

Review Article

MicroRNAs in colorectal cancer

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ABSTRACT

Colorectal cancer (CRC) is the third most common type of cancer worldwide, currently representing the most common gastrointestinal cancer with 13% of all malignant tumors. MicroRNAs (miRNAs) are small non-coding RNAs that repress the translation of target genes. Since their discovery, they have been shown to play an important role in the development of cancer, since they can act as tumor suppressors or oncogenes. A literature review was performed in different databases such as Medline, PubMed, Cochrane, nature, Wolters Kluwer, ScienceDirect, Scopus, SpringerLink, Wiley Online Library. Studies were included from 2003 to 2018. Colorectal cancer presents genetic heterogeneity, because it can develop in different ways, the pathway through which cancer occurs depends on the gene initially altered. The aberrant expression of microRNAs is implicated in the development of colorectal cancer and its progression. Three existing steps in the maturation of the microRNAs have been identified: 1) transcription of the pri-miRNA, 2) cleavage in the nucleus to form the pre-miRNA and 3) a final excision in the cytoplasm to form the mature microRNA. It has been discovered that miRNAs have an impact on cell proliferation, apoptosis, stress response, maintenance of stem cell potency and metabolism, all important factors in the etiology of cancer. The data analyzed in this article highlights the importance of the study of microRNAs in colorectal cancer, however, for the carcinogenic process, progression, therapeutic management and prognosis, more multicenter randomized clinical trials are needed with a detailed analysis.

Keywords: Biomarkers, Colorectal cancer, Diagnosis, MicroRNAs, Prognosis, Survival

INTRODUCTION

Colorectal cancer (CRC) is the third most common type of cancer worldwide, currently representing the most common gastrointestinal cancer with 13% of all malignant tumors.^{1,2} This cancer is the fourth most

common cancer in the United Kingdom and the main cause of death due to malignant neoplasms.³ According to data from the Surveillance, Epidemiology, and End Results Program (SEER) of the United States, in 2015 an estimated 132,700 new cases of colorectal cancer were diagnosed, representing 8% of all new cases of cancer,

with an estimated 49,700 deaths (8.4% of all cancer deaths in the United States).⁴

The incidence of colon cancer in 2016 of 95 270 and 49 190 deaths associated with this pathology, without showing a significant predominance associated with gender. Incidence has decreased since the mid-1980s, from 2008 to 2012 around 4.5% per year in adults over 50 years of age, but increased 1.8% annually in patients under 50 years of age, with a mortality rate tending to decline 2.8% annually from 2003 to 2012.⁵

The mutational mechanisms associated with CRC include epigenetic (DNA methylation) and genomic instability, which is divided into: chromosome instability and instability of microsatellites.^{6,7} CRC can be of non-hereditary or sporadic cause related to errors in DNA methylation, transcriptional silencing of tumor suppressor genes, genes involved in cell cycle control, repair of genetic material and apoptosis or of genetic origin related to mutations of both tumor suppressor genes or the presence of oncogenes, chromosomal anomalies, gene mutation, differentiation, apoptosis and angiogenesis.^{8,9} The instability of microsatellites is also known as a mutator pathway, caused by errors in the repair system due to DNA damage, mainly due to the failure of base complementarity, generating the expansion of short sequences in tandem and an increase in the number of mutations.^{10,11}

METHODS

A literature review was performed in different databases such as Medline, PubMed, Cochrane, nature, Wolters Kluwer, ScienceDirect, Scopus, SpringerLink, Wiley Online Library. The keywords microRNAs, colorectal cancer, survival, prognosis, diagnosis, biomarkers were used. The experimental and review studies from 2014 to 2018 were included in which specific regulations of certain MicroRNAs are specified for the diagnosis, prognosis and/or development of colorectal cancer.

