Epigenetics and Cellular Metabolism

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Contributor: zhang xiaolin

Epigenetics refers to the regulatory code that dictates gene expression or not and can be stably inherited in the absence of a constant genomic sequence. The current research content of epigenetics mainly includes DNA methylation and hydroxylmethylation, histone modifications, chromosome remodeling, and non-coding RNA regulation. In the early stage of CRC, DNA methylation status begins to change abnormally, mainly through the hypermethylation of some CpG islands leading to the down-regulation of gene expression and genome-wide hypomethylation, which cause genome instability to participate in tumorigenesis and development.

Keywords: colorectal cancer ; epigenetics ; cellular metabolism ; targeted therapy ; tumorigenesis

1. Introduction

Colorectal cancer (CRC), a multi-step, multi-factor complex disease, is a common malignant tumor of the digestive tract. It has become the world's third most common cancer and the second most common cause of death from cancer [1]. Both genetic and environmental risk factors play essential roles during the development of CRC [2]. In recent years, there have been large advances in cancer diagnosis technology. However, because the early symptoms are not dominant, most patients are diagnosed at an advanced stage, which affects the prognosis. Therefore, it is urgent to reduce the high incidence and mortality of CRC, and to develop advanced prevention and treatment strategies. For decades, people have elucidated many aspects of CRC biology, including genetics, epigenetics, metabolism and signaling pathways. Among them, epigenetic changes and cellular metabolic reprogramming play a key role in the occurrence and development of CRC, which is becoming more and more important.

Epigenetics refers to the regulatory code that dictates gene expression or not and can be stably inherited in the absence of a constant genomic sequence. The current research content of epigenetics mainly includes DNA methylation and hydroxylmethylation, histone modifications, chromosome remodeling, and non-coding RNA regulation. In the early stage of CRC, DNA methylation status begins to change abnormally, mainly through the hypermethylation of some CpG islands leading to the down-regulation of gene expression and genome-wide hypomethylation, which cause genome instability to participate in tumorigenesis and development [3][4]. Histone modifications are often closely related to DNA methylation and act together in the process of gene transcription. Covalent modifications in histones includes acetylation, methylation, phosphorylation, ADP-ribosylation, ubiquitination, succinylation and myristoylation, etc. Histone methylation modifications mainly include the monomethylation, dimethylation or trimethylation of histone H3 or H4, such as H3K4me2, H3K4me3, H3K9me3 and H3K27me3. Histone acetylation modifications mainly include histone H3 and H4 acetylation. Histone modification significantly affects gene expression; therefore, there are obvious histone modification abnormalities in CRC [5]. MicroRNA (miRNA) is a small single-stranded non-coding RNA that can regulate the expression of various oncogenes and tumor suppressor genes after transcription. The dysregulated expression of many miRNAs has been shown to mediate important signaling pathways in the multi-step carcinogenesis of CRC [6]. In recent years, long non-coding RNA (lncRNA) has also been shown to be highly associated with the tumorigenesis of CRC [7][8]. Even in mitochondrion, epigenetics also plays a fundamental role in energy hemostasis [9].

Cell division and proliferation requires a large amount of protein, lipid and nucleic acid as molecular raw materials and adenosine triphosphate (ATP) as energy, leading to the reorganization of anabolic flow in tumor cells. Metabolic reprogramming contributes to tumor progression and metastasis, which is considered to be an important hallmark of cancer [10]. The most dominant metabolic reprogramming is the aerobic glycolysis, also called the Warburg effect. Tumor cells increase glucose consumption to promote glycolysis, converting pyruvate to lactic acid even under aerobic conditions, which is different to that of the normal cells. However, glutamine metabolism and oxidative phosphorylation (OXPHOS), as well as lipometabolism and one-carbon pathways, are also altered in some tumor cells because of genetic heterogeneity and microenvironmental discrepancy [11][12][13][14][15]. Cellular metabolism is exquisitely modulated. Nonetheless, the regulatory axis in tumors are usually disorganized. This is the reason why dysregulated cell metabolism

is observed in tumors. Cell metabolism is one of the essential factors contributing to carcinogenesis, and is also a result of malignancy [16][17]. Studies have found that metabolic reprogramming is widespread in CRC. In different types of cancers, including CRC, dysregulated metabolic pathways such as abnormal glycolysis, glutamate and lipid synthesis are often observed, leading to unlimited tumorigenesis [18].

