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Research Progress of Epigenetics in Liver Cancer

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Abstract

Epigenetic changes are changes in gene expression by regulating gene transcription and translation without changing the nucleotide sequence of the genome. Although the genome itself changes during the occurrence and development of most malignant tumors, recent studies have found that epigenetic changes also play an important role in the occurrence and development of tumors. Epigenetic modification mainly includes DNA methylation, histone modification and miRNA regulation. This review focuses on the role and mechanism of epigenetic modification in the occurrence, metastasis and invasion of hepatocellular carcinoma (HCC), and summarizes the latest methods for the treatment of HCC by restoring dysregulated epigenetic modification. It provides a theoretical basis for revealing the pathogenesis of liver cancer and developing new methods of diagnosis and treatment.

Keywords

Epigenetics, Hepatocellular Carcinoma, DNA Methylation, Histone Modification, miRNA Regulation

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common tumors of the digestive system. Data showed that liver cancer new were reported for 840,000 S account for 4.7% of the incidence of malignant tumor new 780,000 death cases for liver cancer, 8.2% of malignant tumor mortality [1]. The Hepatocellular carcinoma SHCC hepatocellular carcinoma is the most common type of primary liver cancer histological accounted for about 85% to 90% [2]. Hepatocellular carcinoma (HCC) is one of the most common lethal tumors worldwide. Its occurrence is a progressive, multistage progression from chronic hepatitis/cirrhosis and dysplastic nodular hyperplasia to liver cancer. A clear pattern has not yet

been established. It is gradually recognized that the formation of liver cancer is closely related to allele loss, chromosome abnormality, gene mutation and epigenetic changes [3]. Previous studies mostly focused on genome and gene sequence changes, in contrast to the rise of epigenetics research in recent years, that is, on the basis of not changing the gene sequence, through a variety of ways to change the function and characteristics of genetic genes, and can be inherited through the cell division and proliferation cycle of genomic modifications. Epigenetics can regulate gene expression through DNA methylation, histone modification, chromatin remodeling and non-coding RNA [4]. In recent years, the research progress of liver cancer epigenetics focuses on the following aspects.

2. The Concept of Epigenetics

With the deepening of human studies on the pathogenesis of cancer, it has been clearly recognized that the occurrence and development of cancer is not only related to genetic regulation disorders caused by nucleotide sequence changes such as gene mutation and deletion in cells, but also related to epigenetic regulatory imbalance. Waddington [5] first proposed the phenomenon of epigenetic changes in 1939. Nowadays, epigenetics has become a hot topic in cancer research. At present, the more recognized definition of epigenetics refers to the discipline that affects the change of related gene expression without changing the DNA sequence of related genes in the process of cell division and proliferation, and such changes can be inherited through mitosis and meiosis [6] [7], which mainly studies gene expression unrelated to DNA sequence variation. The nature, function, formation mechanism of heritable phenomena and their role in the occurrence and development of diseases. DNA methylation, egg self-modification, miRNA regulation, chromosome remodeling, and gene imprinting are all obvious features of abnormal epigenetic spectrum of tumor cells.

Hepatocellular carcinoma (HCC) is a malignant tumor with high morbidity and mortality. The key to treatment is early diagnosis. DNA methylation is one of the most important mechanisms of epigenetics. Exploring the change of the carcinogenic mechanism of DNA methylation can provide theoretical basis for the diagnosis of hepatocellular carcinoma. Meanwhile, the methylation level of specific genes can also be used as biomarkers for the early diagnosis and prognosis assessment of hepatocellular carcinoma.

They are involved in cell differentiation, morphogenesis, variability, and adaptability of organisms, and can be affected by genetic and environmental factors. The current research focuses on DNA methylation, histone modification and miRNA regulation, which play an important role in the regulation of mammalian gene expression.

3. DNA Methylation and Liver Cancer

In recent years, with the gradual deepening of research, DNA methylation as an important epigenetic molecular mechanism in tumor has received continuous

attention. DNA hypermethylation: DNA methylation is a form of chemical modification of DNA that can alter genetic expression without altering the DNA sequence. The so-called DNA methylation refers to the covalent binding of a methyl group to cytosine 5 carbon of CpG dinucleotide under the action of DNA methylation transferase. A large number of studies have shown that DNA methylation can cause changes in chromatin structure, DNA conformation, DNA stability and DNA-protein interaction, thus controlling gene expression.

