**Name of Journal:** *World Journal of Gastrointestinal Oncology*

**Manuscript NO:** 62989

**Manuscript Type:** REVIEW

**Metabolism-associated genes in occurrence and development of gastrointestinal cancer: Latest progress and future prospects**

Miao YD *et al*. Metabolism-associated genes in GI cancer

Yan-Dong Miao, Lin-Jie Mu, Deng-Hai Mi

**Yan-Dong Miao, Deng-Hai Mi,** The First Clinical Medical College, Lanzhou University, Lanzhou 730000, Gansu Province, China

**Lin-Jie Mu,** The First Affiliated Hospital, Kunming Medical University, Kunming 650000, Yunnan Province, China

**Deng-Hai Mi,** Dean’s office, Gansu Academy of Traditional Chinese Medicine, Lanzhou 730000, Gansu Province, China

**Author contributions:** Mi DH designed the research; Miao YD and Mu LJ performed the writing and data analysis, and prepared the figures and tables; Miao YD and Mu LJ contributed equally to this work; all authors approved the final manuscript.

**Corresponding author: Deng-Hai Mi, MD, Chief Doctor, Dean, Professor,** The First Clinical Medical College, Lanzhou University, No. 1 Donggang West Road, Chengguan District, Lanzhou 730000, Gansu Province, China. mi.dh@outlook.com

**Received:** January 22, 2021

**Revised:** February 27, 2021

**Accepted:** June 23, 2021

**Published online:**

**Abstract**

Gastrointestinal (GI) cancer remains one of the most prevalent cancers in the world. The occurrence and progression of GI cancer involve multiple events. Metabolic reprogramming is one of the hallmarks of cancer and is intricately related to tumorigenesis. Many metabolic genes are involved in the occurrence and development of GI cancer. Research approaches combining tumor genomics and metabolomics are more likely to provide deeper insights into this field. In this paper, we review the roles of metabolism-associated genes, especially those involved in the regulation pathways, in the occurrence and progression of GI cancer. We provide the latest progress and future prospects into the different molecular mechanisms of metabolism-associated genes involved in the occurrence and development of GI cancer.

**Key Words:** Gastrointestinal cancer; Gastric cancer; Colorectal cancer; Metabolism-associated genes

Miao YD, Mu LJ, Mi DH. Metabolism-associated genes in occurrence and development of gastrointestinal cancer: Latest progress and future prospects. *World J Gastrointest Oncol* 2021; In press

**Core Tip:** Metabolic reprogramming is one of the hallmarks of cancer and is intricately related to tumorigenesis. Many metabolic genes are involved in the occurrence and development of gastrointestinal (GI) cancer. This state-of-the-art review comprehensively describes the latest progress and prospects into the different molecular mechanisms of metabolism-associated genes involved in the occurrence and development of GI cancer.

**INTRODUCTION**

Since the first suggestion that patients with gastric cancer (GC) have metabolic dysfunction and the metabolism study of patients with gastrointestinal (GI) tumors, nearly 80 years have passed[1-3]; however, studies on the role of metabolic processes and associated genes in the occurrence and development of GI tumors and the signal transduction pathways related to regulation have been ongoing. With the development of metabolomics, remarkable progress has been made in comprehending the relationship between metabolic regulation and GI cancer. GC is the ultimate result of a series of events that take decades to happen and result from the accumulation of multiple epigenetic and genetic changes. These changes are essential for tumor cells to accelerate and maintain a series of cancer development pathways, such as angiogenesis, DNA repair, cell cycle, metabolism, apoptosis, cell-to-cell interactions, and immunity surveillance. Besides, epigenetic and genetic changes have an essential role in immunity[4,5]. Previous research has shown that some critical metabolites of epigenetic modification of the genome play a role in the deposition of epigenetic markers that regulate T cell and macrophage activation[6-8]. Camacho-Ordonez *et al*[9] have identified the importance of DNA methylation, chromatin remodeling, histone modifications, mRNA, and non-coding RNA processing for immunity[9]. Targeting cancer epigenomes effectively controls tumor growth. Therefore, the combination of immunotherapy and epigenetic therapy is an attractive approach to overcome the limitations of immunotherapy alone[5,10,11]. Epigenetic gene regulation is associated with the stability and plasticity of T cell memory and may provide the potential to selectively alter T cell memory in diseases *via* targeting epigenetic mechanisms[12]. Extensive research also indicates that the amplified *c-yes-1* was involved in the progress of GC[13]; high levels of c-Ha-ras p21s was related to the invasiveness and metastasis of human GC[14].

The development of colorectal cancer (CRC) has long been known to involve a series of cascading events (*i.e.*, the adenoma-carcinoma sequence): Transformation from normal colonic epithelium to adenoma intermediately and finally into adenocarcinoma[15-17]. This process involves genetic, lifestyle, and environmental risk factors[18]. The continuous accumulation of mutations in the epidermal growth factor receptor (EGFR), P53, Wnt, and transforming growth factor (TGF)-β signaling pathways results in the occurrence and development of CRC. Early *APC* gene mutations occur in 70% of colorectal adenomas[19]. Bell *et al*[20] first found that polyadenylation polymorphism in the *NAT1* gene increases CRC risk[20]. Recently, the application of various “omics” techniques has opened up a new field to study GI cancer mechanisms.

The recombination of cell metabolism represents the basic characteristics of most cancer cells. Studies in the past decades have shown that this metabolic reprogramming is an active process controlled by oncogenes and tumor suppressor genes. It provides energy for cancer cells and reduces equivalent substances and biosynthetic precursors[21]. Cancer cells use most core metabolic pathways, including glutamine, glucose, serine/glycine, amino acid, and lipid metabolism, to maintain their high cell division rate[22]. Extensive research has also shown that metabolic reprogramming is one of the hallmarks of cancer[23] and is intricately related to tumorigenesis[24,25] and cancer immune escape[26,27]. Metabolic remodeling can lead to epigenetic changes in tumors that affect cancer cell proliferation, differentiation, and therapy[7]. Metabolomics can provide biomarkers that can be used to identify early GC, thereby potentially meeting important clinical needs[28]. Research methods combining tumor genomics and metabolomics are more likely to provide deeper insights into this field. We obtained metabolism-related genes from the Molecular Signatures Database, and differentially expressed metabolism-associated genes in GC and CRC of The Cancer Genome Atlas database were obtained by bioinformatics methods. In this review, we mainly summarize the latest progress on how these differentially expressed metabolism-related genes affect the initiation and progression of GI tumors, and discuss the possible mechanisms behind these changes. The up-regulated metabolism-related genes in GC [log fold change (FC) > 1 and false discovery rate (FDR) < 0.05, Table 1] and CRC (Log FC > 1.5 and FDR < 0.05, Table 2) are shown in Figure 1.

**metabolic genes involved in development of GC**

Up to now, many metabolic genes involved in the occurrence and development of GC have been confirmed. Tsai *et al*[29] have reported that *ASS1*, a rate-limited enzyme in arginine biosynthesis, promotes GC progression by enhancing the aggressiveness caused by the accumulation of active β-catenin[29]. The most important cause of sporadic distal GC is *Helicobacter pylori* (*H. pylori*) infection[30]. Duringthecarcinogenic process of *H. pylori* infection, various factors interact to promote damage repair. Possibly altered cell proliferation, apoptosis, and certain epigenetic modifications to tumor suppressor genes may eventually lead to inflammation-related tumors[31]. *PSAT1*, a metabolic gene, is involved in the chronic inflammation induced by *H. pylori* infection and the subsequent carcinogenesis[32]. Similar phenomena can also be found in another metabolic gene-*MIF*. In *H. pylori*-induced gastric inflammation, the expression of *MIF* is significantly increased in gastric epithelial cells, which suggests that *MIF* is involved in gastric carcinogenesis[33]. *TYMS* plays a vital role in folate metabolism, DNA synthesis, and repair[34], and genetic polymorphisms of *TYMS* were related to a better clinical outcome in advanced GC treated with fluorouracil (FU)-based chemotherapy[35]. MTHFD2 is the crucial enzyme in folate metabolism and methyl donor SAM production, which significantly promotes the proliferation of GC cells[36]. Phosphoribosylaminoimidazole carboxylase (PAICS), an essential enzyme for *de novo* purine biosynthesis, promotes the occurrence of GC and is involved in DNA damage reaction by interacting with histone deacetylase 1/2[37]. Xiao *et al*[38] found that PYCR1, a key enzyme in intracellular proline synthesis, is highly expressed in GC, which induces cancer progression by increasing tumor proliferation and reaction to metabolic stress[38]. Another metabolic gene, known as the *ODC1*, has been reported to contribute to the risk of GC by regulating the biosynthesis of ornithine decarboxylase polyamines or by the interaction between isoflavones and NQO1, OAZ2, and AMD1[39]. In summary, all these studies emphasize the tight connection between metabolic genes and the formation of GC, indicating that changes in specific metabolic pathways may influence the occurrence of GC. These previously unresearched metabolic genes are worthy of further exploration of their role in the occurrence and development of GC.

