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REVIEW ARTICLE

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Current insights into the epigenetic mechanisms of skin cancer

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Abstract

Skin cancer is a manifestation of tumors. The different types of skin cancer are named according to their source of tumor cells. Currently, there are three main types of skin cancer. They are squamous cell carcinoma, basal cell carcinoma, and melanoma. Their epidemiological characteristics, clinical classifications, and treatment methods are somewhat different. The epigenetic modifications are also different in these three types of skin cancer. Epigenetics is the change in gene expression and function and the generation of a heritable phenotype without changing the DNA sequence. The phenomenon of epigenetics involves a variety of processes, including the methylation of DNA and RNA, histone modifications, RNAi, and chromatin remodeling. Researchers have found that DNA, RNA, histone, and chromatin level modifications cause heritable changes in gene expression patterns. This review will introduce the role of epigenetics in skin cancer from the three following angles: DNA methylation, histone modifications, and RNA methylation.

KEYWORDS
epigenetics, RNA methylation, skin cancer

1 | INTRODUCTION

The skin is the organ that is the most exposed to the external environment, and its integrity and the extent of interaction with environmental factors affect the health of organisms (Table 1). It has a rich supply of blood vessels, and its structure is quite complex. At times, it falls a victim to different kinds of skin lesions, of which, skin tumors are the most noticeable because they affect the aesthetics of the skin and also threaten human health.

Most skin cancers originate from the epidermis. Basal cell carcinoma is the most common type, and this type is derived from the basal cells near the epidermis-dermis junction. The second most common type is squamous cell carcinoma, which is derived from keratinocytes. The third is melanoma, which is derived from basal intercellular melanocytes (Law & Jacobsen, 2010).

Skin cancer mainly occurs between the ages of 30 and 70. Its incidence is higher with increasing age. However, there are many differences in skin cancer types. Many external factors can cause skin cancer, such as ultraviolet radiation, chemical carcinogens, ionizing radiation, viruses, and other diverse environmental carcinogenic factors. It is also closely related to genetic characteristics, immune function, and hormone levels. Epigenetic modifications are important modifications in the pathogenesis of skin cancer (Figure 1). Epigenetics is the study of heritable changes in gene expression and cell phenotype caused by mechanisms other than DNA sequence changes. Epigenetic phenomena involve DNA methylation, histone modifications, RNA methylation, RNAi, chromatin remodeling, and so on. DNA methylation is one of the most common posttranscriptional and postreplication modifications. According to the definition, DNA methylation is a heritable epigenetic mechanism that limits the covalent addition of a methyl group to the 5th carbon of cytosine in a CpG dinucleotide. Abnormal DNA methylation is an important epithelial characteristic of tumors. It participates in the occurrence and development of tumors (Hartman & Czyz, 2015). Histones are the main carriers of epigenetic information. A covalent modification on the terminal amino acid tail has a significant impact on the control of chromosome structure and on the regulation of gene transcription. It is a control switch that determines whether the gene is expressed or not. The N-terminal amino acid residues of histones are posttranscriptional modification sites and undergo chemical modifications, such as acetylation, methylation, phosphorylation, adenylation,

TABLE 1 Factors and treatment of three different types of skin cancer

Skin cancer	BCC	SCC	Melanoma
Influencing factors	UV, sunlight, ionizing radiation, various harmful chemicals, and dust intake	UV, petroleum, asphalt, tar, arsenic, fluorene, phenanthrene	UV, family medical history, trauma, hormones
Types	1. Shallow 2. Nodular 3. Pigment 4. Hard spot	1. Shallow 2. Deep 3. Transfer	1. Nodular 2. Superficial diffuse 3. Malignant freckles 4. Acral melanoma
Treatment methods	1. Surgical: Scraping, freezing, radiation, surgical resection, MMS. 2. Nonsurgical: Radiation, photodynamic therapy, drugs	1. Drugs 2. Radiation 3. Gene 4. Photodynamic therapy 5. Surgical treatments	1. Chemical drug, 2. Immunotherapy, 3. Antibody drugs 4. Chinese traditional medicine treatments

Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

ADP ribosylation, and ubiquitination (Kouzarides, 2007). The transcription of many key genes plays a vital role in the occurrence and progression of tumors (Khan, Reddy, & Gupta, 2015). The presence of RNA methylation modifications has been known for decades; RNA methylation occurs in different RNA types in many species, and their distribution is species specific. RNA methylation-mediated epigenetic transcriptome regulation and function has become a new field of RNA biology. The newly discovered RNA epigenetic modification N6-methyladenosine is a heritable marker that can be used to study the regulation of eukaryotic gene expression after transcription. The modification of m6A is reversible and dynamic in mammalian cells. It has been presented as another epigenetic regulation similar to histone and DNA modifications. m6A RNA methylation is involved in all phases of the RNA life cycle, including nuclear export, RNA processing, RNA degradation, translation, and regulation. m6A methylation has been discovered to affect tumor initiation and progression through multiple mechanisms.