Existing studies have shown that in humans, DNA methylation mainly occurs on cytosine of CpG dinucleotide (also known as CpG island) at the DNA 5' end of DNA [8], CpG islands. The distribution of CpG dinucleotides in the human genome is very uneven, and in some parts of the genome, CpG remains at or above normal probability, and these regions are called CpG islands. Methylation is provided by S-adenosylmethionine. The enzymes that catalyze the methylation process mainly include DNA methyltransferases (DNMTS) and DNA methyl-binding enzymes (MBPs). The former has been found to have 5 families: DNMTl, DNMT2, DNMT3A, DNMT3B and DNMT3L. The latter mainly includes the MBD family (MBDl, MBD2, MBD3, MBD4 and MECP2) and the ZBTB family (ZBTB4 and ZBTB38) [9]. DNA methylation does not change genomic information, but only down-regulates the transcription of messenger RNA (mRNA) by changing the readability of DNA, thus inhibiting gene expression. In humans and mammals, DNA methylation plays an important role by methylating CpP islands in promoters, which can lead to X chromosome inactivation in females, silencing of allelic imstamped genes, insertion of viral genes, and inhibition of replication elements. DNA methylation has two forms, namely DNA hypermethylation and DNA hypomethylation. Similarly, the above two forms of hepatocellular carcinoma also exist and play an important role.

3.1. DNA Hypermethylation

Hypermethylation of promoter CpG island inactivates some tumor suppressor genes and tumor-related genes by down-regulating mRNA transcription, and the inactivation of these genes plays an important role in tumor formation, tumor suppressor genes: Tumor suppressor genes, also known as tumor suppressor genes, or commonly known as anticancer genes, are a class of genes present in normal cells that can inhibit cell growth and have potential cancer suppressor effects. Tumor suppressor genes play a very important negative regulatory role in controlling cell growth, proliferation and differentiation. They interact with proto-oncogenes to maintain the relative stability of positive and negative regulatory signals. When these genes are mutated, missing or inactivated, they can cause malignant transformation of cells and lead to the occurrence of tumors cell cycle regulation, DNA repair, and changes in cell adhesion. Like other malignant tumors, HCC also has some abnormal methylation modifications of TSG (tumor-specific glycoprotein) genes and tumor-related genes, including RASSFlA, hMLHl, SOCSl, etc. [10]. The hypermethylation of CpG island not only exists in

HCC, but also in some precancerous lesions of HCC, such as cirrhosis. Hypermethylation of CpG islands plays an important role in regulating the proliferation and apoptosis of ttCC cells. p16 and p14 genes are important tumor suppressor genes in human body, and p16 inhibits the binding of CDK4 (cyclin-dependent protein kinase 4) to cyclin Dl to inhibit the cell cycle [11] [12]. By binding with MDM.2, p14 inhibits the degradation of p53, thereby causing cell cycle arrest [13] [14] [15]. It has been found that the expression of p16 and p14 is down-regulated in HCC, and this down-regulation is mainly caused by epigenetic changes caused by abnormal methylation of p16 gene promoter, without gene deletion or mutation. Cspase8 (CASP8), a key apoptosis gene in human body, as the initiator of apoptosis process, plays an important role in both cell death receptors and apoptotic mitochondrial pathway [16]. In pediatric neuroblastoma, abnormal hypermethylation of the promoter of CASP8 gene can cause the silencing of CASP8 [17]. In HCC, this abnormal methylation modification of CASP8 gene has also been found, and it is speculated that it can also inhibit apoptosis by down-regulating the expression of CASP8 gene [18]. Abnormal methylation of the promoter of the preapoptotic gene TMSl has also been found in HCC [19], which can cause silencing of the gene in ovarian cancer, melanoma and lung cancer, and further demethylation agent DNA 5' has been applied in HCC. AZA and tidecin can restore the transcriptional activity of TMSl gene, suggesting that abnormal methylation of TMSl gene promoter in HCC can also inhibit the expression of this gene and thus inhibit cell apoptosis [20]. Some studies have also shown that the hypermethylation modification of CpG island also plays an important role in regulating the adhesion and invasiveness of HCC cells [21], which is mainly mediated by E. Abnormal hypermethylation of the promoter of cadherin (CDHl) gene inhibits its activity [22], and the inactivation of the latter can reduce the intercellular adhesion and thus increase the aggressiveness of cancer cells, ultimately leading to distant metastasis of HCC.