**metabolic genes involved in regulatory pathways of GC**

The occurrence and progression of GC involve multiple events, including the activation or deactivation of multiple signal transduction pathways, such as PI3K/Akt signaling pathway[40], Hedgehog signaling pathway[41], EphA2-to-YAP pathway[42], Wnt/β-catenin pathway[43,44], mitogen-activated protein kinase (MAPK) signaling pathway[45], HGF/MET pathway[46], AKT1/mTOR pathway[47], *etc.* As mentioned in the beginning, metabolic genes are closely related to the occurrence and development of GC. For example, ASS1, a signaling pathway involved in the regulation of metabolic genes, promotes GC invasion and progression mainly through the regulation of autophagy[29]. *TYMS5* is involved in the fluorouracil conversion pathway，which is associated with chemoresistance and treatment failure by 5-FU in GC[48]. Kong *et al*[49] reported that *MIF* is associated with the p53 pathway in GC[49]. *PYCR1* expression was significantly correlated with PI3K/Akt axis in GC[38]. Previous research found that overexpressed *RRM2* in GC cells promotes their invasiveness *via* the AKT/nuclear factor-kappaB (NF-κB) signaling pathway[50].

**metabolic genes involved in development of CRC**

The development of CRC has long been known to involve a series of cascading events, including the metabolic process. Therefore, metabolic genes play a very crucial role in the occurrence and development of CRC. Previous reports indicate that *CA9* expression was up-regulated in ulcerative colitis-associated CRC[51]. *PSAT1* is overexpressed in colon tumors, promotes cell growth, and enhances chemoresistance of colon cancer cells[52]. *SULT2B1*, an estrogen metabolic pathway gene, was significantly highly expressed in colorectal tumor tissues and related to susceptibility to and survival of CRC[53]. Agarwal *et al*[54] had reported that MTHFD1L, a folate cycle enzyme, is involved in the progression of CRC[54].

Emerging evidence suggests that abnormal alternative splicing (AS) is an ordinary event in the development and progression of cancer. The AS event of *ALDH4A1* wasdiscovered in carcinogenesis and prognosis of CRC[55]. Notably, *GPT2* is involved in the glycolysis activation to drive the application of glutamine as a carbon source for the abnormal tricarboxylic acid cycle in colon cancer cells. The Warburg effect supports oncogenesis by coupling pyruvate production and glutamine catabolism mediated by GPT2[56]. Mutation of the oncogene *PIK3CA* reprogrammed glutamine metabolism in CRC[57].

Further studies have shown that GPT2-mediated glutamine utilization enhancement is a fundamental metabolic feature of colorectal signet-ring cell carcinoma[58]. PHGDH catalyzes the first committed step to synthesize glucose-derived serine catalyzed by the phosphate serine pathway related to colon cancer[59]. FADS2is overexpressed in CRC and promotes the proliferation of CRC cells and the growth of xenografts *in vivo* and *in vitro* by promoting the metabolism of PGE2 (a carcinogenic molecule associated with colorectal carcinogenesis)[60]. Macrophage ABHD5 promotes the growth of CRC by inhibiting the production of spermidine by SRM[61]. SphK1overexpression and activation facilitate and enhance the development and progression of colon cancer[62] and are associated with the survival of CRC patients[63]. RRM2 is a ribonucleotide reductase small subunit, and its high expressioncaninduce cancer and promote tumor growth and invasion. The transcription factor E2F1 regulating the transactivation of RRM2can promote the proliferation, migration, invasion, and metastasis of CRC cells[64].

Cyp enzymes in digestive tract epithelial cells play an essential role in the oxidative metabolism of various exogenous substances containing carcinogens and endogenous compounds. Knockdown of *CYP2S1*, a CYP family member, promotes cell proliferation and xenograft tumor growth by enhancing the level of endogenous PGE2[65]. *MTHFD2* encodes a nuclear-encoded mitochondrial bifunctional enzyme with methylenetetrahydrofolate dehydrogenase and methyltetrahydrofolate cyclohydrolase activities. Overexpression of *MTHFD2* can enhance the proliferation and migration of CRC cells, promote the cell cycle, and inhibit apoptosis[66,67]. Cytokine MIF, a lymphokine involved in cell-mediated immunity, immunoregulation, and inflammation, is expressed throughout the human GI tract. MIF expression is enhanced in sporadic colorectal adenomas, and exogenous MIF promotes the tumorigenic behavior of epithelial cells *in vitro*. MIFalso promoted intestinal tumor occurrence (primarily through angiogenesis) in ApcMin/+ mice[68]. PSPH*,* which belongs to a subfamily of the phosphotransferases, regulates the synthesis of serine and glycine in cells and promotes tumor growth. PSPH is overexpressed in most CRC cell lines and enhances the anticancer efficacy of 5-fluorouracil in CRC[69]. *PPAT*, an amino acid/nucleotide metabolism-related gene, is mutated in GC and CRC, acquires somatic mutations in MSH-H GCs and CRCs[70]. The phosphoribosylaminoimidazole carboxylase and PAICS were overexpressed in 70% of CRCs. Regardless of p53 and microsatellite status, increased PAICexpression is associated with proliferation, growth, invasion, and migration of CRC cells[71]. Glutathione S-transferase (GST) catalyzes the reaction between lipophilic and glutathione compounds with electrophilic centers, thereby neutralizing toxic compounds, exogenous substances, and oxidative stress products. Patients with wild-type *GSTP1* had a significantly lower risk of TP53 mutations in CRC than patients with mutated genotypes[72]. GSTP1is up-regulated in CRC tissue samples and facilitates the proliferation, invasion, and metastasis of CRC cells[73].

**Metabolic genes involved in regulatory pathways of CRC**

CRC is a heterogeneous disease that develops *via* the gradual accumulation of well-defined genetic and epigenetic alterations. CRC progression involves multiple genetic events accompanied by genomic instability and mutations [74]. The main signal transduction pathways leading to somatic inheritance of sporadic CRC are as follows: (1) *APC*[75] and *BRAF* gene mutations cause traditional adenomas or serrated polyps, respectively[76,77]; (2) chromosomal instability (CIN) pathway[78]. CIN, observed in 65% to 70% of sporadic CRCs[79,80], is characterized by chromosome changes that include somatic copy number alterations caused by aneuploidy, insertions, amplifications, deletions, or loss of heterozygosity[81]. The Wnt pathway is activated in almost all CIN tumors, and APC mutations are found in about 80% of these tumors[82]; (3) serrated adenoma pathways[83-85]. Serrated polyps are thought to cause nearly 15% of CRCs through serrated neoplasia pathways[86]. The serrated pathway is a unique mechanism of CRC. A prominent feature of the serrated pathway is the activating V600E mutation in BRAF, a component of the MAPK pathway[87]. BRAF mutation occurs in most sessile serrated adenomas but rarely in conventional adenomas, which supports the view that the serrated pathway is an alternative pathway for CRC[88]. The MAPK pathway is located downstream of numerous growth factor receptors, including epidermal growth factor. The EGFR signaling pathway regulates proliferation, growth, and cellular differentiation in CRC cells[89]; and (4) microsatellite instability (MSI) pathway. Unlike the CIN pathway, characterized by changes in gene copy number, CRC can also develop through highly mutated pathways characterized by frequent somatic DNA base-pair mutations[81]. In sporadic CRC, mutations often occurred in the DNA mismatch repair (MMR) pathway (Figure 2). MSI is observed in nearly 15% of sporadic CRC cases. Besides, germline *MMR* mutations are related to Lynch syndrome, the most ordinary hereditary CRC form[90]. CRCs with MSI phenotype usually have high levels of methylation in the regulatory region of the entire genome, including CpG island methylation phenotype (CIMP)[81,91]. CIMP-hypermethylation is found in approximately 20% of CRCs, and this hypermethylation is most often associated with BRAF mutations and MLH1 hypermethylation, characteristics that describe a large proportion of MSI-H tumors[92,93].

