ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 9, Issue, 02, pp.47156-47160, February, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

A REVIEW ON MOLECULAR MARKERS OF COLORECTRACL ACANCER

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ARTICLE INFO

Article History:
Received 23rd November, 2016
Received in revised form
11th December, 2016
Accepted 20th January, 2017
Published online 28th February, 2017

Key words:
Colorectal Cancer,
APC gene, RAS family,
MSI, MMR, Mutation.

ABSTRACT

In the present review, we accumulated the information on cancer, the second largest killer disease (the first being coronary heart disease) in the developed countries, and its prevalence in different regions of the world. Cancer is characterized by loss of control of cellular growth and development leads to excessive proliferation and spread of cells. This review mostly focused on the colorectal cancer, one of the most familiar cancers and cause of cancer death in developed countries. In India it has 6.3% out of an all 28 cancer reported. This review also revealed strongly the role of APC gene for the wide dispersal of colorectal cancer. APC gene is the most important gatekeeper of colonic epithelial cell proliferation and is responsible for controlling the onco protein called β-catenin. Microsatellite instability (MSI) occurs in 10−20% of colorectal cancers (CRC), and has been attributed to both *MLH1* promoter hyper methylation and germ-line mutation in the mismatch repair (MMR) genes. It may support and paved the way for the therapeutic targets.

Citation: Nivetha, A., Karthika, B., Kadheeja Roshni, M., and Vinayaga Moorthi, P. 2017. "A review on molecular markers of colorectracl acancer", *International Journal of Current Research*, 09, (02), 47156-47160.

INTRODUCTION

Cancer is a group of diseases which share similar characteristics. Cancer can affect all living cells in the body, at all ages and in both male and female. The causation is multifactorial and the disease process differs at different sites. Tobacco usage remains the first and most important identified risk factor for cancer. A host of other environmental exposures, certain infections as well as genetic predisposition play an important role in carcinogenesis. More than two decades of successful research the effective implementation of knowledge requires control of cancer. This is currently familiar that over common fraction of cancers area unit preventable, and common fraction probably curable provided they're diagnosed early in their course (Nair *et al.*, 2005). Loss of function in APC gene leads to the increasing level of β-catenin.

Global and Indian scenario

In 2012, International Agency for Research on Cancer figures of global cancer burden estimates were 14.1 new million cases and 8.2 million cancer deaths. Globocan (2012) estimates a substantive increase to 19.3 million new cancer cases by 2025.

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On the Indian scenario, 1.1 million new cancer cases were estimated contributing to 7.8% of global cancer burden (Saranath and Khanna, 2014). Globally Lung (1,824,701, 13%) and breast cancer (1,676,633, 11.9%) are the majority diagnosed cancers and therefore the most important causes of cancer death in men and women in both developed and less developed countries. Prostate cancer is the most frequently diagnosed cancer among men and lung cancer is the leading cause of cancer death among women in more developed countries (Ferley *et al.*, 2014). Other frequently diagnosed cancers are colorectal cancer (1,360,602, 9.7%), stomach cancer (8.5%) and liver cancer (7.5%) respectively. In India, five most common cancers in both sexes were cancers of breast (14.3%), cervix uteri (12.1%), lip oral (7.6%), lung (6.9%) and colorectal (6.3%) of all 28 cancers reported.

Colorectal cancer

Colorectal cancer (CRC) is one of the most prevailing cancers with most rate of mortality in the developed countries. If CRC is detected in early stage it can be cured and this is also one of the most curable cancers through regular colonoscopy. Genetic mutations play important roles in CRC development. Recently, different initiating genes have been found to be involved in different categories of CRC and most of the genetic mutations are somatic with no implication for future generations. A study conducted in monozygotic twins shows 35% of CRC to genetic proneness. In association with this the CRC development can

be manipulated by genetic-environment (Walther *et al.*, 2009). Two categories of CRC has been noticed one related to hereditary while another is non-hereditary (sporadic). Hereditary CRC will be classified into two sub-groups, i.e., Hereditary Non-polyposis Colorectal Cancer (HNPCC) which includes concerning one to 6 p.c of all body part cancer and multiple polyps CRC, which includes familial adenomatous polyposis (FAP), hamartomata's polyposis syndrome and MUTYH-associated adenomatous polyposis. Conventionally, test such as colonoscopy, fecal occult blood testing (FOBT) is a tool which is widely used for non-invasive screening for CRC. Mostly colonoscopy is more operational and delicate and understanding the molecular basis of CRC the molecular signs may be formed as an alternate to FOBT and other screening (Tsang *et al.*, 2014).

