Therapeutic strategy in colorectal cancer based on Traditional Chinese and Western Medicine: from the lipid metabolism perspective

Qian-Qian Niu, and Yuan-Hong Zhao

Abstract—Colorectal cancer (CRC) is a major cause of morbidity and mortality and is closely associated with lipid metabolism, of which fatty acid metabolism, the release of fat factors and the abnormal level of blood lipids are all important pathogenic mechanisms. With the increasing awareness of lipid metabolism, advances in lipid-regulating therapy have made it possible for anti-tumor effect in CRC. However, there are still many research gaps and limitations. Given the complexity and uncertainty of targeted lipid-regulating therapy for CRC, traditional Chinese medicine (TCM) may have a leg up when it comes to the theory of “holistic concept” and “treatment based on syndrome differentiation”. Meanwhile, proper dietary direction, healthy lifestyles, and normal serum lipid levels contribute directly to the prognosis of CRC patients.

Key words—Lipid metabolism, Colorectal cancer, Lipid-regulating therapy, Treatment strategies, Traditional Chinese medicine

Highlights—Lipid metabolism is closely associated with colorectal carcinogenesis and development, which emerges as a potential therapeutic target gradually. Besides, in view of the complexity and uncertainty of targeted lipid-regulating therapy for colorectal cancer, traditional Chinese medicine might provide novel insights, explanations and directions to the lipid-regulating therapy in colorectal cancer.

INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignant tumors with the third morbidity and fourth mortality in the global world [1]. The etiology of CRC is unknown but closely related to the environment, heredity, lifestyle and diet [2], as well as metabolic diseases such as obesity, hyperlipidemia, hypertension and diabetes [3]. Lipid metabolism is emerging as a potential therapeutic target gradually. Besides, TCM might provide novel insights, explanations and directions to the lipid-regulating therapy. Therefore, this study reviewed and investigated the mechanism of lipid metabolism and TCM comment.

LIPID METABOLIC ALTERATIONS OF TUMOR CELLS

Tumor metabolism is more exuberant than that of normal cells, with obvious differences in energy metabolism such as sugar, lipid, nucleic acid and protein. Since Weinberg put forward the anaerobic glycolysis of tumor cells, researches on tumor metabolism have been deepened. Lipids play an essential role in the cellular structure and function, involved in biofilm formation, signaling and energy supply.

Lipid metabolic alterations are the key feature of tumor cells, which is mainly characterized by the enhancement of de novo synthesized fatty acid to promote early tumor progression mediated by various transcriptional factors and lipid metabolic enzymes [4], also closely related to tumor cellular growth, proliferation, apoptosis, migration, inflammatory response and antineoplastic drug resistance.

CRC AND ADIPOSE TISSUE

Adipose tissue formed by the accumulation of adipocytes stores energy for the body, and as the important endocrine organ, which regulates immunity and autophagy [5] by secreting a large number of adipokines and cytokines such as tumor necrosis factor (TNF-α), interleukin (IL)-6 and IL-8. Moreover, long-standing inflammation of adipose tissue also induces colorectal carcinogenesis and progression [6, 7].

CRC AND THE LEVEL OF BLOOD LIPID

The elevated level of free fatty acid (FFA) in serum may induce oxidative stress, lipo-toxicity or hypertriglyceridemia [5]. FFA4 is highly expressed in colorectal cancer cell lines and animal models with unclear mechanism [8].

Epidemiological studies have found that the level of serum lipid metabolism was closely linked to CRC. Elevated high-density lipoprotein (HDL) level was the protective factor for CRC [9], while total cholesterol (TC) was the risk factor [10]. Additionally, triglyceride (TC) is currently uncertain [5] and may be associated with the occurrence of colorectal adenomas [11].

