Global Journal of Medical Research: B
Pharma, Drug Discovery, Toxicology and Medicine
Volume 14 Issue 4 Version 1.0 Year 2014
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

An Insight into the Genetic Study and Pathogenesis of the Colorectal Cancer

By Tapan Behl, Ishneet Kaur, Heena Goel & Rajesh K. Pandey
Delhi University, India

Abstract- Colorectal cancer is defined as the cancer of the large intestine or the rectum – thus attributing to some other names related to this cancer such as – bowel cancer or rectal cancer, depending on the site where the tumor has occurred. It mostly begins as a benign tumor with then turns into a carcinoma.Colon cancer and rectal cancer are related in terms of their genetics and thus are studied together as allied tumors. Although some other factors such as age and lifestyle are also concerned with the progression of this cancer, a minority group of people acquire it because of certain genetic predisposition, which is focused upon in this review. Initially it was thought only to occur because of certain mutations in a specific gene called adenomatous polyposis coli (APC) gene which are responsible for initiating the characteristic events which lead to the progression of this tumor.The cases affected by this pathway were called the LOH group. But further researches concluded that there is another different pathway which can lead to the occurrence of this tumor apart from the one briefly stated above.

Keywords: adenomatous polyp, APC gene, LOH group, MSI-positive group, beta-catenin.

GJMR-B Classification : NLMC Code: QZ 20.5, QZ 40, QZ 52

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An Insight into the Genetic Study and Pathogenesis of the Colorectal Cancer

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Abstract- Colorectal cancer is defined as the cancer of the large intestine or the rectum – thus attributing to some other names related to this cancer such as – bowel cancer or rectal cancer, depending on the site where the tumor has occurred. It mostly begins as a benign tumor with then turns into a carcinoma.Colon cancer and rectal cancer are related in terms of their genetics and thus are studied together as allied tumors. Although some other factors such as age and lifestyle are also concerned with the progression of this cancer, a minority group of people acquire it because of certain genetic predisposition, which is focused upon in this review. Initially it was thought only to occur because of certain mutations in a specific gene called adenomatous polyposis coli (APC) gene which are responsible for initiating the characteristic events which lead to the progression of this tumor.The cases affected by this pathway were called the LOH group. But further researches concluded that there is another different pathway which can lead to the occurrence of this tumor apart from the one briefly stated above. The rest of the cases which were affected by this second pathway were named as the MSI-positive group. Since diagnostic techniques for detecting this cancer, like colonoscopy, as well as its treatment by employing chemotherapy are readily available, it should be considered prime priority to get to know about this tumor at the early stage.If diagnosed earlier, this cancer can be checked upon and thus could make the concerned person survive for a longer time with improved quality life.

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I. Introduction

Colorectal cancer – also known as colon cancer or rectal cancer – is a lethal type of cancer which might occur in the colon or rectum (or both). It initiates as a small benign (non-carcinogenic) bundle of outgrown cells called adenomatous polyp which might then, with time, turn into a carcinogenic cluster and metastasize to other regions of the body such as adjacent lying lymph nodes, liver, lungs and various other sites. Almost 50% of the total cases of primarily benign colorectal neoplasm progress to develop metastatic cancer. It constitutes approximately 10-15% cases of all cancers prevalent and is the second most preeminent cause of deaths, after lung cancer, occurring due to any type of cancer in the western countries[1]. Advancing age is, so far, regarded as the greatest risk-factor for being prone to the occurrence of this tumor. Apart from this, the reasons for the development of this tumor might be both- environmental as well as genetic. Despite of the availability all the required diagnostic technologies as well as suitable treatments, the mortality rate of the patients suffering with this cancer remains quite high. Thus, it is generally advised to detect the tumor at earliest stages and commencing the treatment as soon as possible so that best possible recovery could be achieved because diagnosing the tumor at its advanced stages have shown to leave very little possibility of the survival of the patient even after sufficient treatment [2].

