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Review article

Colorectal cancer: Etiology, pathogenesis and current treatment

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Abstract

Colorectal cancer is define by partial suppression of apoptosis. This can give advantages to survival in tumours but cause the ineffective approach of chemotherapy treatment. New development in the research provide the novel approach of the new target therapy for the colorectal cancer treatment. The novel approach of the targeting therapies leads the new pathway treatment for the colorectal cancer and give the promising results. Progressive inhibition or evasion of apoptosis has been found during the transformation of colorectal epithelium to carcinoma, indicating that dysfunction of apoptosis has an important role in colorectal tumourigenesis. In this review the etiology, pathogenesis and current treatment is discussed.

1.1 Introduction

The cancer is a class of diseases. In the cancer diseases the growth of the uncontrolled cells and this group of cells affect to the normal cells and destroy it and start creating the tumours. This may lead to metastasis, or spread to other locations in the body via lymph or blood. These malignant properties of cancers differentiate them from benign tumours, which do not invade or metastasize (Figure 1). Cancer is fundamentally a disease of failure of regulation of tissue growth [1]. In order for a normal cell to transform into a cancer cell, the genes which regulate cell growth and differentiation must be altered [2, 3].

1.2 Colorectal Cancer (CRC)

Colorectal cancer is characterized by neoplasia in the colon, rectum, or vermiform appendix. Colorectal cancer is the third most commonly diagnosed cancer in the world, but it is more common in developed countries [4]. GLOBOCAN estimated that, in 2008, 1.23 million new cases of colorectal cancer were clinically diagnosed, and this type of cancer killed more than 600,000 people [5, 6].

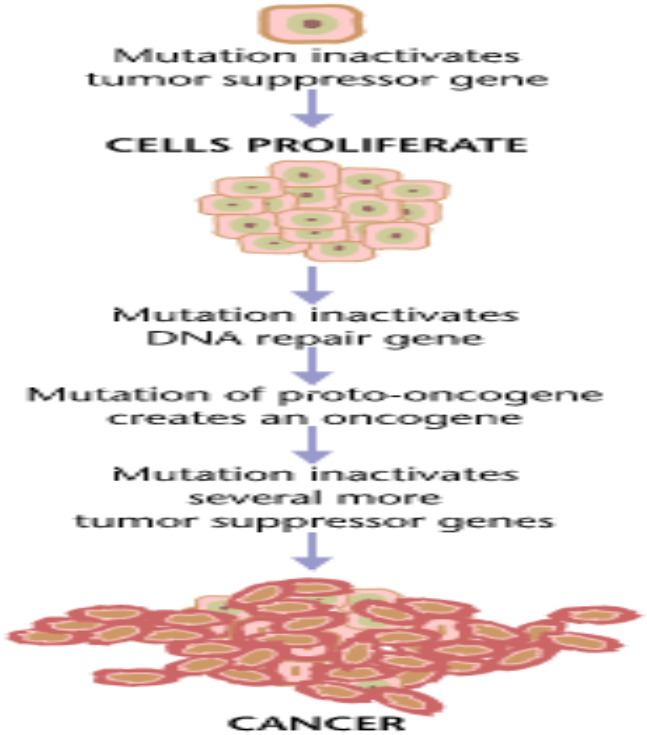


Figure 1. Development of cancer [11].

Colorectal cancers begins in the lining of the bowel, if left untreated, it can increase into the muscle layers underneath and then through the bowel wall. Most begin as a small growth on the bowel wall which is called a colorectal polyp or adenoma.

The growth of the mushroom shaped is usual but after a long time it start the producing the cancer. The colonoscopy is one the examined method for localized bowel cancer. Invasive cancer can be treating with surgery. If the cancer is not treated at the stage I and stage II it will spread to stage III at regional lymphy nodes. Cancer that metastasizes to distant sites (stage IV) is usually not curable [7, 8].

1.2.1 Intestinal anatomy and physiology

Before discussing the staging of CRC it is important to briefly describe the normal anatomy and physiology of the intestine. The intestine consists of three layers. The outer layer consists of two bands of smooth muscles at a right angle to one another, between the muscle layers nerve plexus is located which help to control the peristaltic function of these muscle layers. Outside the muscle layers there is a layer o adipose and connective tissues of variable thickness, this is covered by the peritonefum for the majority of the length of the intestine. Moving inwards the next layer is the sub-mucosa, which consists of connective tissue, blood and lymphatic vessels. Payer's patches, which are an important part of the immune system, also lie within the sub-mucosa. Superficial to the sub-mucosa is the mucosa. This is the layer of cells which carry out most of the varying functions of the intestine. In the small intestine the mucosa is projected into folds and invaginations called villi and in the colon only crypts are seen and the villi are replaced by flat inter-crypt spaces [9].

