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Immune response and therapies involved in colorectal cancer (CRC)

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Abstract

Colorectal cancer (CRC) is one of the third most common cancer in the world. Most of the ceases of CRC is detected in the western countries. The risk of developing colorectal cancer is approximately 4-5%. The front-line treatment is dose-limiting toxicities often occur in colorectal cancer, including chemotherapy and radiation therapy in CRC patients which is beneficial for the patient mortality rate, but because of the slows treatment progression and slow therapeutic effect the chemotherapy and radiation therapy is not satisfactory; hence immunotherapy came into the picture. Immunotherapy includes treatment with antibodies, or small molecules to activate the immune system for deteriorating the cancer cell. The clinical research on colorectal cancer immunotherapy includes immune checkpoints, anti- immune checkpoint, monoclonal antibodies, cancer vaccines and immune system modulators. This review describes the preclinical clinical trial investigating the immune response of CRC patients and various others therapy for treatment and prognosis of colorectal cancer biomarkers of response to these treatments.

Keywords: Colorectal cancer, Immune Checkpoints, T-Lymphocytes, PD-1/PD-L1 and CTLA-4

Introduction

The third most prevalent disease in the world, colorectal cancer (CRC) is a common illness that affects people all over the world. Each year, almost 2 million new cases are diagnosed. The majority of colorectal cancer cases (55%) are seen in western nation. The likelihood of developing colorectal cancer is 4-5% globally. The personality and habits of an individual are regarded as a risk factor for colorectal cancer since they raise the possibility of polyp growth. The following are the main CRC risk factors:

Age: Colorectal cancer is uncommon in those under 50 (excluding the hereditary cancer). Persons with ulcerative colitis who have a history of inflammatory bowel disease (IBD) or CRC are 3.7% more likely to get colon cancer, whereas people with Crohan's disease are 2.5% more likely to develop colon cancer. Chronic inflammation in IBD leads to dysplastic cell growth, which is referred to as dysplasia. Since the dysplastic cells have not yet differentiated into malignant cells, they are more prone to do so and form tumors (Ishida & Koda, 2019)[7]. The family history of CRC among close relatives, particularly those who were under 50 at the time of diagnosis, is another risk factor for the disease. Changing modest aspects of one's lifestyle**,** such as one's food and exercise routines, can help minimize one's chance of developing CRC. The anabolism rate and intestinal motility are prolongedly increased by mild activities, which also lower blood pressure.

