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Micropeptides Related to Tumors: Candidates for Tumor Targeted Therapies and Diagnostic Biomarkers

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Abstract

A number of RNAs, which have been annotated as non-coding RNA, encode proteins less than 100 amino acids. The ORFs less than 100 codes are called small open reading frames （sORFs）. sORFs encode proteins called micropeptides. Though many micropeptides have been identified in several species, there are gaps in mining micropeptides from thousands of ncRNAs. But developing technologies help us to find more and more sORFs and micropeptides. To date, micropeptides are found to involve in various cancers, and can be used as prognostic biomarkers and therapeutic targets. This review discusses the micropeptides which have been discovered in cancers. However, there are gaps that remain unclear. The resulting picture is micropeptides need to be deep-going. And in the future, the research of micropeptides related to cancers also will be a hot topic.

Keywords: sORFs, micropeptides, cancer, diagnostic biomarker, Targeted Therapies, ncRNAs

1. Introduction

Many RNAs have been annotated as no-coding RNA while these nucleotide sequences actually contain sORFs which are less than 300 nt [1]. Recently, many sORFs that can encode peptides have been found. These sORF-encoded peptides are called micropeptides. They are identified to be involved in many biological processes, such as muscle metabolism, inflammation, diseases, and cancer [2]. Among the various effects, the mechanism of micropeptide-related tumors is striking. Tumors are sophisticated diseases related to multiple organs that are hard to cure and bring a heavy burden. Tumors have always been concerned about not only how to reduce complications, but also how to alleviate the discomfort of patients. Many studies start with the mechanisms of tumorigenesis and try to find therapeutic targets. Then, it is found that sORFs have been shown to regulate tumor by affecting proliferation, differentiation, stem cells, migration, invasion, and apoptosis [3]. But not all of the effects of tumors are clear currently. And not all sORFs are identified to encode micropeptides. With the development of technology, we may identify more micropeptides which used to be identified as non-coding sequences. The computational prediction helps us to select and locate sORFs. There are many databases which can provide tools for analyzing the coding potential of sORFs.

Therefore, the results on tumor-related micropeptides that can be detected presently are pioneering and valuable resources. In this review, we will focus on the micropeptides which have been discovered in tumors and discuss the roles of micropeptides in cancers.

2. Micropeptides Identified From Tumors

2.1 Micropeptide identified from neck squamous cell carcinoma (HNSCC)

The micropeptide MIAC (Micropeptide Inhibiting Actin Cytoskeleton) encoded by lncRNA RP11-469H8.6 was found in the differential expression analysis between samples of HNSCC and normal tissues [4]. And data analysis showed that these differences are significant. MIAC and AQP2 can interact with each other. And some aquaporins (AQPs) family members are known to be involved in different tumors [4]. Overexpression of MIAC or knockdown of

AQP2 was found to significantly inhibit the expression of ITGB4 and Sept2, resulting in decreased filamentous actin stress fibers [4]. Therefore, the study concluded that MIAC binds to AQP2 and leads to regulate SEPT2/ITGB4 pathway. Finally, it affects actin cytoskeleton and suppress HNSCC proliferation and metastasis [4]. It was found that knockdown of MIAC promoted proliferation and migration of HNSCC in vivo and in vitro experiments. And over expression of MIAC inhibited HNSCC growth [4]. Although this new treatment needs to be further verified by clinical experiments, the mechanism by which MICA reduces tumor metastasis has been demonstrated, and MICA may make its way into using for patients in the future.

2.2 Micropeptide identified from renal cancer

Recently, a study found that micropeptide named MIAC was remarkably under-expressed in renal cancer（RCC）, which is encoded by lncRNA AC025154.2. Moreover, they found that the expression of MIAC was different in patients with different stages[5]. The more advanced RCC was, the lower expressed of MIAC. It's demonstrated that the micropeptide MIAC can directly bind to AQP2 protein, and finally plays a role in inhibiting the occurrence and development of renal cancer by inhibiting the expression of EREG and EGFR and the activation of downstream signaling pathways [5]. The repressed phenomenon of RCC appears when endogenous over expression of MIAC, as well as in chemically synthesized MIAC polypeptide treatment [5]. In animal models, it was found that effects of current first-line therapeutic drugs, such as Sunitinib and Axitinib, were inferior than that of MIAC [5]. So MIAC can provide a new treatment strategy for kidney cancer, as well as biomarkers for kidney cancer diagnosis and prognosis, but we need animal experiments to verify its effect.