MicroRNAs

The micro-RNAs (miRNAs) are small non-coding RNAs that repress the translation of target genes. Since its discovery it has been shown that they play an important role in the development of cancer, since they can act as tumor suppressors or oncogenes; the oncogenic activity in miRNAs can be dependent on the type of tissue. Currently, its usefulness has been determined as biomarkers for diagnosis and as therapeutic targets in pathologies such as CRC.¹²

MicroRNAs play an important role in physiological and pathological processes, due to their post-transcriptional and regulatory function of genes, found in plants, animals and humans.^{13,14} It has been discovered that miRNAs have an impact on cell proliferation, apoptosis, stress response, maintenance of stem cell potency and

metabolism, all important factors in the etiology of cancer.¹⁵

Three existing steps in the maturation of the miRNAs have been identified: 1) transcription of the pri-miRNA, 2) excision in the nucleus to form the pre-miRNA and 3) a final excision in the cytoplasm to form the mature miRNA.^{16,17}

MicroRNAs in colorectal cancer

Each cellular process is probably regulated by a miRNA, and an aberrant expression of some miRNA is a hallmark of several diseases, including cancer.¹⁸ The alteration in the expression of miRNA in relation to the CRC was reported for the first time in 2003 by Michael et al, stating the decrease in the expression of miR-143 and miR-145.¹⁹ The miRNAs; miR-27a, miR-30b and miR-124 have been identified as suppressors of migration and invasion of several cell lines in CRC.²⁰

Slattery et al, report the expression of 94 miRNAs differentially between tumors with stable and unstable microsatellites for colon carcinomas and 41 for rectal carcinomas.²¹ miRNAs involved in CRC, regulated at discharge, have been described as; miR-135b, miR-21, miR-17-92, miR-95, miR-183, miR-31, miR-201 and miR-196a, being down-regulated miR-143, miR-145, miR-101, miR-34, miR-200, miR-195, miR-145, miR-378 and miR-212.^{22,23} The increase in the expression of miR-224 in colorectal adenomas has been described by Bartley, suggesting that it is an early event in the development of colorectal cancer, as well as having function by repressing the tumor suppressor gene, inhibiting metastasis by dissociating the interaction between RAF1 and MEK.^{24,25} Currently, different over-expressed microRNAs have been collected in colorectal neoplasms: miR-15b, miR-17-5p, miR-19a, miR-20, miR-21, miR-29a, miR-31, miR-92, miR-96, miR-135b, miR-148a, miR-181b, miR-182, miR-183, miR-191, miR-200b, miR-200c and miR-212. On the contrary, in values lower than those existing under normal conditions are: miR-1, miR-9-1, miR-30a-3p, miR-30a-5p, miR-30c, miR-34a-c, miR-126, miR-129, miR-133a, miR-133b, miR-137, miR-139, miR-143, miR-145, miR-195, miR-342, miR-422a, miR-422b.²⁶⁻²⁸

DISCUSSION

The CRC presents genetic heterogeneity, because it can be developed by different routes, the pathway through which the cancer takes place will depend on the initially altered gene; for example, if an alteration occurs in a tumor suppressor gene or in a protooncogene, such as APC or K-RAS respectively, the suppressor pathway is developed; if, on the contrary, the mutation occurs in a repair gene such as MLH1 or MSH2, the mutator path is triggered, whereas if inactivation occurs in gene expression by epigenetic mechanisms, the cancer could develop via of methylation.¹² The aberrant expression of

microRNAs is implicated in the development of colorectal cancer and its progression, therefore, studies have been conducted to use circulating microRNAs in serum and the expression of faecal genes as non-invasive markers for possible early detection.²⁹ Proper control of the expression of microRNA genes is essential to maintain a stable state of the cellular machinery. Recently, it was discovered that extracellular microRNAs circulate in the blood of healthy and diseased patients, and their ribonuclease is present in plasma and serum. The majority of circulating microRNAs are included in lipids or complex lipoproteins, such as apoptotic bodies, microvesicles, or exosomes, and are, therefore, highly stable. The existence of circulating microRNAs in the blood of cancer patients has raised the possibility that they can serve as a diagnostic marker.³⁰

CONCLUSION

In the diagnosis and current medical management of the CRC, the understanding of molecular and genetic factors regarding the pathology involved in oncology is of great importance, expanding our understanding of the implications of the expressed microRNAs and the impact according to their expression levels., requiring exhaustive analysis of the differential expression by molecular phenotype of the tumor. The data analyzed in this article, highlight the importance of the study of microRNAs in colorectal cancer, however, for the carcinogenic process, progression, therapeutic management and prognosis, more randomized multicenter clinical studies are needed with a detailed analysis.

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