Inactive lifestyle: Visceral adipose tissue (VAT), a kind of body fat that accelerates the development of colorectal cancer by secreting proinflammatory cytokines that induce inflammation in the colon and rectum, is connected to an inactive lifestyle and the risk is enhanced by eating habits and the amount of it.Another risk factor for CRC is food, which is related to it in a way that makes it more likely that people would get the disease if they consume an unhealthy diet. For instance, the creation of heme groups in the colon after consuming red meat promotes the development of cancer-causing substances like N-nitroso. Both alcohol intake and smoking are risk factors for CRC; in the case of alcohol consumption, aldehydes have been classified as carcinogenic due to the dependence of the growth of colorectal cancer on polymorphism of alcohol metabolism enzymes. Due to the high concentration of nicotine in tobacco, smoking raises the CRC by 10.8%, and the metabolism of tobacco readily causes polyps to invade the gut. Colorectal cancer (CRC) initiates a complex immune response involving both innate and adaptive immune systems. This intricate interaction between the tumor and the host's immune defenses is crucial for disease progression and treatment outcomes. The tumor microenvironment, a dynamic area surrounding cancer cells, significantly influences this immune response. Within this environment, various immune cells, such as T lymphocytes, natural killer cells, and macrophages, play a vital role in tumor progression and patient prognosis. T lymphocytes, especially cytotoxic CD8+ T cells and helper CD4+ T cells, are essential components of the adaptive immune response against CRC. These cells can identify tumor-specific antigens and launch targeted attacks on cancer cells. Natural killer cells, part of the innate immune system, can detect and destroy tumor cells without prior sensitization. Macrophages, which can have both pro- and anti-tumor functions depending on their polarization, add to the complexity of the immune response in CRC.The aim of immunotherapies for CRC is to boost this natural immune response while overcoming the immunosuppressive strategies tumors use to avoid detection and destruction. One promising approach in CRC immunotherapy is the development of checkpoint inhibitors. These drugs target specific molecular pathways that tumors use to suppress T cell activity. In particular, inhibitors targeting the PD-1/PD-L1 and CTLA-4 pathways have shown significant promise in treating a subset of CRC patients, especially those with microsatellite instability-high (MSI-H) tumors.MSI-H tumors, characterized by defects in DNA mismatch repair, usually have a higher mutational burden and therefore present more neoantigens, making them more vulnerable to immune recognition and attack. This trait explains their generally better response to checkpoint inhibitor therapy compared to microsatellite stable (MSS) tumors. Beyond checkpoint inhibitors, several other innovative immunotherapeutic strategies are being explored for CRC treatment. Adoptive cell transfer involves extracting a patient's immune cells, expanding and sometimes genetically modifying them outside the body, and then reinfusing them to enhance anti-tumor immunity. Cancer vaccines, designed to stimulate the immune system to recognize and attack cancer cells, are another area of active research in CRC. Bispecific antibodies, which can simultaneously bind to tumor cells and immune effector cells, represent another promising immunotherapeutic strategy. Recognizing the potential limitations of single-agent approaches, researchers are increasingly exploring combination therapies. These strategies often involve combining immunotherapy with conventional treatments like chemotherapy or targeted therapies. The rationale behind these combinations is to create synergistic effects, potentially enhancing the efficacy of both treatments. For instance, certain chemotherapies may increase tumor immunogenicity, making subsequent immunotherapy more effective. Despite these significant advancements in CRC immunotherapy, several challenges remain. One major obstacle is identifying reliable predictive biomarkers that can accurately predict which patients are likely to respond to specific immunotherapies. This is crucial for optimizing treatment selection and minimizing unnecessary side effects in non-responsive patients. One of the major hurdles is crafting effective immunotherapy strategies for microsatellite stable (MSS) colorectal cancer (CRC), which constitutes the majority of CRC cases. In contrast to MSI-H tumors, MSS tumors usually exhibit a lower mutational load and tend to be less responsive to existing checkpoint inhibitor treatments. Addressing this challenge is a primary focus of current research, with efforts directed towards combination therapies and innovative immunotherapeutic methods. To sum up, although immunotherapy has transformed the treatment landscape for certain groups of CRC patients, especially those with MSI-H tumors, there is still considerable work needed to broaden these advantages to a wider patient base. Ongoing research into the intricate interactions between CRC and the immune system, along with the creation of new immunotherapeutic strategies, offers hope for enhancing outcomes for patients across the colorectal cancer spectrum.

Molecular Process Implicated in Crc

There are three distinct routes that colorectal cancer can take microsatellite instability (MSI), chromosomal instability (CIN), and the CpG island methylator phenotype. One of these pathways' important characteristics is the pathogenic process that results in genomic stability (CIMP).

1. Classical/CIN pathway

Up to 80–85% of CRC cases are caused by the Classical/CIN pathway, which is characterized by chromosomal instability, polyploidy (imprinting), and a paucity of heterozygous alleles (Pino & Chung, 2010). Telomere mutation, DNA damage response, and modification in the separation of genetic materials are all components of the CIN pathway mechanism, and all of these changes have an impact on crucial genes involved in maintaining healthy cell function, including; (Lin *et al*, 2003)[10] APC—due to its mutation, β-catenin is translocated to the cell nucleus, where it increases the transcription of genes related to tumors, invasions, and mutations.KRAS and PI3K are both associated with increased cell proliferation and persistent MAP kinase activity.A critical cell cycle checkpoint called p53, which is encoded by TP53, becomes dysfunctional as a result of mutations.

2. Microsatellite instability pathway

The human genome has both coding and non-coding areas that include small tandem repeat DNA sequences called microsatellites (Shimizu *et al*., 2002). They range in length from one to tetra base pairs. Due to their repetitive structure, microsatellites are particularly vulnerable to replication faults, which the Mismatch Repair (MMR) mechanism often corrects. The detection and subsequent repair of mismatched bases, which most likely developed during DNA replication, genetic recombination, or physical or chemical damage, are the results of MMR, a highly conserved biological process involving several proteins. Microsatellite instability (MSI), which is caused by extensive length polymorphisms of microsatellite sequences resulting from DNA polymerase slippage, is a powerful mutator trait caused by deficient MMR (dMMR). As a molecular marker of hereditary nonpolyposis colorectal cancer (HNPCC), commonly known as Lynch syndrome, MSI is acknowledged as one of the main carcinogenetic routes of colorectal cancer (CRC).

