Characteristics of amino acid metabolism in colorectal cancer

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Abstract：

In recent years, metabolomics research has become a hot spot in the screening and treatment of cancer. It is a popular technique for the quantitative characterization of small molecular compounds in biological cells, tissues, organs or organisms. Further study of the tumor revealed that amino acid changes may occur early in the tumor [1]. The rapid growth and metabolism required for survival make tumors exhibit an increased demand for amino acids. An abundant supply of amino acids is important for cancer to maintain its proliferative driving force. Changes in amino acid metabolism can be used to screen malignant tumors and improve therapeutic outcomes. Therefore, it is particularly important to study the characteristics of amino acid metabolism in colorectal cancer. This article reviews several specific amino acid metabolism characteristics in colorectal cancer.

Keyword：metabolomics; amino acid metabolism; colorectal cancer

INTRODUCTION：

A comparison of cancer data between China and the U.S. in 2022, published by the National Cancer Center in ChineseMedicaiJoumal, showed that

colorectalcancer (CRC) was the second most newly added cancer in China, compared to fourth in the U.S. At present, the early screening of CRC mainly relies on endoscopy. Due to the shortage of hospital resources, the limited physical conditions of patients, and the existence of many serious complications, its development is limited. Clinically, currently popular biomarkers CEA, CA724 and CA199 for gastrointestinal tumors have been widely used as markers for the diagnosis, screening and monitoring of CRC, but the positive rate is low in the early stage of CRC [2]. Therefore, finding simple and convenient screening tools with high sensitivity and specificity is our primary goal to reduce the case fatality rate of CRC. The expression of genes and proteins is amplified metabolically through complex biochemical processes, and metabolomics has been used to screen for CRC. Amino acids are essential for metabolism in almost all types of cells. The study of amino acids in malignant tumors is of great significance for understanding the metabolic changes of tumors.

Glutamine and colorectal cancer:

Glutamine (Gln) provides energy to mammalian cells and is a direct nitrogen source for purine and pyrimidine biosynthesis in cancer cells [3]. Glutamine transporters transport GLN into cancer cells, where GLS are converted to glutamate under the action of glutaminase (GLS) and deaminated by glutamate dehydrogenase (GDH). Form alpha-ketoglutaric acid (α-KG) and NADH/NADPH into the tricarboxylic acid cycle (TCA) to produce ATP or convert to glutathione (GSH) by glutamate-cysteine ligase. In the Gln metabolic pathway, GLS, as its key enzyme, is highly expressed in CRC and is positively correlated with the occurrence and development of CRC [4]. When Gln metabolism is inhibited, protective autophagy is produced to degrade excess proteins and organelles in cells to help tumor cells survive the stress process safely [5]. Li et al. found that Gln deprivation significantly reduced the cell growth and viability of SW480 and SW620 cells [6], while the intracellular levels of ATP and α-KG were also reduced, confirming the importance of glutamine on energy metabolism and cell viability of CRC cells. Glutamate dehydrogenase (GDH) is a key enzyme that also catalyzes the final reaction of the Gln metabolic pathway and has been reported to be involved in tumor growth and metastasis. Liu et al. Detected the expression of GDH in CRC cells by qRT-PCR and immunohistochemistry. It has been found that GDH is upregulated in CRC cells and can induce epithelial-mesenchymal transformation (EMT) to improve the proliferation and migration of CRC cancer cells [5].

Alanine-serine-cysteine transporter 2 (ASCT2) is Gln transporter [7]. As a medium for Gln uptake and metabolism, ASCT2 affects Gln metabolism and signal transduction. ASCT2 silencing will lead to abnormal cell metabolism. ASCT2 was highly expressed in CRC compared with normal colorectal tissue. ASCT2 is essential for the growth and reproduction of

