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RESEARCH ARTICLE

Epigenetic Alterations and Gene Regulation in Colon Cancer: Exploring Targets for Early Detection and Therapeutic Intervention

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Abstract: Colon cancer, a major root of cancer-related deaths, is noticeable by uncontrolled cell growth in the colon or rectum. In 2023, around 12,370 new cases were reported, with 12% in individuals under 50. Lifestyle issues such as obesity, inactivity, smoking, alcohol use, and poor diet play significant roles in its development. Current findings also highlight the gut microbiome's role and its interaction with inflammation and signaling pathways. The Fearon and Vogelstein model highlights genetic mutations in APC, KRAS, DCC, and p53 as key drivers of tumorigenesis. Microsatellite instability, often due to flawed mismatch repair, further contributes to genetic errors. While surgery and chemotherapy remain standard treatments, early detection is limited, with only 40% diagnosed early. Recurrence risk also remains high. This review focuses on epigenetic alterations and gene regulation in colon cancer, aiming to identify targeted therapies that enhance early detection and reduce recurrence.

Keywords: Colon cancer; Fearon and Vogelstein model; Genetic mutations; Signaling pathways; Treatment.

INTRODUCTION

Colon cancer stands as a significant cause to both illness and fatalities on a global scale. It ranks as the fourth most prevalent form of cancer and third most common cause of cancer-related deaths globally. In 2023, an estimated 12,370 new cases highlighted its widespread impact, with a striking 12% occurring in individuals under 50 years old. This highlights the prevalence of colon cancer as a significant health concern for both genders, with 6,410 men and 5,960 women affected (1). In many countries, the prognosis of patients with colon cancer has gradually but noticeably improved during the last few decades (2).

Lifestyle factors significantly contribute to the development of colon cancer. Many research indicates that being overweight, leading a sedentary lifestyle, smoking cigarettes, consuming alcohol, and following unhealthy dietary patterns (such as a diet lacking in fiber, fruits, vegetables, calcium, and high in red and processed meat) raise the risk of developing colon cancer. Over recent years, there has been a growing importance on the significance of the microbiome in the onset of colon cancer. It is widely recognized that the gut microbiome plays a crucial role in the carcinogenic processes of colon cancer, initiating inflammation and influencing various signaling pathways (3) (Figure 1).

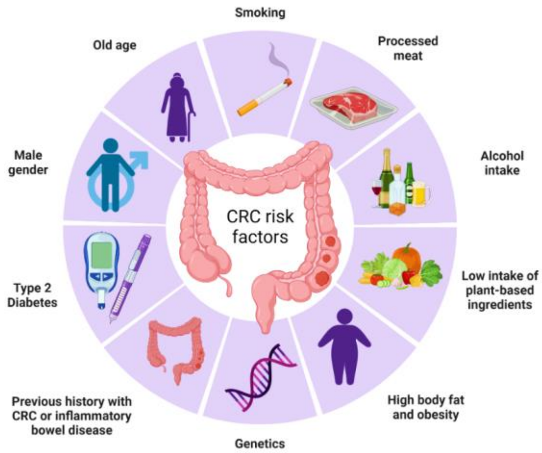

Figure 1: Causes of Colorectal Cancer

Colorectal cancer (CRC) stands out as the inaugural extensively characterized molecular model in the history of cancer research. Fearon and Vogelstein (4) emphasized that CRC serves as an exceptional model to elucidate the impact of genetic alterations on the intricate process of tumor formation. According to Fearon and Vogelstein model Colon tumors are primarily initiated by oncogenic mutations and the inactivation of suppressor genes. For the development of a malignant tumor, a minimum of 4–5 genes must undergo mutations; a lower number of changes are adequate to give rise to a benign tumor. Although genetic alterations often occur in a preferred order, the biological characteristics of the tumor are determined by the total number and types of acquired lesions, not their specific sequence. In certain instances, mutant suppressor genes exhibit a phenotypic effect even when they are in the heterozygous state (5).

