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Review

The role of microRNAs in colorectal cancer

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ABSTRACT

Colorectal cancer (CRC) is still the third most common cancer in the world. Mechanism of CRC tumorigenesis has been widely studied at the molecular levels, and has been recently entered the area of microRNAs. MicroRNAs are small 19 to 22 nucleotides of RNA that engage in the regulation of cell differentiation, apoptosis, and cell cycle progression. MicroRNAs are similar to small interfering RNA (siRNA), that post-transcriptionally regulate gene expression and control various cellular mechanisms. They are important factors in the carcinogenesis of CRC, one of the most important factors includes microRNA. MicroRNAs have been linked to CRC development, and these molecules have been recently studied as new potential biomarkers in diagnosis and treatment of CRC. Specific microRNA expression patterns help distinguish CRC from other colon related disease, and may be used as a prognostication factor in patients after treatment with different chemotherapy drugs. More over the newest molecular therapy via tumor suppressor micro RNA replacement can be new insight in molecular therapy of CRC. This review summarizes the potential roles of microRNAs as potential biomarkers for CRC diagnosis, and treatment.

Contents

1. Introduction

Colorectal cancer (CRC) is the second most common cancer in the world. The incidence of this cancer is increasing in the developing countries [1]. CRC is a heterogeneous population of cells with different characteristics [2] which occurs following the growth of cancer cells in the colon, rectum and appendix.

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Environmental and genetic factors are among the factors influencing the incidence of this cancer [3,4].

Unfortunately, despite the availability of treatments such as surgery and chemotherapy, the prognosis of this disease is still unpromising and in many patients who undergone surgery, the cancer relapse or metastasis occurs after a while. One of the major clinical challenges of this malignancy is late diagnosis. Therefore, molecular studies leading to the identification of biological biomarkers have clinical significance. Extensive studies thus far have shown that miRNAs are novel and useful biomarkers for early detection, prognosis and treatment of colon cancer.

MicroRNAs (miRNAs) are a group of noncoding RNA containing approximately 18–25 nucleotides long that affect post-translational gene expression. They act by binding to the complementary sequences which are often located in the 3′UTR (the three prime untranslated region) of target mRNAs [5–7].

In fact, some studies also indicated the presence of these complementary sequences in coding regions, 5′ UTR and even promoter [8,9]. Hundreds of genes in the human genome encode these RNAs. It is estimated that about 30 percent of the genome encoding the protein is controlled by miRNAs [10,11]. Recent studies have shown several important roles in many biological functions for this class of RNAs including proliferation, differentiation, development and metabolism. In addition, miRNAs are involved in processes related to cancer and even diseases such as diabetes, autism, fragile X syndrome, Alzheimer's as well as heart disease [8,12]. Given the importance of this category of RNAs in different diseases, including colorectal cancer, our goal here is to provide more accurate identification of miRNAs and understanding their role in the development of colorectal cancer.

2. MicroRNAs: structure and biogenesis

Most of the genes encoding miRNA are located in intergenic regions, while some of them are located in intragenic regions. In general, the transcription of miRNAs are carried out by RNA polymerase II (RNA Pol II) while a small group of miRNA genes, which are surrounded by repetitive sequences such as Alu, are transcribed by RNA Pol III. The transcription product by any of these polymerases called primary miRNA (pri-miRNA) which includes 5′ cap and polyadenylate (poly-A) tail [5,13]. MicroRNAs are first processed in the nucleus. At this stage pri-miRNA is cleaved by RNase called Drosha and its protein cofactor DGCR8 in hairpin region and a loop of approximately 70 nucleotides which is liberated from pri-miRNA termed as a precursor miRNA (pre-miRNA). DGCR8 interacts with single strand region of RNA and orients Drosha to the intended location. Then pre-miRNA is exported to the cytoplasm for further processing by Exportin-5 [12,14,15]. In fact, some variants of miRNA are accumulated and act in nucleus. These contain additional sequences that determine their subcellular position. After the release of pre-miRNA in cytoplasm, the second stage of processing is performed by a cytoplasmic endonuclease called Dicer. The Dicer function yields a double-stranded RNA with a length of about 18 to 25 nucleotides, which include a leading strand or miR and a passenger strand or miR*.One of the strands of the duplex degrades following the attachment to argon-binding proteins (AGO) and another strand is incorporated into the RNA-induced silencing complex (RISC) [15,16]. Thermodynamic stability of both ends of the duplex determines which strand to be degraded. The evidences have shown that the strand with more unstable 5′ (weaker base-pairing) has lower chance of degradation (Fig. 1) [15].