2 | SKIN CANCER

2.1 | Basal cell carcinoma

Basal cell carcinoma (BCC) is a skin malignancy from the basal cells near the epidermis-dermis junction, which was first reported by Kropecher in 1903. It grows slowly and rarely migrates. It occurs in the skin where there is often exposure to the sun, especially in the face and neck. The incidence was 726 cases per 100,000 people in Australia, 165 cases per 100,000 people in Minnesota, and 114.2 cases per 100,000 people

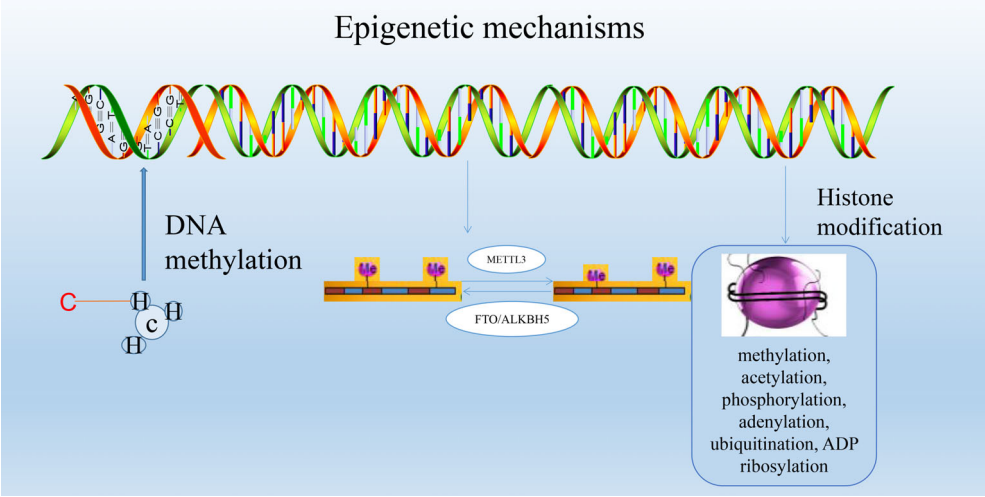

FIGURE 1 The landscape of epigenetic mechanisms. DNA methylation, histone modification, and RNA methylation are the three epigenetic mechanisms that are described in this review. One of the most studied epigenetic mechanism is DNA methylation, which occurs mainly on CpG islands located in different repetitive genome regions or, more commonly, in promoter regions. Histone modifications are also a part of the epigenetic mechanism and mainly include the methylation, ubiquitylation, acetylation, sumoylation, and phosphorylation of the histone tails. Due to the type of modification, these mechanisms can result in the inverse blockage of function or the increased activity of the specific DNA segment. N6-methyladenosine (m6A) is the most common mRNA modification. m6A modification is conducted by its "readers," "erasers," and "writers" to remove, add, or preferentially bind to m6A. m6A methylation occurs at once after pre-mRNA transcription by METTL3-containing methyltransferases, while the demethylation of m6A is by FTO and ALKBH5

in South Wales (Holmes, Malinovszky, & Roberts, 2000). In China, the incidence of skin cancer was lower compared to the incidence in other locations. The incidence was only 1.53 cases per 100,000 people in Shanghai. It has also been found that the incidence is higher in males than that in females, and the incidence in elderly people is higher than that in younger people. Ultraviolet radiation is the main precipitating factor of BCC. Other factors also affect the occurrence of BCC, including high-energy diets (especially high fat, low vitamin intake), various harmful chemicals, and dust intake. BCC is divided into the four following types in clinical practice: the shallow, nodular, pigment, and hard spot types. The treatment of BCC falls into two general categories: surgical and nonsurgical therapies.