Apart from the lifestyle factors, mutation in some genes may also lead to colon cancer. Mutation in genes like APC, KRAS, DCC and p53 leads to the formation of colon polyps. Cancer-related microsatellite instability (MSI) arises from frameshift mutations within tandem repeat sequences, commonly referred to as microsatellites. These mutations occur due to polymerase slippage during replication. Normally, the DNA mismatch repair proteins correct such replication errors. However, when components of this repair pathway are lost, impairing its function, the correction mechanism is hindered. Consequently, MSI accumulates throughout the genome in cancer cells, affecting both coding and noncoding sequences (6). The functional impairment of the DNA mismatch repair (MMR) system occurs when an MMR gene is deactivated through mutation or transcriptional silencing, resulting in the accumulation of errors during DNA replication. Several proteins, including members of the MutS family (MSH2, MSH3, and MSH6) and the MutL family (MLH1, MLH3, PMS1, and PMS2), play crucial roles in mediating DNA repair within the MMR pathway. Particularly, MLH1, MSH2, MSH6, and PMS2 are the most significant regulators of MMR (7). Surgery along with chemotherapy have respectively been used as the first methods of treatment for people with cancer for a long time. Advances in both initial and additional treatments have increased the survival duration of patients with colorectal cancer. In most situations, resection is needed to remove the tumor completely (8). Just 40% of colon cancer patients may now be detected in the beginning stages by diagnostics, and colon cancer may reoccur after surgery and post-operative care. Monitoring average-risk persons is the most efficient way to avoid colon cancer and lower the number of deaths associated with colon cancer in general. Colon cancer prevention is primarily dependent on adenomatous screening procedures (9). This review focuses on the epigenetic modification and regulation of genes that are involved in the different stages of colon cancer (Figure 2).

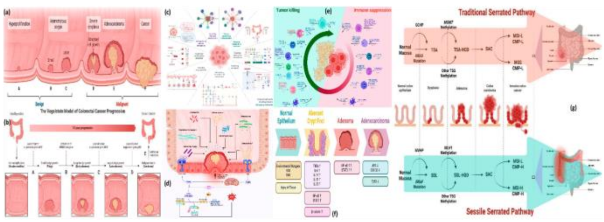

Figure 2: Epigenetic modification and regulation of genes that are involved in the different stages of colon cancer

(a) Adenoma–carcinoma sequence pathway of colorectal cancer development; (b) Vogelstein model of colorectal cancer progression; (c) Hallmarks of colorectal cancer progression; (d) Gut microbiome–host interactions in colorectal cancer development; (e) Tumor–immune interactions and the dynamic interplay between tumor killing and immunosuppressive mechanisms; (f) Colitis-associated cancer pathway in inflammatory bowel disease; (g) Serrated neoplasia routes.

Colon cancer

The colon is a component of the digestive system, also known as the digestive tract, which comprises organs responsible for processing food for energy. Colon cancer initiates when the normal cells lining the colon undergo uncontrolled growth and alterations. Over an extended period, these cells develop into a tumor, which may be benign or malignant, with the progression often spanning several years. The development of colon cancer is influenced by both genetic alterations and environmental factors. Although it remains a significant cause of mortality across all genders, recent advancements in screening methods and treatment modalities have contributed to enhanced survival rates (10).

Causes

Colon cancers frequently arise due to DNA mutations that disable tumor suppressor genes or activate oncogenes, promoting the proliferation and viability of malignant cells. The advancement of colon cancer commonly involves changes in multiple genes (11). Colon cancer has been linked to inadequate physical activity, consistent meal patterns, low-fiber diets, diminished dietary calcium levels, and insufficient beta-carotene intake. Approximately 90% of colon cancers are attributed to environmental factors, such as a history of low-fiber, high-fat diet, alcohol consumption, and tobacco use, often manifesting many years prior to the diagnosis. Recent studies have established a connection between dietary metabolites and their impact on creating either a protective or pro-carcinogenic environment in the colon, a dynamic influenced by an individual's microbiome. A stimulating feature of colon cancer lies in its close connection with the gut microbiota, an integral component of the tumor microenvironment. Many Studies conducted in the last decade have revealed that alterations in gut bacteria, fungi, viruses, and Archaea, known as dysbiosis, coincide with the development of colon tumors. These shifts in microbial composition may play a causal role in tumorigenesis (12).

Fearon and Vogelstein model

Fearon and Vogelstein initially introduced a multistep genetic model of colorectal carcinogenesis in 1990, which has since become a widely accepted model for understanding the progression of solid tumors. The colon carcinogenesis model, originally suggested by Fearon and Vogelstein, has gained widespread acceptance and serves as a context for understanding the progression of solid tumors. In this proposed sequence, the initial step involves the inactivation of APC, succeeded by the occurrence of oncogenic KRAS mutations in the adenomatous stage. Subsequently, as the transition to malignancy unfolds, there is the eventual deletion of chromosome 18q and inactivation of the tumor-suppressor gene TP53 on chromosome 17 (13) (Figure 2b).

Different stages of colon cancer

Cancer staging serves to characterize the extent of cancer spread within the body, assisting in determining its severity and the most suitable treatment approach. Additionally, it is a crucial factor used by medical professionals in assessing survival rates. As outlined by the American Joint Committee on Cancer Tumor-Lymph Node-Metastasis (TNM) system, most cancers are categorized into five distinct stages: Stage 0, I, II, III, and IV. The staging system reveals specifics about the location of cancer, size, penetration into nearby tissues, potential spread to nearby lymph nodes or other body parts, and influences the identification of cancer spread markers (Figure 3).