The purpose of this micro-anatomy is to greatly increase the intestinal surface area and therefore increase the absorptive capacity of the intestine. The cells lining the crypts and villi are specialized and play very specific functions. At the base of the crypts are the paneth cells; these secrete various peptides involved in anti-microbial and other activity. Above the Paneth cells are the intestinal stem cells, which give rise to all of the cell lineages making up the intestinal epithelium. Enterocytes make up the majority of cells in the villus and are predominantly involved in nutrient absorption. Goblet cells produce mucus, which forms a protective layer over the epithelium and finally the enteroendocrine cells produce hormones including Substance P and serotonin [9, 10].

1.2.2 Signs and Symptoms

The symptoms of colorectal cancer depend on the location of tumour in the bowel, and whether it has spread elsewhere in the body (metastasis) [11]. Local symptoms are change in bowel habit, a feeling of incomplete defecation, lower gastrointestinal bleeding including the passage of bright red blood in the stool and melena, black stool with a tarry appearance may indicate colorectal cancer. The entire lumen fill with tumour and it may cases bowel obstruction. This situation is characterized by constipation, abdominal pain, vomiting and abdominal distension. If a tumour has caused chronic occult bleeding then iron deficiency anemia may occur; this may be experienced as fatigue, palpitations and noticed as pallor (pale appearance of the skin). Colorectal cancer may also lead to weight loss, generally due to a decreased appetite [12].

1.2.3 Risk factors

Certain factors increase a person's risk of developing the disease [13] These include:

1. Age: The risk of developing colorectal cancer increases with age [14].
2. Polyps of the colon: Particularly adenomatous polyps are a risk factor for colon cancer.
3. History of cancer: Individuals who have previously been diagnosed and treated for colon cancer are at risk for developing colon cancer in the future.
4. Heredity:
   a) Family history of colon cancer [15].
   b) Familial adenomatous polyposis (FAP) carries a near 100% risk of developing CRC.
   c) Hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome.
   d) Gardner syndrome.
5. Smoking: Smokers are more likely to die of colorectal cancer than nonsmokers.
6. Diet: Studies show that a diet high in red meatand low in fresh fruit, vegetables, poultry and fish increases the risk of colorectal cancer.
7. Viruses: Exposure to some viruses (such as particular strains of human papilloma virus) may be associated with colorectal cancer.
8. Inflammatory bowel disease: About one percent of colorectal cancer patients have a history of chronic ulcerative colitis. The patients with ulcerative colitis and colorectal Crohn's disease have risk of the colorectal cancer. However, colorectal Crohn's disease has higher chances of CRC than ulcerative colitis disease.
9. Environmental factors: Industrialized countries are at a relatively increased risk compared to less developed countries that traditionally had high-fiber/low-fat diets.
10. Alcohol: Drinking, especially heavily, may be a risk factor.

1.2.4 Etiology and Pathogenesis

The CRC disease originating from lining the colon, epithelial cell and rectum of the gastrointestinal tract. A model explaining the interplay between tumour

suppressor genes and oncogenes in colorectal carcinogenesis was first proposed by Vogelstein et al (Figure 2) [16]. Mutations of four to five of the genes outlined in the genetic model are required for the formation of a colorectal carcinoma. Thus, genetic alterations of the tumour suppressor genes APC, DCC (deleted in colon cancer), p53, and MCC (mutated in colon cancer) as well as the oncogenes K-RAS and N-RAS have been shown to directly contribute to the adenoma-carcinoma sequence of CRC [17].

The most common mutation is in the Wnt-signaling pathway in CRC. The mutations can be in the intestinal cryptstem cell and it is inherited. The most commonly mutated gene in all colorectal cancer is the APC gene (Adenomatous Polyposis Coli gene), which produces the APC protein. The APC protein is a "brake" on the accumulation of β-catenin protein; without APC, β-catenin accumulates to high levels and moves into the nucleus then binds to DNA and activates the transcription of genes which are normally important for stem cell renewal, differentiation and cell growth. But when unsuitably expressed at high levels can cause cancer.