Metabolism-related genes are also involved in several pathways that regulate the development of CRC. The mRNA level of Wnt signaling factor AXIN2 was significantly increased in CA9+ population[94]. As we know, the Wnt pathway is involved in the control of gene expression, cell behavior, cell polarity, and cell adhesion. Wnt signal inhibits the degradation of β-catenin, regulating the transcription of multiple CRC-associated genes[95]. As we know, *PYCR1* exerts a crucial role in various cancers; knockdown of *PYCR1* inhibits EMT, proliferation, and drug resistance in CRC cells by regulating p38 MAPK and NF-κB signaling pathway mediated by STAT3[96]. PIK3CA mutation reprogrammed glutamine metabolism by up-regulating *GPT2* in CRC cells[57]. Overexpression of SHMT2 regulates the AMPK/mTOR pathway[97]. Angiogenesis is a fundamental event in the growth and metastasis of CRC. The vascular endothelial growth factor (VEGF) pathway is one of the pivotal regulators of this process. VEGF-receptor pathway activation triggers a network of signaling processes that promote endothelial cell growth, migration, and survival of the original vascular system[98]. VEGF are transcriptional targets of the STAT3 signaling pathway[99]. SPHK1 is involved in the regulation of the STAT3 signaling pathway[100]. The expression of asparagine synthetase (ASNS) was up-regulated by mutated Kirsten rat sarcoma 2 viral oncogene homolog (KRAS), and ASNS expression was induced by the KRAS-activated signaling pathway, especially the PI3K-AKT-mTOR pathway in CRC cells[101]. KRAS activation mutations usually occur after APC mutations and are found in nearly 40% of CRCs. KRAS is a component of several growth factor signaling pathways, including the EGFR pathway. In this pathway, activation of KRAS results in constitutive activation of the Raf–MEK–ERK pathway, PI3K signaling *via* mTOR, and the transcription factor NF-kB[81,102]. CYP2S1regulates CRC growth *via* the PGE2-mediated activation of the β-catenin signaling pathway[65]. Upregulation of CYP2S1 is associated with p53 status in CRC cell lines[103]. The p53 mutation is found in approximately 60% of CRC patients. Mutant p53 combined with Kras activation and TGF-β inhibition promotes tumor metastasis[104]. The TGF-β signaling pathway is an essential regulator of many cellular processes involved in CRC carcinogenesis[105,106].

**CONCLUSION**

The occurrence and progression of GI cancer involve multiple events. The improvement of the overall survival rate of patients with GI cancer will depend on the inherent characteristics of different subtypes of GI tumors and the development of treatment strategies based on these differences. The further identification of GI tumor subtypes and the role of specific types of genes (including metabolism-associated genes) in the occurrence and development of GI tumors is an essential area of future research. When we clarify the impact of metabolism on GI cancer risk, we have to understand how diet, obesity, and sedentary behavior contribute to the development of GI cancer. The association of *H. pylori*, *Clostridium pylori*, and other GI microorganisms with the risk of GI cancer will lead to many studies of the influence of microbiota on GI epithelial cell transformation and cancer development. As we learn more about the pathogenesis of GI cancer and different types of GI tumors, new treatments and diagnostic approaches will emerge.

**REFERENCES**

1 **Ariel I**, Pack GT, Rhoads CP. Metabolic studies in patients with cancer of the gastro-intestinal tract: vii-the influence of gastric surgery upon the chemical composition of the liver. *Ann Surg* 1942; **116**: 924-927 [PMID: 17858155 DOI: 10.1097/00000658-194212000-00017]

2 **Abels JC,** Ariel IM, Rekers PF, Pack GT, Rhoads CP. Metabolic abnormalities of patients with cancer of the gastro-intestinal tract; review of recent studies. *Arch Surg* 1943; **46:** 844

3 **Young NF**, Abels JC, Homburger F, Collier V, Green J. Studies on carbohydrate metabolism in patients with gastric cancer. defective hepatic glycogenesis; effects of adreno-cortical extract. *J Clin Invest* 1948; **27**: 760-765 [PMID: 16695599 DOI: 10.1172/JCI102026]

4 **Sayaman RW**, Saad M, Thorsson V, Hu D, Hendrickx W, Roelands J, Porta-Pardo E, Mokrab Y, Farshidfar F, Kirchhoff T, Sweis RF, Bathe OF, Heimann C, Campbell MJ, Stretch C, Huntsman S, Graff RE, Syed N, Radvanyi L, Shelley S, Wolf D, Marincola FM, Ceccarelli M, Galon J, Ziv E, Bedognetti D. Germline genetic contribution to the immune landscape of cancer. *Immunity* 2021; **54**: 367-386.e8 [PMID: 33567262 DOI: 10.1016/j.immuni.2021.01.011]

5 **Hogg SJ**, Beavis PA, Dawson MA, Johnstone RW. Targeting the epigenetic regulation of antitumour immunity. *Nat Rev Drug Discov* 2020; **19**: 776-800 [PMID: 32929243 DOI: 10.1038/s41573-020-0077-5]

6 **Etchegaray JP**, Mostoslavsky R. Interplay between Metabolism and Epigenetics: A Nuclear Adaptation to Environmental Changes. *Mol Cell* 2016; **62**: 695-711 [PMID: 27259202 DOI: 10.1016/j.molcel.2016.05.029]

7 **Kinnaird A**, Zhao S, Wellen KE, Michelakis ED. Metabolic control of epigenetics in cancer. *Nat Rev Cancer* 2016; **16**: 694-707 [PMID: 27634449 DOI: 10.1038/nrc.2016.82]

8 **Phan AT**, Goldrath AW, Glass CK. Metabolic and Epigenetic Coordination of T Cell and Macrophage Immunity. *Immunity* 2017; **46**: 714-729 [PMID: 28514673 DOI: 10.1016/j.immuni.2017.04.016]

9 **Camacho-Ordonez N**, Ballestar E, Timmers HTM, Grimbacher B. What can clinical immunology learn from inborn errors of epigenetic regulators? *J Allergy Clin Immunol* 2021; **147**: 1602-1618 [PMID: 33609625 DOI: 10.1016/j.jaci.2021.01.035]

10 **Topper MJ**, Vaz M, Marrone KA, Brahmer JR, Baylin SB. The emerging role of epigenetic therapeutics in immuno-oncology. *Nat Rev Clin Oncol* 2020; **17**: 75-90 [PMID: 31548600 DOI: 10.1038/s41571-019-0266-5]

11 **Jones PA**, Ohtani H, Chakravarthy A, De Carvalho DD. Epigenetic therapy in immune-oncology. *Nat Rev Cancer* 2019; **19**: 151-161 [PMID: 30723290 DOI: 10.1038/s41568-019-0109-9]

12 **Tough DF**, Rioja I, Modis LK, Prinjha RK. Epigenetic Regulation of T Cell Memory: Recalling Therapeutic Implications. *Trends Immunol* 2020; **41**: 29-45 [PMID: 31813765 DOI: 10.1016/j.it.2019.11.008]

13 **Seki T**, Fujii G, Mori S, Tamaoki N, Shibuya M. Amplification of c-yes-1 proto-oncogene in a primary human gastric cancer. *Jpn J Cancer Res* 1985; **76**: 907-910 [PMID: 3935622]

14 **Tahara E**, Yasui W, Taniyama K, Ochiai A, Yamamoto T, Nakajo S, Yamamoto M. Ha-ras oncogene product in human gastric carcinoma: correlation with invasiveness, metastasis or prognosis. *Jpn J Cancer Res* 1986; **77**: 517-522 [PMID: 3089984]

15 **Morson B**. President's address. The polyp-cancer sequence in the large bowel. *Proc R Soc Med* 1974; **67**: 451-457 [PMID: 4853754]

16 **Muto T**, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. *Cancer* 1975; **36**: 2251-2270 [PMID: 1203876 DOI: 10.1002/cncr.2820360944]

17 **Cooper HS**, Patchefsky AS, Marks G. Adenomatous and carcinomatous changes within hyperplastic colonic epithelium. *Dis Colon Rectum* 1979; **22**: 152-156 [PMID: 446245 DOI: 10.1007/BF02586805]

18 **Brenner H**, Kloor M, Pox CP. Colorectal cancer. *Lancet* 2014; **383**: 1490-1502 [PMID: 24225001 DOI: 10.1016/S0140-6736(13)61649-9]

19 **Kinzler KW**, Vogelstein B. Lessons from hereditary colorectal cancer. *Cell* 1996; **87**: 159-170 [PMID: 8861899 DOI: 10.1016/s0092-8674(00)81333-1]

20 **Bell DA**, Stephens EA, Castranio T, Umbach DM, Watson M, Deakin M, Elder J, Hendrickse C, Duncan H, Strange RC. Polyadenylation polymorphism in the acetyltransferase 1 gene (NAT1) increases risk of colorectal cancer. *Cancer Res* 1995; **55**: 3537-3542 [PMID: 7627961]

