Betatrophin and Lipid Metabolism Disorder in Colorectal Carcinoma Onset Metabolic Syndrome

Hendra Susanto[1], Ahmad Taufiq[2], Dwi Listyorini[1], Adeodatus Yuda Handaya[3,4], Nia Lukita Ariani[5]

1) Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Negeri Malang, Indonesia
2) Department of Physics, Faculty of Mathematics and Natural Sciences, Universitas Negeri Malang, Indonesia
3) Department of Digestive Surgery, Dr. Sardjito Hospital, Yogyakarta, Indonesia
4) Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta Indonesia
5) Faculty of Health Sciences, Universitas Tribhuwana Tunggadewi, Malang, Indonesia

Abstract

Metabolic syndrome is the global health problem worldwide and significantly associated with lipid metabolism disorder resulted in glucose intolerance and obesity leading to cancer incidence. Long-standing glucose intolerance is recognized as a crucial event in the process of cancer development. Recently, betatrophin, a novel liver-derived hormone, promotes β-cell proliferation and improves glucose intolerance. Betatrophin is a newly identified liver-derived hormone that is associated with glucose homeostasis and lipid metabolism. In the recent clinical exploration, metabolomics is a robust, high-throughput approach to identifying metabolic signatures that are associated with disease development. The detailed assessment of biochemical pathways and novel metabolic intermediates may provide valuable new insights into the mechanisms of tumorigenesis with additional broader implications for other malignancies. However, the interconnection between metabolites alteration and betatrophin in the pathogenesis of colorectal carcinoma (CRC) onset metabolic syndrome (MS) is not fully understood. In our previous study, we found that statistically significant associations between plasma acylcarnitine and amino acid alteration with colorectal cancer risk in patients with onset MS ($p< 0.05$). These findings provide preliminary evidence that there are significant differences in levels of a specific metabolite in colorectal cancer subject onset MS compared to healthy control. We suggest that betatrophin may be suggestive of novel prognostic biomarkers in colorectal cancer associated metabolic syndrome. However, to verify and characterize the observed associations between these metabolites, betatrophin, and colorectal cancer development, an excellent evaluation is necessary with detailed profiling of metabolites to provide multiple comparisons and established colorectal carcinoma risk factors in subjects onset MS.

Keywords: Betatrophin, lipid metabolism disorder, metabolic syndrome, colorectal carcinoma

1. Colon Cancer Prevalence, Etiology, Pathogenesis, and Clinical Prognosis

Colorectal cancer (CRC) is categorized as the most common cancer with a higher mortality rate worldwide, the third rank of cancer cause death in patients, and poor prognosis in the early stages of clinical studies (Brenner, Kloor, & Pox, 2014; Welch & Robertson, 2016). The prevalence of colorectal cancer is half million cases per year and increased significantly in the more elderly population (Davies, Miller, & Coleman, 2005). Globally, it was reported that the incidence of CRC about 900,000 cases per year and become the most common cancer in men than in women (Rustgi, 2007). The rapid increased of colon cancer incidence was reported in East Asia due to change of dietary patterns in the majority of the population (Brenner et al., 2014). Importantly, a diet rich in unsaturated fats and red meat, total energy intake and excessive food/caloric intake (BMI > 30), race and ethnicity, abuse alcohol consumption, and reduced physical activity are the most significant dietary and lifestyle risk factors for colorectal cancer (Fearon, 2011; Strum, 2016). Even though the mortality rate of colorectal cancer tends to decrease in the higher income countries, in contrary the rate of mortality caused by colorectal cancer is still higher in areas with inadequate health care resources (rural areas) of individual countries in Asia (Brenner et al., 2014). According to the GLOBOCAN online database, it was predicted in 2015; there are 61, 228 new colorectal cancer cases in Asia. The increasing of colon cancer mortality incidence was associated with poor prognosis and lack of information in the early stages of cancer development. Indeed, although the prognosis and clinical management of patients with colon cancer were steadily increasing in developed countries, however, there is a significant problem remained. Almost less than 50% of colon cancer patients in the lower income countries is uncovered by a reliable prognostic on a clinic. It has correlated to the decreasing survival rate in these populations during the past decades. Decreased patient survival number was associated with age and gender, in which the susceptibility to cancer progression in the male is higher than female (Brenner et al., 2014).