II. Epidemiology

Colorectal cancer is one the most common form of cancer found in the different populations worldwide. It affects both the sexes but the incidence rate in men is almost double that of the women. The high risked population is affected by colon cancer and rectal cancer in 2:1 ratio i.e., colon cancer occurrence is double than the rectal cancer. This fact is supported by an epidemiological data of the colorectal cancer collected by conducting a study in The United States. According to this study, about 136,830 new cases of colorectal cancer were diagnosed in a specific year out of which, 96,830 cases were of colon cancer while the remaining 40,000 cases were of rectal cancer, thus, giving a clear indication of the accuracy of the above estimated ratio [3]. In Germany, about 57,000 cases of colorectal cancer are reported every year. Thus, the data suggests that this cancer constitutes the most common type of cancer prevalent in Germany, even encompassing other most severely prevalent cancers in the world like breast cancer (whose prevalence in Germany is only 46,000 cases per year) and lung cancer (amounting up to just 37,000 cases per year). The mortality rate among the total cases of colorectal cancer reported in Germany is around 26,500 deaths per year [4]. The global statistical epidemiological data of colorectal cancer is extremely greater than this above stated data. Also, it has been seen that different geographical regions are affected differently by this cancer due to the variations in the environment as well as diverse dietary patterns among various populations.

Author α: Department of Pharmacology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi. e-mail: tapanbehl31@gmail.com
Author σ: Department of Pharmacy, Chandigarh College of Pharmacy, Mohali, Punjab.
Author ρ: Department of Animal Husbandry, Junga, Shimla, Himachal Pradesh.
Author ω: All Excel Inc, 135 Wood St. West Haven CT 06410 USA.

This fact is supported by the evidencethat countries like Australia, New Zealand, Europe and North America have the highest incidence rate of this cancer in the world whereas in some regions of Africa and South-Central Asia, the occurrence rates are very low [5].

III. Signs and Symptoms

In the initial stages of the tumorigenesis, the colorectal cancer may remain assymptomatic i.e., the patient may exhibit no signs or symptoms. When presentation of signs and symptoms start, they generally depend on the site of the occurrence of tumor and the extent to which it has metastasized.On the advent of the production of characteristic sign and symptoms, the patient may experience the following listed adversities: -

- Alterations in the bowel movement are the first manifestation of the colorectal cancer which is generally characterized by –
  - ✓ melena (black and tarry stools) due to the oxidation of the blood which was present along with stools
  - ✓ Prolonged and severe constipation in which the bowel movement may be blocked to a great extent due to the narrowing of the colon or rectum
  - ✓ Unrelenting diarrhea
  - ✓ Chronic bleeding in the colon or rectum which may lead to anemia
  - ✓ Presence of mucus in the stools
  - ✓ Increased urge of defecating frequently
  - ✓ Feeling of unempty bowel even after defecating
- Sensation of discomfort, pain, bloating or fullness in the abdomen. Cramps may also be experienced by the patient. In some cases, a lump may also be felt in any region of abdomen.
- The patient may experience loss of appetite and may continuously feel nauseous and frequent vomiting may also occur.
- Fatigue or weakness in the whole body (especially the limbs) may occur due to the anemia caused by severe blood loss.
- Weight loss and fever are another such common features associated with almost all the cases of colorectal cancer.
- Perforation caused by some kind of piercing in the bowel is a medical emergency which requires immediate surgery because it might lead to further complications such as peritonitis and formation of abscess [6-8].

IV. Causes

Age is attributed to be the foremost cause of the development of colorectal cancer even in persons having any other kind of predisposition for its development. In as estimate made, about 9 people out of 10 diagnosed with colorectal cancer are above 50 years of age. However, the exact reason behind the occurrence of this cancer in old-aged people is still unknown [9]. Apart from age, there are numerous other factors which may attribute to the progression and development of colorectal cancer. These causes are described below: -