LIPID LOWERING THERAPY OF CRC

Decreasing origins of lipids

Limiting external lipid uptake ω-3 and ω-6 polyunsaturated fatty acids are essential fatty acids that can only be obtained from food. The former is mainly ingested from vegetable oil, walnut and green vegetables, while the latter is more common in animal fats [5]. Findings have shown that diets rich in ω-6 fatty acids promoted inflammation, cardiovascular disease and cancer, while ω-3 fatty acids exerted anti-inflammatory actions, inhibition of IL-1β, IL-6, and TNF-α, and diminished the risk of CRC [12]. Recent studies also found that the incidence of CRC in Asia was on the rise, which might be caused by excessive intake of animal fat [1]. Overall, it is very vital to keep a balanced diet and optimize the intake ratio of essential fatty acids. Overexpression of CD36 induces tumor metastasis, a transmembrane channel protein [13] that promotes the absorption of lipids in the extracellular
Drug Combination Therapy

environment, which also develops the anti-tumor therapy and cure.

Limiting de novo synthesized fatty acid The augmented levels of fatty acid synthesis enzymes are common in malignancy, including fatty acid synthase (FASN), acetyl-CoA synthetase (ACS), ATP citrate lyase (ACL), fatty acid CoA ligase (ACSL) and acetyl CoA carboxylase (ACC) [4]. FASN is the most extensively studied therapeutic target at present. Several kinds of FASN inhibitors, such as cyanin, C75 and orlistat, have entered the clinical trials [14]. And TVB3166 [15], the new FASN inhibitor, also showed strong anti-tumor activity in CRC cells. Furthermore, inhibition of the synthesis of these lipids might be a therapeutic strategy in the treatment of antiangiogenic therapy resistance. In addition, studies have shown that human breast cancer and colon cancer cells progressed after sunitinib exhibited increasing fatty acid synthesis, and FASN inhibitors might mitigate this growth and metastasis [16]. ACSL4 is upregulated in some colon adenocarcinomas, and inhibitors of ACSL4 attenuates the proliferation of tumor cells [17]. Sterol regulatory element binding proteins (SREBPs) are the key regulators of cellular lipid homeostasis, with high expression in CRC cells. Hence, their further proliferation may be limited by blocking the transcription SREBPs 4. Additionally, liver X-activated receptor (LXR) activates fatty acid synthesis by inducing SREBP-1c. And SR9243, an LXR inverse agonist, could inhibit lipids synthesis and promote cell apoptosis [18].

Inhibition of fatty acid desaturation Stearoyl-CoA desaturase (SCD) catalyzes the synthesis of monounsaturated fatty acids (FAs) for further synthesis of glycerophospholipid, sphingolipid and other lipids. Researches have demonstrated that SCD was a risk factor for poor prognosis and progression of patients with CRC [19]. And betulinic acid (BetA), an inhibitor of SCD, causes apoptosis in CRC cells [20].

Limiting the synthesis of CHO Dysregulation of the mevalonate (MVA) pathway and 3 Hydroxy-3-Methylglutaryl-CoA Reductase (HMGR) may be the essential mechanism for carcinogenesis. Statins are inhibitors of HMGR, which may inhibit tumor growth, cause apoptosis, and suppress angiogenesis [21]. Moreover, intestinal dysbacteriosis arose in patients with colorectal precancerous or cancerous patients [22]. And statins have been proved effective in balancing the intestinal flora [23], which remained to be verified to be the valid anti-tumor target. A meta-analysis also showed patients treated with statins before the diagnosis of CRC were associated with lower mortality [24]. However, large heterogeneity existed between the results of individual studies, statins are still not a common treatment regimen for patients with CRC.

Blocking utilization of lipids Sphingomyelin and CHO act as bioactive signaling molecules, hence, inhibition of signaling pathways by interfering with metabolism and supply, it is considered an efficient approach for suppression of cancer growth and metastasis [25]. Fatty acid oxidation (FAO) confers energy to supply life activities, which is important to cancer cells. Therefore, inhibition of FAO may reduce the risk of tumorigenesis [26]. However, in certain settings increase of FAO facilitates hydrolysis, thus decrease the level of FAs in cancer cells for tumor-suppressive effect.

Blocking formation and hydrolysis of lipid droplets Lipid droplets (LDs) are cytoplasmic lipid storage organelles. LDs overexpress in CRC relative to normal tissues, which may be closely linked to the progression of CRC [27]. Moreover, excess LDs also leads to the resistance of some antitumor agents [28, 29].