In the pathogenesis of colorectal cancer, it was initiated by a benign adenomatous polyp that progress to an advanced adenoma with high-grade dysplasia. As the final stages, an advanced adenoma will develop into invasive cancer. The typical molecular involvement of some essential genes and growth factors in the pathogenesis of colorectal cancer is shown in **Figure 1.** Genomic instability induced a higher prevalence of chromosomal instability, which causes numerous changes in chromosomal copy number and structure. As the results, the physical loss of a wild-type copy of a tumor-suppressor gene, such as APC, TP53, and SMAD family member 4 (SMAD4) will direct to the malignant phenotype (Markowitz & Bertagnolli, 2009).

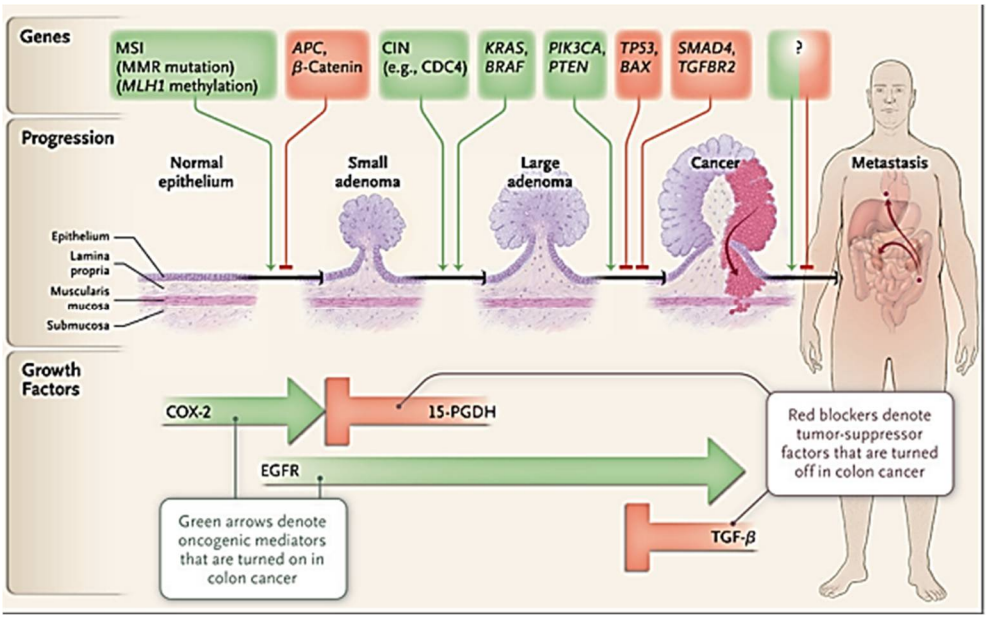

Figure 1. Genes and growth factor involved in the progression of colorectal cancer (Markowitz, S.D. and Bertagnolli, M.M., N Engl J Med, 2009)

The accumulation of both acquired genetic and epigenetic changes was observed enhance the transformation of normal glandular epithelium into invasive adenocarcinoma. Colorectal carcinoma can classify into several categories/groups depend on the type of genomic instability, such as aneuploidy and chromosomal gains and losses associated with microsatellite instability (MSI), dysplastic aberrant crypt foci in adenomatous polyposis coli (*APC*) gene (the central suppressor gene in colorectal cancer) (Rustgi, 2007), and mutation in other genes of the Wnt signaling pathway (*KRAS* or *TP53*). As the results, almost 30% of CRCs cases caused by TGFβ1 signaling activation due to *KRAS* and *TP53* genes mutation (Lao & Grady, 2011; Walther et al., 2009). Several studies have shown that *KRAS* mutation in exon two codons 12 significantly associated with the early event of CRC (one-third of CRC cases) and become the priority target of CRC combine therapy with EGFR inhibitor. Almost 99% of CRC patients with KRAS mutation are resistance to EGFR inhibition (Walther et al., 2009). The involvement of APC and β-catenin in colorectal cancer pathogenesis is strongly associated with the Wnt signaling pathway and induced cell cycle alteration. Also, the potential role of *TP53* gene mutation in CRC pathogenesis offered an alternative genetic target for CRC therapy. TP53 was addressed as a prognostic factor and predictor of response to treatment. However, some discrepancies are still unsolved which is the genetically changes/mutation of APC related β-catenin and TP53 insufficiently validated in clinical management (Walther et al., 2009).