It is worth noting that certain metabolic changes are known to occur at the epigenetic level, so that epigenetics and metabolism are highly intertwined in a mutually beneficial manner [19]. Metabolites produced in metabolic pathways, such as glycolysis cycles and OXPHOS, can be used as cofactors for epigenetic regulation [20]. Studies have also shown that epigenetics can regulate the expression of metabolism-related genes and affect the metabolic reprogramming of tumor cells [21][22][23]. Since many metabolic changes and epigenetic regulation are common in multiple cancer types, they become promising targets for tumor therapy. The purpose of this review is to describe the interactions between epigenetic changes and metabolic reprogramming, and to list the research progress of drugs targeting epigenetics and metabolism in CRC.

2. Epigenetics in CRC

2.1. DNA Methylation and Hydroxymethylation in CRC

2.1.1. DNA Methylation in CRC

DNA methylation is the covalent bonding of a methyl group at the 5′ carbon position of the cytosine of CpG dinucleotides under the action of DNA methyltransferases (DNMTs) to form 5-methylcytosine (5mC). DNMTs are mainly divided into two categories: DNA methylation maintenance enzyme DNMT1 and DNA de novo methylase DNMT3A, DNMT3B and DNMT3L [24]. In the human genome, CpG dinucleotides account for 10% and exist in two forms. One is dispersed in DNA and accounts for 70% to 80% of CpG dinucleotides, and this form is in the form of methyl. Another form, where CpG sites are highly clustered, is called CpG islands, which only account for 1% to 2% of the genome. They are mostly found in the 5′ promoter region of the gene, and can also extend to the exon region of the gene. Changes in normal DNA methylation patterns include DNA hypomethylation, which occurs in normal unmethylated regions of the genome, and DNA hypermethylation, which usually occurs on CpG islands [25].

Recent studies have shown that inactivation of multiple tumor-suppressor genes due to abnormal methylation of CpG islands plays an important role in the development of CRC [26]. DNA methylation has a unique subtype in CRC, which is called the CpG island methylation phenotype (CIMP) [27]. CIMP has been considered a significant direction for CRC research [28]. Evidence shows that this abnormal methylation has been found in the promoter regions of some vital tumor suppressor genes in CRC, including O6-methylguanine-DNA methyltransferase (MGMT), thrombospondin 1 (THBS1), tissue inhibitor of metalloproteinases 3 (TIMP3), $p14^{ARF}$, $p15^{INK4B}$ (cyclin dependent kinase inhibitor 2B), $p16^{INK4a}$, adenomatous polyposis coli (APC), deleted in colorectal carcinoma (DCC), MutL homolog 1 (MLH1), insulin-like growth factor 2 (IGF2), suppressor of cytokine signaling 1 (SOCS-1) and Runt-related transcription factor 3 (RUNX3) genes. The CpG island methylation in the promoter region of the above genes may play a crucial role in the occurrence and development of CRC, and the hypermethylation of the p16 promoter region is common in CRC. Moreover, hypermethylation of the p16 promoter region is widespread in CRC, and p16 methylation can be considered as an indicator of the prognosis of CRC [29].

Genome-wide hypomethylation is aberrant and involves early epigenetic changes during the development of CRC [30]. There are few studies into molecular events related to human genome hypomethylation, but there is evidence that gene-related specific hypomethylation changes are closely related to the development of CRC. In tumor cells, oncogenes are in a state of hypomethylation, and so they are activated. Abnormal hypomethylation of some genes, such as mothers against decapentaplegic homolog 3 (SMAD3), long interspersed nucleotide element-1 (LINE-1) and GDNF family receptor alpha 1 (GFRA1) genes, have been shown to be associated with the poor prognosis of CRC [31][32][33].