LDs are hydrolyzed by several lipases such as adipocyte triglyceride lipase (ATGL), hormone-sensitive lipase (HSL) and monoacylglycerol lipase (MAGL), leading to the production of free fatty acids. Interestingly, despite many studies on these tumor-associated lipolytic enzymes, the previous conclusions didn’t seem to be consistent. ATGL and Abhd5 (activation of ATGL) have been proved to inhibit colorectal carcinogenesis and progression [30]. MAGL was highly expressed in high invasive tumor cells [31], and JZL184, a MAGL inhibition, inhibited colon cancer cell proliferation through epithelial-mesenchymal transition and enhanced the chemosensitivity of cancer cells to 5-fluorouracil [32]. Additionally, autophagy plays a great role in regulating lipid homeostasis, which may induce the neoplastic type and development [33] in CRC.

Challenges and limitations of lipid-regulating therapy There have already been some cancer therapeutic targets in the area of lipid-modulating therapy, yet, the development of which does not seem substantial. Moreover, there are many limitations to the previous studies [26]. On the one hand, it is very difficult to selectively inhibit the lipid metabolism of tumor cells. FASN is not only highly expressed in tumor cells, but also necessary for the normal proliferation of neural stem cells and progenitor cells [34]. Due to this, the blinded lipid-regulating may cause the disorder of whole metabolic. On the other hand, the lipid acquisition of tumor cells is flexible and complex, when a pathway is inhibited, or transmitted into the other one rapidly with poor stability. The studies of lipid metabolism in cancer need to be carried out under the condition of tumor microenvironment without the utilization of exogenous lipids, which limited the development of pharmaceutical researches [35].

TCM COMMENTS

CRC was widely and profoundly understood in TCM over the last thousands of years. The etiology, pathogenesis and therapy of CRC have been recorded in many famous works of TCM. Ancient doctors have realized that unclean and overfeeding diets were the root cause of CRC, with the main pathogenesis of spleen deficiency, involved blood stasis and turbidity (It means the pathological characteristics of CRC in TCM.)

Hyperlipidemias is the most common dyslipidemia, similarly compared with CRC in TCM. Both of pathogenesis are complicated, involving a disease argued deficiency in origin and excess in superficiality (Bexu Biaoshi in TCM, the phrase “excess in superficiality” is used to describe dampness-heat and static toxicity in the
body, and the phrase “deficiency in origin” is used to describe the dysfunction of Qi, Xue, Yin and Yang. Therefore, the theory of “motivating yang of spleen and removing blood stasis and turbid” (It means improving immune and digestive function as well as regulating the level of serum lipid.) may be an important direction in the treatment of them.

**PROSPECTS OF TCM THERAPY**

The deficient metabolism of glucose and lipid is induced by more caloric intake, and excessive caloric intake causes fatty liver. Excess fat in the liver can secrete adiponectin and inflammatory cytokines, which promoted vicious cycles of lipotoxicity. We have worked together toward fatty liver and alcoholic fatty liver disease (AFLD), and developed the TCM empirical formula Yigan Jiangzhi Formula (liver-supplementing lipid-lowering formula, YGJZF) based on the nuclear TCM pathogenesis, consist of 6 TCM ingredients, with the effects of antioxidation, lipid-lowering, liver protection and prevents CRC liver metastases in mice [36]. Also, this theory was followed and applied in previous clinical practice with optimistic therapeutic effect, which proved the validity of TCM lipid-regulating in antitumor therapy.

Additional, numerous effective chemical components targeted to CRC by the lipid pathway in herbs have been identified by modern pharmacological studies on TCM. Luteolin [37] might suppress the proliferation of CRC by targeting lipid peroxidation. Previous studies have reported that emodin and lucid extract achieve anti-tumor effects by inhibiting the activation of SREBPs [38, 39].

Overall, lipid metabolism is closely related to colorectal carcinogenesis and development, which emerges as a potential therapeutic target gradually by regulating abnormal signaling pathways, enzymes and metabolites. To date, the basis of lipid metabolism is poorly understood, the most of the researches are still at the preclinical stage, making it difficult to assess the clinical value. The theory of “motivating yang of spleen and removing blood stasis and turbid” may be an important direction in the treatment of CRC in TCM. So far, higher-quality researches are required to verify its efficacy. Clinicians should promote a healthier diet, physical activity, and lifestyle habits, and focus on the blood lipid levels following TCM and dynamic variation rules. We aim to fully play the role of TCM to prevent disease progression, targeting complex etiopathogenesis and insufficient medication of CRC.