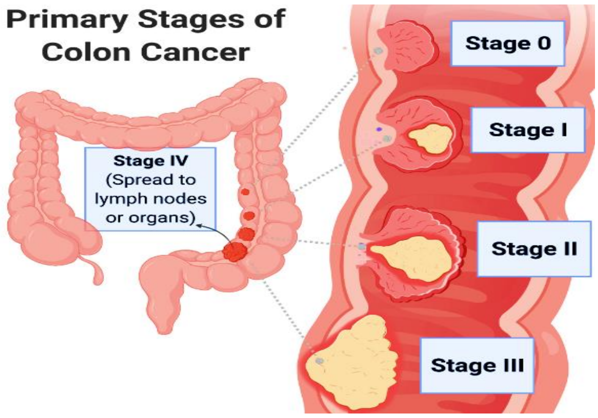

Figure 3: Various stages of colon cancer

It reveals the different stages of colon cancer from stage 0 to IV. Stage 0 is the early stage of colon cancer and it can be cured easily. Stage I is also an early stage but it spreads all over tissues. In stage II it spreads in the outermost layer. In stage III, the outer layer of the colon got penetrated by cancer. In stage IV, it starts spreading everywhere (14).

Stage 0 / I

This stage also referred to as colon carcinoma in situ, implies the presence of abnormal cells within the innermost layer (mucosa) of the colon wall. These irregular cells possess the potential to develop into cancer and invade surrounding healthy tissue. Adenomatous Polyposis Coli (APC) gene is known to have a substantial impact on colon cancer progression, especially in the initial stage. When the APC gene undergoes mutations, it is linked to familial adenomatous polyposis (FAP), an inherited disorder marked by the occurrence of multiple polyps in the colon (15). Normally, the APC gene plays a role in controlling cell growth and division. Mutation in this gene can cause cells to grow uncontrollably, resulting in the development of polyps.

APC (Adenomatous Polyposis Coli) gene

Figure 4 depicts the Wnt/β-catenin pathway in which it works through Wnt binding to its central receptor complex LRP5 or LRP6 which are the members of the Frizzled protein family. In the absence of a Wnt ligand, cytoplasmic β-catenin undergoes phosphorylation arranged by a complex including GSK3β, CKIα, Axin and APC. Axin functions to facilitate complex formation with GSK3β and APC. Within this complex, GSK3β prompts β-catenin phosphorylation in the cytoplasm while APC helps in linking phosphorylated β-catenin to the ubiquitin-mediated proteolytic pathway in the cytoplasm.

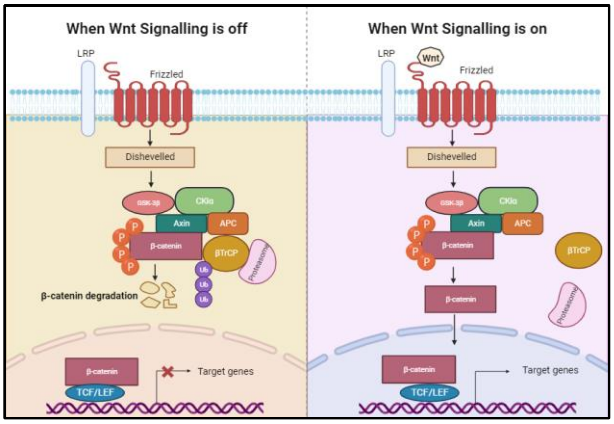

Figure 4: Wnt / β-catenin pathway

However, when Wnt protein ligands are present, they bind to the core receptor complex, activating Wnt signaling. This activation involves engaging cytosolic protein, blocking the formation of the Axin/GSK3/APC complex. Consequently, this inhibition stops β-catenin degradation, leading to its accumulation in the cytoplasm. Subsequently, the cytoplasmic β-catenin translocate to the nucleus, where it associates with the transcription factor TCF/LEF, thereby initiating the expression of Wnt target genes. The Wnt/β-catenin pathway plays a critical role in determining cell proliferation, survival, and differentiation (16).

Treatment

- ❖ The management of stage 0 (carcinoma in situ) may involve the following surgical interventions.
- ❖ Local excision or simple polypectomy
- ❖ Involves the removal of the localized or superficial tumor.
- ❖ Typically employed when the tumor is small and confined to a specific area.

