Saudi Journal of Biological Sciences (2017) **24**, 466–476

King Saud University

Saudi Journal of Biological Sciences

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ORIGINAL ARTICLE

Establishment of apoptotic regulatory network for genetic markers of colorectal cancer

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Received 3 November 2016; revised 25 December 2016; accepted 6 January 2017
Available online 26 January 2017

KEYWORDS

Colorectal cancer;
Genetic marker;
Meta analysis;
GO analysis;
KEGG analysis

Abstract Our purpose [illegible] to sc[illegible]out genetic markers applicable to early diagnosis for colorectal cancer and to establish ap[illegible]pte[illegible] regu[illegible]tory network model for colorectal cancer, thereby providing theoretical e[illegible] and ta[illegible]eted therapy for early diagnosis of colorectal cancer. Taking databases including [illegible]NKI, [illegible]IP, Wa[illegible]ang data, Pub Med, and MEDLINE as main sources of literature retriev[illegible] literatu[illegible] associate[illegible] with genetic markers applied to early diagnosis of colorectal cancer we[illegible] sea[illegible]ed[illegible] perform[illegible]omprehensive and quantitative analysis by Meta analysis, hence screening genetic [illegible]kers used in early diagnosis of colorectal cancer. Gene Ontology (GO) analysis and [illegible]oto Encyclo[illegible]dia of Genes and Genomes (KEGG) analysis were employed to establish apoptot[illegible]egulatory network model based on screened genetic markers, and then verification experiment was c[illegible]ducted. Through Meta analysis, seven genetic markers were screened out, including WWOX, [illegible]ras, COX-2, p53, APC, DCC and PTEN, among which DCC shows highest diagnostic efficiency. GO analysis of genetic markers found that six genetic markers played role in biological process, molecular function and cellular component. It was indicated in apoptotic regulatory network built by KEGG analysis and verification experiment that WWOX could promote tumor cell apoptotic in colorectal cancer and elevate expression level of p53. The apoptotic regulatory model of colorectal cancer established in this study provides clinically theoretical evidence and targeted therapy for early diagnosis of colorectal cancer.

1. Introduction

Colorectal cancer, as a common malignant tumor in digestive system, ranks third among male common malignant tumors and ranks second among female common malignant tumors in terms of morbidity in worldwide. In 2008, there were 1.2 million new cases of colorectal cancer globally, among which 609 thousand died of the disease (Jemal et al., 2011). In China, colorectal cancer mainly attacks people aged 40–60 years old and due to its occult onset and low awareness,

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.sjbs.2017.01.014
1319-562X

most patients have been in advanced stage when diagnosed, and metastasis has occurred in about 25% patients when first diagnosed. Therefore, elevation of early diagnostic rate for early treatment and improvement of prognosis for colorectal cancer are focuses in current and further colorectal cancer prevention and control.

Meta analysis refers to a quantitative literature review which takes multiple independent research results for the same topic as objects, and based on strict design, it employs proper statistical methods to perform systematic, objective, quantitative and comprehensive analysis, aiming to promote statistical test efficacy, evaluate inconsistency or contradiction of research results and discover disadvantages in individual research. In addition, it can process a large quantity of literatures without number limitation. Therefore, Meta analysis plays a significant role in clinical diagnosis, treatment, risk assessment, prevention and intervention, health service as well as decision-making (Zhou et al., 2010). Meta analysis not only promotes efficacy of statistical inference thus lessening inconsistency of single research and draw more comprehensive and reliable conclusions (Zhang et al., 2013; Chaiyakunapruk et al., 2014), but also puts forward some novel research subjects, guiding direction for further study.

Gene Ontology (GO) database (Hill et al., 2016) is a structured standard biological model established recently by GO organization, aiming to build a standard system of genes and their biological productions to analyze genes and their cellular component, molecular function and biological processes they are involved in.

