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

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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 prospect 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

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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

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mechanisms of metabolism-associated genes involved in the occurrence and development of GI cancer.

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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-Ordóñez *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

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.

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 THE 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]. During the carcinogenic 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

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.

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- κ B) signaling pathway[50].

METABOLIC GENES INVOLVED IN THE 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* was discovered 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]. *FADS2* is overexpressed in CRC and promotes the proliferation of CRC cells and the growth of

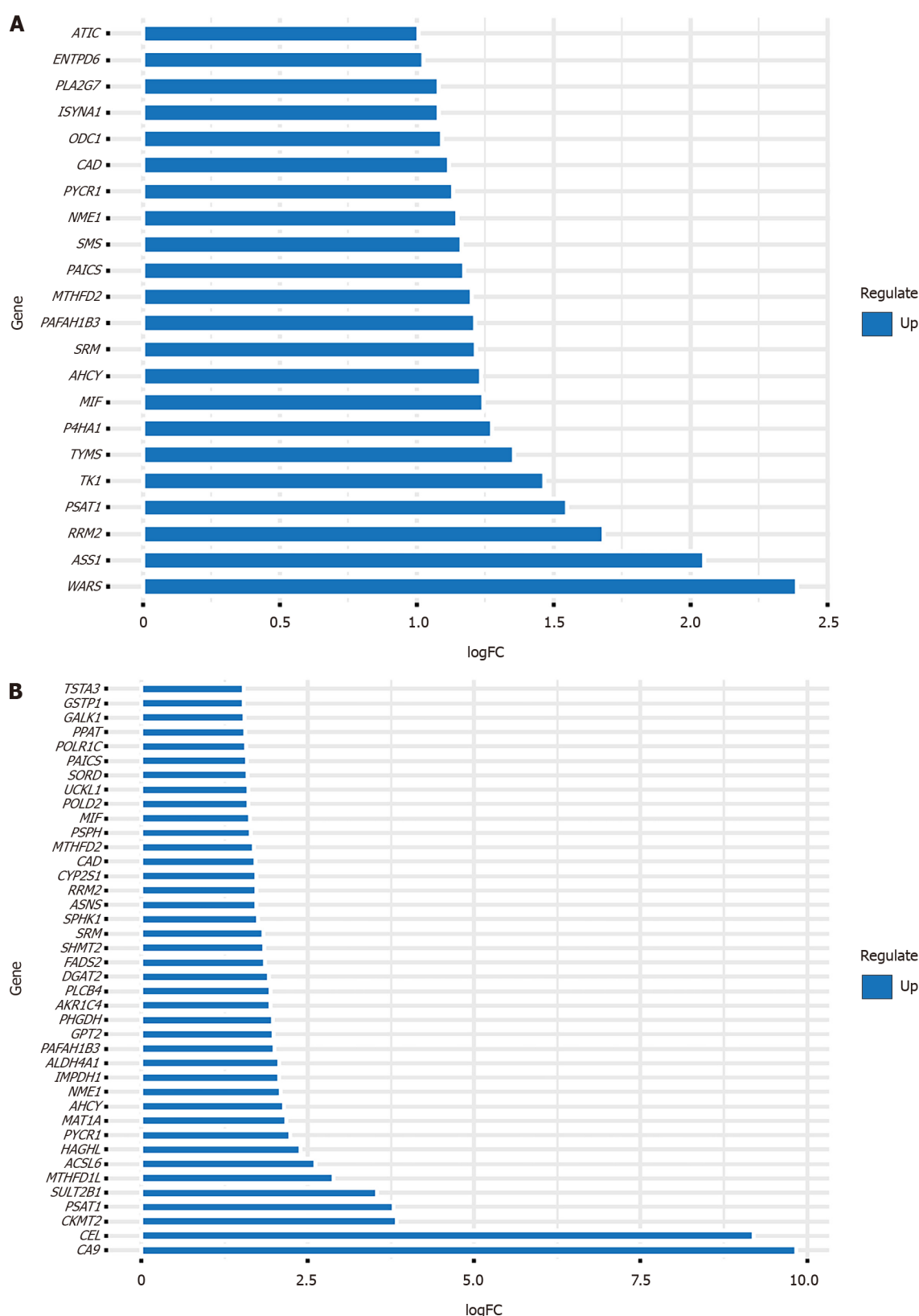


Figure 1 Differentially expressed metabolic genes in gastric cancer and colorectal cancer based on The Cancer Genome Atlas database.