Resection and anastomosis

- ❖ Implemented when the tumor is too large for removal through local excision.
- ❖ In this procedure, the affected portion of the tissue is excised, and the remaining healthy sections are rejoined using an anastomosis.
- ❖ In the treatment of this stage, surgery is the predominant and only therapeutic approach. The primary method involves the removal of the colon

polyp, which is a cluster of cells, or the cancerous area within the colon, performed through a procedure known as a polypectomy. This surgical intervention is often conducted during a colonoscopy. In cases where the cancer is too large for a polypectomy, they may choose for a partial colectomy. This procedure involves the removal of a segment of the colon, eliminating the cancerous section. Following the removal of the cancer, they may reconnect the healthy portions of the colon through a procedure called anastomosis. This comprehensive surgical approach addresses stage 0 colon cancer, ensuring the removal of cancerous tissues and promoting the restoration of normal colon function(17).

Genomic instability

Genomic instability incorporates a spectrum of genetic and genomic modifications, ranging from tiny point mutations to extensive chromosome rearrangements. Aneuploidy, on the other hand, specifically denotes an abnormal count of chromosomes without involving polyploidy. In colon cancer, genomic instability falls into two primary categories: Chromosomal Instability and Microsatellite Instability. Chromosomal Instability is predominantly defined by its functional and mechanistic characteristics, representing a sustained high frequency of chromosome missegregation. This condition results in alterations in chromosome count, such as gains or losses. Consequently, the Chromosomal Instability phenotype strictly aligns with aneuploidy or shares identical features. Conversely, Microsatellite Instability is commonly defined by its phenotypical attributes, suggesting repetitive expansions and contractions of DNA within the cell. Molecularly, the Microsatellite Instability phenotype arises from deficiencies in DNA replication and repair mechanisms. Etiologically, Chromosomal Instability conquers over Microsatellite Instability in colon cancer. Approximately 85% of colon cancers exhibit Chromosomal Instability, while the remaining 15% manifest Microsatellite Instability characteristics (18).

Generally, DNA remains primarily restricted within the nucleus and mitochondria. Yet, under conditions involving genomic or chromosomal instability associated with cancer, DNA might be liberated into the cytoplasm. This release predominantly occurs through the creation of micronuclei, which are structures outside the nucleus containing DNA. Micronuclei resulting from defects in DNA repair often consist of acentric chromosome fragments, while chromosomal instability primarily results in micronuclei that enclose complete chromosomes. Particularly, chromosomal instability also induces DNA damage, causing micronuclei to contain acentric chromosome fragments. A significant portion of these micronuclei typically experience an irreversible breakdown of compartmentalization during interphase, attributed to the collapse of the micro nuclear membrane. While entire micronuclei maintained nuclear function to a certain extent, this functionality significantly reduced in disrupted micronuclei. Moreover, disrupted micronuclei exhibit deficiencies in both transcription and replication, leading to a substantial build-up of DNA damage. Consequently, micronuclei are increasingly recognized as a crucial origin of cytoplasmic DNA (19).

Stage I / II

In this stage of colon cancer, tumors have penetrated deeper layers of the colon wall but haven't extended beyond the colon wall itself or into nearby lymph nodes. This stage incorporates cancers that originated as polyps. Complete removal of the polyp during a colonoscopy, without any cancer cells at the margins of the removed tissue, may not be required for further treatment. However, if the cancer within the polyp is high grade, or if cancer cells are present at the edges of the polyp, additional surgery could be recommended.

Kirsten Rat Sarcoma (KRAS) is one of the most mutated oncogenes in colon cancer, affecting about 40% of CRC patients with activating missense mutations, predominantly at codons 12, 13, and 61. Individuals with KRAS-mutant colon cancer generally experience a less favorable prognosis compared to those with KRAS-wild-type colon cancer, particularly in cases of metastatic disease. The presence of KRAS mutations in colon cancers has been linked to reduced survival rates and sensitive tumor aggressiveness. Moreover, these mutations in colon cancer contribute to resistance against certain treatment approaches (20).

KRAS (KIRSTEN RAT SARCOMA)

KRAS plays a key regulatory role in cellular signal transduction pathways, including PI3K-Akt and RAS-RAF-MAPK signaling, which are essential in cell proliferation. In colon cancer, mutations in KRAS result in the abnormal activation of the RAS/RAF/MEK/ERK signaling pathway, impacting the tumor microenvironment. Particularly, colon cancer exhibits distinctive metabolic features in the presence of KRAS mutations, contributing to metabolic development. Various researches have demonstrated the crucial role of KRAS in regulating cancer metabolism by modulating diverse metabolic processes. KRAS mutations induce glucose uptake, increase glutamine metabolism, and enhance autophagy. In colon cancer, KRAS mutations correlate with elevated glycolysis and increased expressions of proteins involved in glutamine metabolism (Figure 5).

