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Review Article

MicroRNA and colorectal cancer

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ABSTRACT

Colorectal cancer is still the third most common cancer in the world. Its carcinogenesis has been extensively studied at a molecular point of view, and has recently entered the era of microRNAs, a class small non-coding RNAs that post-transcriptionally regulate gene expression and control various cellular mechanisms. Because they control biological processes that are implicated in carcinogenesis (as developmental transitions, organ morphology, apoptosis and cell proliferation), microRNAs have been linked to cancer development, and these molecules have been recently studied as new potential biomarkers to better characterise tumour prognosis and to predict response to the different active chemotherapy.

This review summarizes the potential roles of microRNAs as potential biomarkers for colorectal cancer diagnosis, prognosis and drug-response prediction.

Through the literature there is evidence that some microRNA could be used as biomarkers in colorectal cancer; however, there are some discrepancies amongst the different studies. These differences could partially due to heterogeneity between the different series associated with tumour stage, tumour location, genetic background of the tumours and technical issues. More progress is needed before microRNAs can be used in clinical practice. Accumulation of further data will allow to determine the most relevant microRNAs as biomarkers and also to better understand their role in colorectal carcinogenesis.

1. Introduction

Colorectal cancer is the third most common cancer in the world. Despite progress in diagnosis and treatment overall 5 years survival is 40% and approximately 50% of patients will die because of the development of distant metastases. The unique curative treatment of colorectal cancer patients remains surgery. Chemotherapy efficacy has made progress during the last 20 years with an improvement of median overall survival of advanced colorectal cancer patient from 6 to 24 months with the introduction of targeted therapies as anti-VEGF or anti-EGFR associated with irinotecan or oxaliplatin. Colorectal cancer carcinogenesis has been extensively studied at a molecular level in recent years and has recently entered the era of microRNAs (miRNAs). MiRNAs dysregulation has been described in different types of cancers [1–4] including colorectal cancer and these molecular entities constitute new potential biomarkers to better characterise tumour and to predict response to the different active chemotherapy. MiRNAs are a family of small non-coding RNAs that post-transcriptionally regulate gene expression and control various cellular mechanisms including developmental transitions, organ morphology, apoptosis and cell proliferation. MiRNAs regulate about 30% of human genes [5]. Typically, pri-miRNAs are successively processed in the nucleus and the cytoplasm by 2 endonucleases (Drosha and Dicer RNase III) resulting in mature miRNAs which may inhibit the translation of mRNA by directing a RNA-induced silencing complex to the target mRNA. MiRNAs maturation is a complex process involving different steps. First transcription by polymerase II results in high length primarily transcript (pri-miRNAs) (up to 1 kb), second processing in the nucleus by Drosha leads to a 70-nt-long precursor (pre-miRNA) and finally, in the cytoplasm pre-miRNA undergo modifications by the RNAse III Dicer to become mature miRNAs. They are then incorporated into the RNA-induced complex (RISC), composed of the Transactivation Responsive RNA-Binding Protein (TRBP) and Argonaute 2 [6]. The mature strand composed of 19–25 nucleotides recognized complementary sequences in the 3′ untranslated region of target mRNAs, and guides the miRNAs–RISC to repress gene expression by inhibiting translation and inducing mRNA degradation (Fig. 1).

Because they control biological processes that are implicated in carcinogenesis, miRNAs have been linked to cancer development. Depending on targeted genes they can either be considered as tumour suppressors or oncogenes. Aberrant expression of miRNAs has been shown in various types of cancer, as breast, brain, lung, pancreas, thyroid, haematological malignancies, and colon. The

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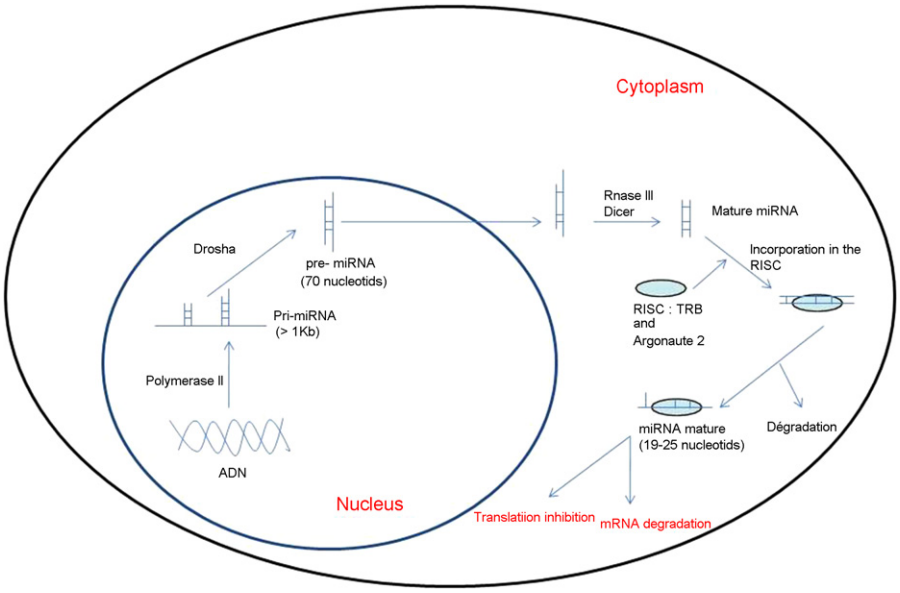