CRC cells. microRNA is a class of small molecular RNA that blocks the expression of mRNA degradation regulatory genes, and abnormally regulated mirnas are involved in the occurrence of tumors. In colorectal cancer, there are a large number of abnormally regulated mirnas, and mir-137 is one of them. Studies have determined that mir-137 regulates CRC glutamine metabolism by targeting the 3'UTR region of ASCT2[8]. Amplification of the oncogene c-myc has been reported in primary CRC, and c-myc overexpression has been observed in 60% of CRC patients. As key transcription factors, many glucose and Gln metabolizing genes are directly regulated by c-myc, such as ASCT2 and GLS1[9]. c-myc can increase Gln metabolism by up-regulating GLS expression, which leads to Gln entering the TCA cycle as α-KG[10]. TranTQ demonstrated that the glutamine-Akg axis contributes to Wnt signaling and cell differentiation in CRC[11], providing compelling evidence for the key role of Gln and aKG homeostasis in regulating carcinogenic Wnt signaling and CRC progression. Many mechanisms have been proposed regarding Gln metabolism in CRC, such as glutamine addiction, increased glutamine decomposition, and the effect of autophagy activation on cancer cell survival and proliferation[6]. Although the specific mechanism is not clear, it can be confirmed that Gln plays a crucial role in CRC cell metabolism.

Anastomotic fistula is one of postoperative complications of CRC. Yang et al. found that glutamine supplementation could effectively reduce the incidence of anastomotic fistula. This can be attributed to several factors[12]. On the one hand, glutamine can increase collagen synthesis, thereby accelerating intestinal mucosal healing and regeneration. On the other hand, supplementation with glutamine may reduce the inflammatory response in cancer patients. Inflammation is a key factor in the proliferation and invasion of CRC, and severe inflammation can lead to cancer progression and worsen a patient's prognosis. The severity of inflammation is also one of the important factors affecting the healing of intestinal anastomosis[13]. Kozjek et al. found that enteral glutamine supplementation had anti-inflammatory activity and reduced hormonal stress responses in rectal cancer patients receiving preoperative chemoradiotherapy compared to placebo treatment[14]. It can be seen that glutamine can reduce inflammatory damage and oxidative stress, and protect the healing of anastomosis, which is conducive to CRC surgery.

Serine and colorectal:

Serine (Ser) are non-essential amino acids that act as a major donor of a carbon unit, whose main roles include the synthesis of amino acids, nucleotides, glutathione and participating in biological methylation modification, and the production of NADPH for antioxidant defense[15]. Serine can be taken up from the external environment or synthesized by endogenous pathways, which mainly include de novo synthesis, proteolytic recovery and glycine conversion. Under fasting conditions, most of the intracellular Ser

derived from de novo synthesis pathway (SSP)[16]. SSPS are produced by 3-phosphoglycerate (3PG), an intermediate product of glycolysis. First, phosphoglycerate dehydrogenase (PHGDH) oxidizes 3PG to form 3-phosphohydroxypyruvate (3PHP), which accepts the amino group of glutamic acid, 3-Phosphatidylinic acid (3P-Ser) and α-ketoglutaric acid (α-KG) were produced under the catalysis of phosphoserine aminotransferase 1 (PSAT1). Finally, phosphate phosphatase (PSPH) dephosphorylates 3P-Ser to produce Ser. The established growth-promoting role of Ser in cancer cells, previous evidence that Ser levels are increased in CRC, and the discovery that increased expression of genes controlling Ser synthesis enhances xenograft growth suggest that this pathway plays a role in the progression of CRC[17].

As a key enzyme in de novo synthesis of Ser, PHGDH plays an important role in tumor cell proliferation and migration. The study found that CRC patients with high PHGDH expression levels tended to have stage III/IV CRC and larger tumors, and that high PHGDH levels were significantly associated with lower survival rates for CRC and were independent predictors of poor prognosis for CRC[18]. MontroseDC et al. demonstrated significant increases in PHGDH and PSAT1 in adenomatous polyps compared to normal tissues, and PSAT1 was the strongest and consistently increased gene compared to PHGDH and PSAT1. PSAT1 levels in the cytoplasm of CRC cells were elevated compared to normal adjacent tissues. Elevated Ser has been found in mouse colorectal tumors and human CRC, and limiting endogenous and exogenous sources of Ser maximizes the possibility of inhibiting CRC cell proliferation and enhancing the effectiveness of 5-FU in treating CRC patients[16]. 5-FU is a chemotherapy agent used as part of first-line treatment in most CRC patients, and its main mechanism of action is to induce nucleotide imbalance and DNA damage, leading to cell death[19]. PranziniE et al. demonstrated that interfering with the availability of Ser enhanced the antitumor effects of 5-fluorouracil (5-FU) in both in vitro and in vivo CRC models[20], he proved that a shift toward mitochondrial serine metabolism promotes 5-FU resistance in CRC by supporting purine nucleotide biosynthesis and allowing resistant cells to prevent the accumulation of drug-induced DNA damage.