3.2. DNA Hypomethylation

In human malignant tumors, DNA hypomethylation can lead to a decrease in genomic stability, mainly affecting DNA repeats, tissue-specific genes and proto-oncogenes. Moreover, the increase of DNA hypomethylation can lead to the evolution of malignant tumors [23]. Similar to other malignant tumors, Lin CH *et al.* found that the methylation degree of DNA 5' telocyridine was significantly reduced in HCC, and the degree of reduction was related to the size and malignancy of the cancer [24]. However, the specific mechanism of DNA hypomethylation modification in HCC has not been clearly studied, and further exploration is needed.

4. Histone Modification and Liver Cancer

In the cytoplasm, histones and DNA constitute the chromatin of cells, and histones can be divided into H1, H2A, H2B, H3, H45 kinds. Among them, two H2A

and H2B dimers and one H3. H4 tetramer together form the nucleosome of chromatin, which is surrounded by a DNA fragment about 147 bp in length, and each nucleosome is connected by a complex chain structure composed of histone H1 and DNA [25]. The structure of chromatin determines whether changes in histone proteins can cause chromatin remodeling, resulting in reversible heritable epigenetic changes in gene function. The structure of the amino terminus of histones H3 and H4 leads to the epigenetic modification of histones, mainly covalent modification, including histone methylation, histone acetylation, histone phosphorylation and histone ubiquitination, etc. Among them, the methylation and acetylation of lysine residues of histones H3 and H4 are mainly studied in depth. Enzymes involved in these modification processes mainly include histone acetylases (HATs), histone deacetylases (HDACs), and histone methyltransferases (HMTs) and histone demethylases (HDMTs) [26]. Histone modification changes gene expression by causing chromatin remodeling without affecting the nucleotide sequence of the genome. This epigenetic change plays an important role in the occurrence and development of many malignant tumors. Studies have shown that histone modification also exists in HCC.

4.1. Histone Methylation

Histone methylation is involved in chromatin formation and maintenance, DNA repair, chromatin imprinting, transcription, and X chromosome inactivation [27]. Histones are methylated on lysine and arginine residues by histone methylation transferase. Lysine can form monomethyl, dimethyl, or trimethyl, whereas arginine can only form monomethyl or dimethyl, and methylation of histone lysine residues is associated with different transcription readings during transcription. Histone methyltransferases are a general term for a group of enzymes containing conserved SET catalytic domains, including: MLL, SETD, SET, EZH, NSD, WHSC, SUV, EHMT, SMYD family, and the histone lysine methyltransferase DOTlL. There are also family members without SET domains, including PRDM and PFM families. Recently, histone lysine demethyltransferases have been identified, including the KDMl/LSDl and JMJD protein families, the latter consisting of JHDMl. 4 and JARIDl [28] [29]. It has been reported that HBX promotes the occurrence and development of liver cancer by up-regulating the expression of SMYD3 in liver cancer cell lines. Tandem repeat polymorphisms of the number of common variables in SMYD3 are susceptibility factors for hepatocellular carcinoma cell lines and Hela cell lines. At the same time, it was found that SMYD3 has histone methyltransferase activity and plays a significant role in transcriptional regulation as a member of the RNA polymerase complex. The activation of SMYD3 plays a decisive factor in inducing hepatocellular carcinoma [30]. In nude mice, RIZ sites are often absent in hepatocellular carcinoma, and RIZl causes cell cycle arrest and apoptosis, thereby inhibiting the formation of hepatocellular carcinoma [31]. Due to complex epigenetic regulation in Ash2 and LSDl, high levels of H3K4 demethylation are significantly reduced