2.2 | Squamous cell carcinoma

As the second highest incidence of skin cancer, squamous cell carcinoma (SCC) has also increased every year. According to Robberst, the rate of SCC in the United Kingdom is 35.8 cases/10 million people, and this is one of the most common malignancies in the United Kingdom. The data show that the incidence has increased rapidly in those who are older than 60 years old and that the incidence is higher in men than it is in women. Asians appear to have the greatest levels of exposure. Excessive sun exposure can cause skin inflammation, metabolic abnormalities in tissues, and lower immune system functions; this leads to cell mutation and canceration. According to the area of the SCC, the depth and scope of invasion can be divided into three types as follows: the shallow, deep, and transfer types. The treatment methods include drug, radiation, gene, photodynamic, and surgical treatments.

2.3 | Melanoma

Melanoma is an epithelial malignant tumor derived from melanocytes originating in the nerve ridge. Among malignancies, the proportion of malignant melanoma is 1–2%. It has a high degree of malignancy, is highly invasive, and has the greatest rates of mortality. It occurs mainly in the vulva, eyes, skin, sinuses, lungs, throat, digestive tract, and reproductive tract and can also occur in the anus and rectum. There is a gender difference in the occurrence of melanoma. The incidence of melanoma in men is higher than that in women, and the number of new cases in men is 1.6 times that of women. Caucasians have the highest incidence among all races. In addition, according to data released by the NCI Monitoring Research Project, the occurrence of cutaneous melanoma has a certain age trend. Among people under the age of 75, new cases increase with age. The new cases in the 65–74 age group were the most common, reaching 22.7%, and the median age of onset was 64 years. In males, it often occurs on the skin of the ears, neck, back, and shoulders, while the predominant sites for women are the lower extremities, perineum, and anal skin. Similar to other cancers, the occurrence of melanoma is mainly caused by genetic mutations and environmental factors. UV irradiation is closely related to the occurrence of melanoma. However, UVA does not directly affect mutations or damage DNA. Instead, it generates reactive oxygen species through non-DNA photoreceptors in the body. The resulting oxygen radicals cause DNA damage and fragmentation, resulting in gene mutations (Tawee et al., 2015). According to the pathological type, melanomas can fall into the following four types: superficial diffuse, acral, malignant freckles, and nodular melanoma. The clinical treatment of melanoma includes chemical drugs, immunotherapy, antibody drugs, and traditional Chinese medicine treatments.

3 | EPIGENETIC

3.1 | DNA methylation

DNA methylation is a natural modification of DNA (Sun et al., 2012). DNA methylation refers to the covalent attachment of a DNA methyl group to the 5th carbon on the cytosine of a CpG dinucleotide, and this reaction is catalyzed by a DNA methyltransferase. The distribution of CpG dinucleotides in the human genome is not uniform. It often accumulates in certain places and forms DNA fragments (300–3,000 bp) with high CG content. DNA methylation mainly occurs in CpG dinucleotides. DNA methylation is involved in various physiological processes, such as differential gene expression, chromosome inactivation, aging, and cancer development. It can also cause changes in molecular biology, such as the interaction with protein, chromatin structure, DNA stability, and conformation. In addition, the methylation of gene promoter CpG islands participates in the process of the tumor cell cycle, gene transcription, DNA damage repair, cell differentiation, and anticancer drug metabolism. In mammals, there are three major known transferases regulating DNA methylation (DNMT1, DNMT3a, and DNMT3b), which are overexpressed in human tumor cells (Song et al., 2015). DNMT catalyzes DNA methylation, and DNMT activity has a significant impact on DNA methylation (Sun et al., 2012). Among them, the methylation status of the genome is mainly maintained by DNMT1, and it plays a vital role in inhibiting the expression of tumor suppressor genes in human cancer cells. Its increased activity is considered to be a feature of early molecular changes in tumor cells (Seo, Choi, Moon, Kim, & Park, 2017). DNMT1 plays an important role in the hypermethylation of gene promoters and is associated with the malignant transformation of human malignancies. DNMT3a and DNMT3b mainly mediate the methylation of new CpG sites. Although DNMT3a has low expression levels in the various tissues of the body, it has the effect of remethylation and maintains the remethylation status of tissue cells. At the same time, reducing the expression level of DNMT3a can restrain the metastasis and growth of melanoma tumor cells to an extent.

