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Chapter

Colorectal Cancer Stages, Progress, Genetic Predisposition, and Immune Surveillance

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Abstract

Colon cancer (CC) is highly malignant and is considered the second cause of death worldwide. However, the overall CC survival rate is improving due to the rapid development of screening tools and improved treatment options. This raised the need to develop effective approaches for medical intervention. Moreover, CC is classified into four stages: stages I, II, III, and IV. On the other hand, the driver genes played vital regulatory roles in essential pathways for cellular division, cell survival, fate, and genome stability. For example, the RAS mitogen-activated protein kinase is essential for cellular division. Additionally, carcinogenesis is linked to the mutations, which are reported in the Kirsten rat sarcoma viral oncogene homolog gene, Adenomatous Polyposis Coli gene, Tumor Protein 53 gene, and SMAD family member 4 genes, Mothers against decapentaplegic homolog 4 gene. In addition, the immune system reactions have different impacts on CC growth and management. The inflammation process is described as one of the innate responses. The inflammation process is initiated and exacerbated by various types of immune cells included the macrophages, and neutrophils for their activation, margination, extravasation, and migration to the damaged tissue. The preferred role of inflammation against cancer is at stages I and II.

Keywords: colorectal cancer, genetic predisposition, immune surveillance, oncogene, tumor suppressor gene, immunostimulatory cytokines, immune inhibitory cytokines

1. Introduction

Colon cancer (CC) is highly malignant and is considered the second cause of death worldwide. For 2018 new cases, 10% of the newly recorded cases were dead [1]. However, the overall CC survival rate is improving due to the rapid development of screening tools and improved treatment options. This raised the need to develop effective approaches for medical intervention [2]. Moreover, CC is classified into four stages: stages I, II, III, and IV (Figure 1). Stage I includes the cancer growth through the mucosa, invasion of the muscular, and development through the colon or rectum wall, which is not infused into nearby tissue or lymph nodes. For stage II, cancer has infused through the colon or rectum wall and grown into nearby structures. In stage III, the cancer of the colon has spread to four or more lymph nodes, which may be
metastasized to adjacent organs. Finally, cancer has spread to one or more distant organs in stage IV and may be diffused to the peritoneum [4].

According to the American Cancer Society, surgery may be the sole therapy for stage 0–I colon cancer. In most situations, this is accomplished by removing the polyp or eliminating the cancerous region with a colonoscope. However, if the malignancy is too big to be treated with local excision, a portion of the colon must be removed (partial colectomy) [5].

In stage I–II CC, on the other hand, surgery is a viable option for removing malignant tissue and adjacent lymph nodes, and it may be the only treatment required. Adjuvant chemotherapy is also suggested after surgery if the malignancy is at high risk of recurrence. 5-Fluorouracil with leucovorin, oxaliplatin, and capécitabine are the most common chemotherapeutic treatments. However, additional combinations may be employed. The typical treatment for stage II–III is a partial colectomy to remove the area of the colon with cancer as well as adjacent lymph nodes, followed by adjuvant chemotherapy. The FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin), and CapeOx (capécitabine and oxaliplatin) regimens are the most often utilized adjuvant chemotherapy regimens. However, depending on their age and medical conditions, some people may be able to receive 5-Flourouracil in combination with leucovorin or capécitabine alone [6].

In stage IV, CC most commonly spreads to the liver, but it can also extend to the lungs, brain, peritoneum (the lining of the abdominal cavity), or distant lymph nodes. Surgery is usually unlikely to cure certain tumors. This will entail surgery to remove the piece of the colon harboring cancer, adjacent lymph nodes, and any regions of cancer metastasis. Following that, chemotherapy is usually administered. If the malignancy has progressed to the liver, hepatic artery infusion may be utilized in some circumstances. If the metastasis cannot be eliminated because the tumorous tissues are too big or numerous, chemotherapy may be administered prior to surgery (neoadjuvant). If the tumors diminish, surgery to remove them may be attempted. Chemotherapy may be administered again following surgery. Ablation and embolization are two alternative options for destroying liver tumors. Furthermore, chemotherapy is the primary treatment if the disease has gone too far for surgery to be effective [7].