**ACKNOWLEDGMENT**

The authors did not receive any funding for this study.

**Abbreviations:** CRC, colorectal cancer; TCM, traditional Chinese medicine; TNF α, tumor necrosis factor α; IL, interleukin; FFA, free fatty acid; HDL, high-density lipoprotein; TC, triglyceride; T-CHO, total cholesterol; FASN, fatty acid synthase; ACS, acetyl-CoA synthetase; ACLY, ATP citrate lyase; ACSL, fatty acid CoA ligase; ACC, acetyl CoA carboxylase; SREBP1c, sterol regulatory element binding proteins; LXR, liver X-activated receptor; SCD, stearoyl-CoA desaturase; FAs, fatty acids; BetA, betulinic acid; MVA, mevalonate; HMGCR, 3 Hydroxy-3-Methylglutaryl-CoA Reductase; LDs, lipid droplets; ATGL, adipocyte triglyceride lipase; HSL, hormone-sensitive lipase; MAGL, monoacylglycerol lipase; AFLD, alcoholic fatty liver disease; YGJZF, Yigan Jiangzhi Formula.

**Competing interests:** The authors declare that they have no conflict of interest.

**Citation:** Niu QQ, Zhao YH. Therapeutic strategy in colorectal cancer based on Traditional Chinese and Western Medicine: from the lipid metabolism perspective. Drug Combination Therapy. 2021;3(4):16. doi: 10.53388/DCT2021110501.

**Executive editor:** Jin-Feng Liu.

**Submitted:** 22 June 2021, **Accepted:** 13 October 2021, **Online:** 18 October 2021

© 2021 By Authors. Published by TMR Publishing Group Limited. This is an open access article under the CC-BY license (http://creativecommons.org/licenses/BY/4.0/)

**REFERENCES**

[1] M. Arnold, M. S. Sierra, M. Laversonne, I. Soerjomataram, A. Jemal, and F. Bray. “Global patterns and trends in colorectal cancer incidence and mortality,” *Gut*, vol. 66, no. 4, pp. 683–691, 2017.

[2] J. D. Horton, J. L. Goldstein, and M. S. Brown, “SREBP: activators of the complete program of cholesterol and fatty acid synthesis in the liver,” *The Journal of clinical investigation*, vol. 109, no. 9, pp. 1125–1131, 2002.

[3] K. Ishino, M. Mutoh, Y. Totsuka, and H. Nakagama, “Metabolic syndrome: a novel high-risk state for colorectal cancer,” *Cancer letters*, vol. 334, no. 1, pp. 56–61, 2013.

[4] E. Currie, A. Schulze, R. Zechner, T. C. Walther, and R. V. Fares Jr., “Cellular fatty acid metabolism and cancer,” *Cell metabolism*, vol. 18, no. 2, pp. 153–161, 2013.

[5] A. Pakiet, J. Kobiela, P. Stepnowski, T. Sledzinski, and A. Mika, “Changes in lipids composition and metabolism in colorectal cancer: a review,” *Lipids in health and disease*, vol. 18, no. 1, pp. 29, 2019.

[6] L. Kern, M. J. Mittenbü hler, A. J. Vesting, A. L. Ostermann, C. M. Wunderlich, and F. T. Wunderlich, “Obesity-Induced TNFα and IL-6 Signaling: The Missing Link between Obesity and Inflammation-Driven Liver and Colorectal Cancers,” *Cancers*, vol. 11, no. 1, pp. 24, 2018.

[7] K. M. Nieman, I. L. Romero, B. Van Houten, and E. Lengyel, “Adipose tissue and adipocytes support tumorigenesis and metastasis,” *Biochimica et biophysica acta*, vol. 1831, no. 10, pp. 1533–1541, 2013.