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.

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]. SphK1 overexpression 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 expression can induce cancer and promote tumor growth and invasion. The transcription factor E2F1 regulating the transactivation of RRM2 can 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 methyl-ene-tetrahydrofolate dehydrogenase and methyl-tetrahydrofolate 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*. MIF also 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 PAIC expression 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]. *GSTP1* is 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 primary 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].

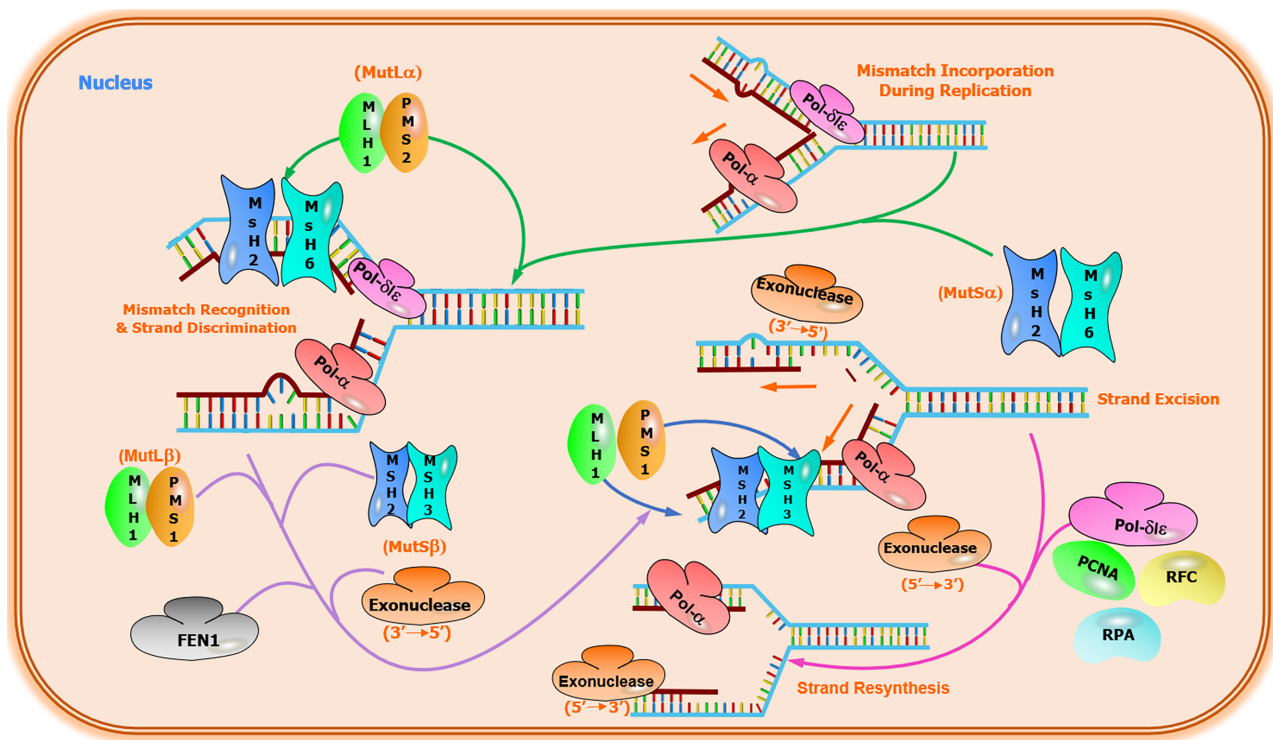


Figure 2 Mismatch repair in eukaryotes. Mismatch repair (MMR) removes nucleotides mispaired by DNA polymerases and insertion/deletion loops (IDLs) ranging from one to ten or more bases that result from slippage during replication of repetitive sequences or during recombination. Defects in this system 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 mismatch 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.

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 the 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, *PCYR1* exerts a crucial role in various cancers; knockdown of *PCYR1* 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-κB[81,102]. CYP2S1 regulates 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. Improving 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 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.

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