in liver cancer compared to other cancers [32]. Recent studies have found that the expression of JHDMlD in HepG2 cells under nutritional starvation is nearly doubled [33]. Compared to DNA methylation and HDAC inhibitors, the search for HMT inhibitors is still in its infancy. Many histone lysine methyltransferase inhibitors have been discovered, including choritin, BIX.01388 and BIX.01294. Choritin was the first HMT inhibitor to be developed. This complex has a selective effect on SUV39 HMT [34]. Recently, arginine methyltransferase inhibitors AMI-1 and AMI-5 have been discovered. In addition, recent studies have reported that DZNeP can consume components of PRC2 complex in cultured hepatoma cells, affect cell growth and anchor-dependent spheroid formation, and reduce the number of epithelial cell adhesion molecules [35]. In non-obese diabetic combined with severe immunodeficient liver cancer cells implanted in mice, the treatment of DZNep inhibited tumor formation [36]. This finding reinforces the therapeutic potential of HMT inhibitors and reveals the need for the development of new specific histone methylation inhibitors.

4.2. Histone Acetylation

The acetylation status of histones depends on the balance between histone acetyltransferases (HATs) and histone deacetylases (HDACs). HATs found today are mainly divided into two categories according to their localization in cells, namely class A HATs in the nucleus and class B HATs in the cytoplasm [37]. The former regulates gene transcription through acetylation of histone proteins, while the latter mainly catalyzes the acetylation of non-histone proteins in the cytoplasm. Currently, HATs has been found mainly in the GNAT family (GCN5-related histone amino terminal acetyltransferase), MYST family and CBP (p300/CREB binding protein) family. HDACs are mainly divided into four categories according to their structure and localization in the cell: class I (including HDACl, HDAC2, HDAC3, HDAC8), class II (including class Ila: HDAC4, HDAC5, HDAC7, HDAC9; classIIb: HDAC6, HDACl0), class III (SIRT 1-7), and classlV (HDACll) [38]. Transcriptional inhibition of HDACs may play an important role in regulating the process of cell growth inhibition, cell differentiation and apoptosis. Lei W *et al.* found that HDACl can promote T6F131-induced EMT expression and induce hepatocyte migration, and HDACl is highly expressed in HCC. It is also possible to promote HCC invasion through up-regulation of EMT expression [39]. Bhaskara *et al.* found that the deletion of HDAC3 gene can increase the acetylation levels of histones H3K9, H3K14, and H4K5 in the S phase of the cell cycle, and this effect can induce the occurrence of HCC [40]. By comparing HCC with normal liver tissues, Choi *et al.* found that the expression of SIItin l was significantly increased in HCC, and silencing SIIul gene could induce the growth arrest of HCC cells, indicating that SIRTl played an important role in the evolution of HCC [41]. Further studies have found that the up-regulation of SIRTl expression is related to the malignancy of HCC, and inhibition of SIRTl expression can induce senescence and apoptosis of HCC

cells, and further inhibit the progression of HCC [42]. With the deepening of research on histone acetylation, people began to explore drugs targeting HATs and HDACs for tumor treatment. Among all the agents, the research of HDAC inhibitors has made breakthrough progress. Most HDAC inhibitors affect HDAC associated with zinc finger structure. The first clinical drug approved by the US FDA is SAHA, which is mainly used in the treatment of patients with aggressive, persistent or recurrent cutaneous T-cell lymphoma [43]. Loss of histone acetylation contributes to the silencing of genes in cancer, and treatment with HDAC inhibitors can re-establish normal histone acetylation patterns, thereby exerting anti-tumor properties, including increased apoptosis, induced growth arrest, and reduced induced differentiation [44]. Most HDAC inhibitors affect gene expression by blocking one or more HDACs. The dose-dependent properties of TSA, ITF2357 and SAHA in inducing apoptosis in human hepatocellular carcinoma were investigated [45]. In vivo and in vitro, oral administration of HDACi AR42 has been shown to act by inhibiting HDACs and regulating the signaling pathway of cancer cell survival [46]. The combination of leucophage inducer, HDACi OSU.HDAC42 and SAHA increased the anti-cancer efficacy of OSU.HDAC42 and SAHA. In Hep3B and HepG2 hepatocellular carcinoma cell lines, the combination of HDACi MS-275 and CDK inhibitor CYC.202 produced a stronger pro-apoptotic effect than either drug alone. Dose-dependent VPA inhibited the proliferation of tumor cells by activating caspase.3 apoptotic pathway and inhibiting NotchmRNA levels [47].