2.3. Micropeptide related to Esophageal Squamous Cell Carcinoma（ESCC）

A micropeptide was found that can bind Yin Yang 1 (YY1). YY1 is a transcription factor which contributes to enhancer-promoter structural interactions [6]. So, it was designated YY1BM (Yin Yang 1 binding micropeptide) which is encoded by LINC00278 [7]. Some transcription factors are involved in carcinogenesis, and those transcription factors, such as eEF2K, which can promote the survival of cancer cells, can be activated by YY1. And the higher the expression of eEF2K, the higher the testosterone level of men in ESCC samples. However, YY1BM can combined with YYI [7], that is to say, YY1BM combines YY1 and suppresses the transcription of eEF2K [7]. It causes apoptosis of ESCC. In the mouse ESCC model, the research found that the survival rate of transplanted ESCC male mice was

improved after treatment of YY1BM injection [7]. Therefore, YY1BM can be used as a prognostic biomarker and therapeutic target for male ESCC.

2.4 Micropeptides identified from breast cancer

There are three micropeptides related to breast cancer, which have been proved to be directly related to the development of cancer. The first one is CIP2A-BP (protein phosphatase 2A binding micropeptide), which is encoded by LINC00665 [8]. TGF-β (transforming growth factor β) is known to promote breast cancer. And TGF-b regulates CIP2A-BP translation through Smad pathway, which leads to decrease of CIP2A-BP [8]. The expression of CIP2A-BP in patients with triple-negative breast cancer (TNBC) was found to significantly decrease unsurprisingly. CIP2A-BP was found to inhibit migration and invasion of TNBC by binding to CIP2A, which is an oncogene [8]. Direct injection of CIP2A-BP or overexpression of CIP2A-BP reduced lung metastasis and improved survival in experiments [8]. So CIP2A-BP expression could be used as a prognosis marker among TNBC patients. And it is a possible treatment for TNBC metastasis.

The second one is a short transmembrane protein which is encoded by CASIMO1(Cancer-Associated Small Integral Membrane Open reading frame 1) [9]. Enhanced expression of CASIMO1 was found at all tumor stages with breast tumor sample data. In the study, they cloned the CASIMO1-encoded sequence and constructed its expression in cells [9]. Finally, a small protein between 10-15 kDa was found to be generated with Western blotting detection. This micropeptide was detected to be closely adjacent to and partially overlapping with lysosome-associated membrane protein 1 (Lamp1) [9]. Lamp1 is thought to be associated with cytoskeletal signaling, lysosome-associated and tumor metastasis. The research detected dysregulation of the actin cytoskeleton, and cells stopped dividing with knockdown of CASIMO1. CASIMO1 can interact with SQLE (squalene epoxidase) protein [9]. Overexpression of CASIMO1 results in accumulation of SQLE, which is critical for cholesterol synthesis as well as an identified factor in breast cancer. Its knockdown leads to decreased proliferation in multiple breast cancer cell lines [9].

The third micropeptide is XBP1SBM (Spliced X-box binding protein 1 binding micropeptide), which can interact with XBP1S(Spliced X-box binding protein 1) [10]. XBP1S is known to be a transcription factor which involves in numerous signaling pathways. XBP1s is associated with many diseases, including cancer. And transcription of XBP1s leads to the expression of

XBP1SBM, which retained XBP1s in turn [10]. The result is increasing expression of VEGF and promoting cancer. The promoting angiogenesis and metastasis effects of TMP1 in TNBC were confirmed in cell experiments as well as mouse models [10].

2.5 Micropeptide related to Hepatocellular carcinoma (HCC)

There are some micropeptides related to HCC. The first is JunBP (Jun binding micropeptide), which relates with TGF-β [11]. TGF-β is known to have relation to the pathogenesis of chronic liver disease and cancer. TGF-β can promote the invasion-metastasis cascade by activating lincRNAs. Zhang et al. studied TGF-β Regulated lincRNA, and found LINC02551. They found JunBP which is transcription product J of LINC02551 in HCC tissues and HCC cell lines [11]. In addition, c-Jun is a vital mediate molecule of mitogen-activated protein kinases (MAPK) signaling pathway and TGF-β could act as one of the extracellular ligands that activate this pathway. The study showed that JunBP binds to c-Jun and promotes its phosphorylation and activation subsequently results in metastasis of HCC [11]. The effect of JunBP in promoting HCC metastasis was confirmed in mouse model.

The second is CIP2A-BP. When studying patients with liver cancer at different stages, it was found that the more advanced the liver cancer was, the more expression of LINC00665 was [12]. And CIP2A-BP was overexpressed in HCC cells. In the CCK-8 experiment, with inhibiting the relative expression level of LINC00665 in HCC cells, and the cell proliferation activity was significantly inhibited [13]. The results of CCK-8 experiment showed that CIP2A-BP increased the number of hepatocytes. It was found that the invasion and migration of cells were significantly increased with transfection of over-CIP2A-BP in transwell experiment [13].