Among the cancer types, colorectal remains, in third position, most common cancer in men (6, 63, 000 cases, 10.0% of all cancer cases) and in women it is the second most common cancer (5, 71, 000 cases, 9.4% of all cancer cases) worldwide. Almost 60% of cases are encountered in developed countries. The number of CRC-related deaths is estimated to be approximately 6, 08,000 worldwide, accounting for 8% of all cancer deaths and creation CRC the fourth most common cause of death due to cancer. The annual prevalence rate for colon (AARs) and rectal cancer in India in men are 4.4 and 4.1 per 1, 00, 000, correspondingly. The AAR cancer in women is 3.9 per 1, 00, 000. The cancers affecting men Colon cancers is more predominant than colorectal cancer and it ranks 9th among men. In the 2013 report, the maximum AAR in men for CRCs was recorded in Thiruvananthapuram (4.1) followed by Banglore (3.9) and Mumbai (3.7). The highest AAR in women for CRCs was (5.2) followed by Aizwal (4.5) (Shukla *et al.*, 2014). Colorectal cancer (CRC) is a heterogeneous disease, developing through a multi pathway raised frameshift-to-inframe ratios, and lower transcript levels than wild-type allele sequence of events guided by clonal selections. CRC developmental pathways include (a) genomic instability, chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phonotype (CIMP), (b) genomic mutations including suppression of tumor suppressor genes and activation of tumor oncogenes.

Pathways included in the development of CRC may be broadly categorized into (a) genomic instability, including chromosome instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP), (b) genomic mutations including suppression of tumor suppressor genes and activation of tumor oncogenes, (c) microRNA, and (d) epigenetic changes (Kanthan *et al.*, 2011). Detection of CRC in stages can reduce both the prevalence and mortality of the disease. Molecular symbols that discover gene mutation in the primary steps of CRC can be used as non-invasive screening tests for early detection of CRC, followed by aggressive positive tests such as colonoscopy for individuals with positive results. Choice of biomarkers is very important. In order to develop a new diagnostic method, suitable biomarkers which are biological substances that can be used to indicate the biological state of a patient, must be identified stage so that diseases can be cured effectively. Regarding CRC detection, since CRC is believed to be developed slowly via accumulation of genetic mutations, detection of the disease at earlier stage is the key concern for developing new diagnostic methods. In selection of novel biomarkers, in terms of CRC detection, a good marker must be skilled of cultivated among CRC patients and healthy individuals significantly (Tsang *et al.*, 2014).

Global and Indian scenario

Colorectal cancer is the third most common cancer in men (6, 63, 000 cases, 10.0% of all cancer cases) and the second most common in women (5, 71, 000 cases, 9.4% of all cancer cases). The CRC-related deaths is estimated to be approximately 6, 08, 000 worldwide, accounting for 8% of all cancer deaths which makes CRC the fourth most common cause of death due to cancer (Shukla *et al.*, 2014). The highest incidence rates were estimated in Australia/New Zealand and Western Europe, the lowest in Africa (except Southern Africa) and South-Central Asia. CRC is the third most commonly diagnosed cancer and the third leading cause of cancer death in both men and women in the US. The American Cancer Society estimates that 1, 36,830 people will be diagnosed with colorectal cancer and 50,310 people will die from the disease in 2014 (Alteri *et al.*, 2014). In India, the annual incidence rates for colon cancer in man affected in 4.4 and 4.1 per 1, 00, 000, respectively and the AAR for colon cancer in women is 3.9 per 1, 00,000. Thus Of the cancers affecting men Colon cancers is more predominant than colorectal cancer. In the 2013 report, the maximum AAR in men for CRCs was recorded in Thiruvananthapuram (4.1) followed by Bangalore (3.9) and Mumbai (3.7) whereas the highest A maximum AAR in Nagaland the maximum AAR in CRC for women reported to be high (5.2) followed by Aizwal (4.5).