Kyoto Encyclopedia of Genes and Genomes (KEG (Kanehisa and Goto, 2000) is a database that integrates ge ome, chemistry, and information of system function, whic links gene catalogs obtained from genome that ha n completely sequenced to system function of higher l el of ce species and ecosystem. It is characterized by owerful image function, enabling people to have an intuitive d co prehensive understanding of the metabolic pa ways th study.

Taking databases including CN VIP, Wan g data, Pub Med, and MEDLINE as ma sour s of literatur retrieval, literatures associated with enetic mark s that are applied to early diagnosis of colo tal cancer were s rched to perform comprehensive and uantitati e analysis by Meta analysis, hence screening gene mar rs which can be used in early diagnosis of colorectal ca Regardi g the screened seven genetic marker ncluding WO K-ras, COX-2, P53, APC, DCC d PTE , their a ptotic regulatory network model in c rectal was established by GO analysis and KEGG a ys, and then verification experiment was conducted. The odel defines programed death regulatory mechanism for colo tal cancer cell, hence directing the individual diagnosis and targeted therapy of colorectal cancer.

2. Material and methods

2.1. Subjects

With CNKI, VIP and Wanfang databases were regarded as primary sources for Chinese literatures retrieval, literatures published between 1st January 1990 and 31 December 2013 were searched under key words of colorectal cancer, genetic markers, and early diagnosis. Regarding English literatures, Pub Med and MEDLINE were considered as main sources, and literatures published between 1st January 1990 and 31 December 2013 were searched with key words "colorectal cancer", "genetic markers" and "diagnosis". All literatures meeting inclusion criteria were carefully read, including the whole text and references, and related literatures were searched as well. The full text of included literatures were either in Chinese or in English and concerning researches made by the same institution or on the same subject but published on different journals, the latest and the most complete report was adopted.

Inclusion criteria for literatures: (1) the literature should be in English or in Chinese, with content of application of genetic markers in early diagnosis of colorecta ; (2) the research type is retrospective study; (3) the g d standar in literature is histopathology or operative diag sis, and the l rature takes patients with colorectal ca er as xperiment group and healthy people or patients th benign mor a ontrol group, and objects with no res ction of ation, s well as sex; (4) literature should provi diag se results of colorectal cancer separately diagn d by etic ma ers; (5) true positive (TP), false pos e (FP), fal egat e (FN) and true negative (TN) of pati ts th colorecta ncer that is separately diagnosed by genetic ma ers can be obtained directly according to the lit e or by ca lation; (6) the literature employs correc methods and the study has normative process, and regardin researches m ltiply made by the same institution or on the sa e subject but ublished on different journals, the latest and the st compl e report was adopted. All included literatures in this re published full text in Chinese or in English l all data were obtained from the original text.

Ex sion criteria for literatures: (1) the literature involves either an unoriginal or repetitive research, or serious design defect, or incomplete data; (2) the type of literature is review or abstract; (3) cases are not diagnosed by gold standard; (4) subject is colon cancer or rectal cancer; (5) no control group is set in the study; (6) the literature studies application of genetic markers in postoperative recurrence diagnosis of colorectal cancer; (7) the literature shows no results of separate diagnosis but only combined diagnosis results of genetic markers for colorectal cancer.

2.2. Data extraction and quality assessment

Data extraction of included in literatures: (1) general data, including authors, published time, published journal, title, the numbers of cases in experimental group and in control group; (2) methodological characteristics: cutoff value; (3) characteristics of research results: diagnostic results of genetic markers for colorectal cancer, including TP, FP, FN and TN.

Quality assessment of included literatures: included literatures were separately and independently assessed and performed cross-check by two professional reviewers using quality assessment of diagnostic accuracy studies (QUADAS) developed by Whiting et al. (2003). QUADAS consists of 14 assessment indicators. Regarding each indicator, "Yes" indicates meeting the standard; "No" indicates not meeting the standard, "Not clear" indicates insufficient information can be got from the literature to determine whether the standard is met.