Figure 1.
Colon cancer stages, development, and survival rates [3].
To manage the malignancy, most stage IV patients will get chemotherapy and/or targeted treatments such as FOLFOX (leucovorin, 5-fluorouracil, and oxaliplatin “Eloxatin”), FOLFIRI (leucovorin, 5-fluorouracil, and irinotecan “Camptosar”), CAPEOX or CAPOX (capecitabine (Xeloda) and oxaliplatin), and FOLFOXIRI (leucovorin, 5-fluorouracil, 5-Fluorouracil, oxaliplatin, and irinotecan) [8]. Targeting medicines can be coupled with the regimens listed earlier. Bevacizumab (Avastin), ziv-aflibercept (Zaltrap), and ramucirumab (Cyramza) are drugs that target vascular endothelial growth factor (VEGF). On the other hand, cetuximab (Erbitux) and panitumumab (Vectibix) are drugs that target EGFR. 5-Fluorouracil and leucovorin with a targeted medication, capecitabine with a targeted drug, irinotecan with a targeted drug, cetuximab alone, and panitumumab alone are examples of the targeted regimens combinations with the chemotherapy. Several variables influence regimen selection, including past treatments [6].

After all, CC genetic predisposition and the host’s immune responses influencing cancer growth were discussed and illustrated to understand the best management approach depending on the CC stage and pathogenesis.

2. Genetic predisposition of colon cancer

2.1 Genes involved in colon cancer expansion and prognosis

The driver genes played vital regulatory roles in essential pathways for cellular division, cell survival, fate, and genome stability. For example, the RAS mitogen-activated protein kinase (MAPK) is essential for cellular division. Additionally, carcinogenesis is linked to the mutations, which are reported in the Kirsten rat sarcoma viral oncogene homolog gene (KRAS), Adenomatous Polyposis Coli gene (APC), Tumor Protein 53 gene (P53), and SMAD family member 4 genes, Mothers against decapentaplegic homolog 4 gene (SMAD4). Additionally, epigenetics in conjunction with intestinal dysbiosis, bacterial drivers, and persistent mucosal inflammation are all contributing factors to CC [9, 10].

On the other hand, KRAS, nuclear factor-κB gene (NF-κB), signal transducer and activator of the transcription-3 gene (STAT-3), B-cell lymphoma type-2 gene (BCL-2), BCL-2-associated protein X gene (BAX), and the transforming growth factor-β gene (TGF-β) were selected in the molecular testing for their correlation in the CC predisposition and progression [9–11].

2.2 Kirsten rat sarcoma viral oncogene (KRAS)

Regarding CC, genes enrolled in cancer development are proto-oncogene (KRAS), tumor suppressor gene (P53 and APC), antiapoptotic gene (BCL-2), and proapoptotic gene (BAX) [10]. Mutations in the KRAS oncogene are common in human malignancies, notably those of the pancreas, gallbladder, bile duct, thyroid gland, and non-small cell lung cancer with CC. These mutations may influence prognosis and medication responsiveness to anticancer agents targeting the KRAS protein pathway [12].

KRAS mutations are considered an early influencer in CC that happened in 30 to 40% of patients. On the other hand, the KRAS gene activates NF-κB signaling in cancerous cells and triggers several proinflammatory mediators [9, 10, 12, 13].

The conventional first-line treatment for advanced CC is chemotherapy based on 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX). KRAS mutations, particularly
G12D, are associated with a poor response to the conventional treatment and a significant risk of recurrence. Furthermore, KRAS mutations are strong indicators of EGFR inhibitor therapy success in individuals with CC. Monoclonal antibodies targeting EGFR have been shown to assist CC patients who had failed previous treatments. Cetuximab and panitumumab are EGFR-targeting drugs used to treat KRAS mutations. LUMAKRAS™ (sotorasib), also known as AMG 510, recently received accelerated approval from the US Food and Drug Administration (FDA) for the treatment of adult patients with KRAS-G12C mutations who have received at least one prior systemic therapy [14, 15].