Glycine and colorectal cancer:
Glycine (Gly), in addition to being a component of glutathione, is the most abundant amino acid in the body and is involved in a variety of metabolic and pathophysiological processes that are important for the growth and survival of proliferating cells, including cancer cells[21]. Gly can be synthesized from a variety of sources and can be synthesized from choline, serine and threonine through a range of pathways. Serine is particularly important for glycine synthesis. The conversion of Ser to Gly is catalyzed by serine hydroxymethyltransferase (SHMT), and SHMT1 and SHMT2

proteins are mainly confined to the cytoplasm and mitochondria, respectively. SHMT2 regulates the activity or expression of proteins that allow tumor cells to survive in the face of hypoxia or nutrient deficiency. In contrast to normal enzymes, SHMT2 is overexpressed in CRC tissue and is involved in colorectal cancer progression[22]. SHMT2 knockdown significantly inhibits a variety of signaling pathways, including TGF-β, Notch and Wnt pathways, which are closely associated with CRC progression, especially the Wnt/β-catenin pathway. In human CRC tissues, both SHMT2 and β-catenin expression are elevated and closely related to CRC progression and metastasis, and SHMT2 expression is negatively correlated with survival[22]. The RedalenKR et al. study reported an association between pre-treatment tumor metabolic profile and treatment outcome in locally advanced CRC patients undergoing radical surgery after combined neoadjuvant therapy, providing the first clinical evidence of high tumor Gly concentration as an adverse prognostic factor. Treatment with Gly alone resulted in a significant 43% reduction in tumor volume. This decrease is associated with decreased MVD and proliferation index in tumor tissue[23]. Gly is known to deactivate VEGF-stimulated endothelial cell growth, migration, and angiogenesis through mechanisms involving receptor-dependent pathways[24]. Jacob et al. reported that Gly has a protective effect on mesenteric ischemia/reperfusion (I/R) injury, and one of the mechanisms is to down-regulate lethal signaling and eliminate the apoptotic cascade in the I/R injury model[25]. The promising efficacy of Gly supplements in the prevention of several intestinal diseases suggests that Gly could in principle be a target for therapeutic intervention[21].

FOLFOX chemotherapy (CTx) has been shown to be effective for the treatment of liver metastases (CRLM) in colorectal cancer[26]. The side effect of cardiotoxicity is one of the reasons that may limit the use of FOLFOX. Currently, there are no effective strategies to prevent FofOLx-induced cardiotoxicity. Gly has been shown to protect the liver from CTX-induced damage and oxidative stress, as well as reduce platelet aggregation and improve microperfusion. Dietary Gly protects the heart from Folfox-induced damage during CRLM treatment. The findings of ManeikyteJ et al. suggest that Gly is involved in the process of cardiac protection by reducing the level of Folfox-induced fibrosis and apoptosis in myocardial tissue and retaining LVEF[27]. Interestingly, markers of myocardial damage were significantly elevated after FOLFOXCTx, regardless of diet, but significantly decreased in the animals receiving Gly. Gly appears to be a promising substance for limiting Fofolfox-induced cardiotoxicity, which requires further investigation.

Arginine and colorectal cancer：
Arginine (Arg) are semi-essential amino acids, important precursors for the production of proteins, polyamines, creatinine and nitric oxide, and

are involved in all aspects of tumor metabolism[28]. Args come from a variety of sources including dietary intake, protein breakdown and endogenous de novo synthesis. Endogenous ArGs are mainly produced in the gut and kidney. The conversion of intestinal citrulline to Arg in the kidney mainly involves two steps: aspartic acid and citrulline under the action of succinic acid synthetase 1(ASS1) to arginine succinic acid, and rapid conversion to arginine and fumarate by arginine succinic acid lyase (ASL). ASS1 is a rate-limiting step in catalytic de novo arginine biosynthesis. Several cancers are characterized by low ASS1 expression, including hepatocellular carcinoma, pleural mesothelioma, and prostate cancer[29]. In these cancers, the promoter of the ASS1 gene is usually epigenetically silent[30], ASS1 silencing is associated with tumor progression, possibly due to increased pyrimidine synthesis due to higher availability of aspartic acid[31]. In contrast, Colorectal cancer shows increased expression of ASS1[29]. Histological data from normal and primary CRC tissues indicate that ASS1 is strongly stained in primary CRC and that protein levels in CRC significantly up-regulate ASS1 compared to normal colorectal tissue[32]. A more in-depth study of clinical histology in about 600 samples of ASS1 independently supported this finding[33].