3. The CpG island methylator phenotype (CIMP)

another characteristic of the CRC, is caused by epigenetic instability. Hypermethylation of oncogene promoters, which results in gene silence and loss of protein production, is a key characteristic of CIMP tumors. Today, a subset of CRCs known as DNA hypermethylation in CpG-rich promoters is acknowledged. According to their level of methylation, malignancies may be categorized, and those with high levels of methylation (referred to as the CpG island methylator phenotype, or CIMP), represent a clinically and aetiologically different category that is marked by "epigenetic instability. The degree to which CIMP has been accurately described varies among investigations. Actually, the biggest difficulty in analyzing and investigating CIMP tumors is determining which particular methylation loci should be used to identify CIMP. The standard panel, which typically includes the following five loci: hMLH1, p16, MINT1, MINT2, and MINT31, has been used in the majority of research. (Pancione *et al*., 2012).

Function of Immune Response

The interaction between the malignant cell and the host immune cell in a tumor microenvironment is that cancer cell invasion from the immune cell responses has been acknowledged as an independent sign of the malignancy. Since many distinct cell types and cell products interact during the immune response to cancer cells, it is impossible to separate the effects of cell-mediated and antibody-mediated responses. However, cytotoxic T lymphocytes (CTL) are widely acknowledged as one of the most significant effector pathways of anti-tumor immunity. Through the use of their clonal T cell receptors (TCR), which were created using a somatic recombination mechanism, CTL are able to execute tumor-specific recognition. By releasing lytic agents and engaging in direct cell-cell contact, activated CTL can facilitate the targeted death of tumor cells.CTL are typically CD8+ and consequently class I MHC-restricted, while occasionally CD4+ class II MH are present. Additionally, cytolytic actions by limited T lymphocytes have been observed. Specifically, through producing cytokines that act on CTL to improve their cytolytic potential CD4+ T cells shows an important role while developing and maintaining the protective immunity against malignant cells. Their existence is not necessary for lytic activity, though. Due to their unique genetic profiles and markers, cancer cells should be destroyed by the immune system in order to safeguard our bodies. Contrary to this reality, however, the most common method of interaction involves decreasing too permissive immune responses or tolerance, in which cancer cells are identified as self-cells. Under normal circumstances, T cells move throughout the body to detect pathogen-derived antigens on the surface of antigen-presenting cells (APCs). The antigen stored in the MHC complex on the surface of the APC is bound by the T cell receptor (TCR) on CD4+ helper T cells and CD8+cytotoxic T cells. There have been significant improvements in the knowledge of immune-oncology and immunotherapy. Inhibitors of immune checkpoints are promising immunotherapeutic strategies (Tiwari *et al*., 2020a).

1. Anti-Tumor immune response in CRC

The anti-tumor activity of CD8+ cytotoxic T lymphocytes (CTLs) is the major focus of cancer immunotherapy. If the tumor cells are carrying identifiable antigens, CTLs can directly attack all tumor cell types. But CD4+ T cells also contribute significantly to anti-tumor immunity. In secondary lymphoid organs or the tumor, CD4+ T cells can either inhibit or enhance the anti-tumor CTL response.

1.1. Cancer immune surveillance: The patient's immune system demonstrates the body's defense against the tumor. There is widespread agreement that the immune system, by the help of its innate and adaptive effector mechanisms, permits early detection and elimination of altered cells during the early stages of cancer. The immune system acts as a stimulator of cell transformation, a regulator of unchecked proliferation, and a regulator of immunogenicity.

1.2. Immunoediting: The process of immunoediting includes the immune system and malignant cells inside the tumor microenvironment and is then divided into three phases: elimination phase, equilibrium phase, and escape phase (Figure-01). Immunoediting modifies the tumor responses of cancer cells through a mechanism that has not yet been fully understood. During the elimination phase, the tumor cells get eliminated after the recognition by the immune system. This phase has “two signals theory” thus by the help of major histocompatibility complex (MHC) the tumor antigen is represented to the T-cell receptors this is termed as first signal and binding of co-stimulatory factors which causes the activation of T-lymphocytes and is termed as second signals.In equilibrium phase, to govern immune responses and produce an active state of the immune systems in responsiveness, the aberrant development of the cells during the equilibrium phase activates a number of metabolic pathways. The diminished helper T-cells or effector T-cells, however, are no longer helpful in tumor suppression. This phase of cancer immunoediting is the most extensive since immune cells are still moving about in tumors and keeping cancer cells dormant despite their inability to kill them (Passardi *et al*., 2017). During the escape phase, Cancer cells use physiological pathways created to maintain tissue in homeostasis condition and prevent healthy tissue from any form of distortion during the escape phase to evade the immune system. Cancer cells also use several mechanisms to suppress the immune response both directly and indirectly. At this stage, cancer cells connect to and activate co-stimulatory molecules on the surface of T lymphocytes. They also produce immune suppressive mediators including indoleamine-2,3-dioxygenase (IDO) and inhibitory co-receptors such programmed cell death protein ligand 1 (PD-1), and are in charge of transforming growth factor- (TGF-beta) and other anti-inflammatory cytokines, which are produced when tumours are present (IL-10). These co-inhibitory molecules, also referred to as immunological checkpoints, are crucial in suppressing immune responses (Passardi *et al*., 2017).