Fig. 1. MiRNAs biosynthesis. MiRNAs maturation is a complex process involving different steps. First transcription by polymerase II results in high length primarily transcript (pri-miRNAs) (up to 1 kb), second processing in the nucleus by Drosha leads to a 70-nt-long precursor (pre-miRNA) and finally, in the cytoplasm pre-miRNA undergo modifications by the RNAse III Dicer to become mature miRNAs. They are then incorporated to the RNA-induced complex (RISC), composed of the TRBP (Transactivation Responsive RNA-Binding Protein), and Argonaute 2. The mature strand composed of 19–25 nucleotides recognized complementary sequences in the 3′ untranslated region of target mRNAs, and guides the miRNAs–RISC to repress gene expression by inhibiting translation and inducing mRNA degradation.

mechanisms of miRNA deregulation in cancer are closely related to the genetic alterations observed in cancer cells and more than half of known miRNAs are located in regions of loss of heterozygosity (LOH), regions of amplifications, and at common cancer associated chromosomes breakpoints [2]. These genetic alterations may directly modify miRNA expression. Other alteration mechanisms could explain modifications of miRNA expression, as methylation abnormalities, and epigenetic regulation of miRNAs.

Colorectal cancer is a cancer type for which genetic alterations have been extensively studied. At least three different molecular types of colorectal cancer have been individualized based of genetic profiling alteration during the last 20 years. Typically the most abundant group is represented by the Chromosomal Instability phenotype (CIN). This group shows chromosome alterations such as frequent losses of 17p, 18q, 5q, 8p and 20q, a high rate of *APC* and *TP53* inactivating mutations, frequent *KRAS* and rare *BRAF* activating mutations. These tumours are more frequently located in the distal part of the colon [1]. The second group is associated with a genetic instability leading to high microsatellite instability phenotype (MSI-H) owing to a mismatch repair deficiency. In sporadic cases this phenotype is linked to a hypermethylation of the hMLH1 gene promoter whereas in familial cases inactivating mutations of mismatch repair genes are found. MSI-H cancers are characterised by an accumulation of gene mutations in repeated mononucleotide sequence such as those found in *TGFRII*, *BAX* or *IGFR* coding sequences. The prevalence of *TP53 APC* and *KRAS* mutations is significantly lower in this group than in microsatellite stable group (MSS) and, on the contrary, BRAF mutations are more frequent in the MSI-H colon cancer group. This tumour phenotype is more frequently observed in proximal part of colon and in elderly women [7]. Finally the last group is associated with a CpG island methylator phenotype (CIMP). It overlaps partially to the previous one but presents some specificity such as an association with a poor prognosis.

MiRNAs have been studied in colorectal cancer although the validation of miRNA as potential biomarkers of diagnosis, prognosis or response to treatment needs to be analysed taking into account the different colorectal tumour phenotypes since the genetic alteration mechanisms are widely different.

1.1. Cancer diagnosis

The diagnosis of colorectal cancer based on a molecular signature implies that a specific expression profile is found in tumour as compared to non-tumour cells. Several studies suggested such differences [8–24]. Up to now, 35 miRNAs were found up or down regulated in colorectal cancer cells as compared to non tumour cells in at least 2 independent series (Table 1). Amongst them, hsa-miR 20a, hsa-miR-21, hsa-miR 25, hsa-miR-31, hsa-miR-93, hsa-miR 106 (includes 106a and 106b), hsa-miR-183 and hsa-miR-203, were unambiguously up-regulated in colon cancer as stated by 5–9 independent studies and hsa-miR-1, hsa-miR-126, hsa-miR-30a (included hsa-miR-30a-3p and hsa-miR-30a-5p), hsa-miR-143, hsa-miR-145, hsa-miR-191 and hsa-miR-192 were down regulated, as stated by 3–5 different studies. The down-regulated miRNAs were clearly associated with frequently deleted chromosomal region and up-regulated miRNAs with chromosomal regions showing frequent copy number increase (Table 1).

Nevertheless there are some discrepancies between studies that may be explained by different factors. First, tumour location could play a role in the heterogeneity of the results. Indeed, in a series studying the over-expression of miRNAs in rectal and colon cancers as compared to match normal tissues only 10 miRNAs were found over-expressed in both locations [8]. At the opposite no difference seems to exist between proximal and distal colon tumour [8].

The genetic background could also influence miRNA dysregulation. Cancer miRNAs could differ between MSI and CIMP tumours. Different studies have shown that miRNAs over or under expressed vary between MSS and MSI samples. It was found that only 19 out of the 60 miRNAs dysregulated in colon cancer were found both in MSS and MSI-H subtypes [9] and that the relative expression to normal tissues of hsa-miR-26b, hsa-miR-31, hsa-miR-92, hsa-miR-155, hsa-miR-196a and hsa-miR-223 was significantly different between MSI-H and MSS subgroup of tumours [10]. A miRNA signature composed of four miRNAs, under-expressed in MSS subgroup, compared with MSI subgroup (hsa-miR-142-3p, hsa-miR-212, hsa-miR-151, hsa-miR-144) was unequivocally associated with the microsatellite instable status with a cross-validated performance of 84% accuracy, 81% specificity, 92% sensitivity [9].