2.1.2. DNA Hydroxymethylation in CRC

During active and passive demethylation pathways, there are several kinds of intermediates, such as 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), 5-carboxylcytosine (5caC) and 5-hydroxymethyluracil (5hmU) [9]. Recently, DNA 5hmC is also found to be a biomarker for tumors and may play an important role during tumorigenesis [34]. 5hmC regulates intestinal differentiation in adults, and its aberrant alterations lead to the disorder of gene expression in CRC [35]. Besides, DNA 5hmC is associated with malignant tumor behavior in patients and is considered to be an independent prognostic factor for overall survival, indicating that down-regulation of DNA 5hmC may be a useful biomarker for prognostic assessment of CRC [36]. Aberrant hydroxymethylation of arachidonate 15-lipoxygenase

(ALOX15), growth hormone releasing hormone receptor (GHRHR), tissue factor pathway inhibitor 2 (TFPI2) and transketolase like 1 (TKTL1) at some genome position is correlated with CRC [37]. These lines of evidence indicate that 5hmC in genomes may be a promising biomarker for the diagnosis and prognosis of CRC.

Abnormal 5hmC modifications often occur at transcription start site (TSSs) regions and proximal regions closer to TSSs than that of the abnormal methylation [37]. Some studies have shown that promoters with 5hmC have a natural resistance to hypermethylation in CRC [38]. This result means that 5hmC also functions as an important regulator during transcription, and can be used as a therapeutic target. Vitamin C can promote decitabine or azacytidine-induced DNA 5hmC, leading to subsequent reactivation of $p21^{WAF1}$ (CDKN1A), an epigenetically silenced tumor suppressor in CRC [39]. Treatment with anti-cancerous omega-3 polyunsaturated fatty acids in CRC shows an increase in the genomic DNA 5hmC [40].

2.2. Histone Post-Translational Modification

Histone modification is mainly the various modifications of the free N-terminal, including acetylation, methylation, phosphorylation, ubiquitination and so on. These modifications direct the fate and function of histones, which further alter the chromosomal substructures and subsequently gene transcription. Histone modification can catalyze the change of gene expression through histone modification enzymes, including writers, erasers and readers, which play important roles in the occurrence and development of malignant tumors. Therefore, the dysregulation of histone modification in CRC may change the expression of corresponding genes. Histone modifications can result in the activation or inhibition of transcription, depending on the location and type of modification [41]. The acetylation of lysine residues is related to transcriptional activation and is considered an “activation marker” [42]. Studies have shown that the acetylation level of H3K27 in CRC is significantly higher than that in normal tissues [43]. Ashktorab et al. demonstrated that H3K12 and H3K18 acetylation are significantly increased in moderately and well-differentiated colon cancer, and are decreased in poorly differentiated colon cancer [44]. However, lysine methylation can cause many consequences, such as promotion of transcriptional activity, regulation of transcriptional inhibition and so on. H3K4me3 is enriched in transcriptionally active gene promoters, while H3K9me3 and H3K27me3 are present in transcriptional repressive gene promoters. Benard et al. demonstrated that the high expression of activated histone modification H3K4me3 and the low expression of silent modification H3K9me3 may be related to the poor clinical outcome of CRC [45].

Histone modification is dynamically regulated by a variety of enzymes. For example, histone methyltransferases (HMTs) and histone demethylases (HDMs) are responsible for increasing and removing methyl groups, respectively. Histone acetyltransferases (HATs) can increase the acetyl groups of lysine residues, while histone deacetylases (HDACs) can remove acetyl groups. The dynamic balance of these two enzyme activities maintains the proper state of histone acetylation. Therefore, the dysregulation of histone modification-related enzyme activities is related to the development of cancer [46]. For instance, H3K9 methyltransferase G9a promotes gastric cancer progression and suppresses its autophagy by activating mTOR signaling [47]. H4K16 acetyltransferase MYST1/KAT8 contributes to glioblastoma progression by activating EGFR signaling [48]. H3K9 deacetylase SIRT6, one of the class III HDACs, are important for melanoma and gliomblatoma progression via inhibition of the transcription of glycolytic genes [49][50]. In CRC, epigenetics also functions as a fundamental role during carcinogenesis and subsequent tumor development and metastasis. For instance, H3K79 methyltransferase DOT1L supports CRC cancer progression via epigenetically promoting c-Myc expression [51]. Histone demethylase JMJD2D can interacts with β-catenin, activating the transcription of its target genes, which further supports cell proliferation, migration, and invasion of CRC [52]. Histone deacetylase SIRT1 inhibits CRC metastasis by transcriptional repression of miR-15b-5p [53]. These results indicate that post-translational modifications of the histone are important for CRC tumorigenesis and may be used as therapeutic targets for targeted therapy. Importantly, inhibitors targeting histone deacetylase have become promising drugs for the treatment of CRC [54].