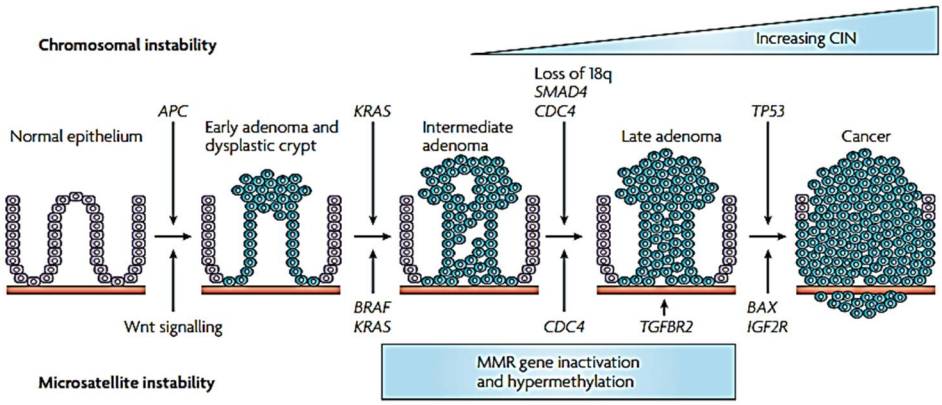

Figure 2. The general pathogenesis scheme of adenoma-carcinoma in CRCs (Walter et al. Nat Rev Cancer, 2009)

Colon cancer is a clinically various disease with empirical genetic heterogeneity result in difficulty to determine a useful adjuvant therapy for patients (Felipe De Sousa et al., 2013). Indeed, the global problem of colorectal cancer prognosis is the sensitivity and specificity of some prognostic factors to detect the early stages of this cancer in patients. In clinical prognosis process for colorectal cancer, screening management was divided into two main categories: stool tests (occult blood and exfoliated DNA tests) and structural examinations (flexible sigmoidoscopy, colonoscopy, and computed tomographic colonography). Stool tests were considered to detect cancer, and structural analyses were used to detect cancer and premalignant lesions (Quintero et al., 2012; Strum, 2016). In the recent clinical trial study, it was reported that flexible sigmoidoscopy was significantly correlated with decreased colorectal incidence and mortality in patients (Schoen et al., 2012). In addition, it was claimed that removal of low-risk adenomas by resection method reduces the risk of death from colorectal cancer over a period of 8 years to a level below the risk in the general population (Loberg et al., 2014). Even though several previous studies was proposed some prognostic methods, however, it is not yet clear whether screening should target early cancers or pre-malignant adenomas, and the stable clinical protocol based on serological screening is not entirely determined. Furthermore, there is an opportunity to use serological metabolites as a potential alternative biomarker to detect the early stages of colorectal cancer (CRC). Thus, the exploration of a novel serological biomarker for colorectal cancer is primarily required to improve the quality of life in CRC patients.

2. Metabolic Syndrome and Colorectal Cancer Development

Metabolic syndrome probably can be considered as a surrogate marker for other cancer risk factors due to lack of physical activity, change of daily intake by high-calorie consumption, high fat intake, decrease fiber diet, and increase oxidative stress. Visceral obesity and chronic

systemic inflammation caused by adipose tissue dysfunction will create a pro-tumorigenic environment of a cancer stem cell. The alteration of pro- and anti-inflammatory cytokine expression due to the excess fat amount in the visceral site will trigger insulin resistance as a core component of the metabolic syndrome associated with obesity. Obesity as the leading cause of metabolic syndrome is also known involved in the pathogenesis of specific cancer. Previous studies have shown that 14% of cancer deaths in men and 20% in women could be attributed to obesity, and excess weight also has been considered associated with specific cancer due to dyslipidemia (Cohen & LeRoith, 2012; Nguyen, Nguyen, Lane, & Wang, 2011). Furthermore, almost one-third of the 571,950 cancer death cases in the US until 2011 was related to overweight-obesity and physical inactivity. Also, higher rates of cancer-related mortality have been seen in patients with T2DM.