3.2 | Histone modifications

The addition of a histone modification is a significant method of epigenetic regulation and has special physiological and biochemical functions. According to the ratio of the basic amino acids contained and the difference in the molecular weight, histones are mainly divided into five types: H1, H2A, H2B, H3, and H4. The nucleosome is the basic unit of chromatin and is formed around the octahedral core that

consists of 145–147 pairs of DNA bases entangled in two units of histone H2A, H2B, H3, and H4. The nucleosomes are linked by DNA sequences of approximately 60 bp in length. Histone H1 binds to these linker DNAs. The histone tail interacts with DNA, regulatory proteins, enzymes, and other chromatin proteins, and most of the posttranslational modifications of histones occur at the 15th to 38th amino acid residues of this domain (Furumatsu & Ozaki, 2010). In addition, histone tails play a key role in the process of chromatin assembly and aggregation into highly ordered structures. The extent of chromatin condensation directly affects DNA replication, recombination, and transcription. Histone modifications can change the structure and function of chromatin, can affect the transcription of many key genes, and play a significant role in the occurrence and progression of tumors (Khan et al., 2015). The N-terminal amino acid residues of histones are posttranscriptional modification sites. They can undergo chemical modifications, such as acetylation, methylation, phosphorylation, adenylation, ADP ribosylation, and ubiquitination (Kouzarides, 2007). Currently, the most studied are methylation and acetylation modifications. Histone acetyltransferase and histone deacetylase (HDAC) regulate histone acetylation. Histone acetylation plays a significant biological role in many cellular processes, such as nucleosome assembly, gene transcription, and changes in the chromatin state. Histone methylation modification refers to the process of the methylation and demethylation of the amino acids of histones H3 and H4 under the action of histone methyltransferases and histone demethylases. This process is mainly for the modification of the N-terminal arginine and lysine residues. The enzyme that catalyzes arginine methylation is from the HRMT family. The enzyme that catalyzes lysine methylation is from the HKMT family (Varier & Timmers, 2011). Histone methyltransferases regulate the cell cycle. The abnormal expression of gene expression and the overexpression of histone methyltransferases are present in many tumors.

3.3 | RNA methylation

There are hundreds of modifications in RNA, many of which have been revealed by the function of RNA modification. There are simple modification groups, such as methyl and acetyl groups, but there are also some complex modifications with heterocycles. These diverse modifications make RNA have complex regulatory functions. Chemical modifications on RNA mainly occur on tRNA followed by rRNA; approximately 1/3 of the RNA modifications occur on it, and approximately 10% of the modifications occur on mRNA. There are also some modifications found on noncoding RNAs. Of the numerous RNA modifications, currently, the most interesting is the highly conserved N6-methyladenosine (m6A), which is the most abundant in eukaryotes. m6A was originally identified in 1974. It is the most extensive base modification on all RNA types, including rRNA, mRNA, tRNA, snoRNA, and ncRNA and accounts for ~0.2–0.6% of all adenosines in mammalian mRNA. There are three nucleotides in each of the consensus sequences: G(m6A)C (70%) or A(m6A)C (30%) in each transcript (Molinie et al., 2016). m6A has a high content and is relatively conservative in distribution; but more importantly, m6A is the first RNA methylation modification found to have a dynamic, reversible modification process. High-throughput sequencing has shown that the distribution of m6A in mature transcripts is not random but mainly occurs in the 5′ and 3′ untranslated regions (5′ and 3′ UTRs) and within long internal exons (Batista et al., 2014); consequently this influences the function and processing of RNAs, including mRNA translation (Kloor & Osswald, 2004), RNA stability (Chen et al., 2014), alternative splicing (Zhao et al., 2014), and polyadenylation (Gordon et al., 2003). m6A is regulated in vivo by three effector proteins: the writer, eraser, and reader proteins (Fu, Dominissini, Rechavi, & He, 2014). m6A methyltransferase is a METTL3-METTL14 complex (Ping et al., 2014). There are two m6A demethylases: ALKBH5 (Zheng et al., 2013) and fat mass and obesity associated (FTO) (Jia et al., 2011). They belong to the Alkb double oxidase family; the m6A reader contains a YTH domain (Wang et al., 2014). The m6A methylase complex consists of at least five "writer" proteins, of which, METTL3 acts as the catalytic core. METTL14 is supported as a structure for METTL3, while WTAP stabilizes the core complexes. The "erasers" consist of FTO and ALKBH5. They act as demethylases to reverse m6A modifications (Zheng et al., 2013). The functional interaction between m6A demethylases and methyltransferases may determine the dynamic regulation of m6A modifications.