Gene markers in colorectal cancer

Chromosomal instability

The most common alleles lost are from chromosomes 5, 8, 17 and 18, and the most corporate single defect is mutation of the Kirsten ras (K-ras) oncogene on chromosome 12. RAS family is a series of genes including *HRAS*, *NRAS* and *KRAS.* The oncogenic mutation of RAS family leads to the activation of RAS genes that promote cell survival and suppress apoptosis. KRAS mutation analysis is widely used as a prognostic and predictive biomarker of anti-EGFR monoclonal antibodies like cetuximab and panitumumab to predict the therapeutic effectiveness in CRC in clinical applications. APC gene is the most important gatekeeper of colonic epithelial cell proliferation and is responsible for controlling the onco protein called β-catenin. The loss of function in *APC* gene may lead to the development of adenoma due to the up-regulation of β-catenin. Germline APC mutations usually give rise to FAP. Therefore mutations in the APC gene are respectable biomarkers for isolating people at risk of CRC in patients' families. P53 gene located in chromosome 17p is found in active to 75% of belongings of colorectal cancer. It is a tumor suppressor gene encodes a nuclear protein that functions as a transcriptionfactor.p53 is regarded as one of the most important tumor suppressor genes with a key number of cellular functions such as DNA damage repair, initiation of programmed cell death and cell cycle checkpoint control. Loss of material from the long arm of chromosome 18 is found in approximately 70% of cases of colorectal cancer and 50% of adenomas. The 18q segment contains three candidate tumour suppressor genes: *DCC* (deleted in colon cancer gene) and *Smad 2* and *Smad 4* (initially described as *DPC4*) genes. These proteins are involved in signaling from TGF-β receptors and

regulate transcription of key target genes such as c-*myc*, *CBFA1*, *FLRF* and *furin* (Mc.Dermott *et al.*, 2002).

Adenomatous Polyposis Coli gene

APC gene is a tumor suppressor gene located in chromosome 15q 22.1. Germline mutations in the APC gene results in Familial Adenomatous Polyposis. APC stimulates phosphorylation and degradation of β-catenin, also controls its distribution between nucleus and plasma membrane. Mutations in APC have been found in approximately 60% of sporadic carcinomas and adenomas (Powell *et al*, 1992). APC is a multi-domain protein that contains binding sites for numerous proteins including microtubules, onco-protein such as β-catenin (Aoki and Taketo, 2007). It is considered as the most important gate keeper of pathway. Loss of function in APC gene leads to the increasing level of β-catenin. Wagner *et al.* (2003) studied the germ-line mutations in families with HNPCC. In 45 (92%) of the 49 Amsterdam-criteria–positive relations and in 7 (70%) of the 10 Amsterdam-criteria–negative relations, a mutation was identified in one of the three investigated MMR genes**.** Forty-nine alterations existed in MSH2 or MLH1, and individual three were in MSH6. A extensive quantity (27%) of the mutations was genomic movements (12 in *MSH2* and 2 in *MLH1*).