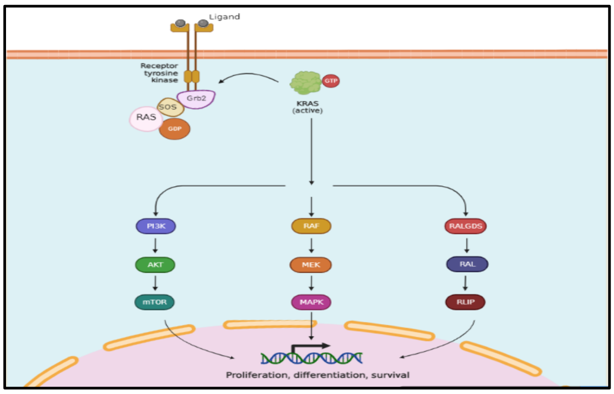

Figure 5: KRAS signaling pathway

The majority of variations observed in KRAS within colon cancer occur in tumors located on the right side of the colon, with codons 12, 13, and 61 responsible for approximately 85% of all KRAS alterations. Specifically, alterations in the region 12 constitute the dominant portion, accounting for about 65% of the total KRAS alleles. Among the prominent colon cancer subgroups, G12V (glycine 12 to valine) and G12D (glycine 12 to aspartic acid) are obvious. This illustrates the prevalent trend and range of KRAS modifications in colon cancer. Especially, the P loop, essential for maintaining a nucleotide in an active state, includes G12 and G13 [20]. Except for KRAS G12C, which exhibits GTPase activity equivalent to the wild type, modifications in codon 12 typically result in a reduction in both intrinsic and GAP-mediated degradation without altering the nucleotide transfer rate. Conversely, alterations in codon 13 increase the efficiency of fundamental transfer while simultaneously decreasing degradation. The N-terminus of switching II is host to Q61, participating in conformational changes in the locality during transitions between molecular states. Mutations in codon 61 disrupt GTP hydrolysis while enabling GDP-GTP exchange. Furthermore, Q61 mutations have the lowest degradation rate among all KRAS genes (20).

Treatment

In this stage, colon cancer imposes a surgical approach similar to that of previous stage. Here, the cancer has progressed deeper into the layers of the colon wall but has not extended beyond the colon wall or into nearby lymph nodes. This stage incorporates cancers that were initially part of a polyp. If a complete removal of the polyp during a colonoscopy reveals no cancer cells at the margins of the excised piece, additional treatment may not be necessary. However, if the cancer within the polyp is of high grade or if cancer cells are present at the edges of the polyp, further surgery might be recommended. Additional surgical intervention may also be advised if the polyp could not be entirely removed or if it had to be excised in multiple pieces, making it challenging to determine the presence of cancer cells at the edges. For cancers not within a polyp, the standard treatment involves a partial colectomy, a surgical procedure meant at removing the section of the colon containing the cancer along with adjacent lymph nodes (21).

Stage II / III

As per the current NCCN (National Comprehensive Cancer Network) Guidelines for colon cancer, stage II/III is characterized by complete penetration of the bowel wall by the tumor without any lymph node metastases. This stage is further categorized into IIA, involving T3 lesions that invade through the muscularis propria into peri colorectal tissues; IIB, encompassing T4a lesions that directly penetrate to the surface of the visceral peritoneum; and IIC, involving T4b lesions that directly invade or adhere to other organs or structures. The classification is based on the location of the primary tumor (T3 and T4). Additionally, the presence of lymphovascular invasion (LVI) is determined when tumor cells are identified within an endothelium-lined space, or if the lymphovascular wall is disrupted by tumor cells .

Loss of heterozygosity (LOH) is characterized by the absence of one of the two gene copies or alleles, often leading to mutation affecting the remaining allele. In advanced colon cancer, LOH is predominantly found in the 18q region, affecting approximately 70% of cases. This occurrence is linked to reduced prognosis in colon cancer. The presence of LOH at 18q signifies the involvement of various tumor suppressor genes, such as Deleted in Colorectal Carcinoma (DCC), SMAD2, and SMAD4. The loss of expression associated with 18q LOH significantly contributes to the pathogenesis of colon cancer (22). DCC is considered as a transmembrane receptor, distributing structural similarities with members of the neural cell adhesion molecule family. Recent studies indicate that DCC functions as a ligand-dependent receptor, requiring the presence of an available ligand to enable cellular survival. This particular role may attribute a tumor suppressor function to DCC, as it potentially eliminates abnormally growing cells under conditions of low ligand levels (23).