3. Identification of microRNA target molecules

The detection of target molecules is one of the most important issues related to miRNA. Complementary base-pairing is essential for interactions between miRNAs and target molecules sequence. In most cases, complementary base pairing involves 6–7 nucleotides which is usually consists of nucleotides 2 to 9 of the miRNA 5′ end. This region is called “seed”. Other bases of miRNA have a limited capacity to pair with UTR3′ sequences adjacent to the seed region. This temporary attachments allows miRNA to connect to multiple internal sites in one UTR3′. Different calculation methods are used for prediction of miRNA target regions including computer algorithms, but as the pairing with the target sequence is incomplete and limited. Thereby, the exact prediction of miRNA target sites is still difficult. One of the predictive algorithms for target molecules is designed based on the pairing and protected seed sequence of miRNA in UTR3′ of different species [17]. mRNAs that are preferentially paired with 7–8 nucleotides of seed sequence are classified based on the criteria such as being protected target sequence developmentally, thermodynamic stability of the interactions occurred between the rest of the miRNA bases and sequences in both sides of UTR3′. Several bioinformatics analysis software is used to detect miRNA targets based on sequence of seed. For example, 1000 miRNA genes estimated to account for 1% of the human genome and it is likely that more than one-third of the human genome is regulated by miRNAs [18–21].

4. Cancer and microRNAs

Cancer is caused by the exit of cells from controlled regulatory, proliferative and differentiating pathways. Self-efficacy in growth signals, insensitivity to growth-inhibitory signals, avoiding programmed cell death, infinite proliferative potential, maintaining angiogenesis, tissue invasion and metastasis are responsible for cancer malignancy [21,22]. The role of miRNAs has demonstrated in development, apoptosis, differentiation and cell proliferation through miRNAs interaction with target genes and this confirms the direct function of miRNAs in cancer. Hence, dominant miRNAs expression can be used for classification of cancer in different groups with distinct characteristics such as cell type and etiology. MicroRNAs compared with mRNAs are more appropriate for tumors classification. This is due to the incomplete coupling between miRNAs and target mRNAs. Hence, several hundred genes and pathways in one sample can be determined by miRNAs microprobes whereas only small amount of total RNA is required. MicroRNAs structure and their function indicate that many miRNAs are abnormally expressed in cancer samples. Furthermore, the functional differences between different tumor types and stages of cancer shown to be associated with miRNAs expression. Differences in miRNAs expression in different types of cancer could be due to differences between origin of cancer cell and its surrounding stromal tissue. Changes in miRNA expression by reducing the expression of essential genes involved in proliferation or survival of cells, leads to tumor formation. However, this does not mean that miRNA directly contribute to cancer progression or tumorigenesis. Although not fully understood yet that altered miRNA expression is the result of pathological state of a cancer or the cancer is the direct cause of the changes in miRNA expression. However, many changes occur in cancer cells that can in a direct or indirect way affect miRNA expression. Genomic rearrangements, abnormalities in miRNA genes or proteins involved in their construction, alterations in epigenetic regulation of miRNA and gene mutations are examples of these changes. However, the presence of miRNAs in cancer-related genomic regions or genomic fragile areas is a major factor of changing miRNA expression in