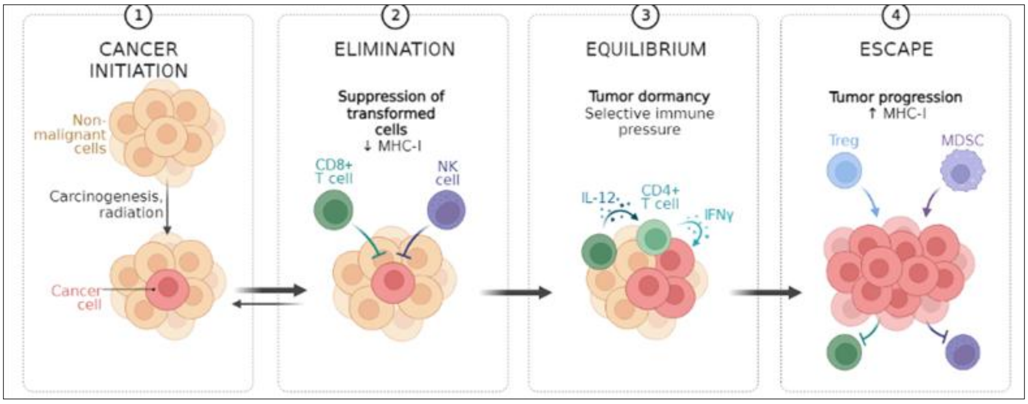

Fig 1: Steps involved in Immunoediting

2. Tumor-associated inflammation

Certain inflammatory patterns can promote the onset and spread of cancer. The target of immunological attack distinguishes the anti-tumor immune response from the immune responses observed in inflammatory bowel disease (IBD). When a person has cancer, the immune system reacts against the altered cell, which is shown by the presence of circulating T lymphocytes that are specific to TAA (tumour associated antigens). On the other side, an unwarranted inflammatory response to gut microorganisms occurs in IBD (Balducci *et al*, 2013) [2]. Reactive oxygen species can cause DNA mutation and thus are thought to contribute to increased cancer risk associated with inflammation, inflammation is connected with increased growth signalling and angiogenesis, and inhibition of apoptosis. Inflammatory cells are important source of cytokines and chemokines (e.g.; IL-1β), proteinases (e.g.; MMPs) and growth factors (e.g.; VEGF) that promotes the tumor growth. Signalling pathways are associated with cancer- promoting inflammation act downstream of oncogene mutation.

3. Immune checkpoints

The immunological checkpoint proteins programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocytes associated antigen 4 (CTLA-4) are released by activated human T cells, and they express and control T-cell function. The release of soluble immunosuppressive mediators can then be aided by cancer by binding to and activating the negative molecules on the surface of T-cells (Passardi *et al*., 2017)

3.1. PD-1

The programmed cell death protein 1, known as PD-1, is primarily expressed by T cells, B cells, NK cells, and activated monocytes. Transmembrane glycoproteins with a 288 amino acid sequence are encoded by a human gene. PD-1 is made up of two ligands, PDL1 (B7H1, CD274), which is expressed constitutively on both hematopoietic and nonhematopoietic cells, and PDL2 (B7DC, CD273), which is expressed on DCs, macrophages, mast cells, and a subset of B cells after being induced. T cell expansion and cytokine production are stifled by the PD-1/PD-L1 interaction. As a result, PD-1 allows tumour cells to evade immune surveillance by controlling immune reactions in an opposite direction. When PD-1 binds to PD-L1, it activates tyrosinase phosphorylation in the B-terminal immunoreceptor tyrosine based inhibitory motifs (ITSM), which interferes with antigen-specific signalling mediated by T cell receptor and inhibits T cell proliferation and differentiation and results in reduced T cell function or apoptosis. As a result, tumour cells are stimulated to escape from healthy immune responses (Figure-02) (Carlsen *et al*., 2022; Singh *et al*, 2015) [3, 15]. The PD-1/PD-L1 signalling pathway (Payandeh *et al*., 2020) involves tumour immune invasion, which may contain the following elements:

a. triggering the loss of T cells,
b. triggering T cell apoptosis,
c. promoting T cell tolerance,
d. preventing the growth of T cells,
e. reducing the activation of T cells,
f. fostering the epidermal mesenchymal transition (EMT).

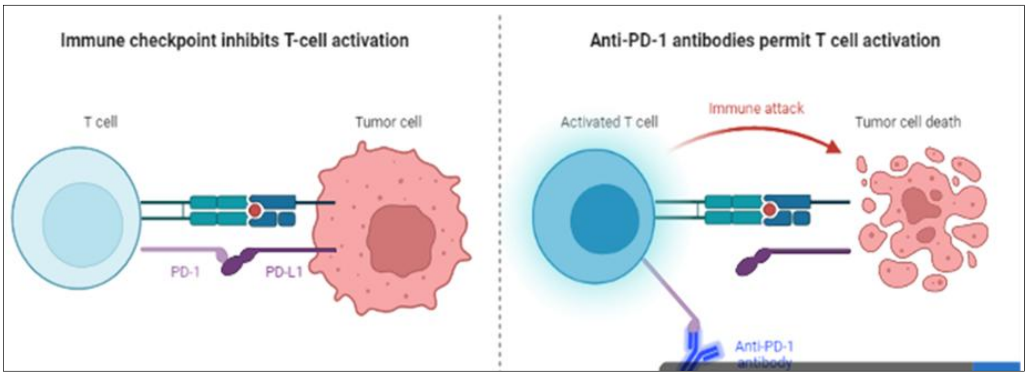

Fig 2: T-cell activation by PD-1 and PD-L1 signalling pathways

3.2. CTLA-4

With a structure similar to CD28, CTLA-4 binds to the B7 ligand and has a greater affinity for the B7 molecules. The immunoglobulin superfamily member CTLA-4 functions as a molecule ligand and is one of its inhibitory molecules. Its expression sends out unfavourable signals and prevents T cells from producing cytokines. When the expression of CTLA-4 is associated with a poor diagnosis of numerous tumours, it is crucial to manage the patient's immune response. Additionally, inhibiting CTLA-4 causes T cells to become active again and allows them to once again target cancerous cells (Singh *et al*, 2015) [16].

4. Immuno-checkpoints inhibitor

Cytotoxic agent and targeted therapy combinations, such as cetuximab or panitumumab for epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) for improved survival of colorectal cancer (CRC) patients, have been tried through the vascular endothelial growth factor receptor (VEGFR) pathway with bevacizumab. Researchers have also looked into using probiotics, anti-inflammatory drugs, and drugs based on gold to lessen the negative effects of multiple drug administration (Grothey *et al*., 2014). However, their restricted clinical utility led to the discovery and development of alternative therapeutic agents, such as immune checkpoint inhibitors.

4.1. PD-1 Blockade / PD-L1 Blockade

It is true that tumour cells expressing PD-L1 and T-cells expressing PD-1 are unable to interact with one another during anti-PD-1 therapy. Anti-PD-1 or anti-PD-L1 therapy had the potential benefit of increasing sensitivity to standard cancer treatments without causing any unwanted side effects. Anti-PD-1 blockade therapies were associated with an increased risk of skin toxicities, which is unexpected.PD-1 Blockade: The first humanised IgG4 monoclonal antibody anti-PD-1 medication is pembrolizumab, which binds to PD-1 with a high affinity and restores the immune response by inhibiting the concomitant expression of PD-1 and PD-L1/2 (Figure-03) (Hamanishi *et al*., 2016a)[5].Nivolumab, another humanised IgG4 monoclonal antibody that inhibits PD-1, is FDA-approved as a second-line treatment for CRC patients by blocking the PD-1/PD-L1 signalling pathways (Hirano *et al*., 2021a).PD-L1 Blockade: A humanised IgG1 monoclonal antibody called atezolizumab targets the interaction of PD-L1 with PD-1 and B7 receptors. This overrides the PD-L1/PD-1 signalling pathways' suppression of the immune response in tumours (Figure-03) (Hirano *et* *al*., 2021b). Atezolizumab combined with chemotherapy is an effective adjuvant therapy for MSI-H III with CRC, according to ongoing research. Atezolizumab has a lot of potential for the treatment of CRC, as seen by its usage in combination with bevacizumab, cobimetinib, and other drugs to treat metastatic CRC.