4 | THE ROLE OF EPIGENETICS IN SKIN CANCER

4.1 | The role of DNA methylation in skin cancer

DNA methylation is a mechanism that regulates gene expression. Abnormal DNA methylation and altered DNA methylation patterns are common epigenetic phenomena in tumor cells. The methylation of gene promoter CpG islands includes the regulation of tumor cell cycle, gene transcription, cell differentiation, DNA damage repair, and anticancer drug metabolism. The occurrence of multiple types of cancer has an important relationship with the abnormal methylation of DNA. Studies have found that the hypomethylation of the entire genome can make the oncogene active and that the hypermethylation of CpG islands can inhibit tumor suppressor genes. Therefore, the hypomethylation of the entire genomic DNA and the hypermethylation of CpG islands can cause cancer (Balgkouranidou, Liloglou, & Lianidou, 2013). Thus far, in cell lines and human melanoma tumors, genome-wide aberrant DNA methylation has been observed. It is associated with the cellular and functional characteristics or the clinical pathology of the disease. In an early study on aberrant melanoma and DNA methylation, methylmion specific PCR was used to determine the methylation status of two regions of the tumor suppressor gene RASSF1A in 44 human melanoma tumors and in 11 melanoma cell lines. Region 1 is located upstream of the transcription initiation codon and has three Sp1 consensus binding sites, and region 2 is located in the first exon (1a) of the open reading frame of the RASSF1A transcript. The proportions of hypermethylation in all cell lines of RASSF1A regions 1 and 2 were observed at 64 and 82%, respectively. Cell lines that are hypermethylated in both regions account for 64%. Similarly, the proportion of the hypermethylation of

RASSF1A regions 1 and 2 was observed in 41 and 50%, respectively, of melanoma tumors, and the proportion of hypermethylation in both regions was 36%. The treatment of melanoma cell lines with the DNA demethylating agent 5-aza-2′-deoxycytidine led to the re-expression of the RASSF1A gene, suggesting that CpG island hypermethylation in the promoter and concomitant gene silencing have predictive value for the development of human melanoma (Spugnardi, Tommasi, Dammann, Pfeifer, & Hoon, 2003). In addition to the MLH1 gene, the hypermethylation of the promoter CpG island was observed in all cancer-associated genes of the melanoma cell line. In addition, the global hypomethylation of the Alu and LINE-1 sequences was discovered in all melanoma cell lines, with an average methylation level of 36% (normal melanocytes were 65%) and 40% (normal melanocytes were 44%). The methylation levels of the Alu and LINE-1 sequences in the melanoma cell line were positively correlated. In both sequences, there was also a direct relationship between global hypomethylation and the number of hypermethylated genes. Moreover, in the test of melanoma cell lines, the MAGEA1 and maspin genes were found to lose their methylation modifications at frequencies of 44 and 25%. Analysis of the gene expression of six hypermethylated genes in melanoma cell lines and the determination of transcriptional gene silencing by RT-PCR correlates with promoter CpG island methylation in each gene (Tellez et al., 2009). This study confirms that the hypermethylation of the promoter regions of cancer-associated genes with transcriptional disorders is often observed in human melanoma.

4.2 | The role of histone modifications in skin cancer

Abnormal histone modifications can cause an imbalance in gene expression and can lead to disease. It plays a key role in the pathological process of tumor and autoimmune diseases (Gray, 2014). At present, the close relationship between histone modifications and abnormal DNA methylation has been well confirmed (Clements et al., 2012). Therefore, studying histone modifications in melanoma will help to explain the available DNA methylation data. Nevertheless, the lack of complex and robust analyses has made it difficult to characterize histone modifications (Greenberg, Chong, Huynh, Tanaka, & Hoon, 2014). The abnormal acetylation of histones is thought to influence the pathophysiology of melanoma by disrupting the same pathways involved in mutations and the hypermethylation of CpG islands (van den Hurk et al., 2012). In melanoma, gene expression profiling shows that the loss of the expression of tumor suppressor genes is a reversible deacetylation of lysine residues in local histones by HDACs (Florenes et al., 2004). HDAC inhibitors are being taken into account for the treatment of melanoma, although data on the posttranslational modifications of histones are limited (Martí, Sorolla, & Yeramian, 2012). Histone hypoacetylation is also associated with the downregulation of certain pro-apoptotic proteins, such as Bak, Bim, and Bax, which belong to the BCL-2 family (Zhang, Gillespie, Borrow, & Hersey, 2004). A recent study has shown that PIB5PA has a tumor suppressive effect and is usually downregulated in melanoma. The downregulation of PIB5PA in a certain proportion of melanoma is due to histone deacetylation by histone hypoacetylation mediated by binding to the transcription factor Sp1 on the PIB5PA gene promoter (Ye et al., 2013). Histone methyltransferase SET Domain, Bifurcated 1 (SETDB1) upregulates melanoma and accelerates tumor progression in a zebrafish melanoma model with the BRAFV600E mutation. SETDB1 catalyzes the trimethylation of histone H3K9, thus promoting the inhibition of target genes (Ceol et al., 2011). Unlike BRAFV600E, which is present in melanoma (Karram et al., 2013), the SETDB1 protein is increased in melanoma but not in benign nevi or in normal melanocytes. This study further demonstrates that epigenetic events interact with genetic mutations during the development of melanoma.