Deleted in Colorectal Carcinoma (DCC)

Loss of heterozygosity (LOH) is a common occurrence observed in advanced stages of colorectal cancer, particularly within the 18q21 region. LOH refers to the loss of one of the two copies or alleles of a gene, frequently accompanied by a mutation affecting the remaining allele. The Deleted in Colorectal Carcinoma (DCC) gene is situated on the extended arm of chromosome 18 (18q21.3), and it is responsible for encoding the transmembrane protein known as DCC. DCC functions as a "conditional tumor suppressor gene."About 70% of colon cancers exhibit loss of heterozygosity (LOH) in the region of the DCC gene. Netrin-1, a protein, is produced in the depths of the colon mucosa crypts. As epithelial cells undergo differentiation and migrate toward the surface, the concentration of netrin-1 decreases. This diminishing concentration gradient is believed to play a role in the normal process of apoptosis and the shedding of epithelial cells. In cases where the DCC gene is mutated, netrin-1 fails to bind to the DCC transmembrane protein, leading to abnormal cell survival. Moreover, an increase in netrin-1 has been observed in patients with advanced colon cancer, potentially overriding the apoptotic effect of DCC. Some studies, though not all, have found a reverse correlation between the survival of colon cancer patients and LOH on chromosome 18q (24).

Treatment

Mostly these stage colon cancers have penetrated the colon wall, possibly extending into nearby tissues, yet they have not metastasized to the lymph nodes. The primary treatment may involve surgery to remove the affected part of the colon (partial colectomy) along with nearby lymph nodes. However, if there is an elevated risk of cancer recurrence, it becomes necessary to undergo adjuvant chemotherapy, which involves administering chemotherapy after surgery.

The guidelines from the American Society of Clinical Oncologists (ASCO) suggest that routine adjuvant therapy is not recommended for individuals with this stage colon cancer at a low risk of recurrence. However, it is advisable for those with stage IIB and stage IIC colon cancer to receive adjuvant therapy. Additionally, patients with stage IIA colon cancer featuring high-risk characteristics may also be considered for adjuvant therapy (25). When chemotherapy is employed, the primary options typically include 5-Fluorouracil and leucovorin, oxaliplatin, or capecitabine. Yet, alternative combinations may also be considered depending on the specific conditions (26).

5-Fluorouracil (5-FU), a potent chemotherapeutic agent, is frequently utilized in the treatment of colon cancer. However, the challenges of its toxicity to healthy tissues and the emergence of tumor resistance constitute significant barriers to achieve effective outcomes in cancer chemotherapy. For the past five decades, 5-FU has been a prevalent approach in the treatment of colon cancer. However, the limitations of its negative effect on normal tissues and the emergence of chemoresistance in colon cancer are the present significant challenges to the success of cancer chemotherapy. Consequently, the clinical use of 5-FU is limited. Therefore, there is a need to identify novel therapeutic agents with potential applications in conjunction with 5-FU during colon cancer treatment. This is essential to enhance patient survival and mitigate adverse effects. An option for patients with high-risk stage II/III colon cancer includes adjuvant chemotherapy based on oxaliplatin. Yet, a significant number of patients experience peripheral sensory neuropathy (PSN) during the 6-month duration of oxaliplatin-based adjuvant therapy, often resulting in adjustments or discontinuation of the treatment (27). In the field of clinical practice, the widespread receiving of capecitabine, administered twice daily at 825 mg/m2 on days of radiation, has gained acceptance as a viable alternative to the continuous infusion of 5-FU. This alteration comes after two phase 3 trials affirmed the non-inferiority of capecitabine as a radiosensitizer when compared to 5-FU (28).

Stage III / IV

This stage of colon cancer refers to the condition where the cancer has extended beyond the lining of the colon and reached nearby lymph nodes. While cancer cells are present in these lymph nodes, the disease has not progressed to distant organs within the body, such as the liver or lungs. Individuals diagnosed with stage I and stage II colon cancer typically do not exhibit noticeable symptoms. In contrast, those with stage III/IV are more disposed to experience observable symptoms such as nausea or vomiting, loss of appetite, bloating, and unintended weight loss. Somatic mutations of TP53 are observed in up to 60% of colon cancer patients, and this is linked to unfavorable clinical outcomes. TP53, often referred to as "the guardian of the genome," plays a crucial role in regulating the cell cycle and maintaining genome stability. Positioned on the short arm of chromosome 17. TP53 is among the extensively studied tumor suppressor genes. The encoded p53 protein, comprising 393 amino acids with four functional domains, features a centrally located sequence-specific DNA-binding domain covering amino acid position 101–306. Mutations in this domain are frequent in p53 mutants, compromising its physiological function.