Recent finding improved that T2DM may be an independent risk factor for cancer and cancer-related mortality. T2DM and obesity have been associated with many different cancers and an increased risk of cancer, such as esophagus, pancreas, colon, gallbladder, endometrial, and rectum; non-Hodgkin's lymphoma; and multiple myeloma in women with elevated BMI. A higher risk of cancers of the liver, pancreas, colon and rectum, kidney, bladder, endometrial, biliary tract cancer, and breast and non-Hodgkin's lymphoma in individuals with diabetes compared with those without diabetes (Cohen & LeRoith, 2012). Epidemiologic data during the last decade showed that the risk of colon cancer increased in those individuals with metabolic syndrome. Metabolic syndrome plasma markers (hypertriglyceridemia, hyperglycemia, low serum HDL cholesterol, hyperinsulinemia, and C-peptide) are considered associated with the development of colorectal cancer. In both sexes, metabolic syndrome was at significantly elevated risk of colon cancer (Giovannucci, 2007). Dietary fat was observed associated with colorectal cancer risk through its involvement in insulin resistance (Lin, Zhang, Cook, Lee, & Buring, 2004). The alteration of hormone homeostasis, for instance, the signaling of insulin, the insulin-like growth factor system, and steroid sex hormones are correlated with cancer incidence. Increased adipose tissue amount within the human body is directly associated with higher levels of inflammation and an increase in oxidative stress. A large population-based study was found that subjects with hyperlipidemia, diabetes, and hypertension are related to hormonal disturbances. Hormonal imbalance during diabetic progression is correlated with cancer development through a specific signaling pathway. For example, increased insulin and IGF-1 or leptin/adiponectin secretion, immune abnormalities including elevated circulating pro-inflammatory cytokines and metabolic alterations are known to stimulate cancer-associate T2DM and metabolic syndrome (Coller, 2014).

An excess of nutrient demand and altered metabolic by-products of cancer cells will trigger a change of their environment, inducing metabolic and secretory adaptations in adjacent non-cancer cells such as fibroblasts, adipocytes, and macrophages. Obesity and hyper nutrition are linearly correlated to a systemic increase in NEFA, glucose, insulin, leptin, and inflammatory cytokine. As a result, it will influence the whole organism homeostasis or metabolic imbalances that directly promote cancer cell survival, proliferation, and malignant progression (Font-Burgada, Sun, & Karin, 2016). Another cohort study showed that metabolic

syndrome in men associated with liver cancer, colorectal cancer, and bladder cancer. On the other hand, the presence of metabolic syndrome in women was linked to endometrial cancer, pancreatic cancer, breast cancer, rectal cancer, and colon cancer. Metabolic syndrome is stronger related to colorectal cancer in women of the European population (Esposito, Chiodini, Colao, Lenzi, & Giugliano, 2012).

The alteration of adipose tissue function, liver and muscle tissues, leading to cachexia, a metabolic syndrome featuring typical diabetic features and responsible for 20% of cancer deaths (Argiles, Busquets, Stemmler, & Lopez-Soriano, 2014). Moreover, glucose intolerance and insulin resistance have been reported significantly correlate to cancer cachexia, while there is incomplete explanation whether insulin resistance plays a pivotal role in the development of cachexia in patients with cancer. Interestingly, in vivo study was shown that cachectic mice induced by colon-26 tumor progress to insulin resistance (Asp, Tian, Wendel, & Belury, 2010). The higher incidence of colon adenoma and advanced adenoma was observed in T2D subjects associated with endogenous hyperinsulinemia and higher levels of insulin growth factor-1 (IGF-1) (Jain, Chhoda, & Uribe, 2016). T2D has been proposed as a risk factor for colorectal cancer and strongly associated with obesity. Patients with T2D who suffered from obesity for more than four years duration will more susceptible develop to colorectal cancer than healthy control (Peeters, Bazelier, Leufkens, de Vries, & De Bruin, 2015). It is hypothesized that glucose intolerance, hyperinsulinemia linked insulin resistance and diabetes is the potential inducer of colon cancer in patients with metabolic syndrome. However, there is no information on how metabolic perturbation in colorectal patients with glucose intolerance and insulin resistance associated with a particular hormone that regulates glucose metabolism and homeostasis.

