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MiniReview

The Relationship between RNA-binding Proteins and Metastatic Process of Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma metastasis is often the leading cause of treatment failure in hepatocellular carcinoma. It is now recognized that metastasis is a complex process involving multiple factors and that aberrant expression or dysfunction of RNA-binding proteins (RBPs), leading to an imbalance in the expression of proto-oncogenes and oncogenes, is inextricably involved in the process of tumor metastasis, which will be discussed in the review. In this review, we will discuss the mechanism and role of RBP in the metastasis of hepatocellular carcinoma. Basic regulatory strategies of RBP most RBPs contain one or more conventional RBDs, which recognize and bind specific sequences in RNAs in order to play their roles. The RBDs, together with some repetitive sequences, form the basic modules, which, through various combinations and permutations, enable the RBPs to accurately search for RNAs for recognition in the cell and participate in regulating RNAs.

Keywords: hepatocellular carcinoma, metastasis, RBP

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1 INTRODUCTION

Eukaryotic gene expression regulation mainly includes transcriptional and post-transcriptional levels and plays a direct role in normal physiological processes and the development of diseases[1,2]. RNA-binding proteins (RBPs) are a class of proteins that regulate gene expression and can specifically bind to RBPs in the normal physiological process[3,4]. RBPs are a class of proteins that regulate gene expression and precisely interact with RNA molecules to participate in RNA processing, modification, and transcription.

Metastasis is an important cause of poor prognosis and death in cancer patients. It is the process by which tumor cells escape from their primary site and spread to distant organs. A small number of cancer cells at the primary site gain the ability to metastasize and grow through the necessary sequential steps[5]. Many genomic, transcriptomic and proteomic factors contribute to cancer cell metastasis. In cancer, dysregulation or dysfunction of RBPs leads to an imbalance in the expression of targeted oncogenes and tumor suppressor genes, which affects cancer-associated phenotypes such as cell proliferation, apoptosis, senescence, angiogenesis, migration, and invasion[6]. There is growing evidence that abnormalities in RBP expression and function are associated with cancer metastasis[7]. Similarly, abnormal

function of RBPs often accompanies the metastatic process of hepatocellular carcinoma[8]. Based on the latest research, this paper summarizes the RBPs related to the metastatic process of hepatocellular carcinoma. It reviews the specific mechanism of their involvement in this process to provide new ideas or methods for new cancer therapy targets. This paper summarizes the RBPs related to liver cancer metastasis based on the latest research. It reviews the specific mechanism of their involvement in this process, intending to provide new ideas or methods for new targets in cancer therapy[9,10].

The RBPs' ability to respond to the target RNAs is also essential. The primary regulatory strategies of RBP on target RNAs are known to be as follows. RNA stability regulation RNA stability mainly depends on the nucleotide sequence and modifications and is determined by its 5′m7G cap and 3′ poly(A) tail. The regulation of RNA stability directly determines the amount of the final product of gene expression and has a crucial impact on many biological behaviors.

2 CANCER METASTASIS IN HEPATOCELLULAR CARCINOMA WITH RBPS

2.1 Rbps Promote Expression of Mrnas

The methods of degrading mRNAs mainly start with poly(A). On the one hand, RBPs can enhance the stability of mRNAs and regulate the protein expression of their target genes; many RBPs have been shown to promote the expression of mRNAs by controlling the stability of mRNAs in the metastatic process of tumors. On the other hand, RBPs can also accelerate the degradation of mRNAs, e.g., IGF2BP1 can reduce the expression of 1.2% of HmU6LAC-modified mRNAs in hepatocellular carcinoma cells—HmU6LAC modification of mRNA stability. RNA modification can affect biological processes, such as transcription, pre-mRNA splicing, RNA export, mRNA translation, and RNA degradation. m6A modification is the most common methylation modification of RNA molecules in eukaryotes, i.e., the introduction of a methyl group at the N6 position of the adenosine molecule is the most common methylation modification[11,12].

Its biological effects are mainly regulated by three essential proteins: methyltransferases, methylation reading proteins, and demethylation enzymes, i.e., writer and eraser. Several studies have shown that such dynamic modifications are associated with the development of liver tumors, and selective splicing, an essential post-transcriptional regulatory mechanism, can regulate the generation of multiple mRNAs and protein products from a single gene[13].

Abnormal or incorrect splicing is one of the major causes of cellular dysfunction and can lead to cancer development. The main types of aberrant splicing in tumors include constitutive splicing, exon skipping, selective 5-splice sites, selective 3-splice sites, intron retention, mutually exclusive exons, etc. Some RBPs can form complexes with splicing-related core proteins and control selective splicing in tumor cells; some RBPs can form complexes with splicing-related core proteins under different conditions and control splicing selectively in tumor cells; some RBPs can form complexes with splicing-related core proteins under different circumstances.