RoyHK et al. demonstrated that increased expression of inducible nitric oxide synthetase (iNOS), a key enzyme in Arg metabolism, is an early event in the development of colon cancer, and the induction of iNOS may play a key role in increasing the blood supply of dysplastic mucous membranes, thus promoting colon cancer[34]. Arginine deprivation has been used as a cytotoxic method to selectively target a large number of arginine-trophic tumors. Studies have shown that[35] diet supplemented with arginine increased the growth of metastatic CRC by 55%, while restriction of arginine inhibited the growth by 78%. Consumption of arginine reduced CRC cell motivity and reduced CRC cell invasive growth, suggesting that arginine is trophic to CRC cells and cannot survive in the absence of an external source of arginine[36]. To assess the need for topical Arg supplements to maintain CRC growth, AlexandrouC et al. cultured CRC cell lines in ARG-free or control media containing all amino acids. It was found that all tested cell lines failed to grow without Arg, indicating that the cessation of cell dystrophy growth was accompanied by the cessation of DNA replication, and the expression of the cell cycle marker cyclin D1 was reduced and restored when supplemented with arginine, demonstrating that nutritional deprivation of Arg was effective in slowing tumor growth, such as the reduction of tumor volume and weight. Arg malnutrition was identified as a metabolic vulnerability for colorectal cancer[33].

Methionine and colorectal cancer：
Methionine (Met) is a sulfur-containing amino acid that is generally considered a general hydrophobic residue involved in the methylation of

DNA, RNA, histones, small molecules, and lipids[37]. Met is synthesized by homocysteine methylation or polyamine biopathway under betaine cofactor and 5-methyl-tetrahydrofolic acid. The methionine cycle is the process by which Met is converted to methyl. Met is used to produce S-adenosine methionine (SAM) by methionine adenosine transferase (MAT) and demethylated to form S-adenosine homocysteine (SAH). After dehydrogenation of S-adenosine homocysteine hydrolase (SAHH), SAH is converted back to homocysteine (HCY), which recombines with methyl groups to regenerate Met and turn the methionine cycle. This circulatory pathway is closely associated with colorectal cancer. In recent years, a growing body of literature has accumulated evidence that SAM exerts anti-proliferative and pro-apoptotic activities in CRC cells, demonstrating its ability to regulate genes responsible for cell invasion and metastasis[38]. Metastasis and diffusion of CRC cells is the major cause of death in patients. We found that SAM significantly reduced vimentin levels and promoted the transformation from n-cadherin to e-cadherin expression in HCT-116 and Caco-2 cells, as demonstrated by comparing the strength of corresponding protein bands in SAM treated and untreated cells. Highlighting SAM's ability to slow CRC cell migration by inhibiting the transition from epithelial to mesenchymal states[39]. SAM inhibits CRC cell growth by reversing the hypomethylation of c-Myc and H-ras promoters, thereby inhibiting the expression of these oncogenes[40]. SAM has been shown to overcome 5-FU chemical resistance in CRC cells by targeting autophagy, P-gp expression, and NF-κB signaling activation, providing important implications for the development of new adjuvant therapies to improve CRC treatment and patient outcomes[38].

Dietary restriction of methionine (MR) is known to extend life and improve metabolic health[41]. Studies have shown that MR Has anti-aging and anti-obesogenic properties, affects cancer outcomes through controlled and repeatable changes in single-carbon metabolism, and is further targeted for a range of cancer interventions such as chemotherapy and radiotherapy[42]. Gao suggests that MR May have broad anticancer properties, providing a tolerable low dose of 5-FU with no effect on CRC tumor growth when used alone; however, MR Synergies with 5-FU therapy, significantly inhibits CRC tumor growth, and has broad effects on tumor, plasma, and liver metabolic pathways. The most significant changes in nucleotide metabolism and REDOX status are related to the mechanistic action of 5-FU and MR, suggesting that dietary MR Works synergistically with 5-FU to inhibit CRC tumor growth and disrupt nucleotide metabolism and REDOX balance[43]. Komninou and colleagues show that Met dietary restriction inhibits the development of CRC in rats, an effect that occurs primarily in the post-initiation phase of carcinogenesis, possibly due to inhibition of CRC cell proliferation, suggesting a potential role for Met dietary restriction in CRC prevention[44].