- *Dietary factors:* It has been long speculated that diet of a person may contribute for some causes which may lead to the progression of colorectal cancer.People having high intake of animal fats and proteins in their daily diet have been linked with the increased risk of developing this cancer but no such confirmation has been given in the medical literature. Some studies have shown that consumption of red meat frequently becomes the promoter of some reasons which further lead to initiation of the tumor while some other studies found no such relation. While some researchers consider fat to be the major harbinger of this cancer, others consider proteins as the same. Apart from the fats and proteins themselves, another group of researchers point out to the way of these substances getting cooked, especially when exposed to very high temperature during the processes of broiling and barbecuing – which results in the production of certain carcinogenic substances as the end products, to be the affecters which need to be considered as the main reasons for the connection between these biomolecules andthe progression of colorectal cancer [10-11].
- *Lifestyle factors:* Smoking is considered as one of the foremost reasons for the development of colorectal cancer. A study conducted on the current and former smokers against life-long non-smokers (which represent a group of people who have consumed at the most 100 cigarettes in their whole lifetime) concluded that the development of colorectal cancer is directly proportional to the duration of smoking i.e., the more a person smoked, the more he is at an increased risk for developing this cancer. According to an estimate, a person who has been associated with smoking for more than 40 years or the people who are not able to quit smoking before the age of 40 are more prone to the progression of colorectal cancer by an increased rate of about five times as compared to non-smokers. Also, the people who quit smoking are related to a decreased risk of developing this cancer, thus validating the factor of smoking as a risk-factor [12]. Heavy alcohol consumption is another such factor. Although the mechanism which alcohol results in the progression of colorectal cancer is not yet clear, it has been speculated that the end product of its metabolism viz., acetaldehyde is responsible for

it. This fact is supported by the evidence of its carcinogenic properties in the animal models [13]. Also, lack of sufficient physical exercise is also associated with an increased risk for developing colorectal cancer [14].

- *Genetic factors:* People who are normally associated with a family which is having a history of colorectal cancer are considered to be at a greater risk than the ones who do not have any such report. Genetic factors accounts for upto 20% of the total cases of colorectal cancer worldwide. Thus, this factor cannot be easily ruled out when considering various risk-factors and causes of this cancer. In case of colorectal cancer, a few inherited conditions, in which there is an early development of the colon polyps due to some genetic predisposition, like familial adenomatous polyposis (FAP) – also known as Gardner's syndrome [15], MYH- associated polyposis (MAP) [16], Turcot's syndrome, Peutz-Jagher's syndrome, juvenile polyposis and Cowden's diseaseare associated with an increased risk of developing colorectal cancer, if not treated at the earliest stages. But the most common inherited condition associated with this cancer is called the hereditary non-polyposis colorectal cancer (HNPCC) – which is also known as Lynch syndrome. HNPCC alone accounts for approximately 2 to 4% of the total cases of the colorectal cancer [17]. According to the genetic studies, there may be two pathways which can be associated with the genetic events occurring in any individual which lead to the progression of colorectal cancer due to the genetic factors. These two identified pathways are described as follows: -

i. LOH group: - LOH stand for loss on heterozygosity. This group of people constitutes approximately 80% of the total cases of colorectal cancer which are caused due to various genetic factors. The characteristic feature of this group is a type of chromosome mutation which results in aneuploidy (i.e., a mutation in which the diploid number of chromosomes are either less or more than the normal value). It is also associated with numerous allelic losses. The tumor caused in this group is activated by WNT/Wingless pathway which is initiated by a mutation caused in the APC (adenomatous polyposis coli) gene [18].

ii. MSI-positive group: - MSI-positive stands for microsatellite instability-positive. This group of people accounts forabout 15% of the remaining cases of colorectal cancer associated with genetic predisposition. The reason for this type of instability caused in the gene is attributed to mismatching repair of the DNA.The tumor formation in this group is reported to occur due to the accumulation of beta-catenin (which acts as the main transcriptional activator of the carcinogenesis occurring in colorectal cancer), which is acquired by a catenin stabilizing mutation caused in the beta-catenin gene [19].