2.2 Human Antigen

The human antigen R gene belongs to the embryonic lethal abnormal vision gene family, also known as ELAV1. Under physiological conditions, its encoded HuR protein mainly involves mRNA splicing and nuclear export[14]. It is closely related to normal physiological processes such as lipid metabolism in the liver protein functions as a post-transcriptional regulator. HuR protein acts as a post-transcriptional regulator, mainly binding to mRNAs in the cytoplasm and stabilizing the structure of target mRNAs to increase their expression levels. HuR is highly expressed in liver cancer tissues, but the specific mechanism of its effect on liver cancer cells is still unclear.

It is now known that HBV-encoded X-protein (HBx) plays a significant role in hepatitis B-associated hepatocellular carcinoma. Its expression is upregulated by HuR protein, and its expression is also upregulated by HuR protein. It is known that HBx plays a significant role in hepatitis B-associated hepatocellular carcinoma development, and its up-regulation of HuR expression enhances the stability of HER2 mRNA and increases the level of HER2 expression, which in turn promotes the migration of hepatocellular carcinoma cells. It has also been demonstrated that HuR is involved in hepatocellular carcinoma cell migration by activating downstream proteins via the STRA6/JAK2/STAT3 signaling pathway. In addition, in the non-alcoholic fatty liver disease experiment, mice with hepatocyte-specific lack of HuR showed prominent fibrosis and tumor development, which suggests that HuR may have a particular impediment to the development of liver tumors by participating in the process of hepatic lipid transport and other processes[15].

2.3 Cytoplasmic Poly

The length of the poly(A) tail at the 3' end of eukaryotic mRNA is closely related to translation initiation and mRNA stability. Cytoplasmic poly (CPEB) family members mainly bind target mRNAs in the cell. There are four members in the CPEB family, and their specific regulatory mechanisms are different.CPEB1/2 is more closely related to breast cancer, while CPEB3 is more closely related to hepatocellular carcinoma, primarily hepatocellular carcinoma metastasis. met adhesin is a direct target of CPEB3, and inhibiting the translation of mRNA of met adhesin will inhibit the translation of mRNA of CPEB, and

then inhibit the translation of mRNA of met adhesin, and then inhibit the translation of mRNA of CPEB. miR-107 down-regulated CPEB3 expression by directly targeting CPEB33′-UTR, which was accompanied by the up-regulation of epidermal growth factor receptor (EGFR), and this process promoted the proliferation and metastasis of human hepatocellular carcinoma (HCC) cells[16].

Similarly, miR-9-5p and miR-20b-5p can promote the metastasis of hepatocellular carcinoma cells by down-regulating the expression of CPEB3. CPEB4 is mainly found in gliomas, breast cancers, other cancer tissues, etc. In recent years, it has been found that the expression level of CPEB4 is significantly upregulated in early-stage hepatocellular carcinoma tissues but decreased in middle- and late-stage hepatocellular carcinoma tissues, which is consistent with the changes in CPEB4 mRNA. This unique biphasic change suggests that CPEB4 plays a complex role in the development of hepatocellular carcinoma, and the decrease of CPEB4 in middle and advanced hepatocellular carcinoma tissues is likely to be related to metastasis.

2.4 Kiaa1429 Upregulated in HCC

KIAA1429 is highly expressed in hepatocellular carcinoma tissues compared with normal tissues. KIAA1429 can inhibit ID2 by participating in the m6A modification of ID2 mRNA, which promotes hepatocellular carcinoma migration and invasion. further demonstrated that KIAA1429 can inhibit the migration and invasion of hepatocellular carcinoma by participating in the m6A modification of ID2 mRNA, which further reveals that KIAA1429 has a complex role in the development of hepatocellular carcinoma[17]. In another study, a cyclic non-coding RNA from KIAA1429 inhibited ID2 in HCC cells and tumors. In another study, a cyclic non-coding RNA from KIAA1429 was upregulated in HCC cells and tumors, named circ_KIAA1429, and its downstream target was Zeb1.

2.5 Methyltransferase-like Family

METTL3 can inhibit the expression of SOCS2 in HCC through the m6A-YTHDF2-dependent mechanism and promote the proliferation and metastasis of hepatocellular carcinoma cells. Another mechanism by which METTL3 is involved in hepatocellular carcinoma metastasis is that it mediates the transcription of the HPS5 gene and promotes the generation of circHPS5 instead of processing it into HPS5 mRNA, and circHPS5 promotes the process of EMT in tumor tissues, which leads to the metastasis of hepatocellular carcinoma. Another study showed that down-regulation of METTL14 expression in liver cancer tissues in vivo and in vitro could enhance the metastatic ability of liver cancer, and METTL14 mainly positively regulated the maturation process of miR-126 together with the microprocessor protein DCGCR8, which had an apparent inhibitory effect on the metastatic ability of liver cancer. Studies have confirmed that the down-regulation of METTL18 gene expression was observed in the process of hepatocellular carcinoma cell proliferation, invasion, and metastasis, and METTL18 is expected to become a new type of tumor cell. METTL18 is expected to become a new marker for evaluating HCC patients[18].