Notably, a deletion surrounding exons 1–6 of MSH2 was distinguished in seven actually separate relations (12% of the total cohort) and was successively confirmed to be a founder. Screening of a second U.S. cohort with HNPCC from Ohio allowed the identification of two additional kind reds with the identical founder deletion. They recognized a common North American removal in MSH2, secretarial for 10% of their cohort. The studies (Genealogical, Molecular and haplotype) represented a pattern of deletion (mutation) which was seen in the 19th century by the North American Founder. Inheritance of a only reformed gene can effect in a marked predisposition to colorectal cancer in two different diseases, Familial Adenomatous Polyposis (FAP) and Hereditary Non-polyposis Colorectal Cancer (HNPCC). The studies demonstrate that the deficiency in FAP causes initiation of tumor by affecting the gatekeeper function of the *APC* gene. In contrast**,** the responsibility in HNPCC mostly affects tumor development by aiming the genome protector part of DNA mismatch repair. Educations of these disorders have providing single visions into together inherited and sporadic methods of human tumor (Kinzler and Vogelstein, 1996). Zhu *et al.* (1998) reported the Smad2, Smad3, and Smad4 transduce signals from the cloning and directed interruption of the mouse Smad3 gene. *Smad3* mutant mice are possible and abundant. The *Smad3* mutant mice become moribund with colorectal adenocarcinomas among 4 and 6 months of age. The neoplasms enter over the intestinal wall and metastasize to lymph nodes. These results directly implicate TGFb signaling in the pathogenesis of colorectal cancer and provide a compelling animal model for the study of human colorectal cancer.

Kim *et al.* (2013) evaluated MSI in 277 colorectal and endometrial cancer genomes. In coding sequences, the frequent MSI occasion indicated tumor sort specificity, raised frameshift-to-inframe ratios and lower transcript levels than wild-type alleles. Moreover, genome-wide study exposed transformations in the circulation of MSI against point mutations, containing overrepresentation of MSI in euchromatic and intronic regions linked to heterochromatic and intergenic regions, correspondingly, and reduction of MSI at nucleosome-occupied sequences. Our results provide a panoramic view of MSI in cancer genomes, prominence their tumor type specificity, effect on gene expression, and the character of chromatin organization. Smith *et al.* (2015) described the current guidelines; a change in our current cervical cancer screening guidelines related to the follow-up of women with a human papillomavirus (HPV)-negative, atypical squamous cells of undermined significance (ASC-US) result; current issues shaping screening for breast, colorectal, and lung cancer; and the most recent data on cancer screening from the National Health Interview Survey.

Hoffmeister (2013) reported mediany 115 cases of 69 years showed MSI-high age mid cases were 69 years and 115 cases were categorized MSI-high. In multivariate investigations, BMI was positively linked with both) risk of MSI-high colorectal cancer [per 5 kg/m2: OR, 1.71; [per 5 kg/m2 or 1.71; confidence interval (CI), 1.35-2.17] are 95%) (OR, 1.20; 95% CI, 1.07–1.33). The suggestion with MSI-high colorectal cancer was imperfect to women (OR, 2.04; 95% CI, 1.50–2.77**;** P interaction ¼ 0.02) and peak distinct between continually consumer of postmenopausal hormone replacement therapy (OR, 4.68; 95% CI, 2.36–9.30; P interaction ¼ 0.01). In case-only analyses, BMI was more strongly related with MSI-high colorectal cancer than with MSS color colorectal cancer among women (OR, 1.84; 95% CI, 1.13–1.82; P interaction ¼ 0.01). Over the past three eras, molecular genetic studies have showed some critical mutations underlying pathogenesis of the irregular and inherited forms of colorectal cancer (CRC). A relatively limited number of oncogenes and tumor suppressor genes—most prominently the *APC*, *KRAS*, and*p53* genes—are mutated in defined a considerable section of CRCs and a larger collection of genes that are mutated in subdivision of CRCs have begun to be defined). Between DNA-methylation and chromatin structure changes, the mutation act to dis-regulate preserved signaling networks that exert context-dependent effects on critical phenotypes, together with the regulation of cellular metabolism, proliferation, differentiation and survival (Fearon, 2011).