5. Non-Coding RNA and miRNA

Non-coding Rnas (Ncrnas) can influence chromatin structure and play a role in a variety of epigenetic phenomena. Ncrnas can be divided into long and short chains according to their size. Long chain Ncrnas play a cis-regulatory role at the level of gene clusters and even the whole chromosome, while short chain Ncrnas regulate gene expression at the genome level, mediate the degradation of mRNA, induce changes in chromatin structure, determine the fate of cells, and degrade foreign nucleic acid sequences to protect their own genomes [48]. DDC (Diethyll, 4-Dihydro-2, 4, 6, -Trimethyl -3, 5-Pyridinedicarboxylate) can denature mouse hepatocytes through epigenetic modification of DNA and histone, and change the cell phenotype. After DDC, three kinds of non-coding RNA can be found abnormal expression. Among them, the ncRNA levels of H19 and antisense insulin-like growth factor 2 receptor (AIR) were up-regulated, and GTL2/MEG3 were down-regulated, and the ncRNA levels of H19 and AIR were continuously up-regulated after withdrawal of the drug for 1 month. Methyl-donor s adenosylmethionine (SAMe) can block the action of DDC. Whether the mechanism is through affecting the transcription of H19 and AIR needs to be further clarified. microRNA (miRNA) is a class of short non-coding Rnas that can regulate gene expression. Short hairpin Rnas (shrnas) can be clipped to form mirnas or Sinas that produce RNA interference. Wang *et al.* [49] confirmed that

the early expression of miR-181b in CDAA (choline deficient and amino acid) diet mice was related to the TGF-J3 signaling pathway, and the expression of its target tumor suppressor gene TIMP3 was significantly inhibited. Up-regulation of miR-181b also enhanced the resistance of HCC cells to adriamycin. Other studies have determined that the overexpression of miR-221 also plays a key role in the formation of liver cancer, suggesting that inhibiting the expression of miR-221 may be a new approach for the treatment of liver cancer. However, Beer *et al.* [50] [51] found that even a small dose of shRNA without sequence correlation can still cause miRNA expression disorder in hepatocytes, induce apoptosis, accompany hepatocyte injury, stimulate the proliferation of adjacent hepatocytes, and accelerate the occurrence of liver tumors. Therefore, this promising biological therapy technology also has great risks.

6. Summary and Outlook

The most exciting development in cancer research over the past 20 years has been the discovery and confirmation of the key role that epigenetic regulation plays in all stages of cancer development and development. At present, it is generally accepted that chromatin structure has an influence on gene expression, and a large amount of information has been obtained about the key role of epigenetic regulation in the various stages of cancer occurrence and development, which is playing an increasingly important role in guiding clinical practice. Tumor epigenetics has become an emerging and hot research field. At the same time, compared with DNA sequence changes, epigenetics is highly reversible and easy to regulate, providing new ideas and broad prospects for cancer prevention, diagnosis, prognostic analysis and treatment. The relationship between epigenetics and liver cancer is very close, and the specific mechanism still needs to be further studied. Existing drugs targeting epigenetic regulation lack specificity and have large toxic side effects. How to design and develop small molecule drugs targeting a specific enzyme protein or even a specific functional group or variant is worthy of further exploration. The apparent changes can be found in the early lesions of tumors, which provide a new idea for the early diagnosis of tumors. However, due to the interaction between various epigenetic modifications and the complexity of tumor etiology, further studies on epigenetic changes in tumorigenesis are still needed to clarify which epigenetic modifications play a major role in tumorigenesis and their main targets, so as to provide a theoretical basis for tumor diagnosis and treatment. With the completion of the mapping of the human epigenome, the use and research of the epigenome will help to better understand the relationship between epigenetics and tumors, and provide a new vision.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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