4.2 CTLA-4 Blockade

A human CTLA-4 blocking antibody called ipilimumab is used to treat metastatic melanoma. Large phase II clinical studies evaluating nivolumab's safety and effectiveness in the treatment of advanced CRC revealed that nivolumab combined with ipilimumab had a higher immune response rate than nivolumab alone.Tremelimumab is a human IgG2 antibody that is meant to block CTLA-4. Tremelimumab failed to exhibit any pharmacological action throughout the phase II studies conducted on patients with metastatic colorectal cancer; as a result, it is no longer recommended for use in the treatment of this disease (Figure-03) (Hirano *et al*., 2021a).

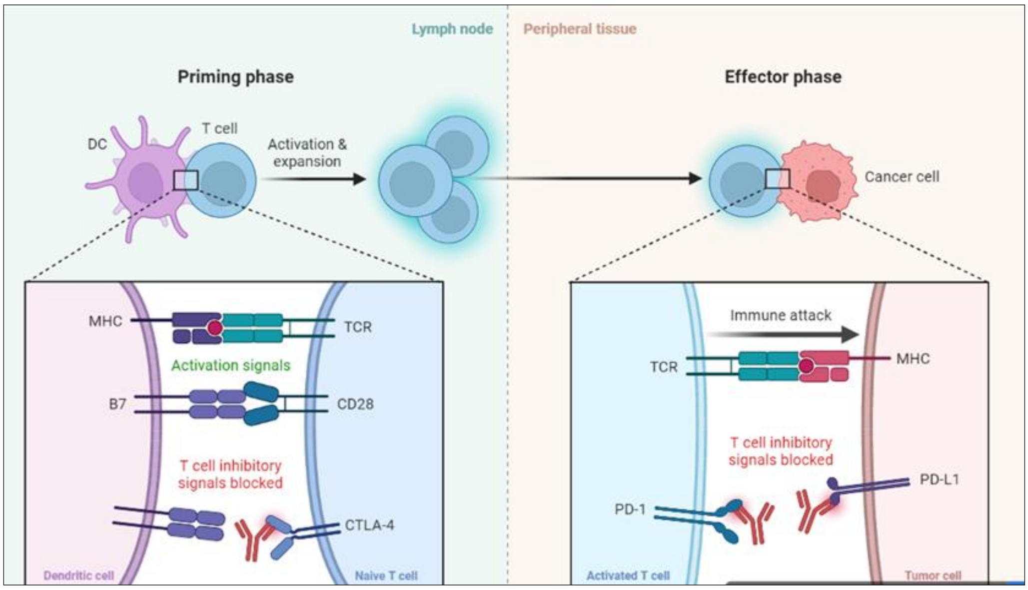

Fig 3: Role of Immune-Checkpoints Inhibitors

Treatment Used for Colorectal Cancer (Crc)

The researcher is utilising a number of methods that have the potential to get a medicine to pass past the colon's epithelial barrier.In the treatment of colon illness, oral delivery of chemotherapeutic medicines to the colonic site is beneficial because it can increase local drug concentration while minimising adverse effects brought on by therapeutic compounds released by upper or systemic absorption of the GIT. To distribute drugs, there are four basic methods that are focused on the oral colon:(Tiwari *et al*., 2020a)(I) medication delivery dependent on local pH changes,(II) timing of drug release (based on release transit time system) (III) Pressure-based system (IV) Drug delivery based on enzymes (degradation of intestinal enzyme and release of prodrug and therapeutic drug) Some others approaches are a pro drug-based system, microbial trigger approach, osmotically control drug delivery, and hydrogen-based system.

1. Polypectomy and Surgery

A polypectomy is the surgical removal of polyps using an endoscope, a colonoscopy, or by surgery. By removing a tiny, confined tumor surgically, CRC patients can receive the right relief (Mönkemüller *et al*, 2009) [11].