21 **Vander Heiden MG**, DeBerardinis RJ. Understanding the Intersections between Metabolism and Cancer Biology. *Cell* 2017; **168**: 657-669 [PMID: 28187287 DOI: 10.1016/j.cell.2016.12.039]

22 **Pavlova NN**, Thompson CB. The Emerging Hallmarks of Cancer Metabolism. *Cell Metab* 2016; **23**: 27-47 [PMID: 26771115 DOI: 10.1016/j.cmet.2015.12.006]

23 **Hanahan D**, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; **144**: 646-674 [PMID: 21376230 DOI: 10.1016/j.cell.2011.02.013]

24 **Xu W**, Yang H, Liu Y, Yang Y, Wang P, Kim SH, Ito S, Yang C, Wang P, Xiao MT, Liu LX, Jiang WQ, Liu J, Zhang JY, Wang B, Frye S, Zhang Y, Xu YH, Lei QY, Guan KL, Zhao SM, Xiong Y. Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of α-ketoglutarate-dependent dioxygenases. *Cancer Cell* 2011; **19**: 17-30 [PMID: 21251613 DOI: 10.1016/j.ccr.2010.12.014]

25 **Yun J**, Rago C, Cheong I, Pagliarini R, Angenendt P, Rajagopalan H, Schmidt K, Willson JK, Markowitz S, Zhou S, Diaz LA Jr, Velculescu VE, Lengauer C, Kinzler KW, Vogelstein B, Papadopoulos N. Glucose deprivation contributes to the development of KRAS pathway mutations in tumor cells. *Science* 2009; **325**: 1555-1559 [PMID: 19661383 DOI: 10.1126/science.1174229]

26 **Dietl K**, Renner K, Dettmer K, Timischl B, Eberhart K, Dorn C, Hellerbrand C, Kastenberger M, Kunz-Schughart LA, Oefner PJ, Andreesen R, Gottfried E, Kreutz MP. Lactic acid and acidification inhibit TNF secretion and glycolysis of human monocytes. *J Immunol* 2010; **184**: 1200-1209 [PMID: 20026743 DOI: 10.4049/jimmunol.0902584]

27 **Herber DL**, Cao W, Nefedova Y, Novitskiy SV, Nagaraj S, Tyurin VA, Corzo A, Cho HI, Celis E, Lennox B, Knight SC, Padhya T, McCaffrey TV, McCaffrey JC, Antonia S, Fishman M, Ferris RL, Kagan VE, Gabrilovich DI. Lipid accumulation and dendritic cell dysfunction in cancer. *Nat Med* 2010; **16**: 880-886 [PMID: 20622859 DOI: 10.1038/nm.2172]

28 **Jayavelu ND**, Bar NS. Metabolomic studies of human gastric cancer: review. *World J Gastroenterol* 2014; **20**: 8092-8101 [PMID: 25009381 DOI: 10.3748/wjg.v20.i25.8092]

29 **Tsai CY**, Chi HC, Chi LM, Yang HY, Tsai MM, Lee KF, Huang HW, Chou LF, Cheng AJ, Yang CW, Wang CS, Lin KH. Argininosuccinate synthetase 1 contributes to gastric cancer invasion and progression by modulating autophagy. *FASEB J* 2018; **32**: 2601-2614 [PMID: 29401583 DOI: 10.1096/fj.201700094R]

30 **Bornschein J**, Selgrad M, Warnecke M, Kuester D, Wex T, Malfertheiner P. H. pylori infection is a key risk factor for proximal gastric cancer. *Dig Dis Sci* 2010; **55**: 3124-3131 [PMID: 20668939 DOI: 10.1007/s10620-010-1351-x]

31 **Van Cutsem E**, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. *Lancet* 2016; **388**: 2654-2664 [PMID: 27156933 DOI: 10.1016/S0140-6736(16)30354-3]

32 **Kim N**, Park WY, Kim JM, Park JH, Kim JS, Jung HC, Song IS. Gene expression of AGS cells stimulated with released proteins by Helicobacter pylori. *J Gastroenterol Hepatol* 2008; **23**: 643-651 [PMID: 18070016 DOI: 10.1111/j.1440-1746.2007.05241.x]

33 **He XX**, Yang J, Ding YW, Liu W, Shen QY, Xia HH. Increased epithelial and serum expression of macrophage migration inhibitory factor (MIF) in gastric cancer: potential role of MIF in gastric carcinogenesis. *Gut* 2006; **55**: 797-802 [PMID: 16488898 DOI: 10.1136/gut.2005.078113]

34 **Shen R**, Liu H, Wen J, Liu Z, Wang LE, Wang Q, Tan D, Ajani JA, Wei Q. Genetic polymorphisms in the microRNA binding-sites of the thymidylate synthase gene predict risk and survival in gastric cancer. *Mol Carcinog* 2015; **54**: 880-888 [PMID: 24756984 DOI: 10.1002/mc.22160]

35 **Shitara K**, Muro K, Ito S, Sawaki A, Tajika M, Kawai H, Yokota T, Takahari D, Shibata T, Ura T, Ito H, Hosono S, Kawase T, Watanabe M, Tajima K, Yatabe Y, Tanaka H, Matsuo K. Folate intake along with genetic polymorphisms in methylenetetrahydrofolate reductase and thymidylate synthase in patients with advanced gastric cancer. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 1311-1319 [PMID: 20447923 DOI: 10.1158/1055-9965.EPI-09-1257]

36 **Tong D**, Zhang J, Wang X, Li Q, Liu L, Lu A, Guo B, Yang J, Ni L, Qin H, Zhao L, Huang C. MiR-22, regulated by MeCP2, suppresses gastric cancer cell proliferation by inducing a deficiency in endogenous S-adenosylmethionine. *Oncogenesis* 2020; **9**: 99 [PMID: 33168819 DOI: 10.1038/s41389-020-00281-z]

37 **Huang N**, Xu C, Deng L, Li X, Bian Z, Zhang Y, Long S, Chen Y, Zhen N, Li G, Sun F. PAICS contributes to gastric carcinogenesis and participates in DNA damage response by interacting with histone deacetylase 1/2. *Cell Death Dis* 2020; **11**: 507 [PMID: 32632107 DOI: 10.1038/s41419-020-2708-5]

38 **Xiao S**, Li S, Yuan Z, Zhou L. Pyrroline-5-carboxylate reductase 1 (PYCR1) upregulation contributes to gastric cancer progression and indicates poor survival outcome. *Ann Transl Med* 2020; **8**: 937 [PMID: 32953737 DOI: 10.21037/atm-19-4402]

39 **Cho LY**, Yang JJ, Ko KP, Ma SH, Shin A, Choi BY, Kim HJ, Han DS, Song KS, Kim YS, Chang SH, Shin HR, Kang D, Yoo KY, Park SK. Gene polymorphisms in the ornithine decarboxylase-polyamine pathway modify gastric cancer risk by interaction with isoflavone concentrations. *Gastric Cancer* 2015; **18**: 495-503 [PMID: 25079701 DOI: 10.1007/s10120-014-0396-5]

40 **Huang Y**, Zhang J, Hou L, Wang G, Liu H, Zhang R, Chen X, Zhu J. LncRNA AK023391 promotes tumorigenesis and invasion of gastric cancer through activation of the PI3K/Akt signaling pathway. *J Exp Clin Cancer Res* 2017; **36**: 194 [PMID: 29282102 DOI: 10.1186/s13046-017-0666-2]

41 **Katoh Y**, Katoh M. Hedgehog signaling pathway and gastric cancer. *Cancer Biol Ther* 2005; **4**: 1050-1054 [PMID: 16258256 DOI: 10.4161/cbt.4.10.2184]

42 **Huang C**, Yuan W, Lai C, Zhong S, Yang C, Wang R, Mao L, Chen Z, Chen Z. EphA2-to-YAP pathway drives gastric cancer growth and therapy resistance. *Int J Cancer* 2020; **146**: 1937-1949 [PMID: 31376289 DOI: 10.1002/ijc.32609]

43 **Liu W**, Chen Y, Xie H, Guo Y, Ren D, Li Y, Jing X, Li D, Wang X, Zhao M, Zhu T, Wang Z, Wei X, Gao F, Wang X, Liu S, Zhang Y, Yi F. TIPE1 suppresses invasion and migration through down-regulating Wnt/β-catenin pathway in gastric cancer. *J Cell Mol Med* 2018; **22**: 1103-1117 [PMID: 28994231 DOI: 10.1111/jcmm.13362]