V. Pathogenesis

The formation of adenomatous polyps in the colon and rectum, which occurs due to mutation caused in the APC gene, is considered to be the basic initiator for the progression of colorectal cancer. These mutations can either be inherited or acquired. Apart from the common mutation of APC gene (which occurs in the majority of cases of colorectal cancer). There may be some other rare mutations such as mutations in beta-catenin gene, various other genes which are anologues of APC such as AXIN1 [20], AXIN2 [21], TCF7L2/TCF4 [22] or NKD1 [23], which might also lead to the progression of colorectal cancer.These various mutations result in dysfunction of the concerned gene which further leads to the activation of certain mechanisms which, at first, lead to the formation of benign adenomatous polyps and then further accounts for the progression of these benign polyps into advanced adenomas which can metastasize into various other sites of the body. After the formation of a malignant tumor, the stage of the tumor decides whether it can be cured or not, e.g., when the tumor is at the initial-most stage (when the invasive cancer is still confined within the walls of the colon and has not broken out of it – known as stage I and II), the tumor is curable. However, if it is left untreated at this stage, anyhow, it could grow further and spread into the lymph nodes lying in the nearby region and mark the advent of stage III of the tumor. This stage is curable in upto approximately 73%of the cases by the employment of adjuvant chemotherapy. After this stage, the tumor rapidly metastasizes into various sites (near as well as distant) of the body which is represented as stage IV of the tumor.Although many advancements have been done till now in the process of chemotherapy, stage IV of the tumor remains incurable [24-27].The various events in the pathogenesis of colorectal cancer can be listed as follows: -

- *Mutational activation of tumor suppressor gene:* The foremost step of the pathogenesis of colorectal cancer is the occurrence of mutations in the various genes associated with tumor suppression. These mutations lead to the dysfunctioning of the concerned genes which, due to their linkage with some other pathways, lead to the progression of the colorectal tumor. The various key factors involved in this process are as follows: -

- ✓ *APC:* APC gene is regarded as the most important factor in the progression of colorectal cancer. The activation of the Wnt signaling pathway – which is responsible for the regulation of gene transcription in the cells, due to the mutations caused in the APC gene, is regarded as the primary step in the tumor formation. The mutation in the APC gene results in the loss of both APC alleles which is further responsible for full-length proteins getting lost in the tumor cells. This leads to various types of physiologic alterations which disturbs the homeostasis of the processes which are responsible for the regulation of growth of the epithelial cells in the colon e.g., Transcription, cell cycle succession, migration, differentiation, and apoptosis. Thus, due to the critical role of APC gene in the monitoring of cell growth in colon because of its ability to control the levels of beta-catenin in the cytoplasm, any kind of mutation may result in unchecked growth and transcriptional activities in the cells present there [28-29]. APC is a component of the degradation complex which degrades beta-catenin, whose role is to bind with certain members of T-cell factor–lymphocyte enhancer factor family and create a specific transcription factor which results in the activation of cellular growth factors. Thus, normal APC gene helps in keeping a check over the levels of beta-catenin in the cytoplasm of the cell whereas mutated APC loses its capability to perform any such regulatory function. Hence, in the absence of normal regulatory mechanisms, the levels of beta-catenin goes up resulting in an unchecked activation of Wnt signaling pathway whose outcome is the initiation of tumor formation [30-31].
- ✓ *TP53:* TP53 gene, also known as tumor protein-53 gene, is another gene whose mutations are responsible for the progression of colorectal cancer. The somatic mutations occurring in this gene are considered to the most common cause of the development of many types of cancers including colorectal cancer. The p53 protein is well-known for its anti-proliferative activity in response to various types of stress conditions as well as during normal physiologic conditions. Therefore, inactivation of this protein is the prime target of various carcinogens. Its inactivation is primarily achieved by single base substitution and allele loss [32]. In the progression of colorectal cancer, this event holds the second most important spot after the inactivation of APC gene. The loss of both the alleles of TP53 gene is generally achieved by a two-step mutation process in which the first step is a missense mutation which inactivates the transcriptional activity of p53 and the second step involves a deletion on the chromosome 17p (where this gene is located) which results in the loss of the second allele. The inactivation of TP53 is often linked with the conversion of large benign adenomas into invasive carcinomas, due to the occurrence of both the events at the same point of time [33-34].
- ✓ *TGF-beta tumor suppressor pathway:* The inactivation of TGF-beta is normally the next step in the progression of colorectal cancer. In one-third of the cases of colorectal cancer, inactivation of TGRBR2 occurs due to somatic mutations. The tumors associated with the mismatch repair defect, distinctive frameshift mutations are responsible for the inactivation of TGRBR2 due to the presence of polyadenine repetition. 50% of the cases comprising of wild-type mismatch repair, the tumor suppressor pathway of TGF-beta is ceased due to inactivating nature of the missense mutations which occur in this gene by affecting the TGRBR2 kinase domain. Another way by which the mutations (or deletions) could affect this pathway is by causing alterations in the SMAD4 component of the TGF-beta pathway or the other transcription factors involved along with it e.g., SMAD2 and SMAD3. The events of mutations occurring in this gene and the consequential alterations in the pathways have been associated with the transition of adenomas to high grade dysplasia or evolution of carcinoma [35].

