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Research Article

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DNA Methylation and Micro RNAS as Biomarkers in Hereditary Nonpolyposis of Colorectal Cancer Patients: A Systematic Review

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Abstract

Introduction: *Colorectal cancer (CRC) is a disease of colon or rectum the part of digestive system. DNA methylation is a process of gene expression by recruiting protein which involve in gene repression, or inhibiting the binding of transcription factors to DNA. MicroRNAs (miRNAs) have been attracting major interest as potential biomarker in cancer. Hereditary nonpolyposis of colorecta cancer (HNPCC) is a type of genetic change (mutation) in a family. Our aims to do a systematic review on DNA methylation and miRNAs serve as candidate clinical biomarkers in HNPCC.*

Materials and Methods: *Electronic databases (Medline, PubMed and Scopus data bases). We searched to identify publication all over the world related colorectal cancer and miRNA. Selection was based on the design (CRC, invasive CRC, Colon or rectum, HNPCC, microRNA, circulating miRNA, non-coding RNA), 87 papers from PubMed and 15 papers from Scopus were selected all over the world. CRC, target antigens, methodologies used for detection and miRNA expression were identified and summarized.*

Results: *A total of 96 articles were searched, 87 articles from Scopus and 9 articles from PubMed. 20 duplicates removed and remain 76, 52 excluded after screened the titles and abstracts; and remain 24, 10 full texts articles were excluded with reason, and 14 identifications were included in the studies.*

Conclusion: *The findings of this systematic review showed that DNA methylation and micro RNA in HNCC patients as a genetic mutation or a promoter in colorectal cancer.*

Keywords: Colorectal Cancer, DNA Methylation, HNCC, Micro RNA, Medline, PubMed, Scopus, Cochrane, Systematic Review

1. Introduction

Colorectal Cancer (CRC) is a disease that are owned by people aged from 50-75 years old [1]. An estimated 1.361.000 are diagnosed with CRC annually; approximately 694.000 people die from CRC annually, and 3.544.000 individually are living with CRC [2]. To know the status of the patients who survive with CRC, requires a blood test, direct endoscopy or colonoscopy test [3]. Blood contains numerous analytes including circulating cell free Deoxyribonucleic Acid (cfDNA), the cfDNA may originate from circulating tumor DNA (ctDNA) [4].

DNA methylation is an epigenetic mechanism involving the transfer of a methyl group onto the C5 position of the cytosine to form 5-methylcytosine [5]. In normal cell, it assures the proper regulation of gene expression and stable gene silencing. DNA methylation is associated with histone modifications and the interplay of these epigenetic modifications is crucial to regulate the functioning of the genome by changing chromatin architecture. The DNA methylation also may occur due to inactivation of certain tumor-suppressor genes occurs as a consequence of hypermethylation within the alteration in promoter region and repetitive DNA sequences, this occur due to associated also with

regulation of expressing of noncoding RNAs like microRNAs [6]. MicroRNAs (miRNAs) are endogenous 21-to22-nucleotide non-coding RNAs that target messenger RNAs (mRNAs) and regulate their expression through complementarity to the 3'-UTRs of mRNAs may serve as biomarkers in Hereditary Nonpolyposis of Colorectal Cancer Patients [4].

This literature review provides an overview of the most important scientific literature on HNPCC and miRNAs. Some systematic reviews have been published in colorectal cancer such as systematic review on the existing screening pathways for lynch syndrome identification and others. However, there is no qualitative scientific systematic review DNA methylation and microRNAs as biomarkers in hereditary nonpolyposis of colorectal cancer patients. Therefore, reviewers concentrated on the scientific systematic review on circulating exosomal miRNAs serves as candidate biomarker in colorectal cancer.

2. Materials and Methods

2.1 Searching Strategy

Reviewers are using the Cochrane guidelines to do a systematic review. The searching strategies used to conduct a systematic computerized search of the PubMed, Science Direct and Google Scholar databases [7]. However, in this review, reviewers accessed publication papers through only PubMed and Science Direct to search the articles. Searching term that used as follows (i) "colorectal cancer" or "colon cancer" or "rectal cancer"; or "lynch syndrome" (ii) "Circulating microRNA" or "microRNA" or "miRNA" or "micro-RNA" or "short RNA" or "small RNA" or "non-coding RNA" (iii) "DNA methylation" or "methyl group" or ". A detailed search strategy and search algorithms are shown in the searching results and summary tables.

2.2 Inclusion Criteria

Research, review and systematic review articles were from reliable journals. These scientific articles involved studies reporting data from published papers including colorectal cancer screening, and DNA methylation biomarkers. The inclusion criteria include: (1) studies must describe in human colorectal cancer; (2) data on the hereditary nonpolyposis of colorectal cancer; (3) data related circulating microRNA in HNPCC; (4) data related DNA methylation in HNPCC.

2.3 Exclusion Criteria

In the exclusion, duplicate papers were removed, mismatch papers excluded based on the titles and abstract, and remain papers assessed for eligibility and included in the studies. Thus, the reviews exclude incredible publication papers on other types of cancer.

2.4 Review Process

Research articles were identified from searches of the electronic databases was imported into ENDNOTE software version X8 (Thomson Reuters, USA). Before the data were extracted, selected articles were read the title and abstract to fulfill the inclusion criteria.

2.5 Data Extraction and Quality Assessment

The inclusion and exclusion criteria were used to find the articles based on titles and abstracts. The selected articles were extracted and collected independently. The extraction data were included of the publication data (Authors, year of study, country of study, sample number, tumor stages, microRNA identified, follow-up months, detected samples, assay methods, normalizer RNA).