44 **Yang XZ**, Cheng TT, He QJ, Lei ZY, Chi J, Tang Z, Liao QX, Zhang H, Zeng LS, Cui SZ. LINC01133 as ceRNA inhibits gastric cancer progression by sponging miR-106a-3p to regulate APC expression and the Wnt/β-catenin pathway. *Mol Cancer* 2018; **17**: 126 [PMID: 30134915 DOI: 10.1186/s12943-018-0874-1]

45 **Li C**, Liu DR, Li GG, Wang HH, Li XW, Zhang W, Wu YL, Chen L. CD97 promotes gastric cancer cell proliferation and invasion through exosome-mediated MAPK signaling pathway. *World J Gastroenterol* 2015; **21**: 6215-6228 [PMID: 26034356 DOI: 10.3748/wjg.v21.i20.6215]

46 **Lordick F**. Targeting the HGF/MET pathway in gastric cancer. *Lancet Oncol* 2014; **15**: 914-916 [PMID: 24965570 DOI: 10.1016/S1470-2045(14)70273-6]

47 **Zhang X**, Wang S, Wang H, Cao J, Huang X, Chen Z, Xu P, Sun G, Xu J, Lv J, Xu Z. Circular RNA circNRIP1 acts as a microRNA-149-5p sponge to promote gastric cancer progression *via* the AKT1/mTOR pathway. *Mol Cancer* 2019; **18**: 20 [PMID: 30717751 DOI: 10.1186/s12943-018-0935-5]

48 **Biagioni A**, Staderini F, Peri S, Versienti G, Schiavone N, Cianchi F, Papucci L, Magnelli L. 5-Fluorouracil Conversion Pathway Mutations in Gastric Cancer. *Biology (Basel)* 2020; **9** [PMID: 32887417 DOI: 10.3390/biology9090265]

49 **Kong F**, Deng X, Kong X, Du Y, Li L, Zhu H, Wang Y, Xie D, Guha S, Li Z, Guan M, Xie K. ZFPM2-AS1, a novel lncRNA, attenuates the p53 pathway and promotes gastric carcinogenesis by stabilizing MIF. *Oncogene* 2018; **37**: 5982-5996 [PMID: 29985481 DOI: 10.1038/s41388-018-0387-9]

50 **Zhong Z**, Cao Y, Yang S, Zhang S. Overexpression of RRM2 in gastric cancer cell promotes their invasiveness *via* AKT/NF-κB signaling pathway. *Pharmazie* 2016; **71**: 280-284 [PMID: 27348973]

51 **Nakada N**, Mikami T, Horie K, Nagashio R, Sakurai Y, Sanoyama I, Yoshida T, Sada M, Kobayashi K, Sato Y, Okayasu I, Murakumo Y. Expression of CA2 and CA9 carbonic anhydrases in ulcerative colitis and ulcerative colitis-associated colorectal cancer. *Pathol Int* 2020; **70**: 523-532 [PMID: 32410301 DOI: 10.1111/pin.12949]

52 **Vié N**, Copois V, Bascoul-Mollevi C, Denis V, Bec N, Robert B, Fraslon C, Conseiller E, Molina F, Larroque C, Martineau P, Del Rio M, Gongora C. Overexpression of phosphoserine aminotransferase PSAT1 stimulates cell growth and increases chemoresistance of colon cancer cells. *Mol Cancer* 2008; **7**: 14 [PMID: 18221502 DOI: 10.1186/1476-4598-7-14]

53 **Li S**, Xie L, Du M, Xu K, Zhu L, Chu H, Chen J, Wang M, Zhang Z, Gu D. Association study of genetic variants in estrogen metabolic pathway genes and colorectal cancer risk and survival. *Arch Toxicol* 2018; **92**: 1991-1999 [PMID: 29766219 DOI: 10.1007/s00204-018-2195-y]

54 **Agarwal S**, Behring M, Hale K, Al Diffalha S, Wang K, Manne U, Varambally S. MTHFD1L, A Folate Cycle Enzyme, Is Involved in Progression of Colorectal Cancer. *Transl Oncol* 2019; **12**: 1461-1467 [PMID: 31421459 DOI: 10.1016/j.tranon.2019.07.011]

55 **Liu J**, Li H, Shen S, Sun L, Yuan Y, Xing C. Alternative splicing events implicated in carcinogenesis and prognosis of colorectal cancer. *J Cancer* 2018; **9**: 1754-1764 [PMID: 29805701 DOI: 10.7150/jca.24569]

56 **Smith B**, Schafer XL, Ambeskovic A, Spencer CM, Land H, Munger J. Addiction to Coupling of the Warburg Effect with Glutamine Catabolism in Cancer Cells. *Cell Rep* 2016; **17**: 821-836 [PMID: 27732857 DOI: 10.1016/j.celrep.2016.09.045]

57 **Hao Y**, Samuels Y, Li Q, Krokowski D, Guan BJ, Wang C, Jin Z, Dong B, Cao B, Feng X, Xiang M, Xu C, Fink S, Meropol NJ, Xu Y, Conlon RA, Markowitz S, Kinzler KW, Velculescu VE, Brunengraber H, Willis JE, LaFramboise T, Hatzoglou M, Zhang GF, Vogelstein B, Wang Z. Oncogenic PIK3CA mutations reprogram glutamine metabolism in colorectal cancer. *Nat Commun* 2016; **7**: 11971 [PMID: 27321283 DOI: 10.1038/ncomms11971]

58 **Wang R**, Xiang W, Xu Y, Han L, Li Q, Dai W, Cai G. Enhanced glutamine utilization mediated by SLC1A5 and GPT2 is an essential metabolic feature of colorectal signet ring cell carcinoma with therapeutic potential. *Ann Transl Med* 2020; **8**: 302 [PMID: 32355746 DOI: 10.21037/atm.2020.03.31]

59 **Guo J**, Gu X, Zheng M, Zhang Y, Chen L, Li H. Azacoccone E inhibits cancer cell growth by targeting 3-phosphoglycerate dehydrogenase. *Bioorg Chem* 2019; **87**: 16-22 [PMID: 30852233 DOI: 10.1016/j.bioorg.2019.02.037]

60 **Tian J**, Lou J, Cai Y, Rao M, Lu Z, Zhu Y, Zou D, Peng X, Wang H, Zhang M, Niu S, Li Y, Zhong R, Chang J, Miao X. Risk SNP-Mediated Enhancer-Promoter Interaction Drives Colorectal Cancer through Both *FADS2* and *AP002754.2*. *Cancer Res* 2020; **80**: 1804-1818 [PMID: 32127356 DOI: 10.1158/0008-5472.CAN-19-2389]

61 **Miao H**, Ou J, Peng Y, Zhang X, Chen Y, Hao L, Xie G, Wang Z, Pang X, Ruan Z, Li J, Yu L, Xue B, Shi H, Shi C, Liang H. Macrophage ABHD5 promotes colorectal cancer growth by suppressing spermidine production by SRM. *Nat Commun* 2016; **7**: 11716 [PMID: 27189574 DOI: 10.1038/ncomms11716]

62 **Sukocheva OA**, Furuya H, Ng ML, Friedemann M, Menschikowski M, Tarasov VV, Chubarev VN, Klochkov SG, Neganova ME, Mangoni AA, Aliev G, Bishayee A. Sphingosine kinase and sphingosine-1-phosphate receptor signaling pathway in inflammatory gastrointestinal disease and cancers: A novel therapeutic target. *Pharmacol Ther* 2020; **207**: 107464 [PMID: 31863815 DOI: 10.1016/j.pharmthera.2019.107464]

63 **Miao Y**, Li Q, Wang J, Quan W, Li C, Yang Y, Mi D. Prognostic implications of metabolism-associated gene signatures in colorectal cancer. *PeerJ* 2020; **8**: e9847 [PMID: 32953273 DOI: 10.7717/peerj.9847]

64 **Fang Z**, Gong C, Liu H, Zhang X, Mei L, Song M, Qiu L, Luo S, Zhu Z, Zhang R, Gu H, Chen X. E2F1 promote the aggressiveness of human colorectal cancer by activating the ribonucleotide reductase small subunit M2. *Biochem Biophys Res Commun* 2015; **464**: 407-415 [PMID: 26093293 DOI: 10.1016/j.bbrc.2015.06.103]

65 **Yang C**, Li C, Li M, Tong X, Hu X, Yang X, Yan X, He L, Wan C. CYP2S1 depletion enhances colorectal cell proliferation is associated with PGE2-mediated activation of β-catenin signaling. *Exp Cell Res* 2015; **331**: 377-386 [PMID: 25557876 DOI: 10.1016/j.yexcr.2014.12.008]