The p53 protein, produced by the TP53 gene (a tumour suppressor gene), normally monitors cell division and kill cells if they have Wnt- pathway defects. Eventually, a cell line acquires a mutation in the TP53 gene and transforms the tissue from an adenoma into an invasive carcinoma (Figure 2).

The TGF-β and Deleted in Colorectal Cancer apoptotic proteins are deactivated in CRC. Other oncogenes such as PI3K, RAF and KRAS proteins encoding genes are highly expressed in CRC resulting in uncontrolled cellular growth [18].

The etiology of colorectal cancer appears multifactorial. At present, colorectal carcinomas are seen in association with familial diseases including, Familial Adenomatous Polyposis Syndrome (FAP) and Hereditary Nonpolyposis Colorectal Carcinoma (HNPCC). Cases of colorectal carcinoma which are not associated with a familial predisposition syndrome are termed sporadic colon carcinomas [19, 20].

1.3 Cancer Management Treatment

The treatment of the colorectal cancer is depending upon the cancer stage if the initial stage of CRC it can be curable otherwise difficult to cured. However, when it is detected at later stages (when distant metastases are present), it is less likely to be curable. Surgery remains the primary treatment, while chemotherapy and/or radiotherapy may be recommended depending on the individual patient's staging and other medical factors [21-23].

1.3.1 Surgery

Surgeries can be categorized into curative, palliative, bypass, fecal diversion, or open-and-close. Laparoscopic-assisted colectomy is a minimally invasive technique that can reduce the size of the incision and may reduce postoperative pain [24, 25].

1.3.2 Chemotherapy

The use of the Chemotherapy in the slow tumor growth, reduced the metastasis developing and shrink tumour size at initial stage. The Chemotherapy treatment is most probably used after surgery but it can be used before surgery as well as primary therapy. US FDA approved the treatment because of this chemotherapy treatment clinical trials show promising results. If the cancer is spread to stage III in lymph nodes the chemotherapy treatment is given after surgery.

1. Adjuvant (after surgery) chemotherapy
a) 5-fluorouracil (5-FU) or capecitabine (Xeloda)
b) Leucovorin (LV, folinic Acid)
c) Oxaliplatin (Eloxatin)
2. Chemotherapy for metastatic disease. Commonly used first line chemotherapy regimens involve the combination of infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) with bevacizumab or infusional 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) with bevacizumab or the same chemotherapy drug combinations with cetuximab in KRAS wild type tumours.

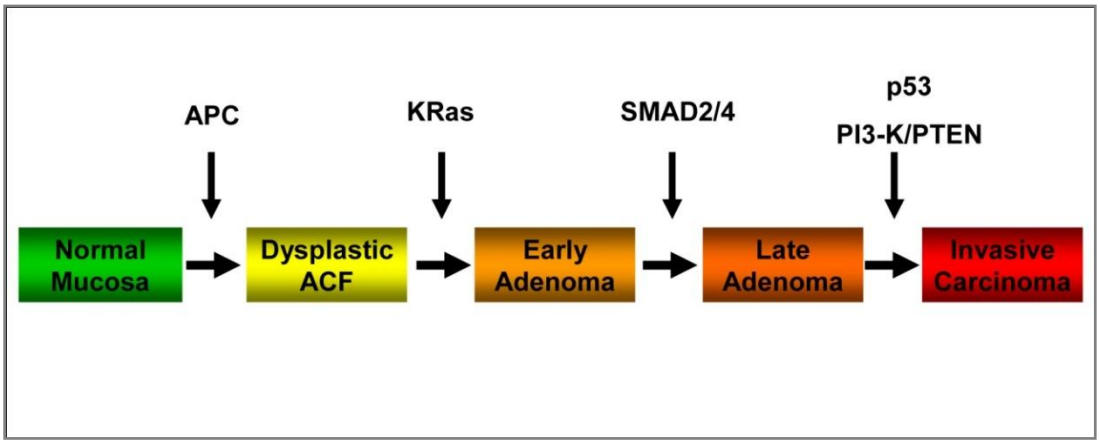


Figure 2. Genetics of colorectal cancer [5].