- *Activation of oncogene pathways:* The activation of several oncogene pathways such as MAPK signaling pathway is normally observed in the patients having colorectal cancer. These pathways are said to be responsible for the overexpression and overactivation of various cellular proliferation processes owing to their location at the downstream of various growth-factor receptors, which includes one of the most important growth factor responsible for excessive cellular proliferation in the colorectal cancer viz., epidermal growth factor [36]. The activation of the below given two oncogene pathways is said to mainly influence and play an important part in the pathogenesis of the colorectal cancer: -

- ✓ *RAS and BRAF:* Among the various oncogenes which play a vital role in the progression of colorectal cancer, the two most important are – RAS and BRAF. The oncogenic mutations caused in RAS and BRAF pathways result in the activation of MAPK (mitogen-activated protein

kinase) signaling pathway in about 37% and 13% of the cases of colorectal cancer, respectively. The mutations in the RAS pathway, particularly in KRAS, leads to the activation of GTPase activity which is responsible for conducting signals to the RAF whereas the mutations caused in BRAF implicates the signaling of BRAF serine-threonine kinase activity, which is further responsible for the activation of MAPK signaling pathway. BARF mutations can be easily detected evn in small-sized polyps and occur more frequently in hyperplastic polyps, serrated adenomas and proximal colon cancers, as compared to the RAS mutations. A medical condition named as hyperplastic polyplosis syndrome is observed in the patients having large sized and large number of hyperplastic lesions. Observations show that these type of patients are at a much greater risk of developing colorectal cancer than the people without hyperplastic polyplosis syndrome because the histologic examinations of the patients suffering from this syndrome shows that the progression of disease in such patients occurthrough an intermediate lesion formation having a serrated luminal borderline around it [37-39].

✓ *Phosphatidylinositol 3-kinase:* The somatic mutations in PI3KCA, which encodes the catalytic subunit of phosphatidylinositol 3-kinase (PI3K), are observed in almost one-third of the total cases of the colorectal cancer, hinting that this might also play a vital role in the progression of this cancer. Apart from this, some less commonly occurring mutationsare also found in place of PI3KCA, such as loss of PTEN – which inhibits the signaling of PI3K, while others include amplification of insulin receptor substrate 2 (IRS2), upstream activation of the signalling PI3K, co-amplification of AKT and PAK4, which act as the downstream mediators of PI3K signaling pathway. Thus, all the mutations and the alterations caused by them are said to play some part, which is not yet well-understood, in the progression of the colorectal cancer [40-41].