In India, the yearly prevalence amounts (AARs) for colon cancer and rectal cancer popular men are 4.4 and 4.1 per 1, 00,000 respectively. The AAR for colon cancer in women is 3.9 per 1, 00,000. Colon cancer grades 8th and rectal cancer grades 9th mid men. Among women), rectal cancer does not figure in the top 10 cancers, whereas colon cancer ranks 9th.In the 2013 report, the maximum AAR among men for CRCs was documented in Thiruvananthapuram followed by Bangalore (3.9) and Mumbai (3.7). In women, the peak AAR was documented in Nagaland (5.2) followed by Aizwal (4.5). In a recently conducted study of 224 colorectal tumors by the Cancer Genome Atlas Network, the pattern of genomic alterations in colon and rectal tissues was found to be similar, regardless of the anatomic location and origin. The researchers concluded that tumors of the colon and rectum can be grouped together. The study identified a set of 24 genes mutated in a significant number of cases. In addition to genes found through prior research (e.g. APC, ARIDIA, TP53, KRAS, and PIK3CA), the researchers identified new genes such as SOX9, FAM123B/WTX, ERBB2, and IGF. These genes were involved in regulating cell proliferation and can therefore serve as potential therapeutic drug targets. Comparative genomic hybridization was helps to diagnose the CRCs for

chromosomal alteration that are linked with metastatic phenotype. In total, 63 tumor samples from 40 patient were investigates, including 30 primary tumor, 22 complete metastases (12 liver, 6 brain, and 4 abdominal wall metastases and 11 lymph node tumors). Using statistical analysis and histograms to estimate the chromosomal differences, overrepresentations were perceived most frequently at 20q11.2–20q13.2, 7q11.1– 7q12, 13q11.2 – 13q14, 16p12, 19p13, 9q34, and 19q13.1 – 19q13.2. Deletions were prominent 9p21, 11q22, and 14q13–14q21.

There are more alteration in hematogenous metastases than lymph node tumors, especially various deletions at 1p, 3, 4, 5q, 10q, 14, and 21q21 and gains at 1q, 7p, 12qter, 13, 22q. Comparing 16, and liver metastases over their conforming primary tumors, mostly deletions at 2q, 5q, 8p, 9p, 10q particularly deletions at 2q, 5q, 8p, and 21q21 and gains at 1q, 11, 12qter, 17q12–q21, 19, and 22q were more frequently perceived. The analysis indicate that the dissimilar pathways of tumor dissemination are revealed by a nonrandom accumulation of chromosomal) modifications with specific alterations being accountable for the altered features of the metastatic phenotype (Knosel *et al.*, 2004). Langan *et al.* (2013) provided CRC evidence based screening modalities, patient stratification and listed the novel concept of putative CRCSC's as prognostic biomarkers. Surinova *et al.* (2015) evaluated a five-protein biomarker signature for colorectal cancer detection. Laczmanska *et al.* (2014) performed chromosomal aberrations using Comparative Genomic Hybridization. Three region amplification comprising genes coding for PTPs that are PTPRZ1(7q313.3, amplified in 23.5% of cases), PTPRQ(12q21.2,amplified in 5.9% of cases) and PTPRT(20q12, amplified in 29.4% of cases along with deletions in the region of PTPRM(18p11.2,deleted in 21,6% of cases) was observed in their present investigation. It suggested that in sporadic colorectal cancer PTPRZ1, PTPRT, PTPRQ possibly act as oncogenes, while PTPRM acts as a tumor suppressor gene. Besides that, advanced on chromosome 20q12 and suffer on chromosome 18p11.2 are linked with the absence of the BRAF mutation and the conventional adenocarcinoma pathway.