1.3.3. Radiotherapy

The utilization of the radiotherapy in cancer vary widely worldwide. It is normally observed that the majority of the patients received the radio therapy for treatment of the cancer. In addition to this the radiotherapy is one the effective treatment for the colorectal cancer, lung cancer and other types of cancers. Thoracic irradiation has traditionally been used in radiotherapy treatment. However this treatment provides a stage III of the cancer. The side effects this treatment are more in comparison to other treatment [9].

1.4 Drawbacks of current therapy

The drawback associated with this therapy is that the drug develops resistance and therapy can not able to treat the disease. Moreover toxicity is the problem. Multidrug resistance (MDR) is a major obstacle to the effective treatment of cancer [26]. Drug resistance to multiple chemotherapeutic agents is considered a major cause of chemotherapy failure in colorectal cancer. Drug resistance can be divided into pharmacokinetic resistance (e.g. low drug concentration at the tumour site, poor tumour vascularisation, high intratumoural pressure), physiological resistance (tumour sanctuaries; influence of pH at the tumour site), tumour cell kinetic resistance (low tumour growth fraction), and cellular resistance [27].

1.5 Approaches for colon targeting

The colon is a site where both local and systemic delivery of therapeutics can take place. Local delivery allows topical treatment of inflammatory bowel disease, colon cancers. Treatment can be made effective if the therapeutics can be targeted directly into the colon, thereby reducing the systemic side effects. In the various types of the bowel diseases the targeted drug delivery into the colon is highly desirable. In order to successfully reach colon in an intact form, the delivery systems should surpass the barriers in the stomach and small intestine [17].

1.5.1 Rational for the development of oral colon targeted drug delivery

1. Treatment of local pathologies
2. Chronotherapy (asthma, hypertension, cardiac arrhythmias, arthritis or inflammation)
3. Greater responsiveness to the absorption enhancers
4. Less enzymatic activity
5. Site for delivery of delicate drugs (Proteins and Peptides) [28]
6. Oral delivery of vaccines as it is rich in lymphoid tissues

1.5.2 Approaches used for site specific delivery to colon:

1. Primary approaches for colon targeting.

- pH Sensitive Polymer Coated Drug Delivery to the Colon.
  The molecules are coated by the suitable polymers and it is delivered to the colon without absorbing the upper part of intestine [29]. The capsule, tablet and pellets are coated by polymer therefore it will delayed released and protect the drug. For the colon targeting the Methacrylic acid esters polymers are used because they are soluble in pH6.

- Delayed (Time Controlled Release System) Release Drug Delivery to Colon.
  In this method the solid dosage form coated with different sets of polymers and the thickness of the outer layer determines the time required disperse in aqueous environment.

- Microbially Triggered Drug Delivery to Colon.
  The use of the biodegradable polymers for the colon specific drug delivery is more effective than other treatment. This polymers are most appropriate because it shield the drug abd protect from the environment. The drug is released in to the colon and reduction in their weight and cinally loss of mechanical strength.

- Prodrug Approach for Drug Delivery to Colon.
  Prodrug is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in vivo to release the active drug. Metabolism of azo compounds by intestinal bacteria is one of the most extensively studied bacterial metabolic process, Azo-Polymeric Prodrugs.

Newer approaches are aimed at the use of polymers as drug carriers for drug delivery to the colon.

2. Polysaccharide based delivery systems.

The use of naturally occurring polysaccharides is attracting a lot of attention for drug targeting the colon since these polymers of monosaccharides are found in abundance, have wide availability are inexpensive and are available in a verity of a structures with varied properties. They modification can be done easily by biochemically and chemically which are safe stable hydrophilic and nontoxic [19]. The polysaccharides made from the plant based, microbial origin and animal. Polysaccharides resist to the digestive action of gastrointestinal enzymes.

1.6 Conclusion

The colorectal cancer and cancer in general is difficult to treat because this cancer disease is complex but also because of its ability to immortalize and continue to divide endlessly. There are various types of treatment available according to the seriousness of the cancer tumors and degree of complication. On the other hand the

treatment effectiveness on the colorectal cancer is depending upon the patient's level of recurrence. The continuous development in the treatment leads CRC evaluation. However, a change in the mentality is begging to prevail, with more and more professionals embracing the idea that individual biomarkers and diagnosis treatment. Also this cancer is growing imperatively and to overcome the limitations of treating the colorectal cancer need to do different combinatorial approach.

Author contributions

All the authors have contributed equally in designing, drafting the manuscript as per the journal submission format. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that there are no competing conflicts of interest.

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