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Review

MiR-146a functions as a small silent player in gastric cancer

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ABSTRACT

Gastric cancer is responsible for approximately one million annual deaths worldwide. Recently, the important roles of miRNAs as vital factors in malignancy processes such as metastasis have identified. They involve in the regulation of different biological procedures such as proliferation, invasion, metastasis and cell survival. MiR-146a has an aberrant expression in different tumors and has different expressions in the gastric cancer cell lines. This microRNA can act as a tumor suppressor and/or oncogene in gastric cancer related cases. Most of the studies have confirmed that miR-146a is downregulated in human gastric cancer cell lines and tissues, significantly and that it has tumor suppressor effects in gastric cancers. On the other hand, the role of miR-146a as an oncogene has been studied in an in-vitro experiment and results showed that over- an expression of miR-146a in gastric cancer tissues inhibits apoptosis and improves cell proliferation of gastric cancer cell. MiR-146a also has been a candidate for diagnosis and prognosis in gastric cancer cases. In this review, we focus on the important roles of miR-146a in tumor genesis of gastric tissues, emphasizing on the involvement of this microRNA in diagnosis, prognosis, chemotherapy response and finally, potential therapeutic applications as an anticancer agent in inhibition of gastric cancer cell metastasis and invasion.

1. Introduction

Gastric cancer (GC) is the fourth most prevalent cancer and the second most significant reason for global cancer-related mortalities. Although, local and regional controlling of tumor and reducing the measure of systemic metastasis can be improved by surgery, radiotherapy, and chemotherapy but outcomes are undesirable, unfortunately, with high relapse rates after total resection. It is essential to improve our knowledge in gastric carcinogenesis to recognize novel molecular biomarkers to progress the current management of gastric cancer related strategies [1].

The microRNAs are small, single-stranded, endogenous, functional RNA molecules consisted of about 22 nucleotides which play significant roles in biological processes and gene expression regulated post-transcriptionally by binding miRNAs to the 3′ untranslated region (3′ UTR) of mRNAs, often but not always happen in 3′ UTR. Considering that a greater number of particular miRNA genes have been recognized, a single miRNA can target numerous different mRNAs, also an individual mRNA can be regulated by various miRNAs [2]. Many processes such as apoptosis, differentiation, metastasis, and proliferation are influenced by miRNAs. Most of the genes of miRNAs are placed in fragile sites or in the regions associated with cancer. Particular features of miRNA correlate with different subsets of solid tumors and hematological disorders [3–6]. One group of microRNAs known as the “tumor suppressor”. When their function is reduced a malignant alteration of a normal cell begins. Tumor suppressor miRNAs typically inhibit tumor progression by negatively preventing oncogenes and/or genes that regulate cell proliferation and differentiation. In contrast, the other group of miRNAs known as oncogenic microRNAs which are able to target mRNAs that have an increased expression in tumors and encoding tumor suppressor proteins [5,7]. These oncogenic miRNAs, known as “oncomirs”, enhance tumor growth by restraining tumor suppressor genes and/or genes that regulate biological processes including cell proliferation and differentiation. Remarkably, an adjusting role for miRNAs in metastasis has been recognized, therefore they have been nominated as metastamiRs, as they have anti- and pro- metastatic roles [7,8].

Some specific miRNAs in gastric cancers are overexpressed or downregulated and these irregularities in miRNAs expression are associated with the beginning and progression of GC [9,10]. Genetic and epigenetic changes of oncogenes and tumor suppressor genes are greatly concerned in gastric carcinogenesis. Because the fundamental transcription mechanism of miRNA is basically similar to that of typical protein-coding genes, both epigenetic and genetic alterations of

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miRNAs lead to gastric cancers development [1]. Although Carcinoembryonic Antigen (CEA), CA19-9 is prevalent biomarkers of GC which are extensively used, these are not appropriate markers. Therefore, searching for novel specific and sensitive markers for GC is essential for finding new screening approaches [11]. Recently, the role of microRNAs (miRNAs) as novel and applied biomarkers has been examined and expanded. Circulating miRNAs may play a role as promising biomarkers in order to improve the early treatment of gastric cancer [12].

MiR-146 like some other microRNAs, is expressed as a family that encoded by dissimilar locus in the genome but shares the similar seed sequence. Certainly, the miR-146a gene is located on mouse chromosome 1that only in two nucleotides is different with the miR-146b that is located on chromosome 19. Most of the studies confirm that miR-146 is a tumor suppressor microRNA and downregulated in approximately in all of the malignancies except for a few of them. Gastric cancer is one of the malignancies that mir-146a is downregulated in most cases but there is a study that confirms its oncomir function in gastric cancer. Pivotal role of miR-146a in gastric cancer attracted the attention of scientists, so that they confirms undeniable prognostic, diagnostic and therapeutic role of miR-146 in gastric cancer, as far as novel studies corroborate miR-146a as a candidate for therapeutic, prognostic and diagnostic purposes of gastric cancer.

In this review, we will have an overview about the role of miR-146a in gastrointestinal malignancy and its prognostic, diagnostic and therapeutic roles will be discussed specially in gastric cancer. Mir-146a maybe performs a vital role as a novel target for targeted therapy of gastric cancer.