2.3 Adenomatous polyposis coli gene (APC)

For carcinogenesis to develop, the Adenomatous Polyposis Coli gene (APC) mutation has to occur before the KRAS mutation. Therefore, the adenoma would not progress to carcinoma if one of the previous mutations happened without the other. APC, KRAS, and P53 are considered the CC driver genes (Figure 2). APC and KRAS mutated as an early event in the transition from normal epithelium to adenoma. However, after mutations or epigenetic silencing, the loss of P53 function can happen as late events. Moreover, P53 mutation makes cancer cells able to invade surrounding tissues and metastasize. As a result, SMAD4 and P53 loss of functions aid for the transformation of adenoma into a carcinoma (Figures 2 and 3) [16, 17].

Moreover, the APC gene is the gatekeeper gene for CC. The APC mutation is considered a frameshift mutation that causes truncation of the APC protein. The APC mutation hinders it from binding β-catenin to the membrane E-cadherin complex’s cytoplasmic domain. As a result, cellular damage occurs [10, 16]. The free cytoplasmic β-catenin molecules, on the other hand, migrate to the nucleus to elicit the Wnt signaling pathway and cancer cell survival. Moreover, TGF-β and β-catenin are indeed cancer resistance indicators [16, 18].

TASIN-1 (Truncated APC Selective INhibitor) is a small chemical that has just been discovered to preferentially destroy cancer cells having APC truncations. TASIN-1 can reduce tumor development of APC shortened CC cells with low toxicity in both xenograft models and a genetically modified CC animal model [19].

Figure 2.
Driver genes mutations of CC and the histopathological impacts [20].
One of the most common events leading to CC transformation, as well as its aggressive and metastatic properties, is P53 tumor suppressor gene dysregulation. P53 reactivator mutant (PRIMA-1\textsuperscript{MET}) has been studied in Phase I/II clinical trials and has shown promising results [15, 20].

2.4 B-cell lymphoma (BCL-2) and BCL-2-associated X protein genes (BAX)

Mutations in genes controlling cell cycle checkpoint proteins (i.e. P53, BCL-2, and BAX) are the genetic drivers of CC and several types of cancers. The low level of BCL-2 expression and high level of BAX expression are correlated for better CC survival and control of cancer. The low BCL-2/BAX expression ratio leads to Cytochrome c (Cyto c) activation after external or internal stimuli. Cyto c is responsible for the Caspase family activation to trigger different cancer cells' apoptosis and phagocytosis (Figure 4). On the other hand, BCL-2 protein inhibits the action of the BAX protein that triggers the cancer cells’ growth [21–23].

3. The influence of the host’s immune responses on colon cancer growth

3.1 Cellular immune rejoinders

The immune system reactions, as innate and adaptive, have different impacts on CC growth and management. The inflammation process is described as one of the innate responses. The inflammation process is initiated and exacerbated by various types of immune cells including macrophages, neutrophils, and mast cells, for their activation, margination, extravasation, and migration to the damaged tissue [24]. The preferred role of inflammation against cancer is at stages I and II. Moreover, the inflammation role was to activate the adaptive immune cells by activating the innate system’s antigen-presenting cells, such as dendritic cells. Additionally, natural killer
(NK) cells and macrophages of the innate system help capturing the cancer cells and releasing immunostimulatory cytokines to activate the adaptive system [25].

On the other hand, cancer is addicted to proliferative and survival signals in the cancer microenvironment as inflammation. Soluble factors, cytokines, and chemokines influence inflammation. They are secreted by cancerous cells with the innate cells recruited to the microenvironment, such as macrophages and mast cells. The depletion of mast cells or macrophages prevented the APC from mutating and preventing intestinal polyps’ initiation. This confirms the role of immune cells and their soluble factors in intestinal cancer initiation and progression [22, 24, 26].