66 **Wei Y**, Liu P, Li Q, Du J, Chen Y, Wang Y, Shi H, Wang Y, Zhang H, Xue W, Gao Y, Li D, Feng Y, Yan J, Han J, Zhang J. The effect of MTHFD2 on the proliferation and migration of colorectal cancer cell lines. *Onco Targets Ther* 2019; **12**: 6361-6370 [PMID: 31496738 DOI: 10.2147/OTT.S210800]

67 **Ju HQ**, Lu YX, Chen DL, Zuo ZX, Liu ZX, Wu QN, Mo HY, Wang ZX, Wang DS, Pu HY, Zeng ZL, Li B, Xie D, Huang P, Hung MC, Chiao PJ, Xu RH. Modulation of Redox Homeostasis by Inhibition of MTHFD2 in Colorectal Cancer: Mechanisms and Therapeutic Implications. *J Natl Cancer Inst* 2019; **111**: 584-596 [PMID: 30534944 DOI: 10.1093/jnci/djy160]

68 **Wilson JM**, Coletta PL, Cuthbert RJ, Scott N, MacLennan K, Hawcroft G, Leng L, Lubetsky JB, Jin KK, Lolis E, Medina F, Brieva JA, Poulsom R, Markham AF, Bucala R, Hull MA. Macrophage migration inhibitory factor promotes intestinal tumorigenesis. *Gastroenterology* 2005; **129**: 1485-1503 [PMID: 16285950 DOI: 10.1053/j.gastro.2005.07.061]

69 **Li X**, Xun Z, Yang Y. Inhibition of phosphoserine phosphatase enhances the anticancer efficacy of 5-fluorouracil in colorectal cancer. *Biochem Biophys Res Commun* 2016; **477**: 633-639 [PMID: 27349874 DOI: 10.1016/j.bbrc.2016.06.112]

70 **Jo YS**, Oh HR, Kim MS, Yoo NJ, Lee SH. Frameshift mutations of OGDH, PPAT and PCCA genes in gastric and colorectal cancers. *Neoplasma* 2016; **63**: 681-686 [PMID: 27468871 DOI: 10.4149/neo\_2016\_504]

71 **Agarwal S**, Chakravarthi BVSK, Behring M, Kim HG, Chandrashekar DS, Gupta N, Bajpai P, Elkholy A, Balasubramanya SAH, Hardy C, Diffalha SA, Varambally S, Manne U. PAICS, a Purine Nucleotide Metabolic Enzyme, is Involved in Tumor Growth and the Metastasis of Colorectal Cancer. *Cancers (Basel)* 2020; **12** [PMID: 32218208 DOI: 10.3390/cancers12040772]

72 **Ferraz JM**, Zinzindohoué F, Lecomte T, Cugnenc PH, Loriot MA, Beaune P, Stücker I, Berger A, Laurent-Puig P. Impact of GSTT1, GSTM1, GSTP1 and NAT2 genotypes on KRAS2 and TP53 gene mutations in colorectal cancer. *Int J Cancer* 2004; **110**: 183-187 [PMID: 15069679 DOI: 10.1002/ijc.20124]

73 **FeiFei W**, HongHai X, YongRong Y, PingXiang W, JianHua W, XiaoHui Z, JiaoYing L, JingBo S, Kun Z, XiaoLi R, Lu Q, XiaoLiang L, ZhiQiang C, Na T, WenTing L, YanQing D, Li L. FBX8 degrades GSTP1 through ubiquitination to suppress colorectal cancer progression. *Cell Death Dis* 2019; **10**: 351 [PMID: 31024008 DOI: 10.1038/s41419-019-1588-z]

74 **Dekker E**, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. *Lancet* 2019; **394**: 1467-1480 [PMID: 31631858 DOI: 10.1016/S0140-6736(19)32319-0]

75 **Balch C**, Ramapuram JB, Tiwari AK. The Epigenomics of Embryonic Pathway Signaling in Colorectal Cancer. *Front Pharmacol* 2017; **8**: 267 [PMID: 28579957 DOI: 10.3389/fphar.2017.00267]

76 **Caputo F**, Santini C, Bardasi C, Cerma K, Casadei-Gardini A, Spallanzani A, Andrikou K, Cascinu S, Gelsomino F. BRAF-Mutated Colorectal Cancer: Clinical and Molecular Insights. *Int J Mol Sci* 2019; **20** [PMID: 31661924 DOI: 10.3390/ijms20215369]

77 **Sanz-Garcia E**, Argiles G, Elez E, Tabernero J. BRAF mutant colorectal cancer: prognosis, treatment, and new perspectives. *Ann Oncol* 2017; **28**: 2648-2657 [PMID: 29045527 DOI: 10.1093/annonc/mdx401]

78 **Pino MS**, Chung DC. The chromosomal instability pathway in colon cancer. *Gastroenterology* 2010; **138**: 2059-2072 [PMID: 20420946 DOI: 10.1053/j.gastro.2009.12.065]

79 **Grady WM**, Carethers JM. Genomic and epigenetic instability in colorectal cancer pathogenesis. *Gastroenterology* 2008; **135**: 1079-1099 [PMID: 18773902 DOI: 10.1053/j.gastro.2008.07.076]

80 **Vogelstein B**, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr, Kinzler KW. Cancer genome landscapes. *Science* 2013; **339**: 1546-1558 [PMID: 23539594 DOI: 10.1126/science.1235122]

81 **Nguyen LH**, Goel A, Chung DC. Pathways of Colorectal Carcinogenesis. *Gastroenterology* 2020; **158**: 291-302 [PMID: 31622622 DOI: 10.1053/j.gastro.2019.08.059]

82 **Cancer Genome Atlas Network.**. Comprehensive molecular characterization of human colon and rectal cancer. *Nature* 2012; **487**: 330-337 [PMID: 22810696 DOI: 10.1038/nature11252]

83 **De Palma FDE**, D'Argenio V, Pol J, Kroemer G, Maiuri MC, Salvatore F. The Molecular Hallmarks of the Serrated Pathway in Colorectal Cancer. *Cancers (Basel)* 2019; **11** [PMID: 31330830 DOI: 10.3390/cancers11071017]

84 **Crockett SD**, Nagtegaal ID. Terminology, Molecular Features, Epidemiology, and Management of Serrated Colorectal Neoplasia. *Gastroenterology* 2019; **157**: 949-966.e4 [PMID: 31323292 DOI: 10.1053/j.gastro.2019.06.041]

85 **Murakami T**, Sakamoto N, Nagahara A. Endoscopic diagnosis of sessile serrated adenoma/polyp with and without dysplasia/carcinoma. *World J Gastroenterol* 2018; **24**: 3250-3259 [PMID: 30090005 DOI: 10.3748/wjg.v24.i29.3250]

86 **Toyota M**, Ahuja N, Ohe-Toyota M, Herman JG, Baylin SB, Issa JP. CpG island methylator phenotype in colorectal cancer. *Proc Natl Acad Sci U S A* 1999; **96**: 8681-8686 [PMID: 10411935 DOI: 10.1073/pnas.96.15.8681]

87 **Davies H**, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, Teague J, Woffendin H, Garnett MJ, Bottomley W, Davis N, Dicks E, Ewing R, Floyd Y, Gray K, Hall S, Hawes R, Hughes J, Kosmidou V, Menzies A, Mould C, Parker A, Stevens C, Watt S, Hooper S, Wilson R, Jayatilake H, Gusterson BA, Cooper C, Shipley J, Hargrave D, Pritchard-Jones K, Maitland N, Chenevix-Trench G, Riggins GJ, Bigner DD, Palmieri G, Cossu A, Flanagan A, Nicholson A, Ho JW, Leung SY, Yuen ST, Weber BL, Seigler HF, Darrow TL, Paterson H, Marais R, Marshall CJ, Wooster R, Stratton MR, Futreal PA. Mutations of the BRAF gene in human cancer. *Nature* 2002; **417**: 949-954 [PMID: 12068308 DOI: 10.1038/nature00766]

88 **Kambara T**, Simms LA, Whitehall VL, Spring KJ, Wynter CV, Walsh MD, Barker MA, Arnold S, McGivern A, Matsubara N, Tanaka N, Higuchi T, Young J, Jass JR, Leggett BA. BRAF mutation is associated with DNA methylation in serrated polyps and cancers of the colorectum. *Gut* 2004; **53**: 1137-1144 [PMID: 15247181 DOI: 10.1136/gut.2003.037671]

89 **Fang JY**, Richardson BC. The MAPK signalling pathways and colorectal cancer. *Lancet Oncol* 2005; **6**: 322-327 [PMID: 15863380 DOI: 10.1016/S1470-2045(05)70168-6]