- *Genomic changes and tumor progression:* According to an initially formulated model of the transformation of adenoma to carcinoma, the role of specific tumor-promoting mutations, which are acquired progressively, was considered. This model states the occurring of certain mutations which governs the characteristics properties of tumor-progression, such as the presence of regional or distant metastases. But according to the results of full-genome examination of the sequences in some patients, from primary benign cancers of colorectal cancer to the distant malignant metastases, there was no new mutations observed during the process of metastases. This observation resulted in the speculation that a new mutation is not necessarily required for the progression of primary tumor into a metastasized form which could progress to distant sites. Also, the finding of the presence of all metastasized mutations in the primary lesions, leads to the conclusion that seeding of metastatic form of tumor is very rapid, which may even take a time span ofless than 2 years to progress into a final staged tumor from a primary one [42].
- *Growth factor pathways:* Various growth factor pathways are considered to be responsible for the cell proliferation process occurring in tumor.

✓ *Aberrant regulation of prostaglandin signaling:* Activation of prostaglandin signaling pathway is considered to be prime step in the development of an adenoma in the pathogenesis of colorectal cancer. Mainly inflammation and mitogen-associated upregulation of COX-2 (which is an inducible enzyme which is responsible for the regulation of the synthesis of prostaglandin E2 – a robustly linked agent in the progression of colorectal cancer) are considered to be responsible for the activation of this pathway. An enhanced activity of prostaglandin E2 is also observed when there is a loss of 15-PGDH (15- prostaglandin dehydrogenase – an enzyme whose role in the process of catalytic degradation of prostaglandin E2 is very critical). An elevation in the levels of COX-2 (cyclooxygenase-2) is seen in almost two-third of the patients of colorectal cancer and a loss of 15-PGDH is observed in about 80% of the cases of colorectal cancer, thus indicating that this mechanism is surely linked in some way in the progression of this cancer. Also, some clinical studies conducted showed that the inhibition of COX-2 is successfully able to suppress the development of new adenomas and also restricts the growth of already formed ones, thus validating its connection with the colorectal cancer [43-44].

✓ *Epidermal growth factor receptor:* EGF (epidermal growth factor) is a soluble protein which exhibits trophic effects on the cells of the colon. Important signaling role has been illustrated for the EGF receptor in a particular subgroup of the colorectal cancer cases. This signaling via EGF receptor (EGFR) is regulated by the activation of MAPK and PI3K signaling pathways (which are already described above).Other clinical studies done lately also

conclude that the anti-EGFR therapies showed no effect on the alterations caused due to various mutations such as in KRAS, BRAF and the p110 subunit of PI3K. Further researches are going on to discover more about the connection and mechanism of EGFR in the progression of colorectal cancer [45-46].

- ✓ *Vascular endothelial growth factor:* VEGF (vascular endothelial growth factor), which is mainly involved in the states of injury, various inflammatory processes and also during the normal physiologic growth of the tissue, is said to be key mediator for the formation of new stromal blood vessels – a process called angiogenesis. The role of angiogenesis has been well established by various clinical studies in the growth of the tumor in colorectal cancer. According to a clinical study, treatment of a patient suffering from advanced colorectal cancer with anti-VEGF antibody bevacizumab lead to an increase of 4.7 months in the average estimated total survival period of the patient viz., 15.6 months after being treated with regular standard therapy. Although much research has been done in this regard, more studies are still need to be done to identify the molecular distinctions between which gain assistance by this treatment and the rest who do not [47].

VI. Conclusion

From all the above discussions we conclude that the genetic factors play a critical role in determining the progression of colorectal cancer in any person. The genetic predisposition of any patient of colorectal cancer might be held responsible for the tumorigenesis. The pathogenesis of colorectal cancer involves the mutations of various significant genes which are responsible for the physiology of various proteins and factors responsible for the regulation of cellular proliferation processes in the colon and rectum. Overactivation of any of these factors results in the progression of the formation of a primary tumor and its transition from a benign adenoma to an invasive carcinoma. Thus, these events should be checked upon by diagnosis as early as possible so that appropriate treatment could be started well in time and at the stage where it could be successfully treated.

VII. Acknowledgement

The authors would like to extend their gratitude towards Dr. Anita Kotwani, Associate Professor, Vallabhbhai Patel Chest Institute, University of Delhi, for sharing her valuable ideas and giving various suggestions without which this article would have been incomplete.

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