lipid levels of patients with CRC and stages in Table 3 revealed significant correlations between the levels of HDL-C, TC/HDL-C and LDL-C/HDL-C and tumor stages. The levels of HDL-C in patients with stage I ( $1.3 \pm 0.35$  mmol/L), II ( $1.22 \pm 0.38$  mmol/L) and III ( $1.2 \pm 0.37$  mmol/L) disease were gradually reduced, and the serum HDL-C level in patients with stage IV disease ( $1.24 \pm 0.37$  mmol/L) was slightly higher than that in patients with stage II and III disease. The differences were significant ( $P < 0.05$ ). TC/HDL-C and LDL-C/HDL-C gradually increased in stage I to stage III in patients with CRC and decreased in stage IV patients, with significant differences ( $P < 0.05$ ).

#### ***Screening of cholesterol metabolism pathway DEGs in CRC***

According to the case analysis results, we deduce that changes in HDL-C levels in patients with CRC may be associated with abnormal expression of cholesterol metabolism pathway genes in colorectal cancer tissues. An online analysis was performed using Oncomine. By comparing the differentially expressed genes (DEGs) of the cholesterol metabolism pathway in Skrzypczak colorectal cancer, we found that the mRNA levels of LRP8 ( $P = 7.77E-17$ , fold change = 3.04), MBTPS2 ( $P = 2.11E-10$ , fold change = 1.73), PCSK9 ( $P = 2.48E-7$ , fold change = 2.15), LDLR ( $P = 2.90E-5$ , fold change = 1.88), FDXR ( $P = 1.71E-4$ , fold change = 1.54), APOL1 ( $P = 2.14E-4$ , fold change = 1.33), and CELA3A ( $P = 3.17E-4$ , fold change = 1.16) were upregulated in CRC tissue, as shown in Figure 1. The mRNA levels of OSBPL1A ( $P = 1.7E-11$ , fold change = -2.37), VLDLR ( $P = 6.17E-8$ , fold change = -2.18), SREBF2 ( $P = 1.01E-6$ , fold change = -1.4), SORL1 ( $P = 8.37E-6$ , fold change = -1.91), HDLBP ( $P = 5.75E-5$ , fold change = -1.25),



ABCA1 ( $P = 2.13\text{E-}4$ , fold change = -1.74) and APOL2 ( $P = 2.75\text{E-}4$ , fold change = -1.21) were downregulated in CRC tissue (Figure 2).

### *Identification of candidate DEGs*

DEGs in CRC were reanalyzed using GEPIA based on TCGA and GTEx datasets for transcriptomic analysis. The results demonstrated that LRP8, PCSK9, and LDLR were upregulated in colorectal cancer tissue compared with normal tissue (Figure 3A, B and C), while MBTPS2 and FDXR showed significantly higher expression only in rectal cancer and colon cancer, respectively (Figure 3D and E). ABCA1 and OSBPL1A were downregulated in CRC tissue (Figure 3F and G), consistent with the results from Oncomine. CELA3A was downregulated (Figure 3H), and SORL1 was upregulated in cancer tissue (Figure 3I), which is the reverse of the above results. The expression levels of APOL1, VLDLR, HDLBP, SREBF2 and APOL2 were comparable between cancer and normal tissues according to the GEPIA analysis results (Figure 3J-N). Therefore, we identified LRP8, PCSK9, LDLR, MBTPS2, FDXR, ABCA1 and OSBPL1A as dysregulated in CRC.

### *Prognostic value of DEGs*

Using the online Kaplan-Meier survival analysis tool Prognoscan, we discovered that high mRNA expression of LDLR (hazard ratio (HR) = 3.12, 95% confidence interval (CI): 1.77-5.49,  $P < 0.001$ ), ABCA1 (HR = 1.66, 95%CI: 1.11-2.48,  $P = 0.012$ ) and OSBPL1A (HR = 1.38, 95%CI: 1.01-1.89,  $P = 0.041$ ) was an unfavorable prognostic factor for disease-free survival (DFS) in CRC patients (Figure 4A, B and C), while high mRNA expression of FDXR (HR = 0.7, 95%CI: 0.47-1.05,  $P = 0.002$ ) was a favorable prognostic factor for DFS (Figure 4D). Unfortunately, LRP8, PCSK9 and MBTPS2 expression could not be used to predict DFS outcome according to the results of this analysis, as shown in Figure 4E, F and G.