The third one is short transmembrane protein 1 (STMP1) which was found to be elevated

different cancer and metastasis [14]. Chen et al. found that STMP1 promoted migration of tumor and fission of mitochondria [15]. In mouse models, overexpression of STMP1 leads to activation of migration and metastasis, STMP1 silencing inhibited tumor metastasis [15]. So JunBP, STMP1 and CIP2A-BP can be served as a candidate of prognostic biomarker and therapeutic target for HCC.

2.6 Micropeptide related to colorectal cancer (CRC)

A research found a micropeptide encoded by LINC00467, which is involved in mitochondrial metabolism and ATP production in CRC progression by promoting ATP synthase activity and cell proliferation [16]. And they designated it ATP synthase–associated peptide (ASAP). ASAP increased mitochondrial ATP and led to further tumor proliferation. The study found that ASAP is more up-regulated in CRC cells than normal intestinal epithelial cell lines [16]. And the tumor-promoting effect of ASAP was significantly blocked when the activity of ATP synthase was inhibited. It can be inferred that ATP synthase inhibitors have antitumor effects. The lack of ASAP inhibited the growth of Patient derived xenograft (PDX) in the mouse experiment [16]. All in all, we can expect potential of targeted therapy with ASAP in CRC.

HOXB-AS3 (homeobox B cluster antisense RNA 3) is an RNA which decreased in cancer. And HOXB-AS3 peptide were found to be low expressed in CRC. This micropeptide can combine with hnRNP A1, which leads to PKM2 (Pyruvate kinase isozyme typeM2) to be at a low level [17]. And PKM2 is known to promote the proliferation and metastasis of tumor [18,19]. This study demonstrated the poor prognosis of CRC patients with low levels of HOXB-AS3's peptide, but they did not use an animal model to verify whether HOXB-AS3 peptides have a

therapeutic effect [17]. So it needs to do more research on HOXB-AS3's peptides to fill in the gap.

2.7 Other cancer related sORFs

Many cancers have been proved to be related to sORFs, but they haven't detected expression of sORFs in some of cancers [20]. For example, the expression of LINC00958 in gastric cancer is significantly increased, and LINC00958 is increasing in many tumors [21]. Another example is LINC00665. There are many tumors related to LINC00665, such as gastrointestinal tumors, breast cancer, osteosarcoma, and liver cancer [22]. However, the peptides encoded by LINC00665 have been reported in experiments related to breast cancer and liver cancer, and the discovery of LINC00665 related peptide has not been explicitly mentioned in other tumors. However, whether these LncRNAs express micropeptides and how they are regulated still need further study.

Table 1. Micropeptides identified from human cancers.