Cysteine and colorectal cancer：

Cysteine (Cys) is a sulfur-containing protein amino acid that plays a uniquely important role in cell response to changes in the REDOX environment.Cys can be derived from protein catabolism or de novo synthesis of methionine.Dietary methionine is converted to homocysteine in two successive steps: first by condensation of homocysteine with serine, it is catalyzed to cysteine β-synthetase (CBS), and then hydrolyzed to cysteine by cysteine gamma-lyase (CSE), thus establishing a link between the trans-vulcanization pathway and the TCA cycle.The trans vulcanization pathway is associated with energy metabolism, tumor angiogenesis, and drug resistance in colon cancer[45].A recent study has shown that the trans-vulcanization pathway directly benefits cancer cells in maintaining REDOX balance and escaping iron death.Studies have shown that many cells require Cys uptake to prevent the onset of iron death[46].Cys is an effective regulator of iron death.Cys levels indirectly control cell susceptibility to iron death through their effects on synthesis of GSH, CoA, Fe/S clusters, and potentially other molecules.These molecules are essential for the continued function of the antioxidant network that prevents iron death, as well as for the management of the intracellular distribution of iron, a key iron death catalyst to which a variety of cancer cells are highly susceptible[47].Many studies have shown that increased Cys uptake is not a universal response to oncogene activation[48]. High levels of Cys input may be an adaptive feature of at least some cancer cells to inhibit iron death or other forms of oxidative stress in the body.

Cys has a major role in cancer cell metabolism: acting as a precursor to glutathione under the action of glutamylcysteine ligase (GCL), contributing to oxidative stress control.Oxidative stress promotes damage to cellular proteins, lipids, membranes, and DNA and plays a key role in the development of cancer[49].It is well known that patients with CRC have higher oxidative stress and lower antioxidant capacity than healthy subjects[50]. One of the reasons for this is that oxidative stress is an important cause of inflammation and may contribute to the development of CRC.Yang et al. observed that Cys may be oxidized more in CRC tissue than in non-tumor tissue, where Cys is usually maintained in reduced form[51].If Cys oxidation promotes free radical production and increases oxidative stress in tumor tissue, tumor cells can protect themselves from higher oxidative stress, and the imbalance between oxidative stress and antioxidant capacity is thought to cause CRC[52].Studies have shown that plasma Cys concentration is inversely associated with the incidence of CRC in postmenopausal women, associated with rectal and proximal tumors, but not distal tumors[49].In addition, this association was significant for local tumors, but not for metastatic tumors, and was not observed in studies conducted in men[53].

Branched amino acids and colorectal：

Branched amino acids (BCAAs) are the building blocks of all life forms, namely valine (Val), leucine (Leu), and isoleucine (Ile), and can be synthesized in bacteria, plants, and fungi, but not in animals. The branched amino acid group is first reversibably transaminated to alpha-ketoglutaric acid by branched aminotransaminase (BCATs) to produce glutamic acid and branched alpha-ketoic acid (BCKAs). BCKAs are then irreversely decarboxylated[54] and dehydrogenated by a branched chain alpha ketoate dehydrogenase (BCKDH) complex that is negatively regulated by BCKDH kinase (BCKDK) phosphorylation [55]. Catalyzed by BCKDH, BCKAs are further oxidized by A variety of enzymes into different substrates for biosynthesis or energy, and the three BCkas can be further decomposed into acetyl and/or succinyl-coA, which will enter the TCA cycle and contribute to energy production. Studies have shown that BCATs1 plays an important role in branched chain amino acid degradation and is considered as a prognostic biomarker for colorectal cancer. Xue Meng et al. found that in 117 patients with CRC, the expression level in BCKDK cancer tissues was higher than that in neighboring tissues, which had a significant impact on survival time, indicating that BCKDK directly phosphorylated MEK at Ser221 to positively regulate MEK/ERK signaling[56]. MAPK has a wide range of functions in cancer cell proliferation, so the BCKDK-MEK1 axis may contribute to the development of CRC. Phosphorylated BCKDK promotes epithelial-mesenchymal transformation (EMT) by regulating EMT genes, leading to CRC metastasis[57].

