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Role of Micro-RNA in Colorectal Cancer Screening☆

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ABSTRACT

MicroRNAs are involved in carcinogenesis through postranscriptional gene regulatory activity. These molecules are involved in various physiological and pathological functions, such as apoptosis, cell proliferation and differentiation, which indicates their functionality in carcinogenesis as tumour suppressor genes or oncogenes. Several studies have determined the presence of microRNAs in different neoplastic diseases such as colon, prostate, breast, stomach, pancreas, and lung cancer. There are promising data on the usefulness of quantifying microRNAs in different organic fluids and tissues. We have conducted a review of the determinations of microRNAs in the diagnosis of colorectal cancer.

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Papel de los micro-RNA en el cribado del cáncer colorrectal

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RESUMEN

Los micro-RNAs son responsables de la regulación de múltiples procesos biológicos de índole metabólica, de proliferación, de diferenciación, de apoptosis, del desarrollo y de la oncogénesis. En la carcinogénesis, los micro-RNA pueden ejercer su función a través de la alteración de los genes supresores de tumores o mediante la interacción con los oncogenes. Se ha determinado la presencia de diferentes micro-RNA en distintas enfermedades neoplásicas como cáncer de colon, próstata, mama, estómago, páncreas, pulmón, etc. Existen datos prometedores sobre la utilidad de cuantificar los micro-RNA en diferentes fluidos orgánicos y tejidos. Se ha realizado una revisión sobre las determinaciones de los micro-RNA en el diagnóstico del cáncer colorrectal.

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Introduction

Across the world, colorectal cancer is the third most frequent cancer in men, second in women and the second cause of death related to tumour disease.[1] In 2013, estimates in the United States showed over 140 000 new cases, with mortality in 50 000 colorectal cancer-related cases.[2]

Early detection of colorectal cancer may reduce the incidence and mortality figures; screening methods bear special importance, because the appearance of signs and symptoms are associated with advanced stages of the disease. Furthermore, follow-up of patients who have suffered colorectal cancer aims to detect those with a greater risk of disease relapse.

Unfortunately, the probability of cure after the onset of symptoms is 50%, whereas 80% can be reached with early diagnosis. Accepted screening methods for colorectal cancer are: occult blood detected in stools, double contrast opaque enema, colonoscopy, and rectal examination. Occult faecal blood testing is a low-cost and simple method, although only 50% of tumours and 10% of polyps bleed enough to be diagnosed by this method.

There is an ongoing debate on colon lesions not diagnosed by faecal blood testing or colonoscopy, because these are non-bleeding lesions, or located in the proximal colon, many with a rather aggressive progression (methylator phenotype, and instability of microsatellites).[3] In spite of the several available diagnostic methods, there is no consensus on new alternatives for detection, or guidelines on neoplastic disease precursors and early lesions. Promising advances in the field of molecular markers could play an important role at this level.

A tumour marker can be defined as an ''identifiable'' component in the tumour cell or secreted by the cellular clones.[4] A tumour marker in supraphysiological quantities indicates neoplasic disease, which contributes valuable information about the tumour's biological behaviour.[5,6] However, the absence of sensitivity and specificity in the initial phases of neoplastic disease strictly limits the systematic use of most tumour markers in screening asymptomatic patients. Disease staging at the time of diagnosis (determined by tumour size, degree of cytological differentiation and lymph node involvement) is the most-used prognostic indicator in colorectal cancer patients. However, certain prognostic markers are evaluated for this purpose, quantified and determined in tumour tissue and peripheral blood.[5]

In 1981, the *National Health Information Centre* (NHIC) proposed monitoring the carcinoembryonic antigen (CEA) as the best non-invasive technique to confirm relapses in patients with a previous diagnosis of colorectal cancer.[7] Later, in 1996, the *American Society of Clinical Oncology* (ASCO) published clinical guidelines based on evidence for using tumour markers in colorectal cancer.[8] In 2007, the *European Group on Tumour Markers* (EGTM) updated the guidelines for using serum, tissue and faecal markers in colorectal cancer.[9]

In spite of having studied a multitude of tumour markers in colorectal cancer, only a few of them are recommended for routine use. The various oncological guidelines accept and recommend: (1) faecal blood testing for early diagnosis in people over 50 years of age; (2) determination of CEA in post-operative follow-up of patients undergoing chemotherapy or surgical resections; (3) instability of microsatellites, through genetic study of MLH1, MSH2, MSH6, PMS2 to identify people susceptible for non-polyposis hereditary colorectal cancer and 4) APC mutation in the diagnosis of familial adenomatous polyposis.[7–9]

Physiologic epigenetic mechanisms that are able to change chromatin structure are, amongst others, modification of DNA methylation, histone and RNA; it has been demonstrated that epigenetic changes are just as important as genetic changes in the origin of neoplastic disease, and both contribute to the progression and development of neoplastic disease.[3] Micro-RNA are molecular structures with 20–22 nucleotides and post-transcriptional activity involved regulating genetic expression. Their participation in different physiological and pathological functions has been shown, such as apoptosis, cellular proliferation and differentiation, and their functionality as tumour suppressor genes or as proto-oncogenes in carcinogenesis has been demonstrated.[10] The medical literature includes various studies focusing on micro-RNA detection in tissue, in stools or peripheral blood, and their values have been linked to the diagnosis and prognosis of neoplastic disease.

Markers in Stools

Different studies have determined faecal DNA to quantify the various values of micro-RNA in stools. Link et al. verified the overexpression of miR-21 and miR-106a in colorectal neoplastic lesions and in adenomas, comparing them with healthy individuals.[11] In their study, Kalimutho et al. evaluated hypermethylation of miR-34b/c promoter in stools; they demonstrated that up to 75% of colorectal cancer patients had promoter hypermethylation correlated to the tumour stage, which led them to propose determining miR-34b/c aberrant methylation in stools as a diagnosis marker. In normal conditions, miR-34 functions as a tumour suppressor by participating in cellular ageing, inducing apoptosis and stopping the cellular cycle. Thus, miR-34b/c aberrant methylation, present in up to 97.5% of colorectal neoplasia, would allow cellular proliferation.[12]

Likewise, over-expression of miR-20a, miR-21, miR-92, miR-96, miR-106a, miR-203 and miR-326 in patients with colorectal tumour disease has been detected in stools, whereas advanced stages of the disease show low levels of

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