2. Radiation Therapy

Ionizing radiation is applied during radiation treatment to treat CRC patients and to inhibit the spread of harmful virus cells. Selective internal radiation treatment (SIRT), trans arterial chemoembolization (TACE), and radiofrequency ablation are all types of radiation therapy (RA) (Ji *et al*., 2018) [8]. In CRC patients with liver metastases, SIRT is utilized instead of surgery. In this radiation treatment, radioactive microbeads are inserted into the hepatic artery. It relies on the liver's particular blood supply, in which metastatic liver tumors are mostly nourished by the branches of the hepatic artery, as opposed to healthy hepatocytes, which are largely nourished by the portal artery. One of the radionuclides used to mark microspheres and release high energy and beta decay photons with little penetration of soft tissue, or estimated -ray transmission range of 2.5mm to 1cm, is yttrium-90 (Y-90). As a result, SIRT with Y-90 may administer ionizing radiation over 100–120 Gy, and because beta radiation only penetrates a small amount of tissue, tumors are still within tissue tolerance (Stubbs & Wickremesekera, 2004).

TACE is a form of blocking chemoembolization of the hepatic artery used to treat liver cancer linked to mCRC. This method entails infiltrating blood arteries in order to restrict the blood supply to the tumor. This procedure involves injecting tiny emboli coated with chemotherapy drugs into specific arteries with a catheter to provide blood to malignant cells. These particles cause cytotoxicity while also cutting off the blood supply. As a result, blood flow and embolization boost the impact and aid in the destruction of tumors from drugs that do not drain out of tumor vasculature. A modified version of the TACE approach was used, and Lipiodol Polymer-based microparticles (DEB) improved medication delivery to tumors while reducing exposure to the general bloodstream (Ishida & Koda, 2019) [8].

When treating CRC with liver metastases, radiofrequency ablation is frequently employed. In this method, frictional forces produced by an alternating current delivered through a closed circuit drive the movement of ions, resulting in tissue heating. Target temperatures are kept between 55 and 100 °C in order to promote protein denaturation, prevent charring and evaporation, and manage radio conduction. Either a temperature gauge or impedance matching can be used for ablation (Ishida & Koda, 2019) [9].

3. Chemotherapy

Table 1: Some of the drug used in Colorectal Cancer and their route of administration

CHEMOTHERAPY	INTRAVENOUS OR ORAL
5- Florouracil	Intravenous
Oxaliplatin	Intravenous
Irinotecan	Intravenous
Cetuximab	Intravenous
Pantitumumab	Intravenous
Capacitabin	Oral
Regorafenib	Oral

It is one of the most crucial types of therapy utilized in the fight against cancer. The medicine is used to stop the division and development of tumors and cancerous cells. Chemotherapy is the primary approach used to treat metastatic cancer. These chemotherapy medications have the potential to interfere with processes other than those involved in cancer cells' cell division, DNA replication, and chromosomal segregation. Medicine treatment has limitations; it targets all rapidly dividing cells within the cell, but only a smaller proportion of the drug actually reaches the body's target organization. Additionally, there is a chance that the surgical procedure will harm healthy tissue.

4. Immunotherapy

Novel immunotherapy strategies have been developed as a result of increased understanding of the intricate interactions between cancer cells and the immune system. With the best clinical effectiveness in melanoma and lung cancer, the use of selective anti-PD1, anti-PD-L1, and/or anti-CTLA-4 monoclonal antibodies (mAbs) has revolutionized the treatment. landscape for a number of cancer types. One of the tumors where immunotherapy has been demonstrated to be less successful is colorectal cancer. Immune checkpoint inhibitors have a definite therapeutic function in individuals with metastatic colorectal cancer that has poor mismatch repair (MMR) or tumors that are highly microsatellite instable (MSI-H) (Amin & Lockhart, 2015) [1], however the great majority of patients with these conditions do not respond well to immunotherapy (Ciardiello *et al*, 2019) [4] IT is a potential therapy for the management of mCRC, particularly in patients with MSI-H tumors. It is based on how the body defends itself, developing immunity and enabling the body to combat cancer cells. It lessens the impact as well. The risk of developing cancer is higher in people with extremely compromised immune systems. Immunotherapy often falls into one of three categories: active therapy, passive therapy, or combination therapy.