2.3. Non-Coding RNAs in CRC

2.3.1. MicroRNAs in CRC

MiRNA is a type of non-coding single-stranded RNA molecule with a length of about 22 nucleotides encoded by endogenous gene. By binding to a specific site in the 3′ UTR region of the target gene’s mRNA, miRNA promotes the degradation of the target gene’s mRNA, thereby exercising the function of regulating gene expression. A large number of studies have shown that the abnormal regulation of miRNAs plays an important role in the development and metastasis of CRC, showing dual effects of promoting tumors or suppressing tumors [55]. Deng et al. proved that overexpression of miR-21 can promote cell proliferation and invasion, and can alleviate the inhibitory effect of the chemotherapy drug 5-fluorouracil (5-Fu), the first-line drug for the treatment of CRC, on the proliferation and invasion of HT-29 cells [56]. The low expression of miR-133b is related to the poor survival rate and metastasis of CRC [57]. In SW620 and HT-29 cell lines, the ectopic expression of miR-133b can effectively inhibit tumor cell proliferation and apoptosis in vitro and in vivo by directly

targeting receptor tyrosine kinases [58]. It has been found that the expression of miR-143 and miR-145 is reduced in CRC. Transfection of miR-143 and miR-145 precursors into HCT116 or SW480 cell lines, respectively, can observe cell growth inhibition and drug sensitivity enhancement [59]. More and more evidence shows that miRNAs can be used as markers for prognostic evaluation and efficacy evaluation of CRC [6]. Therefore, inhibiting oncogenic miRNAs and restoring the tumor-suppressive miRNAs can be used as promising strategies for the treatment of CRC.

2.3.2. LncRNAs in CRC

Long non-coding RNAs (lncRNAs) are transcripts longer than 200 nucleotides that do not encode proteins. They can interact with almost all molecules in cells, including RNA, DNA, proteins, and even metabolites. Recently, lncRNAs such as cancer-susceptibility 15 (CACS15), cytoskeleton regulator RNA (CYTOR), HOX transcript antisense RNA (HOTAIR), metastasis associated lung adenocarcinoma transcript 1 (MALAT1), taurine upregulated 1 (TUG1), nuclear paraspeckle assembly transcript 1 (NEAT1), miR-17-92a-1 cluster host gene (MIR17HG) and so on, have been shown to be tightly correlated with the prognosis of CRC and function as competitive endogenous RNAs (ceRNAs) [60]. These ceRNA networks, formed by the lncRNA/miRNA/mRNA interactions, have been found in a wide range of biological processes in CRC, including liver metastasis, epithelial-to-mesenchymal transition (EMT), inflammation, and chemotherapy/radiation resistance [60]. Moreover, lncRNAs also function as protein partners to regulate protein stabilization. For instance, lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) directly interacts with Ddx5 protein, enhancing its stability, and sequentially activating Wnt signaling in CRC [61]. LncRNA colon cancer associated transcript 1-L (CCAT1-L), which is specifically transcribed from the upstream 515kb site of MYC in human colorectal carcinoma, promotes long-term chromatin looping, which further enhances MYC transcription regulation via long-range interactions between the MYC promoter and its enhancers [62]. These findings indicate that lncRNAs may be potential biomarkers and therapeutic targets for CRC.