90 **Li SKH**, Martin A. Mismatch Repair and Colon Cancer: Mechanisms and Therapies Explored. *Trends Mol Med* 2016; **22**: 274-289 [PMID: 26970951 DOI: 10.1016/j.molmed.2016.02.003]

91 **Liu X**, Zhang T, Li Y, Zhang Y, Zhang H, Wang X, Li L. The Role of Methylation in the CpG Island of the ARHI Promoter Region in Cancers. *Adv Exp Med Biol* 2020; **1255**: 123-132 [PMID: 32949395 DOI: 10.1007/978-981-15-4494-1\_10]

92 **Weisenberger DJ**, Siegmund KD, Campan M, Young J, Long TI, Faasse MA, Kang GH, Widschwendter M, Weener D, Buchanan D, Koh H, Simms L, Barker M, Leggett B, Levine J, Kim M, French AJ, Thibodeau SN, Jass J, Haile R, Laird PW. CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with BRAF mutation in colorectal cancer. *Nat Genet* 2006; **38**: 787-793 [PMID: 16804544 DOI: 10.1038/ng1834]

93 **Hinoue T**, Weisenberger DJ, Lange CP, Shen H, Byun HM, Van Den Berg D, Malik S, Pan F, Noushmehr H, van Dijk CM, Tollenaar RA, Laird PW. Genome-scale analysis of aberrant DNA methylation in colorectal cancer. *Genome Res* 2012; **22**: 271-282 [PMID: 21659424 DOI: 10.1101/gr.117523.110]

94 **Takahashi H**, Suzuki Y, Nishimura J, Haraguchi N, Ohtsuka M, Miyazaki S, Uemura M, Hata T, Takemasa I, Mizushima T, Yamamoto H, Doki Y, Mori M. Characteristics of carbonic anhydrase 9 expressing cells in human intestinal crypt base. *Int J Oncol* 2016; **48**: 115-122 [PMID: 26648507 DOI: 10.3892/ijo.2015.3260]

95 **Moon RT**, Bowerman B, Boutros M, Perrimon N. The promise and perils of Wnt signaling through beta-catenin. *Science* 2002; **296**: 1644-1646 [PMID: 12040179 DOI: 10.1126/science.1071549]

96 **Yan K**, Xu X, Wu T, Li J, Cao G, Li Y, Ji Z. Knockdown of PYCR1 inhibits proliferation, drug resistance and EMT in colorectal cancer cells by regulating STAT3-Mediated p38 MAPK and NF-κB signalling pathway. *Biochem Biophys Res Commun* 2019; **520**: 486-491 [PMID: 31606203 DOI: 10.1016/j.bbrc.2019.10.059]

97 **Liu F**, Liu Y, Gao H, Wang L. [Serine hydroxymethyl transferase 2 regulates the AMPK/mTOR pathway and induces autophagy to promote chemotherapy resistance in colon cancer cells]. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi* 2019; **35**: 344-350; 356 [PMID: 31167694]

98 **Hicklin DJ**, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol* 2005; **23**: 1011-1027 [PMID: 15585754 DOI: 10.1200/jco.2005.06.081]

99 **Jin Z**, Li H, Hong X, Ying G, Lu X, Zhuang L, Wu S. TRIM14 promotes colorectal cancer cell migration and invasion through the SPHK1/STAT3 pathway. *Cancer Cell Int* 2018; **18**: 202 [PMID: 30555277 DOI: 10.1186/s12935-018-0701-1]

100 **Bao Y**, Li K, Guo Y, Wang Q, Li Z, Yang Y, Chen Z, Wang J, Zhao W, Zhang H, Chen J, Dong H, Shen K, Diamond AM, Yang W. Tumor suppressor PRSS8 targets Sphk1/S1P/Stat3/Akt signaling in colorectal cancer. *Oncotarget* 2016; **7**: 26780-26792 [PMID: 27050145 DOI: 10.18632/oncotarget.8511]

101 **Toda K**, Kawada K, Iwamoto M, Inamoto S, Sasazuki T, Shirasawa S, Hasegawa S, Sakai Y. Metabolic Alterations Caused by KRAS Mutations in Colorectal Cancer Contribute to Cell Adaptation to Glutamine Depletion by Upregulation of Asparagine Synthetase. *Neoplasia* 2016; **18**: 654-665 [PMID: 27764698 DOI: 10.1016/j.neo.2016.09.004]

102 **Haigis KM**, Kendall KR, Wang Y, Cheung A, Haigis MC, Glickman JN, Niwa-Kawakita M, Sweet-Cordero A, Sebolt-Leopold J, Shannon KM, Settleman J, Giovannini M, Jacks T. Differential effects of oncogenic K-Ras and N-Ras on proliferation, differentiation and tumor progression in the colon. *Nat Genet* 2008; **40**: 600-608 [PMID: 18372904 DOI: 10.1038/ng.115]

103 **Yang C**, Zhou Q, Li M, Tong X, Sun J, Qing Y, Sun L, Yang X, Hu X, Jiang J, Yan X, He L, Wan C. Upregulation of CYP2S1 by oxaliplatin is associated with p53 status in colorectal cancer cell lines. *Sci Rep* 2016; **6**: 33078 [PMID: 27609465 DOI: 10.1038/srep33078]

104 **Nakayama M**, Oshima M. Mutant p53 in colon cancer. *J Mol Cell Biol* 2019; **11**: 267-276 [PMID: 30496442 DOI: 10.1093/jmcb/mjy075]

105 **Yang H**, Wei Y, Yang Y, Zhang Q, Jia Y, Zang A, Ren L. TGF-β1 suppresses proliferation and promotes apoptosis in colon cancer cell by inactivating ERK pathway. *Panminerva Med* 2020 [PMID: 32000462 DOI: 10.23736/S0031-0808.19.03831-X]

106 **Slattery ML**, Herrick JS, Lundgreen A, Wolff RK. Genetic variation in the TGF-β signaling pathway and colon and rectal cancer risk. *Cancer Epidemiol Biomarkers Prev* 2011; **20**: 57-69 [PMID: 21068203 DOI: 10.1158/1055-9965.EPI-10-0843]

107 **Hoeijmakers JH**. Genome maintenance mechanisms for preventing cancer. *Nature* 2001; **411**: 366-374 [PMID: 11357144 DOI: 10.1038/35077232]

108 **Kolodner RD**. Guarding against mutation. *Nature* 2000; **407**: 687, 689 [PMID: 11048703 DOI: 10.1038/35037701]

**Footnotes**

**Conflict-of-interest statement:** There is no conflict of interest associated with any of the senior author or other coauthors who contributed their efforts in this manuscript.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** January 22, 2021

**First decision:** February 24, 2021

**Article in press:**

**Specialty type:** Oncology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Tanabe S **S-Editor:** Fan JR **L-Editor:** Wang TQ **P-Editor:**

**Figure Legends**

 

**Figure 1 Differentially expressed metabolic genes in gastric cancer and colorectal cancer based on The Cancer Genome Atlas database.** A: Differentially expressed metabolic genes in gastric cancer. False discovery rate (FDR) < 0.05, log fold change (logFC) > 1; B: Differentially expressed metabolic genes in colorectal cancer. FDR < 0.05, logFC > 1.5. Log FC: Log fold change.



**Figure 2 Mismatch repair in eukaryotes.** Mismatch repair (MMR) removes nucleotides mispaired by DNA polymerases and insertion/deletion loops (IDLs) ranging from one to ten or more bases that result from slippage during replication of repetitive sequences or during recombination. Defects in this system dramatically increase mutation rates, fuelling the process of oncogenesis. Four main steps involved in MMR are: (1) Recognition of base-base mismatches and IDLs; (2) recruitment of additional MMR factors; (3) search for a signal that identifies the wrong (newly synthesized) strand, followed by degradation past the mismatch; and (4) resynthesis of the excised tract[107]. There are several mispair-recognizing proteins. The eukaryotic MMR system contains proteins related to the bacterial MutS and MutL proteins but is more complicated than the bacterial system. It involves two different heterodimeric complexes of MutS-related proteins, MSH2-MSH3 (known as MutSBeta) and MSH2-MSH6 (known as MutSAlpha), and each has different mispair recognition specificity. Heterodimer MSH2-MSH6 focuses on mismatches and single-base loops, whereas MSH2-MSH3 dimer (MutSBeta) recognizes ILDs. Similarly, instead of a single MutL-related protein, eukaryotic MMR involves a heterodimeric complex of two MutL-related proteins, MLH1-PMS1 (PMS2 in humans)[108]. Heterodimeric complexes of MLH1/PMS2 (MutL-α) and MLH1/PMS1 (MutL-β) interact with MSH complexes and replication factors. Excision and resynthesis of the nascent strand (containing the mismatch or IDL) are performed by several proteins, including proliferating cell nuclear antigen, replication protein-A, replication factor-C, exonuclease-I, DNA polymerases delta/epsilon, endonuclease flap structure-specific endonuclease-1, and additional factors. MMR components also interact functionally with nucleotide excision repair and recombination. PCNA: Proliferating cell nuclear antigen; RPA: Replication protein-A; RPC: Replication factor-C.