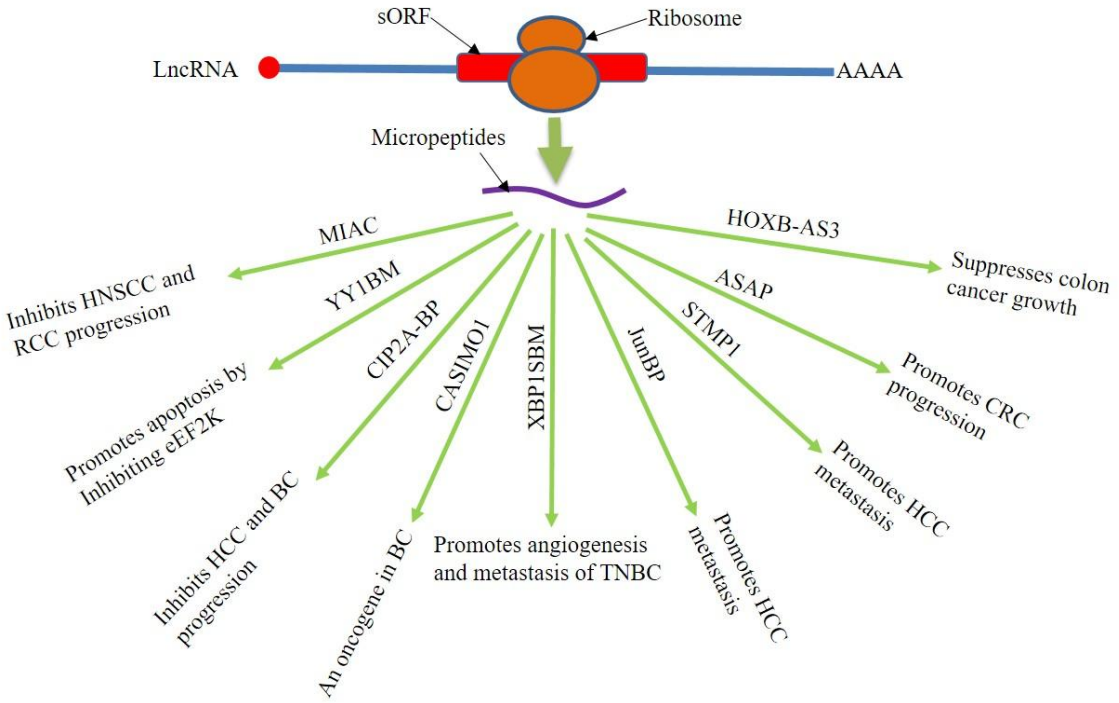
Micropeptide	Tumor TypE	Length (aa)	Sequence	Related lncRNA	Mechanism	references
MIAC	HNSCC RCC	51	MERAGVPGFSPRRSSVEAKMQSTSCSVRK SSTVTAWPAVVLLLSWGQRRGG	lncRNAAC025154.2	Inhibits the activation of the EREG/EGFR signaling pathway	[9],[10]
YY1BM	ESCC	21	MLSGQLQPEGRSALPQPGAAL	LINC00278	Acts as a protective factor to hinder cancer progression by inhibiting the PI3K/AKT/NFκB pathway	[3]
CIP2A-BP	BC, HCC	52	MGRWRVSSVESWPFASTGGKLAIATAGTG TQAAPRPFLIRPPDSWALALALM	LINC00665	Binds tumor oncogene CIP2A to replace PP2A's B56γ subunit, thus releasing PP2A activity that inhibits activation of PI3K/AKT/NFκB pathway	[18]
CASIMO1	BC	83	MAVSTEELEATVQEVLGRLKSHQFFQSTW DTVAFIVFLTFMGTVLLLLLLVVAHCCCCS SPGPRRESPRKERPKGVDNLALEP	CASIMO1	Interact with members of the mevalonate (MVA) pathway in particular with SQLE.	[17]
XBP1SBM	BC	21	-	lncRNAMLLT4-AS1	Enhances the expression of VEGF	[2]
JunBP	HCC	19	-	LINC02551	Acts as a bridge for JNK/c-Jun interaction	[28]
STMP1	HCC	47	MLQFLLGFTLGNVVGMYLAQNYEMPNL AKKLEEIKKDLEAKKKPPSS	lncRNA*1810058I24Rik*	Enhances the phosphorylation of DRP1 at Ser616 and induced mitochondrial fission.	[11]
ASAP	CRC	94	MDKKSTHRNPEDARAGKYEGKHKRKKR RKQNQNQHRSRHRSVTSFSSDDPMFPSSS SSSSGSQTDSSIEDAAKGKIKKKRREKTNK WEKRKDKI	LINC00467	Regulates the production of mitochondrial ATP and enhanced the oxygen consumption of cancer cells.	[7]
HOXB-AS3	CRC	53	MPVLPGTQRYPHQRRRFOAAGGGAESGK RGSEEAPGVAwSGSESGRDAATPAW	lncRNAHOXB-AS3	Switches the ratio of PKM1/Pyruvate Kinase M1/M2.	[25]

3. Conclusions

Many micropeptides have been discovered recently. The micropeptides are fading in people's sight. Micropeptides are often found to regulate the transcription of different target genes by interacting with other proteins to regulate activity [22-24]. Here we have summarized the role what micropeptides play in cancers. Because the regulation mechanism of different micropeptides is often different, the discovered micropeptides are also different in different types of tumors. These differences can better carry out targeted treatment and diagnosis. A micropeptide might involve in different tumors,–but have the exact opposite effects [25]. Accumulating evidence shows that some micropeptides have been proved to regulate the proliferation and diagnosis, and others have the potential to treat tumors. For example, CIP2A-BP reduced lung metastasis and improved survival rate in the research of TNBC, while it promoted HCC carcinogenesis in another research.

Finally, we envision that there are still many shortcomings： Whether micropeptides can be used as tumors criteria and prognostic indicators in clinical practice remains to be further studied [26,27]. At present, the clinical trials of micropeptides also need further experiments. Although many sORFs have been proved to be related to tumors, there is no evidence of their micropeptides. These sORFs also need further research. Because of its small molecular and easy decomposition, some tumor-related peptides may not be detected yet [28,29]. However, the known potential of micropeptides is inestimable and undoubtedly in biological targeted therapy, diagnostic biomarker, prognosis judgment and so on.

In summary, although some tumor-related micropeptides have been discovered and studied, there is still a big gap in the research of micropeptides and sORFs. In terms of the types and clinical applications of micropeptides, the potential of micropeptides in the identification and treatment of tumors is like a treasure awaiting exploration.



Abstract graphic (Diverse functions of recently annotated micropeptides in human tumor)

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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