### *PPI network of DEGs with prognostic value*

LDLR, FDXR, ABCA1 and OSBPL1A were analyzed by STRING to construct protein-protein interaction networks (Figure 5A-D) and predict other possible roles that they may play in addition to cholesterol metabolism. The results implied that FDXR was also

involved in xenobiotic metabolic processes, cellular responses to xenobiotic stimuli and oxidation-reduction processes. ABCA1 was shown to be involved in the steroid hormone-mediated signaling pathway, and OSBPL1A was involved in antigen processing and presentation of exogenous peptide antigens via MHC class II, microtubule-based movement and vesicle-mediated transport.

## DISCUSSION

Cholesterol is the most abundant steroid compound in the human body and is essential for membrane biogenesis, signal transduction, cell proliferation and differentiation<sup>[9]</sup>. When cholesterol is deficient in humans, the normal cell physiological process is disrupted, cellular rigidity is increased, and the cells are easily fractured. Cholesterol is provided by the diet but can also be synthesized by the liver in humans and distributed throughout the body via low-density lipoprotein (LDL) and high-density lipoprotein (HDL) transporters<sup>[10]</sup>, such as LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C). Cancer has been associated with cholesterol, as cholesterol can directly influence cell physiological function and is also the obligatory precursor of steroid hormones, which are involved in tumor promotion and tumor death<sup>[10]</sup>. Hypercholesterolemia was shown to promote mammary tumor growth and invasiveness in several mouse transgenic models<sup>[11]</sup>, suggesting that cholesterol or its metabolites promote CRC.

A large number of epidemiological statistics and basic research suggest that the uptake of cholesterol and serum cholesterol levels are closely related to the occurrence, development and prognosis of colorectal cancer, but there is no consistent conclusion thus far. The main focus of these studies was the association of blood concentrations of total cholesterol (TC) in relation to CRC risk. Findings from three prospective studies on TC concentrations have been inconsistent, showing either a positive association with CRC, colon and rectal cancer risk<sup>[12]</sup>, no association with the risk of colon cancer but a positive association with the risk of rectal cancer in men only<sup>[13]</sup>, or no association at all<sup>[14]</sup>. Regarding triglyceride (TG) concentrations, three cohort studies found no significant associations with the risk of CRC, colon or rectal

cancer. Data on their relationship with the clinical features in CRC patients are scarce. In this study, we found that both TC and TG levels were not associated with the cancer type (colon/rectal, data not shown), tumor size or tumor stage in CRC patients.

HDL-C, as an indispensable form of cholesterol, plays a very important role in some diseases, including arteriosclerosis<sup>[15]</sup>, and has been a subject of intense research in cancer. However, studies of the link between HDL-C levels and colorectal cancer have also led to contrasting results. Yang *et al*<sup>[16]</sup> found that serum HDL-C level reduction was associated with an increased risk of cancer, including CRC. Jafri *et al*<sup>[17]</sup> conducted a large meta-analysis of randomized lipid-altering trials and observed a significant inverse association between baseline HDL-C levels and the risk of developing cancer. In our study, we found that HDL-C is decreased in CRC patients with larger tumors and advanced stages. Although these findings do not seem to have reached a definitive conclusion on whether low serum HDL-C levels should be considered a marker of the presence of cancer or a possible causative factor, several possible mechanisms exist by which serum concentrations of HDL-C may be directly or indirectly involved in colorectal carcinogenesis. Decreased concentrations of HDL-C have been related to increased circulating concentrations of proinflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor- $\alpha$  receptors, which can stimulate cell growth and cellular proliferation and inhibit apoptosis<sup>[18]</sup>. Increased HDL-C levels are associated with increased concentrations of anti-inflammatory cytokines such as IL-10<sup>[19]</sup>, which inhibit the production of these proinflammatory cytokines<sup>[20]</sup>. These observations suggest that HDL may modulate colon carcinogenesis through inflammatory pathways. Another proposed pathway is through modulation of oxidative stress because HDL displays antioxidative activities and is believed to confer protection against oxidation of LDL-C<sup>[21,22]</sup>. A low concentration of HDL-C leads to more oxidized LDL-C<sup>[23]</sup>, which has been described as a cause of increased intracellular oxidative stress, a process that is involved in the pathogenesis of cancer<sup>[24]</sup>. However, as oncogenic processes enable cancer cells to synthesize their own cholesterol, which can be further metabolized and take part in whole-body circulation, and tumor

development may also disrupt intestinal homeostasis, the change in serum HDL-C levels can be a result of CRC from this perspective.