As an important organ in the human body, the gut has the highest level of immune activity, and disruption of intestinal homeostasis is closely associated with the development of obesity, T2DM, IBD, atherosclerosis, and colon cancer[58]. Branched chain amino acids act as regulatory factors that promote intestinal development, nutrient transporters, and immune-related functions, thereby improving intestinal health[59]. However, most studies have focused on Leu function rather than Val or Ile in the gut. Leu supplementation maintains intestinal health by enhancing tight connections in fish, as well as improving intestinal epithelial cell proliferation, villus height, and small intestine growth in pigs. In addition, the high expression of BCAT and BCKDH enzymes in the intestinal tract indicates a certain correlation between BCAAs and intestinal function[60]. A recent experimental study of obesity-related CRC variant models reported that dietary BCAA supplements significantly inhibited the development of chemically induced CRC lesions [61]. All these indicate that there is a certain biological relationship between branched chain amino acids and the occurrence and development of CRC.

CONCLUSION：

Normally, the human body is in a state of equilibrium of amino acids, but malignant tumors often rely on specific amino acids for survival and

proliferation, resulting in an imbalance of amino acids in the blood, urine and body fluids. There is a strong relationship between colorectal cancer and amino acid metabolism, possibly for the following reasons:

1. Amino acid energy: Colorectal cancer cells are highly metabolically active and require a lot of energy to maintain their rapid proliferation and growth. Amino acids can produce energy through the amino acid metabolic pathway, providing cancer cells with the energy they need to survive. In colorectal cancer cells, the degradation of amino acids can be achieved through the involvement of enzymes such as amino acid transaminase and glutaminase, which convert amino acids into energy-producing substances such as pyruvate and lactic acid. 2. Amino acid synthesis: Rapid proliferation and growth of colorectal cancer cells require a large supply of amino acids. In some cases, cancer cells may meet their needs by increasing the synthesis of amino acids. For example, cancer cells can synthesize glutamate and derivatives of glutamate such as glutathione by increasing the glutamate synthesis pathway, thus providing antioxidants and anti-stress substances. 3. Amino acid transport: Amino acid transport also plays an important role in the development of colorectal cancer. Cancer cells increase the uptake and utilization of amino acids by increasing the expression and activity of amino acid transporters. This can provide the supply of amino acids that cancer cells need to promote their growth and proliferation. 4. Regulation of amino acid metabolites: Amino acid metabolites can also affect the development of colorectal cancer. For example, some amino acid metabolites such as glutathione and serine can regulate biological processes such as oxidative stress and apoptosis of cells, thereby affecting the growth and metastasis of colorectal cancer. These characteristics may be closely related to the growth and invasion of tumor cells and the metabolic changes of tumor microenvironment, and have important significance for the occurrence and development of colorectal cancer. Amino acid detection as a simple and convenient means of health diagnosis and tumor screening has a guiding role for the prevention of disease, improve the nutritional status of the body and provide reference for the treatment of tumors. There are currently many therapies for malignant tumors, and amino acid therapy is also crucial as an adjunct therapy. For example, by adjusting arginine in patients, the body can improve resistance and inhibit tumor cell growth, reduce treatment-related side effects, and improve survival. With the absence or inhibition of glutaminase, malignant tumors that rely on exogenous glutamine for energy supply will not be able to utilize this source of nutrients, thus blocking the uptake and utilization of amino acids by cancer cells and inhibiting tumor growth. The methionine-restricted diet resulted in reduced proliferation of colon cells and reduced precancerous abnormal crypt lesions, while overcoming 5-FU chemical resistance in CRC cells. Despite the potential of amino acids in the treatment of colorectal

cancer, further studies are currently needed to verify their efficacy and safety. In addition, factors such as individual differences and tumor heterogeneity may also affect the effectiveness of amino acid therapy. Therefore, according to the specific conditions of different patients, it is very important to develop an individualized treatment plan. At present, we know that specific amino acids are associated with colorectal cancer, but whether these specific amino acid changes can be used as a reliable screening method for colorectal cancer needs further research.

ACKNOWLEDGEMENTS

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