Moreover, T-lymphocytes, T-helper (TH or CD4), NK cells, and dendritic cells are associated with CC survival enhancement regarding the adaptive immune system’s role in controlling CC. Additionally, cytotoxic T-lymphocytes (CTL or CD8) and TH cells enhance the cancer cells’ apoptosis, engulfment, detection, and antibody production against cancer cells. Furthermore, B-cells’ antibodies that target specific surface antigens are limited by the presence of the tumor-specific antigens, such as the carcinoembryonic antigen, to capture it by the antibodies and enhance the cancer cells removal [27].

In terms of CC immunotherapies, numerous FDA-approved vaccinations defend against viruses known to cause certain forms of cancer. Vaccination against human papillomavirus (HPV), for example, can protect against six forms of cancer, while a vaccine against hepatitis B virus (HBV) helps protect against some types of liver cancer. Unfortunately, however, there is no colorectal cancer vaccination available [28].

On the other hand, chimeric antigen receptor-T (CAR-T) cell immunotherapy is a unique technique that is genetically designed to recruit T-cells against malignant
illness. CAR-T cell therapy has led to success in hematological malignancies, and it has long been advocated for solid tumors such as colorectal cancer (CC). However, this strategy did not meet expectations given solid tumors’ intrinsic obstacles provided to CAR-T cells, owing to a lack of tumor-restricted antigens and undesirable adverse effects. New techniques, such as designing T-cells with immune-activating molecules, localized delivery of T-cell, bispecific T-cell engager, and combinatorial target-antigen recognition, are proposed to overcome many hurdles to ameliorate the challenging conditions of CAR-T cells in CC [29].

Furthermore, CAR-natural killer (NK) cells have received widespread interest due to their safety in clinical applications, the method for identifying cancer cells, and the quantity of clinical specimens. CAR-NK cells have been shown in preclinical and clinical trials to be capable of combating hematological malignancies as well as solid tumors such as CC. However, the use of CAR-NK cell therapy in solid tumors presents unique challenges, such as the expansion and activation of primary NK cells in vitro, the selection of CAR targets, the survival time of CAR-NK cells in vivo, NK cell storage and transportation, and the efficiency of NK cell transduction [30].

3.2 Cytokines and chemokines

Cytokines are classified into proinflammatory, immunostimulatory, and immunoinhibitory cytokines. For proinflammatory cytokines, the interleukin (IL)-8 (chemokine), IL-1, IL-6, tumor necrosis factor (TNF)-α, and vascular endothelial growth factor (VEGF) serum levels are associated with cancer development and considered as predictive tools. Moreover, macrophages release IL-1, which contributes to fever and T-cell and macrophage activations. Furthermore, IL-6 is released by macrophages, endothelial cells, and T-cells. IL-6 inhibits the production of acute-phase proteins in the liver and promotes the proliferation of antibody-producing cells. On the other hand, IL-8 is a chemoattractant generated by macrophages that attracts immune system cells and phagocytes to the site of inflammation. Finally, TNF-α is mainly secreted from macrophages and TH cells, which has a cytotoxic reaction against cancer cells and enhances the activity of phagocytic cells. As a result, TNF-α and IL-1β are emerging as potential targets for drug candidates in anticancer therapy [24]. Furthermore, TNF-α antagonists are well studied in the rheumatoid arthritis, and IL-1β antagonists are used for inflammatory disorders characterized by excessive IL-1β production [27]. On the other hand, VEGF is secreted by the cancer cells to improve cancer cell vasculature (angiogenesis) [12].