Active therapy: The body's distinct immune system, which fights cancers, is made possible through active therapy. Exosomes, cell treatments, cancer-specific vaccinations, and supplementary therapy are all included. Exosomes are produced through the processes of endocytosis in the cell membrane, multivesicular body formation that fuses with the plasma membrane, and exocytosis, which releases them into the extracellular fluid. Exosomes contain a variety of host cell components, such as proteins, miRNA, lipids, DNA, etc (Lichtenstern *et al*., 2020) [9]. The therapy of CRC has been investigated using a variety of monoclonal antibodies. Targeted CRC immunotherapy can be used to treat human Achaete Shield Homology 2 (HASH2) and MASH2 (the mouse homolog of HASH2). Additionally, employed for CRC were the peptide- and DC-based vaccinations. Peptide-based vaccinations are made of synthetic peptides that are 8 to 11 amino acids long and can stimulate certain T cells response to antigens unique to tumors. Several common tumor-specific antigens, including; CEA, signal transducer and activator of transcription 3 (STAT3) and survivin (inhibits caspase activation and thus apoptosis), and mucin 1 (cell surface bound MUC1). Patients with metastatic CRC who respond to DC vaccinations had higher post-operative survival rates. Responses to DC vaccinations are impacted by somatic mutations and T-lymphocyte infiltration.

Passive therapy: antibodies made outside the body are referred to as passive treatment when they are administered to confer or support immunity against cancer by transferring immune effectors to the host rather than activating the host's immune system. Adoptive cell therapy (ACT) and immune checkpoint inhibition are two strategies for passive immunotherapy. Due to the great specificity and killing capacity of T-cells, the bulk of adoptive cell treatments predominantly depend on this approach. In ACT, autologous T cells are taken from a patient, activated ex *vivo*, then expanded to produce a high number of T cells. To pvirovide the intended therapeutic effect, they are then implanted into the patient. Autologous T cells were produced as a result, and they express the mouse T-cell receptor (TCR). The human carcinoembryonic antigen (CEA) attaches to TCR in a particular way. Patients with metastatic CRC who didn't improve after receiving conventional medication therapy received these lymphocytes. Immune system checkpoint blockade treatment is a further strategy. Recently, it was revealed that immunotherapy for CRC might be improved by using immune checkpoint blocking treatment in conjunction with chemotherapy.

Combination therapy: Is used to describe immunotherapy that included both active and passive components. Comparing the anti-angiogenic vaccination activity to that of an induced human umbilical vein endothelial cell (HUVEC) vaccine, the latter showed reduced activity. Based on this, a DC vaccination containing the CT26 antigen was created; it is given in conjunction with an inducible HUVEC vaccine (Golshani & Zhang, 2020). It has been demonstrated that this combination vaccination stimulates immune responses against tumor cells and tumor angiogenesis (Basile *et al*., 2017). Increased anticancer activity is brought on by synergistic immune action against tumor cells close to the tumor microvasculature. The clinical therapy of CRC may be studied using this immunotherapeutic combo approach.

Discussion

As we noted, the high death rate of colorectal cancer has made it the most dangerous health issue in the world. The most recent developments in the study of CRC research as well as fresh information on its diagnosis and therapy have been included in this review. It is important to build novel preventative techniques since different combinations of genetic and environmental variables might cause CRC to develop. A more thorough investigation of the interaction between the microbiota, food, and CRC is required due to the fact that the majority of the cancer genes implicated in CRC have been identified under numerous environmental conditions that are yet unclear, necessitating a change in lifestyle to lower the risk of development of CRC. Similar to this, the creation of several sensitive biomarkers is being employed to enhance diagnostic approaches. Until recently, just two mutation techniques—MSI and KRAS mutation—were utilized for diagnosis and therapy. Therefore, if we are talking about the therapies and treatments used for CRC, immunotherapy and personalized medicine are becoming essential tools, therefore it is required to do an extensive investigation of the characteristics of each patient's tumors.

Conclusion

The morbidity and death rates of CRC, a prevalent cancer that threatens human health, are rising yearly. The study of treatments is developing steadily. As the understanding of the causes of CRC has grown, the focus of its treatment has switched from total surgery to radio-chemotherapy. In a number of recent studies, immunotherapy has also been primarily employed, with a focus on immunological checkpoints when assessing MSI-H patients. On MSS patients and other cancer patients, immunotherapy and chemotherapy are coupled as a targeted therapy, offering a fresh approach to treating the disease when earlier treatments for the patient's condition were unsuccessful.

The effectiveness of different immunological checkpoints cannot currently be predicted clinically, and there is still no consensus on how to screen target groups and create the best possible individual treatment plans. To enable individualized therapy, further research is required on the immune response, tumor microenvironment, and drug resistance mechanisms.

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