3. Cellular Metabolism in CRC

3.1. Aerobic Glycolysis in CRC

Current studies have found that the Warburg effect is closely related to the occurrence, invasion and metastasis of CRC [63][64]. Compared with normal mucosa, many metabolic pathways of CRC have changed. The metabolic changes of CRC is the result of metabolic reprogramming guided by the activation of proto-oncogenes and the inactivation of tumor suppressor genes [65]. Many genes and proteins related to glucose uptake and glycolysis are dysregulated in CRC, including K-RAS, hypoxia-inducible factor (HIF), MYC, PI3K/AKT/mTOR axis and their related signaling pathways and tumor suppressor gene p53 [66]. In fact, the dysregulation of many of the above genes is related to tumor aggressiveness and poor prognosis of CRC [67]. For instance, K-RAS mutations occur in approximately 40% of CRCs [68][69]. Yun et al. found that glucose transporter 1 (GLUT1) levels were up-regulated in the transcripts of CRC cell lines in the K-RAS gene mutation state, and K-RAS mutant cells showed increased glucose uptake and glycolysis [70]. Another major gene is HIF, which is stimulated by the hypoxic microenvironment. Up-regulation of HIF-1α expression was found in 55% of CRC biopsies [71]. HIF can up-regulate the expression of hundreds of genes, such as GLUT1, c-Myc, vascular endothelial growth factor (VEGF), and glycolysis-related genes. P53 is also one of the most import and mutant genes in CRCs. More than 40% of CRCs carry mutations in the tumor suppressor gene p53, leading to loss or gain of function [72]. Ma et al. found that the glycolysis of wild-type p53 CRC HCT116 cells contributes about 40% to ATP, while the contribution of p53 mutant cell glycolysis to ATP is up-regulated to about 66% [73].

3.2. Glutamine Metabolism in CRC

In addition to glycolysis, glutaminolysis is also important in CRC. Glutamine is the fastest consumed amino acid in tumor cells. The growth of cancer cells is dependent on glutamine, and tumor cells cannot grow in a medium lacking glutamine. After glutamine enters the cell via the transporter alanine-serine-cysteine transporter 2 (ASCT2), it is hydrolyzed into glutamate and ammonia under the action of glutaminase (GLS), glutamine can be converted into α-ketoglutaric acid (α-KG) and enter the tricarboxylic acid (TCA) cycle, which provides intermediate metabolites and energy for cells [74]. The gene expression of glutamine metabolism-related enzymes in CRC is up-regulated. For example, the level of GLS1 mRNA in CRC is significantly higher than that in neighboring normal tissues [75]. These changes are regulated by oncogenes and tumor suppressor genes. Among them, the proto-oncogene c-Myc is the main transcription factor that promotes the metabolism of glutamine in cancer cells. ASCT2 and GLS1 can be transcriptionally activated by c-Myc, thereby promoting the uptake and metabolism of glutamine [76][77].

3.3. Biosynthetic Metabolism in CRC

In addition to energy catabolism, the biosynthetic metabolism of CRC is also very different from normal human tissues, which is mainly reflected in lipids, proteins and nucleotides. For instance, comparing CRC to normal colon tissue, an integrated analysis of miRNA and mRNA endorses a twenty miRNAs signature, which is tightly correlated with metabolic genes including long-chain acyl-CoA synthetase 6 (ACSL6) and phosphoribosyl pyrophosphate synthetase 1 and 2 (PRPS1/2) [78]. Nucleotides in tumors are mainly synthesized by de novo pathways, and their de novo synthetase activities are relatively high in CRC [79][80].

The lipid metabolism of normal cells is maintained at a low level, and the activity of enzymes related to lipid metabolism is also low. Abnormal lipid metabolism of tumor cells is mainly manifested by de novo fatty acid synthesis and enhanced lipid synthesis [81]. Enzymes related to fatty acid synthesis have been discovered, such as ATP citrate lyase (ACLY), acetyl-CoA carboxylase (ACC) and fatty acid synthetase (FASN) is highly expressed in CRC [82][83]. Nevertheless, several genes, such as acetyl-CoA acyltransferase 2 (ACAA2), acyl-CoA dehydrogenase short chain (ACADS), acetyl-CoA acetyltransferase 1 (ACAT1), acyl-CoA oxidase 1 (ACOX), carnitine palmitoyltransferase 1A (CPT1A) and 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2), were shown to be downregulated in CRC, compared with distant normal colon tissue (NTC) in a transcriptome study [84]. This makes it complex for the relationship of lipogenesis and tumorigenesis in CRC.

Protein homeostasis is also important for cell fate. Interestingly, protein synthesis is also accurately modulated in cells and deregulation of it may be an important cause for carcinogensis. It is showed that the PI3K/AKT/mTOR signaling pathway is abnormally activated in CRC, which not only enhances glycolysis, but also enhances protein synthesis [85]. Activated mTOR can regulate downstream pathways, such as eukaryotic initiation factor 4E binding protein 1 (4EBP1) and S6 kinase 1 (S6K1), which are key regulators of protein translation [86].

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