<sup>2</sup> Investigations at the laboratory level have revealed a more complex map of the influence of cholesterol metabolism on the promotion or suppression of CRC that could account for these conflicting studies. Metabolic reprogramming is a common hallmark of tumors<sup>15</sup>. In addition to the Warburg effect, tumor cells also undergo lipid remodeling, which is mostly characterized by aberrant de novo lipogenesis and cholesterogenesis due to oncogenic-driven lipogenic enzyme overexpression<sup>26</sup>. In this study, analysis of abnormally expressed cholesterol metabolism-related genes in CRC showed that the upregulated genes are mainly involved in the synthesis and uptake of cholesterol, while the downregulated genes are mainly concentrated in the channels of cholesterol transport. Related to the active characteristics, the abnormal expression of these genes is conducive to maintaining intracellular high cholesterol levels to ensure the growth of material and energy needs.

Low-density lipoprotein receptor-related protein 8 (LRP8) and low-density lipoprotein receptor (LDLR) are cell surface receptors and function in signal transduction and endocytosis of specific ligands. LRP8 participates in the development and metastasis of several cancers, such as gastric cancer<sup>27</sup> and melanoma<sup>28</sup>. Some studies have reported the relationship between LDLR and CRC at the *in vitro* and animal levels<sup>29,30</sup>. However, research on the underlying mechanism is still scarce. MBTPS2 encodes a membrane-bound zinc metalloprotease, an endoplasmic reticulum membrane protein, that exhibits a dual function<sup>31</sup>. On the one hand, MBTPS2 activates<sup>8</sup> sterol regulatory element-binding proteins (SREBPs), which are key transcription factors that subsequently promote the expression of cholesterol-related genes<sup>32</sup>. On the other hand, as MBTPS2 can respond to stress in the endoplasmic reticulum and cause cells to cope with stressful conditions, the dysregulation of MBTPS2 can lead to severe disease in humans<sup>33,34</sup>. PCSK9 is a secreted serine protease that is involved in the posttranscriptional regulation of LDR, which can promote intracellular degradation in



acidic subcellular compartments<sup>[35]</sup>. Regarding its LDLR-decreasing function, a study in cancer research showed its inverse correlation with LDLR expression<sup>[36]</sup>. However, in our study, we found that PCSK9 and LDLR are both upregulated in CRC, which is very intriguing. The role of FDXR in CRC has been explored in some studies<sup>[37,38]</sup> before; in our analysis, we also confirmed an increase in FDXR expression, while the high expression level is a favorable prognostic factor for DFS in CRC. <sup>8</sup>ATP-binding cassette transporter (ABCA1) is a transmembrane protein responsible for reverse cholesterol transport and synthesis of HDL-C<sup>[39,40]</sup>. Both the overexpression and the decrease in ABCA1 are associated with tumorigenesis<sup>[41,42]</sup>. OSBPL1A was reported to be involved in <sup>16</sup>ABCA1-mediated pathways of cholesterol efflux and could also impact the biogenesis of HDL-C in the liver and intestine<sup>[43]</sup>; thus, the relationship between the downregulated expression of these two genes and the decrease in serum HDL-C in CRC is worthy of attention.

## **CONCLUSION**

Overall, in this study, we found that serum HDL-C levels are different in colorectal cancer patients with different stages and tumor sizes. LRP8, PCSK9, LDLR, MBTPS2 and FDXR are upregulated, while ABCA1 and OSBPL1A are downregulated in CRC. Among them, LDLR, ABCA1, OSBPL1A and FDXR were valuable prognostic factors of DFS. Our findings provide hypothetical and biological characteristic insight into the role of cholesterol metabolism in CRC, and further molecular-level studies are needed to elucidate potential mechanisms.

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