Throughout the process of carcinogenesis, p53 variations play a crucial role in the adenoma-carcinoma transformation. The underlying mechanism remains unknown, leading to a lower prevalence of p53 mutations, approximately 34%, in proximal colon tumors compared to the higher rate of 45% in distal colon tumors. TP53 alterations involve frameshift changes induced by both insertions and deletions, or missense substitutions, with the latter being more prevalent in colon cancer. In both conditions, the tumor-suppressive functions are hindered, leading to either gain of function or loss of function, eventually promoting tumor genesis and proliferation. Despite being mutants, p53 retains the ability to synthesize a protein-tetramer, indicating that they consist of a combination of altered and normal form p53 peptides (29).

Figure 6 illustrates the p53 signaling pathway and its functions within the tumor-associated microenvironment of colon cancer. In colon cancer, p53 is involved in immune surveillance, blood vessel development, and remodeling of the extracellular matrix (ECM) in both tumor cells and neighboring non-stromal cells. CAFs are cancer-associated tissues; ECM is external matrix; MDM2, E3 ubiquitin-protein ligase Mdm2; TAMs are tumor-associated macrophages; TGF-ß converts development factor beta; and Tregs are regulate T-cells.

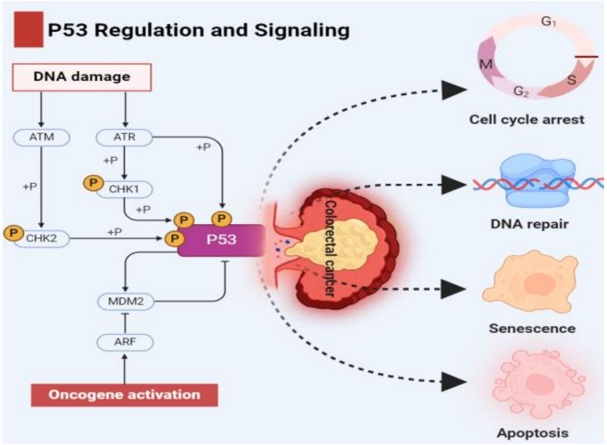

Figure 6: p53 signaling pathway.

Treatment

For individuals diagnosed with stage III colon cancer, the recommended adjuvant chemotherapy involves combining oxaliplatin with a fluoropyrimidine (FOLFOX or CAPOX). Depending on the regimen and the patient's low risk of recurrence, the treatment duration can be shortened from 6 months to 3 months. This adjustment maintains its effectiveness while substantially decreasing the risk of cumulative sensitive neuropathy. Certainly, a maximum of 30% of individuals will develop actual benefits from this adjuvant treatment. Among them, 50% have already achieved a cure through surgery, while 20% still meet disease recurrence despite receiving the adjuvant treatment. Consequently, there is a crucial need to enhance the individual prediction of recurrence risk for each patient and determine the necessity for adjuvant chemotherapy. Moreover, there is a persistent requirement for novel treatment approaches to specific subgroups.

Neoadjuvant radiotherapy is currently established therapy for individuals with stage II/III colon and rectal cancer. It aims to decrease tumor size and eliminate cancer cells that may have dispersed. Following surgical resection, adjuvant radiotherapy is administered post-resection to eliminate any residual cancer cells. This approach is predominantly employed for stage II/III colon and rectal cancers patients who did not undergo preoperative radiotherapy, such as those dealing with bowel obstruction prior to surgery (30).

Stage IV

Stage IV colon cancer develops when cancer originating in the colon metastasizes, spreading to various tissues and organs in the body. Stage IV metastatic colorectal cancer (mCRC) is categorized into subgroups, distinguishing between metastasis to a single site or organ (IVa), multiple sites or organs (IVb), or the presence of peritoneal metastasis (IVc). Beyond the site of metastasis, research indicates that factors such as the timing, number, and original location of metastases can also influence overall survival (31). In addition to the genes mentioned previously, there are other genes involved in the development and progression of colon cancer.

Treatment

Managing metastatic colon cancer presents significant challenges and requires a combination of approaches including chemotherapy, radiotherapy and surgical interventions. A multidisciplinary assessment of patients is imperative, given the absence of a universally effective treatment regimen. Systemic treatment for metastatic colon cancer primarily relies on chemotherapy. Typically, chemotherapy protocols involve combining a fluoropyrimidine (such as 5-FU or capecitabine) with either irinotecan or oxaliplatin in a two-drug regimen (doublet). The treatment regimens may be based on either 5-FU or capecitabine and can include oxaliplatin (FOLFOX or CAPEOX) or irinotecan (FOLFIRI or CAPIRI), with no observed disparities in survival outcomes (31).Coarsely two-thirds of cases are localized in the sigmoid colon, with the majority diagnosed at Stage II or higher. This often necessitates adjuvant chemoradiotherapy following primary surgical intervention. Despite advancements in conventional treatment methods and protocols, concerns persist regarding the side effects of radiotherapy, as well as the risks of local recurrence and distant metastasis in colon cancer. These factors contribute to a diminished quality of life and increased mortality rates among patients.