3. Metabolomics, Cancer Development, and Clinical Prognosis

Nowadays, several non-invasive detection/prognosis method of CRC are being developed mainly based on stool samples, including stool DNA (sDNA) and microRNA (miRNA) testing (Zhu et al., 2014). However, importantly, cancer is characterized by abnormal metabolism due to the alteration of metabolite levels from some critical metabolic pathways. It has been considered as the essential focus of prognosis development in cancer. The change of metabolite levels results in rapid progress in disease biomarker discovery. Metabolomics is a new field in medicine concentrate on examining and analyzing metabolites. Metabolomics, the comprehensive study of small- molecular- weight metabolites and their dynamic changes in biological systems. The development of clinical prognosis approach was initiated to used metabolomics model to elucidate specific biomarkers of disease (Deng et al., 2016; Zhu et al., 2014). Metabolomics was addressed to improve clinical therapy efficacy and outcomes and can be used to explore and identify the potential biomarkers associated with cancer and to get the better understanding of anticancer therapies development (Armitage & Southam, 2016). In the metabolomics approach, it was established that biological fluids primarily used in this procedure, including plasma, cerebrospinal fluid, saliva, and urine. The most common methods of evaluating the composition involve nuclear magnetic resonance (NMR) and

magnetic resonance (MR) with the addition of gas chromatography (GC-MS) or liquid chromatography (LC-MS). The combination approach of metabolomics methods was better than using single NMR or LC-MS and improved predictive accuracy in all the pairwise comparisons among CRC, polyps, and healthy controls (Deng et al., 2016; Hirayama et al., 2009).

Metabolomics is also widely applied in common metabolic diseases, in particular, glucose intolerance associated with diabetes development. The measurement of metabolites levels is provided promising chances for a successful prognosis, diagnosis, and comprehensive monitoring of the progression of disease particularly in cancer development (Holmes, Wijeyesekera, Taylor-Robinson, & Nicholson, 2015). The development of metabolomics will also contribute to the individualization of treatment, proper drugs adjustment, which will make therapy more successful, cause fewer side effects, and improve the quality of patients life (Denkert et al., 2008; A. Zhang et al., 2014). The variability of biochemical processes in tumor cells in comparison to healthy cells is the starting point for metabolomics studies. Indeed, the metabolic changes are observed not only in solid tumors but also in surrounding tissues. Recently, the further research aims to find biomarkers which would help to diagnose a disease quickly, assess its progression, and implement effective treatment. Several clinical investigations have been made to identify the potential prognostic factor by using a metabolomics approach. Metabolomics is capable of characterizing individuals by disease state (early stages) and close to a molecular representation of tumor phenotype (Farshidfar et al., 2016; Goedert et al., 2014). However, all of those studies lack a considerable validation, and there have been few attempts at exploring potential clinical applications. Furthermore, there is still limited information whether metabolic changes in colorectal cancer are associated with liver-specific metabolite that potentially involved in systemic regulation.