4.3 | The role of RNA methylation in skin cancer

m6A is important in a variety of biological processes, mainly due to its regulation of the expression of m6A-related genes (Patil et al., 2016). It has been reported in Arabidopsis, yeast, Drosophila, and zebrafish that WTAP and the m6A methyltransferase METTL3 are essential for development, meiosis, and viability (Hongay & Orr-Weaver, 2011; Ping, 2014; Zhong et al., 2008). In mammalian cells, both METTL14 and METTL3 are essential for the differentiation and self-renewal of mouse embryonic stem cells (Aguilo, 2015; Chen, 2015; Liu, 2014; Wang et al., 2014). Furthermore, silencing METTL3 leads to prolonged circadian rhythm in mice (Fustin, 2013). The modification of m6A in mammalian cells is reversible and dynamic. It has now been used as another epigenetic regulation similar to histone modifications and DNA methylation. It has been discovered that m6A methylation affects tumor progression and initiation through a variety of mechanisms. At present, m6A has been discovered to have different biological regulatory functions at different stages of cancer, and its dysregulated expression is closely related to various cancers. A key regulator of m6A in RNA plays a significant role in the maintenance and progression of cancer stem cells. For example, the inhibition of the RNA demethylase FTO inhibits GSC growth and self-renewal, thereby inhibiting the tumor progression of GBM. Ultraviolet rays are a major environmental factor affecting the occurrence of cancer. Yang Xiang et al. studied the relationship between m6A and UV damage. UV-induced RNA methylation may affect the expression of genes involved in DNA repair. Their results show a new role for RNA methylation in promoting cellular resistance to UV damage and identify a potential novel pathway involving m6A RNA, METTL3, and Polκ in early UV-induced DDR, with a significant role for methylated RNA in recruiting Polκ to the damaged sites for efficient DNA repair (Xiang et al., 2017). Unbalanced m6A regulation will result in defects in RNA metabolism at each step. In conclusion, m6A methylation plays important and broad roles through the functional interaction between m6A demethylases, m6A methylases, and m6A binding proteins (Jia, Fu, & He, 2013). Aberrant m6A methylation levels induced by defects in any factor may result in the dysfunction of RNA and cause diseases. However, few studies have investigated the role of RNA methylation in skin cancer. This will be a direction that is worthy of studying.

5 | CONCLUSION AND OUTLOOK

Epigenetic changes often accompany tumorigenesis and progression. Epigenetic changes play a role in the genetic process of tumors by

affecting key genes and interactions. DNA methylation modifications, histone modifications, and RNA methylation modifications are all mechanisms of the abnormal expression of key genes in tumors. A large number of epigenetic variations respond to changes in the environment by regulating the behavior of the corresponding genes, ensuring that cells have better adaptability; some fraction of epigenetic abnormalities lead to tumor suppressor gene silencing or oncogene activation, which promotes tumorigenesis. In recent years, compared with the studies of DNA methylation and histone modifications, there have been few studies on RNA methylation modifications. However, DNA methylation and histone modifications still need to be further studied. RNA methylation modifications are a relatively new field of discovery, and scholars have gradually revealed that a chemical modification of RNA has an epigenetic significance and have recently focused on m6A. However, there are still many problems in the epigenetic modification of RNA that need further investigation, such as its relationship with some major diseases, its variation in cell differentiation, and so on. Epigenetic modification has gained increasing attention in the regulation of the immune response and tumor immunotherapy. Moreover, reversible epigenetic modifications have become ideal targets for the therapeutic intervention of tumors. Therefore, an in-depth understanding of epigenetic mechanisms in the process of tumor development has important clinical implications for the early diagnosis of tumors, drug treatment of tumors, and improvement of tumor prognosis. Furthermore, the development of cancer immunotherapeutic drugs for key epigenetic variation sites has become a hot topic of study and has good future prospects.

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