Other treatments

In addition to the treatments mentioned earlier, various other therapeutic approaches may be executed.

Gene Therapy

Colon cancer development is impacted by genetic alterations and chromosomal instability. Addressing and rectifying these aberrant genes, as well as preventing the overexpression of certain genes, holds the potential to reduce the incidence of colon cancer. Numerous genes undergo changes, playing a role in the progression of colon cancer. Factors such as point mutations, the activation of cancer-related genes, the suppression or elimination of prototype oncogenes, and the reduction of suppressor-oncogene functionality can all contribute to cancer development. Gene therapy offers a significant advantage by introducing specific genes into targeted tumor cells, thereby regulating the inappropriate activity of mutated genes and diminishing tumor growth.

Immunotherapy

Researchers' fascination with tumor immunotherapy has increased because of its excellent treatment potential for colon cancer. Many clinical trials examining immunotherapies in colon cancer patients are now being developed. Cytokine treatment, checkpoint-based inhibition therapy, inhibition of complement therapies was used to treat colon cancer (32).

Cytokine therapy

In colon cancer, both the inflammatory process and immunogenic responses promote tumor formation, and cytokines are crucial elements of tumor immunology. Due to their stimulation of the primary carcinogenic components nuclear factor-B and inducer of transcription three (STAT3) in intestine cells, which promote growth and inhibit cell death, TNF and interleukin-6 are important contributors in colon cancer (33).

Survival rate of colon cancer

Table 1: Survival rate based on the different stages of colon cancer.

Stages	Survival rate
0/I	92%
I/II	87%
II/III	72%
III/IV	53%
IV	12%

The survival rates for different stages of colon cancer in the United States are shown in Table 1. In the United States, the 5-year relative survival rate for stage 0/I colon cancer is approximately 92%. This rate decreases to 87% for stage IIA and 65% for stage IIB. Stage III-IV is associated with a survival rate of 53%, while the 5-year survival for stage IV, indicating metastatic CRC, is only 12% (34).

Diagnosis

Physicians providing primary care should conduct a thorough physical examination of the abdomen in patients suspected of having colon cancer and explore into the patient's medical history for an accurate diagnosis. Various screening methods for diagnosis include colonoscopy, fecal immunoglobulin test, sigmoidoscopy, and fecal occult blood test. To enhance the diagnostic process, it is essential to gather information about the cancer experiences of first-degree, second-degree, and third-degree family members. Among these diagnostic methods, colonoscopy stands out for its precision in detecting colon tumors. This procedure allows for a comprehensive examination of both the entire large intestine and the terminal part of the small intestine. Biopsy samples can be obtained during the procedure for subsequent histopathological examination. To ensure the effectiveness of a colonoscopy, adherence to hygiene standards is crucial, and it should be performed by a skilled colonoscopy with a commendable polyp detection rate, including a thorough examination of the cecum. Conventional imaging techniques often fall short in detecting tumors. Emerging methods such as activated (FAPI-PET) and diffusion-weighted MRI (DW-MRI) show promise, particularly in cases involving extraperitoneal diseases, owing to their heightened sensitivity and specificity. Recently XGboost an innovative cancer detection method algorithm was proposed by (35) showed 91.2% accuracy in the detection of colon cancer.

CONCLUSION

This review provides valuable insights into the understanding of colon cancer by examining recent advancements in the field. It explores the causes, stages, statistical data, and the genetic factors involved in the onset of colon cancer, as well as the various treatment options available. Identifying new biological pathways is crucial for the development of novel therapeutic strategies. Over the past few decades, breakthroughs in molecular biology have significantly enhanced our understanding of the molecular etiology of colon cancer, leading to the creation of targeted therapies for the treatment of this malignancy. The development of a molecular classification and the identification of key biological pathways in colon cancer have proven essential in advancing personalized treatment approaches. These innovations have opened new avenues for tailoring therapies to specific cancer subtypes, improving outcomes for individual patients. Despite the range of available treatments and medications for colon cancer, there remains a pressing need for the development of more effective drugs, particularly for advanced-stage cancers. The continued research into molecular mechanisms and therapeutic targets is vital for improving the prognosis and quality of life for those affected by this disease.

Conflict of Interest

Authors declare no conflict of interest exists.

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