4. The Role of Acylcarnitine and Amino Acid Alteration in Metabolic Disorder and Cancer Pathogenesis

In the metabolomics study of colorectal cancer, liquid chromatography-mass spectrometry (LC-MS) and nuclear magnetic resonance (NMR) is suitable for the large-scale measurement of metabolite levels in tumor and normal tissues. Importantly, it provides not only direct data on energy metabolism but also the potential reciprocal relationship between metabolic networks and the underlying mechanisms of carcinogenesis. Colorectal cancers (CRC) are significantly correlated to perturbations in cellular amino acids, nucleotides, pentose-phosphate pathway carbohydrates, and glycolytic, gluconeogenesis, and tricarboxylic acid intermediates (Hirayama et al., 2009). Interestingly, colon cancer stem cells showed higher lipid droplet (LD) amount than their differentiated counterparts, and LD-rich cancer cells are more resistant to chemotherapy (Beloribi-Djefaflia, Vasseur, & Guillaumond, 2016). In clinical trial finding, metabolomics data was proved that paired human visceral adipose visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) significantly associated with CRC tumor stages. The inflammation markers of VAT strongly correlate to CRC progression (Liesenfeld et al., 2015). Moreover, fatty acid synthesis and oxidation has been observed play

a significant role in cancer progression through provide nutrients and energy during metastasis. It is well established that systemic mobilization of lipids from adipose tissue fuels tumor growth during cancer-associated cachexia (Röhrig & Schulze, 2016). The clinical observation was claimed that change of carnitine and amino acids levels related to cancer development. Carnitine is a potent antioxidant and anticancer agent. Carnitine (3-hydroxy-4-*N*-trimethylaminobutyric acid) is an essential cofactor to produce energy resulting from lipid metabolism. It is related to the crucial function of carnitine during β-oxidation of fatty acids through facilitating transport of long-chain fatty acids across the mitochondrial inner membrane as acylcarnitine esters and modulating intracellular CoA homeostasis. Moreover, acylcarnitine belong to the core markers of mitochondrial function related to the beta-oxidation of fatty acids. Acylcarnitines (AcylCNs) are synthesized by carnitine palmitoyltransferase 1 (CPT 1), and incomplete fatty acid oxidation results in elevated acylcarnitine concentrations (Mai et al., 2013).

The previous study was mentioned that the combination of butyrate and carnitine has beneficial effects on colon cancer prevention in vitro by inducing colon cancer cell apoptosis through downregulating anti-apoptotic and up-regulating pro-apoptotic genes (Dionne et al., 2012). By contrast, the increasing of acylcarnitine levels has been reported clinical prognostic factors in specific cancer-related metabolic disorder. Alterations in serum levels of several acylcarnitines [tetradecenoylcarnitine (C14:1), tetradecadienylcarnitine (C14:2), octadecenoyl-carnitine (C18:1) and malonylcarnitine/hydroxybutyrylcarnitine (C3DC+ C4OH)] are significantly associated not only with T2DM but also with pre-diabetic states (Mai et al., 2013). Furthermore, plasma acylcarnitine (AcylCN) and branched-chain amino acid have been utilized as biomarkers for insulin resistance and in particular to identify metabolic imbalances in fatty acid oxidation and amino acid catabolism. The increasing of acylcarnitine linear to age and insulin sensitivity in the more elderly population (Consitt et al., 2016), while plasma long-chain acylcarnitine concentrations (C16, C18:1, C18) in obese/T2D were elevated after hyperinsulinemic conditions compared to lean controls (Mihalik et al., 2010). Also, long-chain AcylCNs is the current marker for insulin sensitivity and inflammation caused by metabolic syndrome (McCoin, Knotts, & Adams, 2015). The accumulation of acylcarnitines has represented an inability to convert to carbohydrate substrate and a depletion of TCA intermediates, suggesting that imbalance between fatty acid oxidation (FAO) flux and tricarboxylic acid cycle (TCA) flux, leading to incomplete fatty acid oxidation and insulin resistance (Schooneman, Vaz, Houten, & Soeters, 2013). Despite plasma acylcarnitine metabolomics exploration, several previous studies have been done to propose amino acid as additional metabolic prognostic factors for cancer stages. Physiological amino acid concentrations depend on the organs functions, and pathological conditions can change their metabolism. In the pathogenesis of cancer, it was established that cancer cells need more amino acids to synthesize nucleic acids and proteins implicate to increased metabolism (Simińska & Koba, 2016). Therefore, the alteration of the amino acid profile (Glycine and Tyrosine) was significantly correlated with colon cancer seem like a promising diagnostic power for clinical diagnosis (Leichtle et al., 2012). Interestingly, some of the amino acid levels were decreased in the early stages of colorectal cancer (Leichtle et al., 2012; Simińska & Koba,