For immune system stimulation, IL-2, IL-4, IL-5, IL-12, IL-18, and interferon (IFN)-γ are immune-stimulatory cytokines. The immune-stimulatory cytokines activate the growth, differentiation, and maturation of CTL, TH cells, NK cells, and dendritic cells. Additionally, macrophages, lymphocytes, and NK cells produce IFN-γ, in which IFN-γ is significant macrophage and NK cells activator. As a result, IFN-γ enhances major histocompatibility class I expression to activate CTLs. Moreover, IL-2 is secreted by TH cells and co-stimulates the proliferation of TH cells, CTLs, and B-cells, which activates NK cells. Additionally, IL-18 is primarily secreted by macrophages and promotes NK cells cytotoxicity as well as T-cell’s IFN-γ production. Furthermore, dendritic cells and macrophages release IL-12, which contributed to the TH-1 cell differentiation, NK cell, and T-cell activations. On the other hand, the lymphocytes and macrophages produce IL-4, which is involved in B-cell activation,
differentiation of TH-2 cells, and TH-1 cells suppression. Finally, IL-5 is released by TH cells and mast cells and has the primary activity of activating and chemoattracting eosinophils [22, 31].

The immune regulatory system is activated by the secretion of IL-10 and TGF-β from the cancerous cells, tumor-associated macrophages, or immune cells, such as TH-2 cells. In addition, it enhances the activation and expression of the immune checkpoint molecules, such as cytotoxic T-lymphocyte antigen-4 and programmed cell death protein-1, which can inhibit the immune stimulatory signals activation between antigen-presenting cells and the CTLs to capture the cancer cells [31]. Moreover, IL-10 is involved in suppressing macrophage phagocytosis and B-cells’ activation [11, 12, 27]. To summarize the role of cytokines and chemokines in the CC angiogenesis or immune system recognition, Figure 5 illustrates the recently found relation between the CC and the cytokines [32].

3.3 Inflammatory signaling molecules

Proinflammatory cytokines are like TNF-α, IL-1, and IL-6, and their cell membrane receptors association influences downstream signaling factors activation. Moreover, colon cancer-associated inflammatory molecules are NF-κB and STAT-3, activated by binding the lipopolysaccharides to the toll-like receptor (TLR)-II and IV. NF-κB and STAT-3 actions enhance apoptosis of the cells and increase the expression of TNF-α, IL-1, and IL-6. However, STAT-3 and NF-κB are negatively correlated with the TGF-β release from cancer cells or with the TGF-β receptor expression on cancer cells, especially colon cancer [2, 24].

Figure 5.
The chemokines and cytokines and colorectal cancer growth interrelations [32].
3.3.1 NF-κB and STAT-3

The proinflammatory signaling molecules NF-κB and STAT-3 were associated with multiple types of hyper-inflammatory diseases or hyper-inflammatory foundations, such as inflammatory bowel syndrome, CC, lung cancer, and many other types of cancer. The higher levels of NF-κB and STAT-3 in the long term were correlated with CC angiogenesis and invasiveness. The activation of NF-κB mediator by TNF-α and IL-1β and the activation of STAT-3 mediator by IL-6 have led to cancer growth through the oncogenic signaling pathways activation in cancer cells (i.e. KRAS over-expression). On the other hand, their short-term secretions were reported to induce cancer cell apoptosis (proapoptotic) [13, 23].

3.3.2 TGF-β

The high levels of the immune-inhibitory cytokine (TGF-β) are associated with multiple types of immune deficiency diseases, resistant, and metastatic types of cancer (i.e. CC). This cytokine can be secreted from the tumor-associated macrophages and resistant cancer cells to induce the T-regulatory cells that will inhibit the activation of the CTL and TH cells. As a result, the CTL and TH cells cannot recognize cancer cells to induce apoptosis or their engulfment by the phagocytic cells [2, 18, 22, 33].

On the other hand, TGF-β enhances the VEGF secretions from the cancer cells. The VEGF amplifies the vasculature, the proinflammatory status, and the wound healing environment around the cancerous tissue. As a result, this can promote the cancer growth, metastasis, and activation of the tumor-associated macrophages to escape the immune surveillance for cancerous tissue [22, 25, 34].

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