3. Results

The searching strategy was using PubMed and Scopus. A total of 96 articles were searched, 20 duplicates removed and remain 76 articles, 52 excluded after screened the titles and abstracts, remain 24, 10 full articles were removed with reason. And 14 articles were included in the studies (Figure 1). List of miRNAs identified from the selected articles as shown in Figure 2 and summary description as indicated in Table 1.

4. Discussion

CRC detection may use various clinical samples such as peripheral blood, saliva and urine as well as stool specimen [8]. DNA methylation and microRNAs serve as biomarker in CRC patients due to alteration in promoter region and repetitive DNA sequences, this occur due to associated also with regulation of expressing of noncoding RNAs like microRNAs [4]. MicroRNAs (miRNAs) are non-coding RNAs of 20-22 nucleotides and regulate the translational inhibition of target mRNAs by base-pairing with their 3'-untranslated regions (3'-UTR). They have been associated with numerous molecular mechanisms involving developmental, physiological and pathological changes of cells and tissue [9]. Therefore, peripheral blood, saliva, urine and stool specimen can be used for CRC diagnosis in the future. However, detection of DNA methylation, mutation and microRNAs serve as biomarker in CRC patients to evaluate the effectiveness of the drug and diseases progression still limited. Therefore, reviewers would like to focus on a systematic review of DNA methylation and microRNAs serve as biomarkers in hereditary nonpolyposis of colorectal cancer patients.

4.1 How Microorganisms Cause Cancers

Normally people transmitted by Helicobacter pylori through saliva. The Food and water contaminated with bacteria due to infected fecal. stated that Helicobacter pylori enter the stomach of the host, it's urease activity to neutralize the hostile acidic condition at the beginning of infection [10]. defined namely H. pylori infection substantially contributes to global cancer mortality. Meanwhile, described that Hepatitis B virus (HBV) is one of the choric infections that leading cause for hepatocellular carcinoma (HCC) worldwide. Furthermore, defined explicitly that liver fluke infection causes pathological changes mainly to the bile ducts where the worm can be found, as well as to the liver and gall bladder in both human and animal. The early pathological changes consisted of an acute inflammatory reaction involving the large intrahepatic bile ducts and portal connective tissue. Therefore,

the infection of the bacteria, viruses and parasites may produce specific miRNAs during the infection process that leading to cancers [11,12].

4.2 DNA Methylation and Mutation, Micro RNA in Colorectal Cancer Patients

In the last decade, an increasing number of studies have identified miRNAs as critical regulators of carcinogenesis and tumor progression, affecting tumor growth, progression, metastasis and drug resistance [13,14]. As a result, an increasing number of studies have demonstrated the potential of miRNAs as novel therapeutic targets and diagnostic markers [15,16]. Despite a lack of comprehensive understanding of the mechanisms underlying miRNA dysregulation in cancer, a number of studies have demonstrated that the silencing of specific miRNAs and DNA methylation are strongly associated. For example, in cancer cells, hypermethylated CpG islands are found within the DNA sequences encoding miR-127 and miR-124a [17,18]. The silencing of miRNA expression in cancer appears to be largely mediated by DNA methylation, particularly the methylation of tumor suppressor genes. CRC is often caused by accumulation of genetic/epigenetic changes in genes coding for tumor suppressors, oncogenes and DNA repair pathways [19].

4.3 Candidate Micro RNA in CRC Patients

The miRNAs are a class of non-coding RNAs that paly important role in gene expression, the author also stated that there are various genes that associated with miRNAs such as FOXA1 and Zbtb7a with miR-212 and miR-106a. However, in CRC is one of the most inherited cancer syndromes known, the genes that allied with CRC are MSH2 and MSH6 which combine with human chromosomes [20].

4.4 Micro RNA 127

There were numerous studies have been assessed microRNA 127 which associated with some changes including cell initiation and proliferation. stated that miR-127 is usually expresses as part of a miRNA cluster in normal cells, suggesting that it is subject to epigenetic silencing. However, Mir-127 was downregulation after treatment. Therefore, it is concluded that DNA demethylation can be activate expression of miRNA that may act as tumor suppressor genes [21].

4.5 Micro RNA 124

There were various studies have been assessed microRNA 124 which associated with several changes in cellular process such as cell proliferation, apoptosis, invasion, and metastasis Meanwhile, the author also stated that Mir-124 as tumor suppressor in CRC which inhibit STAT3 to suppress the growth of human CRC. Moreover, Mir-124 also as oncomirs involved in CRC pathogenesis with targets iASSP to regulates the cell proliferation. Therefore, MiRNAs and their expression regulation is more important in several human diseases, and cancer in particular as their involvement in various tumorigenesis processes such as angiogenesis, migration and proliferation [22].

5. Conclusion and Future Prospective

MicroRNAs are non-coding RNAs that regulate gene expression. The uncontrol cells may develop themselves during tumor cell initiation, adaptation, proliferation, and initiation of cell death. The samples that require for CRC diagnosis are body fluids and urine. MicroRNAs 124 and 127 have been diagnosed in down regulation cells in numerous people such as hospitalized and non-hospitalized patients. However, there are no up regulated cells from hospitalized and non-hospitalized patients, screened samples, survey samples and etcetera. Further investigation of the plasma, serum and tissues samples in the laboratory needed performed using real time PCR towards selected candidate miRNAs especially for CRC samples in the future perspective.

Completing Interests

The authors declare there are no competing interests

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