2016), while there is limited information whether the reduction of the amino acid level occurred in the late stages of this cancer development. Also, based on metabolomics approach, it was proved that the levels of branched-chain amino acids and medium acylcarnitine are changed in muscle from insulin-resistant individuals. It is suggested that fatty acid metabolism is impaired in those subjects and seemed to be dependent on variations in the flux of metabolites via the BCAA oxidation pathway (Geach, 2016). The dysmetabolism of branched-chain amino acids (BCAA) provides a new hypothesis in which the accumulation of metabolites (BCAAs and non BCAAs) promotes β-cell mitochondrial dysfunction, stress signaling, and apoptosis associated with T2D (Lynch & Adams, 2014). However, although some previous studies have been done to explore the metabolites profile of plasma acylcarnitine and amino acid in particular cancer, there is lack information whether the alteration of both of these biomarker levels is associated with colorectal cancer progression caused by onset metabolic syndrome, particularly in a subject with glucose intolerance. Thus, metabolomics approach as the early diagnostic method for this cancer and early relapse monitoring after initial therapy is probably the best available options to improve patient survival.

5. Betatrophin, Metabolic Syndrome, and Cancer Development

Betatrophin is a novel recognized liver-derived hormone that has been implicated in both glucose and lipid metabolism (Chen et al., 2014; Wang et al., 2013; Yamada et al., 2015). Betatrophin is 22 kDa liver protein hormone consist of N-terminal secretion and lack of C-terminal fibrinogen-like domain. Betatrophin can control lipoprotein lipase (LPL) activity in the lipid metabolism. A recent study has pointed out that mice treated S961 caused insulin resistance resulting in β-cell proliferation via overexpressing betatrophin (Yi, Park, & Melton, 2013). Moreover, the serum level of betatrophin is positively associated with type 1 Diabetes mellitus (T1DM) and T2DM (Espes, Lau, & Carlsson, 2014; Fu et al., 2014; Yamada et al., 2015), hyperlipidemia (R. Zhang & Abou-Samra, 2014), and indexes of insulin resistance (Fenzl et al., 2014).

Betatrophin/lipasin/C19org80/TD26/RIFL/ANGPTL8/ is a liver hormone that actively regulated plasma triglycerides levels. C19orf80/betatrophin is significantly associated with liver fat. Mice lacking betatrophin showed a reduction in plasma triglyceride levels in response to refeeding, whereas hepatic overexpression of betatrophin caused hypertriglyceridemia without changing glucose metabolism (Wang et al., 2013). Importantly, hepatic expression of betatrophin was elevated in mice with NAFLD including *db/db* or *ob/ob* mice and mice with a high-fat or methionine-choline-deficient diet (Lee et al., 2016). Furthermore, in the clinical trial, is was observed that circulating betatrophin increased in patients with NAFLD induced by endoplasmic reticulum stress in hepatocytes (Lee et al., 2016), and also significantly associated with pancreatic ductal adenocarcinoma in subjects with impaired glucose tolerance and T2D (Susanto et al., 2016).

Indeed, the development of serological prognostic biomarker in the clinic by using betatrophin during cancer development is widely unknown. It was only reported that

betatrophin/lipasin/ANGPTL8/C19orf80/HCC-associated gene TD26 highly expressed in hepatocellular carcinoma and may correlate to HCC incidence (Tseng, Yeh, Chen, & Lin, 2014). Another possible explanation that betatrophin gene is one of the targeted ChREBP genes which regulates gene transcription related to glucose and lipid metabolism (Iizuka, 2016). Considering that plasma levels of ANGPTL8 are highly associated with insulin resistance, ANGPTL8 may also be a biomarker for ChREBP transactivity in patients with metabolic diseases including hypertriglycemia or cancers.

Even though it has been established that betatrophin regulate lipid and glucose metabolism, however, there is a poor explanation of the central role of this liver hormone in colorectal cancer pathogenesis. Further study is needed to deeply explore the contribution of betatrophin in cancer pathogenesis associated with glucose metabolism imbalance progress to insulin resistance and diabetes.