2.6 Yth Domain Family2yth

Domain family2 (YTHDF2), as a methylated reading protein, is also involved in the methylation modification of m6A and mediates the degradation of mRNA, either in vivo or in vitro, through tetranylation or ribonucleic acid (RNA) endocytosis. Both in vivo and in vitro, the YTHDF2 protein inhibits metastasis of hepatocellular carcinoma. One mechanism inhibits the development of tumor cells and vasculature by processing the decay of IL-11 and SERPINE2 mRNA. At the same time, the transcription of YTHDF2 itself is also affected by hypoxia-inducible factor-2 alpha, and the other is to destroy EGFRmRNA in HCC cells by disrupting EGFRmRNA. Another mechanism is that YTHDF2 inhibits the ERK/MAPK signaling cascade in HCC cells by destabilizing EGFR mRNA. the level of miR-145 in hepatocellular carcinoma tissues negatively correlates with the level of YTHDF2 mRNA, i.e., miR-145 regulates the level of m6A modification by targeting to bind to the 3'-UTR of YTHDF2 mRNA in HCC cells.

YTHDF2 can also be involved in liver cancer metastasis by regulating the m6A modification of hepatic tumor stem cell-associated factor OCT4 mRNA.3 RBP-targeted therapy for liver cancer metastasisAs mentioned above, various RBPs are involved in the metastatic process of liver cancer. Therefore, tumor therapeutic strategies developed based on RBPs have the potential to be an effective means of controlling metastasis of liver cancer. This section will review several therapeutic candidates based on the tumor-metastasis-associated RBPs and tumor-associated RBPs. They target tumor metastasis-related RBP.

2.7 Small-molecule Drugs

The HuR protein mentioned above, a variety of small-molecule inhibitors have been identified to inhibit its nuclear/cytoplasmic translocation and its interactions with target RNAs, e.g., KH-3, which inhibits the EMT, migration process of tumors by interfering with the interactions of HuR with the SNAI1 and FOXQ1 mRNAs. However, although many RBPs are involved in tumor metastasis, only a limited number of small molecules with therapeutic potential have been developed, which may be because the polymorphism of RBPs makes the pharmacological action too complicated and produces many unnecessary side effects. The binding domains of homologous proteins co-regulated by multiple RBPs compete for the intracellular binding of small molecule drugs, weakening the effects of the drugs.

2.8 Antisense Oligonucleotides

Antisense oligonucleotides are short synthetic

nucleotides (about 12-30 nucleotides) that bind specific RNA target sequences through the Watson-Crick base-pairing principle, thus playing a role. Because of the limitations of the current development of small molecule drugs, antisense nucleotide therapy may have a better development in the future.

The liver is the largest gland in the human body and is the center of systemic energy homeostasis and regulation of glucose and lipid metabolism, and one of the significant differences between hepatocellular carcinoma and other cancers is that metabolism-related pathways are severely affected in patients. Some scholars have found that miR-103 and miR-107 are associated with hepatic insulin sensitivity, and in hepatocellular carcinoma, many RBPs are associated with hepatic metabolism and metabolic disorders[19]. This may be a direction for targeted treatment of hepatocellular carcinoma by means of RBPs, while the tumor metastasis of RBPs and hepatocellular carcinoma is a complex process involving the regulation of multiple proteins as well as pathways, which still needs to be continuously and consistently explored.

3 CONCLUSION

As shown above, it remains to be researched whether the theory that RBPs can act as an essential intermediate factor connecting the mechanotransduction of tumor cells and metastasis of cancer applies to liver cancer; in addition, many of the RBPs mentioned in this paper can be used to monitor the recurrence of liver cancer in clinical practice. For example, the high expression of ZCCHC4 is closely related to the poor prognosis of HCC patients, and the expression of ZCCHC4 is significantly upregulated in hepatocellular carcinoma cells of patients with advanced HCC who preferred oxaliplatin and other DNA-damaging agents (DDAs), suggesting that the hepatocellular carcinoma cells are resistant to the DDAs chemotherapy. With the deepening of RBP research and the continuous development of drug screening and deepening technology, some RBP-targeted approaches have begun preclinical and clinical trials and are expected to be applied to the clinical treatment of hepatocellular carcinoma. However, the structure and function of RBPs have yet to be recognized. However, our knowledge of the structure and function of RBP is still limited, and exploring its mechanism in the metastatic process of hepatocellular carcinoma is still challenging.

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Conflicts of Interest

The authors declared no conflict of interest.

Data Availability

Data sharing is not applicable to this review as no datasets were generated or analyzed during the current study.

Author Contribution

Chen W drafted the manuscript; Dai J edited and revised the manuscript; Li C approved the final version of the manuscript.

Abbreviation List

RBPs, RNA-binding proteins
HBx, HBV-encoded X-protein
CPEB, Cytoplasmic poly
YTHDF2, Domain family2
HCC, Hepatocellular Carcinoma
DDAs, DNA-damaging agents

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