**Table 1 Up-regulated metabolism-related genes in gastric cancer based on The Cancer Genome Atlas**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Gene** | **Con mean** | **Treat mean** | **Log FC** | ***P* value** | **FDR** |
| *WARS* | 6.463316413 | 33.79933632 | 2.386648392 | 5.39E-08 | 2.60E-07 |
| *ASS1* | 10.23918101 | 42.338062 | 2.047854908 | 5.71E-06 | 1.81E-05 |
| *RRM2* | 4.193381289 | 13.45216754 | 1.681652732 | 7.79E-13 | 9.82E-12 |
| *PSAT1* | 4.984197042 | 14.58683132 | 1.549233513 | 1.15E-07 | 5.23E-07 |
| *TK1* | 9.404335583 | 25.94196676 | 1.463889934 | 1.90E-08 | 9.60E-08 |
| *TYMS* | 5.252256309 | 13.43148698 | 1.354609806 | 8.20E-15 | 1.85E-13 |
| *P4HA1* | 5.096854107 | 12.3340109 | 1.274963063 | 6.70E-16 | 3.11E-14 |
| *MIF* | 19.56229893 | 46.31616492 | 1.243439876 | 3.49E-07 | 1.44E-06 |
| *AHCY* | 14.87041149 | 34.97985067 | 1.234079561 | 2.23E-10 | 1.71E-09 |
| *SRM* | 15.88621779 | 36.86038375 | 1.214295404 | 2.56E-11 | 2.26E-10 |
| *PAFAH1B3* | 7.126421918 | 16.5295421 | 1.213796955 | 4.78E-11 | 4.04E-10 |
| *MTHFD2* | 5.447936287 | 12.51038205 | 1.199344112 | 5.74E-16 | 2.85E-14 |
| *PAICS* | 6.543206722 | 14.74057996 | 1.171723532 | 9.38E-17 | 6.98E-15 |
| *SMS* | 11.67400201 | 26.12997113 | 1.162406309 | 5.45E-15 | 1.35E-13 |
| *NME1* | 6.553254278 | 14.50996199 | 1.146760323 | 5.99E-13 | 7.81E-12 |
| *PYCR1* | 9.159388726 | 20.07643062 | 1.132179571 | 5.23E-06 | 1.68E-05 |
| *CAD* | 4.618217342 | 10.01148028 | 1.116247328 | 3.37E-17 | 3.14E-15 |
| *ODC1* | 14.89150939 | 31.71876297 | 1.090846515 | 1.34E-06 | 4.97E-06 |
| *ISYNA1* | 4.338447403 | 9.180413895 | 1.08138036 | 9.64E-06 | 2.92E-05 |
| *PLA2G7* | 4.093119979 | 8.652040283 | 1.079839426 | 4.65E-13 | 6.29E-12 |
| *ENTPD6* | 7.372506744 | 15.00708695 | 1.025416818 | 5.98E-10 | 4.20E-09 |
| *ATIC* | 8.653344031 | 17.36986424 | 1.005256812 | 1.25E-16 | 8.48E-15 |

Log FC: Log fold change; FDR: False discovery rate.

**Table 2 Up-regulated metabolism-related genes in colorectal cancer based on The Cancer Genome Atlas**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Gene** | **Con mean** | **Treat mean** | **Log FC** | ***P* value** | **FDR** |
| *CA9* | 0.028995 | 26.60655 | 9.841744 | 1.03E-19 | 3.91E-19 |
| *CEL* | 0.024311 | 14.30974 | 9.201191 | 3.23E-15 | 8.41E-15 |
| *CKMT2* | 0.42259 | 6.021372 | 3.83276 | 5.80E-05 | 8.00E-05 |
| *PSAT1* | 1.864971 | 25.85166 | 3.793031 | 4.00E-28 | 5.61E-27 |
| *SULT2B1* | 0.785605 | 9.164399 | 3.544165 | 1.61E-27 | 1.83E-26 |
| *MTHFD1L* | 1.294767 | 9.556751 | 2.883827 | 2.70E-32 | 4.32E-30 |
| *ACSL6* | 0.319928 | 1.964782 | 2.618552 | 2.94E-14 | 7.16E-14 |
| *HAGHL* | 0.505906 | 2.65869 | 2.393775 | 4.07E-29 | 8.58E-28 |
| *PYCR1* | 8.324112 | 39.39321 | 2.242579 | 8.73E-29 | 1.49E-27 |
| *MAT1A* | 0.370363 | 1.67466 | 2.176855 | 5.78E-11 | 1.14E-10 |
| *AHCY* | 26.97523 | 118.8808 | 2.139808 | 3.53E-27 | 3.67E-26 |
| *NME1* | 4.935536 | 21.03672 | 2.091631 | 6.46E-28 | 8.47E-27 |
| *IMPDH1* | 5.830836 | 24.51912 | 2.072133 | 3.42E-27 | 3.60E-26 |
| *ALDH4A1* | 1.84131 | 7.716947 | 2.067297 | 2.97E-23 | 1.57E-22 |
| *PAFAH1B3* | 7.889409 | 31.58688 | 2.001336 | 5.77E-28 | 7.69E-27 |
| *GPT2* | 2.992286 | 11.89982 | 1.99162 | 3.29E-27 | 3.51E-26 |
| *PHGDH* | 2.694106 | 10.59518 | 1.97553 | 5.21E-10 | 9.66E-10 |
| *AKR1C4* | 0.277697 | 1.064175 | 1.938153 | 1.62E-27 | 1.83E-26 |
| *PLCB4* | 5.394957 | 20.64288 | 1.935961 | 7.02E-08 | 1.14E-07 |
| *DGAT2* | 1.148785 | 4.32325 | 1.912007 | 3.09E-25 | 2.11E-24 |
| *FADS2* | 1.408937 | 5.08608 | 1.851947 | 7.10E-08 | 1.15E-07 |
| *SHMT2* | 9.347261 | 33.69678 | 1.849995 | 1.28E-29 | 3.95E-28 |
| *SRM* | 12.16342 | 43.22303 | 1.829251 | 2.61E-25 | 1.80E-24 |
| *SPHK1* | 0.955052 | 3.20702 | 1.747582 | 1.51E-14 | 3.74E-14 |
| *ASNS* | 3.806487 | 12.6208 | 1.729271 | 7.52E-26 | 5.73E-25 |
| *RRM2* | 6.439151 | 21.27979 | 1.724542 | 6.98E-24 | 3.93E-23 |
| *CYP2S1* | 18.50704 | 61.13654 | 1.723961 | 4.76E-19 | 1.75E-18 |
| *CAD* | 3.562422 | 11.69219 | 1.714615 | 5.30E-29 | 1.01E-27 |
| *MTHFD2* | 5.47575 | 17.67988 | 1.69098 | 2.52E-26 | 2.08E-25 |
| *PSPH* | 2.943986 | 9.195503 | 1.643157 | 1.03E-26 | 9.54E-26 |
| *MIF* | 15.24002 | 47.29712 | 1.633887 | 1.32E-19 | 4.97E-19 |
| *POLD2* | 12.58199 | 38.52394 | 1.614396 | 4.91E-28 | 6.66E-27 |
| *UCKL1* | 6.50296 | 19.90328 | 1.613838 | 2.26E-25 | 1.58E-24 |
| *SORD* | 2.751114 | 8.302656 | 1.593557 | 9.78E-27 | 9.20E-26 |
| *PAICS* | 8.498374 | 25.43873 | 1.581768 | 7.60E-27 | 7.33E-26 |
| *POLR1C* | 4.549977 | 13.53895 | 1.573184 | 1.77E-29 | 4.57E-28 |
| *PPAT* | 1.684581 | 4.984275 | 1.564994 | 4.32E-28 | 5.95E-27 |
| *GALK1* | 3.415609 | 10.02022 | 1.5527 | 5.67E-24 | 3.29E-23 |
| *GSTP1* | 100.8606 | 293.7334 | 1.542144 | 1.14E-22 | 5.58E-22 |
| *TSTA3* | 16.08544 | 46.68479 | 1.537197 | 1.03E-20 | 4.26E-20 |

Log FC: Log fold change; FDR: False discovery rate.