6. Significance and Challenges

Colorectal cancer is the most third common malignancy worldwide with more than 1.2 million new cases diagnosed each year. The observed relationships with obesity and metabolic syndrome suggest that metabolic dysfunction plays a significant role in colorectal cancer, but the underlying biological mechanisms are not entirely understood. The application of comprehensive metabolite profiling within the context of a prospective cohort study has the potential to identify novel metabolites and biochemical pathways associated with colorectal cancer development with significant implications for risk prediction and novel prevention strategies. The proposed research is to identify new metabolic processes that lead to colorectal cancer. It will improve our understanding of how an individual metabolism can affect the risk of colorectal cancer development and may allow identification of those at highest risk of developing this common disease. In our study, we performed targeted, quantitative metabolic profiling in colorectal cancer patients and determined the alteration of plasma concentrations of betatrophin, AcylCNs, and amino acids in colon adenoma and colon carcinoma.

Recently, the identification of incomplete fatty acid oxidation has been simplified by using MS/MS of dried blood spot to determine AcylCNs alternations. However, analysis of fatty acid oxidation in vivo in human has entailed a complex and invasive methodologies. Several studies have shown some discrepancies related to altered plasma AcylCNs in a diabetic patient without cancer. It was reported that lower plasma concentrations of short- and medium-chain AcylCNs in T2D patients, while another study observed higher plasma concentrations of short- and medium-chain AcylCNs in T2D. Importantly, increased plasma acylcarnitine was linearly associated with age, aging, and insulin sensitivity (Consitt et al., 2016). Moreover, elevated in very long-chain plasma acylcarnitine concentrations were reported in obese/T2D compared to lean controls (Mihalik et al., 2010). The alteration of long-chain AcylCNs was suggested associated with insulin sensitivity and inflammation caused by metabolic syndrome (McCoin et al., 2015). It has been known that an overload of mitochondrial lipid oxidation results in accumulation of β-oxidation intermediates and the

depletion of Krebs cycle intermediates, resulting in mitochondrial stress and insulin resistance (Koves et al., 2008). However, it is still controversial whether β-oxidation intermediates and AcylCNs are increased in people with diabetes or not. However, it is suggested that the accumulation of acylcarnitine is represented TCA cycle perturbation and imbalance between fatty acid oxidation (FAO) flux and tricarboxylic acid cycle (TCA) flux, leading to incomplete fatty acid oxidation and insulin resistance (Schooneman et al., 2013).

In our recent study, we are the first to report the predictive and basic profile of betatrophin plasma levels, AcylCNs, and amino acid profiles in colorectal cancer patients. We observed that colorectal patients with diabetes had higher plasma concentrations of short- and very long-chain AcylCNs than healthy subjects, but had lower levels of medium-chain AcylCNs. Indeed, we observed that certain short-chain, long- and very long-chain acylcarnitine was significantly higher in colorectal cancer subjects with a person with diabetes than control. These data suggest that colorectal cancer patients with diabetes may enhance fatty acid oxidation rather than reduced utilization of these intermediates of fatty acids for mitochondrial β-oxidation resulting in increased AcylCN intermediates in plasma. On the other hand, we also want to trace the potential role of betatrophin in colorectal cancer pathogenesis associated with impaired glucose metabolism lipid transport.

Conclusion

The increasing prevalence of metabolic syndromes (Mets) such as diabetes mellitus and obesity improves the possible mechanism for cancer risk through various signaling pathways. Abnormal metabolism due to the alteration of metabolite levels is a crucial lead of cancer. Human metabolites draw high attention for a promising prognosis, diagnosis, and comprehensive marker. Recently, betatrophin is identified as a liver-derived hormone that is associated with glucose homeostasis and lipid metabolism. Betatrophin is the potent regulator of lipid transport homeostasis by controlling lipoprotein lipase (LPL) activity in the vascular wall. However, further study is required to improve our hypothesis whether the betatrophin expression in colorectal cancer patients with diabetic will correlate to fatty acid oxidation and it's intermediate.

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Conflict of Interest

There are no conflicts of interest

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