The drug development was aimed to focus particular oncogenic mutations. It has been essential to modified cancer medicine. *BRAF* codes a serine/threonine kinase. RAS was activating this kinase and phosphorylates mitogen-activated extracellular signal–regulated kinase (MEK), leading to downstream activation of the mitogen activated protein kinase (MAPK)/extracellular signal–regulated kinase (ERK) pathway, a key mediator of cellular proliferation. Somatic mutations producing constitutive initiation of BRAF, most ordinarily a valine-to-glutamic acid exchange at codon 600 (V600E), were first defined in human cancer in 2002. 40%-50% of melanomas are BRAF mutations and 40% to 50% are papillary thyroid 40% to 50% of melanomas, 40% to 45% of papillary thyroid cancers, 20% to 25% of anaplastic thyroid cancers, and 5% to 15% of colorectal cancers and are at a lower prevalence in various other tumor types**.** Besides, the V600E mutation is the significant genetic occasion of hairy cell leukemia (Nagaraja *et al.*, 2015). A genome-scale analysis of 276 samples was performed using the exome the sequence, DNA reproduction amount, advocate methylation and messenger RNA and microRNA expression. A subdivision of these samples (97) suffered low distance of analysis complete genome sequencing. In total, 16% of colorectal carcinomas were found to be hyper-mutated: three-quarters of these had the expected high microsatellite instability, usually with hyper-methylation and MLH1 silencing, and one-quarter had somatic mismatch-repair gene and polymerase e (POLE) mutations. Excluding the hyper-mutated cancers, colon and rectum cancers were identified to have significantly related patterns of genomic alteration. Twenty-four genes were significantly mutated, and in addition to the expected TP52, KRAS, APC, SMAD4, PIK3CA and KRAS mutations. Many mutations in FAM123B, ARID1A and SOX9 was also observed. Frequent copy-number alternation include actually drug-targetable amplifications of ERBB2) and newly discovered amplification of IGF2. Recurrent chromosomal translocations include the mixture of NAV2 and WNT pathway member TCF7L1. Integrative analyses proposed new markers for violent colorectal cancer and an important role for MYC-directed transcriptional activation and repression (Cancer Genome Atlas Research Network, 2012).

Microsatellite instability (MSI) occurs in 10−20% of colorectal cancers (CRC), and has been attributed to both *MLH1* promoter hyper methylation and germ-line mutation in the mismatch repair (MMR) genes. They also presented that a large residents- and clinic-based study of MLH1 methylation, immunohistochemistry, and MMR germ-line mutations that enabled us to: 1) estimate the prevalence of MMR germ-line mutations and *MLH1* methylation between MSI-H cases and assist us recognize if all MSI-H CRC is described by these mechanisms; and 2) estimate the relationship among *MLH1 methylation and sex, age, and location of tumor inside the colon*. In CRC, 1,061 population were MLH1 methylation cases and 172 clinic-based cases**.** Generally, it perceived MLH1 methylation in 60 % of population-based MSI-H cases and in 13% of clinic-based MSI-H cases. Inside the population-based belongings with MMR mutation screening and certain IHC grades, Polynter *et al*. (2008) recognized a molecular occurrence in MMR in 91% of MSI-H cases: 54% had MLH1 methylation, 14% were observed with a striking age difference, with the popularity of a MMR germ-line mutation more than four-fold lower and the prevalence of *MLH1* methylation was founded to be more at the age of 50 and it was four fold higher than before the age of 50. They also interpret that MLH1 methylation within the MSI-H subgroups was predominant is female sex (independent predictor). These results reinforce the position of distinct between the notable causes of MSI in studies of etio-pathology and prognosis (Poynter *et al.*, 2008).

Conclusion

Cancer is the heterogonous disease. From this review, it was observed that, the prevalence of colorectal among the other cancer types found slight growth. Tobacco usage remains as the first and most important identified risk factor for cancer. In India, colorectal cancer remains at the fifth position. Colorectal cancer was classified into Heriditary Non-Polyposis and Familial adenomatous polyposis colorectal cancer. K-ras gene mutation was the most common single gene defect recorded. Loss of function of Adenomatous Polyposis coli (APC) gene lead to the upregulation of β-catenin which was one of the marker for diagnostic for colorectal cancer. It was reported that, 70% of the CRC was due to loss in function of gene from long arm of chromosome 18. It was also found that, Smad2, Smad3, and Smad4 transduce signals from the cloning and directed interruption of the mouse Smad3 gene. Besides that,

BRAF, PTP and *MMR* mutations also were reported by the researchers of the world. This review would present the information on the prevalence and molecular pattern with respect to gene mutation, were presented.

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