[8] I. S. Senatorov, and N. H. Moniri, “The role of free-fatty acid receptor-4 (FFA4) in human cancers and cancer cell lines,” *Biochemical pharmacology*, vol. 150, pp. 170–180, 2018.

[9] F. J. van Duijnhoven, H. B. Bueno-De-Mesquita, M. Culligaro, M. Jenab, T. Pischon, and E. H. Jansen, et al., “Blood lipid and lipoprotein concentrations and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition,” *Gut*, vol. 60, no. 8, pp. 1094–1102, 2011.

[10] H. Rodriguez-Broadbent, P. J. Law, A. Sud, K. Palin, S. Tuapanen, and A. Gyllé, et al. “Mendelian randomisation implicates hyperlipidaemia as a risk factor for colorectal cancer,” *International journal of cancer*, vol. 140, no. 12, pp. 2701–2708, 2017.

[11] M. H. Yang, S. Rampal, J. Sung, Y. H. Choi, H. J. Son, H. J. Lee, et al. “The association of serum lipids with colorectal adenomas,” *The American journal of gastroenterology*, vol. 108, no. 5, pp. 833–841, 2013.

[12] A. P. Simopoulos, “The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases,” *Experimental biology and medicine*, vol. 233, no. 6, pp. 674–688, 2008.

[13] N. B. Kuenmerle, E. Rysman, P. S. Lombardo, A. J. Flanagan, B. C. Lipe, and W. A. Wells, et al. “Lipoprotein lipase links dietary fat to solid tumor cell proliferation,” *Molecular cancer therapeutic*, vol. 10, no.32, pp. 427–436, 2011.

[14] N. Koundouros, and G. Poulogiannis, “Reprogramming of fatty acid metabolism in cancer,” *British journal of cancer*, vol. 122, no. 1, pp. 4–22, 2020.

[15] Y. Y. Zaytseva, P. G. Ryachahou, A. T. Le, T. L. Scott, R. M. Flight, and J. T. Kim, et al. “Preclinical evaluation of novel fatty acid synthase inhibitors in primary colorectal cancer cells and a patient-
derived xenograft model of colorectal cancer,” Oncotarget, vol. 9, no. 37, pp. 24787–24800, 2018.

[16] N. E. Sounni, J. Cicmio, S. Blacher, I. Primac, A. Truong, and G. Mazzucchelli, et al. “Blocking lipid synthesis overcomes tumor regrowth and metastasis after antiangiogenic therapy withdrawal,” Cell metabolism, vol. 20, no. 2, pp. 280–294, 2014.

[17] G. E. Mullen, and L. Yet, “Progress in the development of fatty acid synthase inhibitors as anticancer targets,” Bioorganic & medicinal chemistry letters, vol. 25, no. 20, pp. 4363–4369, 2015.

[18] C. A. Flaveny, K. Griffett, B. El-Gendy, M. Kazantizis, M. Sengupta, and A. L. Amelio, et al. “Broad Anti-tumor Activity of a Small Molecule that Selectively Targets the Warburg Effect and Lipogenesis,” Cancer cell, vol. 28, no. 1, pp. 42–56, 2015.

[19] T. Vargas, J. Moreno-Rubio, J. Herranz, P. Cajas, S. Molina, and M. González-Vallinas, et al. “ColoLipidGene: signature of lipid metabolism-related genes to predict prognosis in stage-II colon cancer patients,” Oncotarget, vol. 6, no. 9, pp. 7348–7363, 2015.

[20] L. Potze, S. di Franco, J. H. Kessler, G. Stasi, and J. P. Medema, “Butenin Acid Kills Colon Cancer Stem Cells,” Current stem cell research & therapy, vol. 11, no. 5, pp. 427–433, 2016.

[21] J. W. Clendening, and L. Z. Penn, “Targeting tumor cell metabolism with statins,” Oncogene, vol. 31, no. 48, pp. 4967–4978, 2012.

[22] R. Gao, Z. Wang, H. Li, Z. Cao, Z. Gao, and H. Chen, et al. “Gut microbiota dysbiosis signature is associated with the colorectal carcinogenesis sequence and improves the diagnosis of colorectal lesions,” Journal of gastroenterology and hepatology, vol. 35, no. 12, pp. 2109–2121, 2020.