2. Biogenesis of microRNA

The miRNA transcription is performed by RNA polymerase II, yielding a long primary structure consisted of about 1000 bases called primary microRNA (pri-miRNA). Following this process DROSHA (RNase III endonuclease) influences pri-miRNA, resulting in producing a double-stranded hairpin structure consisted of about 60–70 nucleotides known as pre-miRNA. Following this process, exportin 5 exports pre-miRNA from nucleus to cytoplasm where it will be processed by DICER (RNase III endonuclease) that yields a 17–25 nucleotide double-stranded structure which enters into the RISC complex where the mature strand of miRNA is separated from another short-lived strand and mature strand play a role as a developed miRNA (Fig. 1).

3. MiR-146 and its role in malignancies

Mir-146a was first discussed as an inhibitor of TRAF6(TNF receptor associated factor 6) and IRAK1 (Interleukin-1 receptor-associated kinase 1) in the native immune reaction [13]. The association between cancer metastasis and expression of miR-146a was primarily distinguished in breast cancer [14–16]. However, the participation of miR-146a has also been stated in the beginning and progress of several kinds of cancers, including esophageal, and prostate cancer [17]. MiR-146a perform a tumor suppressor function in gastric cancer and prevents tumor advancement in the breast, prostate and pancreatic cancers [15,16,18,19]. Though in hepatocellular carcinoma miR-146a purportedly is an oncogenic miRNA. Other studies indicated the downregulation of miR-146a in prostate cancer and papillary thyroid carcinoma [19,20]. As it has been revealed downregulation of this microRNA has a vital role in the advancement of papillary thyroid carcinoma [20,21]. Oppositely, miR-146a has high expression level in anaplastic thyroid and cervical carcinomas and plays an oncogenic role in anaplastic thyroid and cervical carcinomas [22,23]. These unpredictable outcomes of miR-146a in cancer progress may reveal the various functions of miR-146a in different kinds of cancer [24].

4. Multiple aspects of miR-146a in cancers of alimentary channel

One of the most common gastrointestinal malignancies is oral cavity cancer. Most prevalent histopathological type of this cancer is Oral Squamous Cell Carcinoma (OSCC) [25,26]. Over 50 microRNAs, including miR-134, miR-7, miR-146a, miR-21, and miR-155 have been stated in OSCC either upregulated or downregulated. Among these microRNAs, miR-146a, as an extremely dysregulated microRNA, has a role in suppression of metastasis and new targets for this microRNA, such as sox2 (sex determining region Y-box 2) are identified [27–29]. Sox2 is a direct mir-146a target which its overexpression is related to the metastasis and invasion of esophagus squamous cell carcinoma and laryngeal cancer development and it can be related to OSCC progression. These findings support that loss of miR-146a can improve OSCC development to metastasis and is a vindicator to OSCC destructive conduct [17,30,31].

One of the lethal cancers in the world is esophageal cancer. Esophageal cancer is derived from epithelium classified into two subtypes: esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). ESCC is the most common subtype of this cancer, internationally, while EAC is dominant in Western population [32–36]. The miR-146a was significantly downregulated in the serum of patients with ESCC and cancerous tissues, which was associated with TNM (Tumor Node Metastasis) stage, and showed the possible relationship between ESCC and miR-146a pathogenesis.

Though the overall role and mechanism of miR-146a in ESCC is unclear, it can influence many different target genes like Notch (Neurogenic locus notch homolog protein), VEGF (Vascular endothelial growth factor), and COX-2 (Cyclooxygenase-2) in ESCC [37,38]. The serum levels of miR-146a can be used as a possible diagnostic factor for the diagnosis of ESCC. The miR-146a can probably become a new therapeutic agent for inhibiting cancer advancement or level of metastasis [32,38].

According to the evidence, about 1.36 million people are affected by colorectal cancer (CRC), each year all over the world [39]. Though surgical excision accompanied by chemotherapy are extensively used for the treatment of the cancers, based on their pathological stages, however, the absence of a primary diagnosis, problems of metastasis and recurrence still cause challenges for therapy.

Anusha Sathyanarayanan et al. showed that the proliferation of CRC cells gets inhibited by ectopic expression of miR-146a while anti-miR-146a has opposite results. In addition, blocking miR-146a-expression improves invasion while miR-146a expression limits it in CRC cells, as well as expression of miR-146a barricade migration while antimiR-146a emphasizes it [40].

Mir-146a modulates the expression of mediators of motility and growth, and CRC tissues have lower expression of this microRNA. Ectopic expression of miR-146a reduces migration, proliferation, and invasion in CRC cells [41]. Mir-146a decreased the expression of RELA (NF-κB pathway), STAT3 (JAK/STAT pathway), CTNNB1 (Wnt pathway) while the expression of tumor suppressor TP53 (Tumor protein p53) improved [40,42,43]. Furthermore, the expression levels of an epithelial-mesenchyme transition (EMT) modulator SNAI1 (Zinc finger protein SNAIL1**)** and cell cycle regulator CCND1 (G1/S-specific cyclin-D2 is a protein encoded by CCND1) were similarly down regulated by the reintroduction of miR-146a in colorectal cancer cell lines [38,40].

In another study, miR-146a upregulated the expression of TP53, while downregulated STAT3 (Signal transducer and activator of transcription 3) expression, fundamental activation of which has been related to the progression and proliferation of CRC signifying that the downregulation of STAT3 can be one of the manners through which it represses proliferation in this cancer [44–46].

Therefore, miR-146a inhibits migration, invasion, and proliferation potentially by modifying the expression of some signaling mediators. Additional studies are necessary To specify the direct targets and other