[23] S. Vieira-Silva, G. Falony, E. Belda, T. Nielsen, J. Aron-Wisnewsky, and R. Chakaroun, et al. “Statin therapy is associated with lower prevalence of gut microbiota dysbiosis,” Nature, vol. 581, no. 7808, pp. 310–315, 2020.

[24] Y. Li, X. He, Y. Ding, H. Chen, and L. Sun, “Statin uses and mortality in colorectal cancer patients: An updated systematic review and meta-analysis,” Cancer medicine, vol. 8, no. 6, pp. 3305–3313, 2019.

[25] Q. Liu, Q. Luo, A. Halim, and G. Song, “Targeting lipid metabolism of cancer cells: A promising therapeutic strategy for cancer,” Cancer letters, vol. 401, pp. 39–45, 2017.

[26] F. Röhrig, and A. Schulze, “The multifaceted roles of fatty acid synthesis in cancer,” Nature reviews. Cancer, vol. 16, no. 11, pp. 732–749, 2016.

[27] S. Koizume, and Y. Miyagi, “Lipid Droplets: A Key Cellular Organelle Associated with Cancer Cell Survival under Normoxia and Hypoxia,” International journal of molecular sciences, vol. 17, no. 9, pp. 1430, 2016.

[28] S. Rak, T. De Zan, J. Stefuèj, M. Kosoviè, O. Gamulin, and M. Osnak, “FTIR spectroscopy reveals lipid droplets in drug resistant laryngeal carcinoma cells through detection of increased ester vibrational bands intensity,” The Analyst, vol. 139, no. 13, pp. 3407–3415, 2014.

[29] H. K. Yosef, L. Mavarani, A. Maghnouj, S. Hahn, S. F. El-Mashtoly, and K. Gerwert, “In vitro prediction of the efficacy of molecularly targeted cancer therapy by Raman spectral imaging,” Analytical and bioanalytical chemistry, vol. 407, no. 27, pp. 8321–8331, 2015.

[30] J. Ou, H. Miao, Y. Ma, F. Guo, J. Deng, and X. Wei, et al. “Loss of Ahh2 Promotes Colorectal Tumor Development and Progression by Inducing Aerobic Glycolysis and Epithelial-Mesenchymal Transition,” Cell reports, vol. 24, no. 10, pp. 2795–2797, 2018.

[31] D. K. Nomura, J. Z. Long, S. Niessen, H. S. Hoover, S. W. Ng, and B. F. Cravatt, “Monounsaturated Fatty Acid Lipidomics Reveals Increased Lipid Peroxidation in Human Colon Cancer,” Cell, vol. 140, no. 1, pp. 49–61, 2010.

[32] M. Ma, J. Bai, Y. Ling, W. Chang, G. Xie, and R. Li, et al. “Monounsaturated Fatty Acid Lipidomics Reveals Increased Lipid Peroxidation in Human Colon Cancer,” Cell, vol. 140, no. 1, pp. 49–61, 2010.

[33] M. Amao, J. H. T. Peters, M. Dutta, and A. D. Patterson, “Lipid metabolism and lipophagy in cancer,” Biochemical and biophysical research communications, vol. 504, no. 3, pp. 582–589, 2018.

[34] M. Knobloch, S. M. Braun, L. Zurkirchen, C. von Schoultz, N. Zamboni, and M. J. Araújo-Bravo, et al. “Lipid metabolism and lipophagy in cancer,” Biochemical and biophysical research communications, vol. 504, no. 3, pp. 582–589, 2018.

[35] S. Ros, C. R. Santos, S. Moco, F. Baenke, G. Kelly, and M. Howell, et al. “Functional metabolic screen identifies 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4 as an important regulator of prostate cancer cell survival,” Cancer discovery, vol. 2, no. 4, pp. 328–343, 2012.

[36] Y. H. Zhao, Q. Q. Niu, Q. Z. Li, J. H. Yin, Y. Lu, and Z. Li, “The inhibitory effects of Yigang Jiangzi formula on hepatic metastasis of colorectal cancer,” TMR Integrative Medicine, vol. 4, pp. e20009, 2020.