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TARGETED DRUG DELIVERY SYSTEM FOR COLON CANCER

Nandini Vilassingh Rajput, Dipali shegar, Mitali Santosh Hire, Smita Sitaram Andhale
B-pharmacy, Professor
Matoshri institute of pharmacy

ABSTRACT:

Even with all of the breakthroughs in treatment, colon cancer continues to rank third globally in terms of cancer-related mortality. One of the main issues with chemotherapy is the toxicity of conventional medications. The mechanism of targeted delivery involves the concentration of drug in the targeted tissues while decreasing the concentration in the other tissues. The medicine molecule is assisted by this delivery method in ideally reaching the intended location. By lowering the need for a greater dosage of the medication, the targeting will decrease the frequency of dosages. The current review focuses on the various aspects of targeted drug delivery, such as the medication selection criteria and factors that influence it. It also briefly discusses the various targeted drug delivery strategies for colon cancer therapy.

Keywords: colon cancer, targeted drug delivery, chemotherapies.

1.1 INTRODUCTION:

Hippocrates, known as the "Father of Medicine," lived from 460 to 370 B.C. and is credited with creating the term "cancer." Greek word karkinos (carcinos), meaning crab or crayfish, was used by Hippocrates to describe a range of cancer forms[1''2].Cancer is a frequent condition that is believed to be associated with instances of excessive mortality, despite ongoing study. Worldwide,

6.35 million new cases of cancer are expected to be diagnosed annually; emerging nations account for half of these cases[3]. According to a 1998 survey, there are approximately 0.609 million cancer patients in India, including 0.315 million men and 0.294 million women[4]. According to some estimates, after cardiovascular disorders, cancer is the second leading cause of mortality worldwide. Unchecked cell proliferation is a sign of cancer, which develops into a primary tumor that invades and kills other tissues. It is characterized by the absence of the regulatory mechanism that in complex multicellular organisms regulates cell formation and maturation, which is necessary for

homeostasis. When the body needs them, normal cells multiply to increase in quantity before dying. once the prerequisite has been met7. When healthy cells in a specific area of the body begin to proliferate uncontrollably, cancer results. The body uses care and assistance to regulate the proliferation of cells in response to specific needs. In healthy, mature cells, the rate of proliferation is equal to the rate of cell death; in cancer, however, the rate of proliferation is

higher than the rate of death. Tumors are lumps that arise in the body due to abnormal alterations in normal cells. Cancers come in several forms; all cancer cells proliferate, divide, and then divide again to create new, aberrant cells in their place. Certain types of cancer cells often spread to different parts of the body through lymphatic or blood vessels (metastasis), where they begin to grow and can impact the nervous system, digestive tract, and circulatory system. Typically, cancerbegins as a solid tumor.[2]

Several characteristics set tumor cells apart from normal cells:

a) They can secrete their own growth factor, which makes them an independent growth factor that promotes cellular proliferation.

b) Tumor cells are independent of the extracellular environment, whereas normal cells needit to proliferate.

c) Tumor cells lack this property and grow over or under each other, whereas normal cells respond to the presence of other cells in culture by forming a monolayer.

d) Tumor cells continue to proliferate while normal cells cease once they reach a certaindensity.[6]

There are many different kinds of cancer, including prostate, lung, colon, and breast cancer. Colorectal cancer is the third most common cancer in the United States. The progression of development from the colon or rectum is termed as colorectal tumor, or colon malignancy[7]. It results from abnormal cell proliferation that can spread to different parts of the body. Fatigue, loss of weight, and blood in the stool are possible symptoms and side effects[8]. Only a small percentage of colorectal disorders are inherited; the majority are caused by factors in daily life. A few of the causes include eating habits, smoking, and lack of exercise. Red meat and alcohol are two dietary practices that can be dangerous[9].The gastrointestinal tract's colon or rectum are the site of colorectal cancer, which is mostly caused by mutations in the Wnt signaling pathway, which increases signalling activity[10,11,12].Both acquired and hereditary alterations are possible[13]. The APC gene, which produces the APC protein, is the mutant gene in colorectal cancer cases. The β- catenin protein cannot assemble because of the APC protein[14,17]. In the absence of APC, β-catenin accumulates to elevated levels, enters the nucleus, attaches itself to DNA, and ultimately triggers the transcription of proto-oncogenes[16].

These genes are generally required for the differentiation and renewal of stem cells, but excessive expression of them can lead to cancer. Molecular model explaining how colorectal cancer developed via the adenoma-carcinoma series Fig. 1.[17] illustrates:

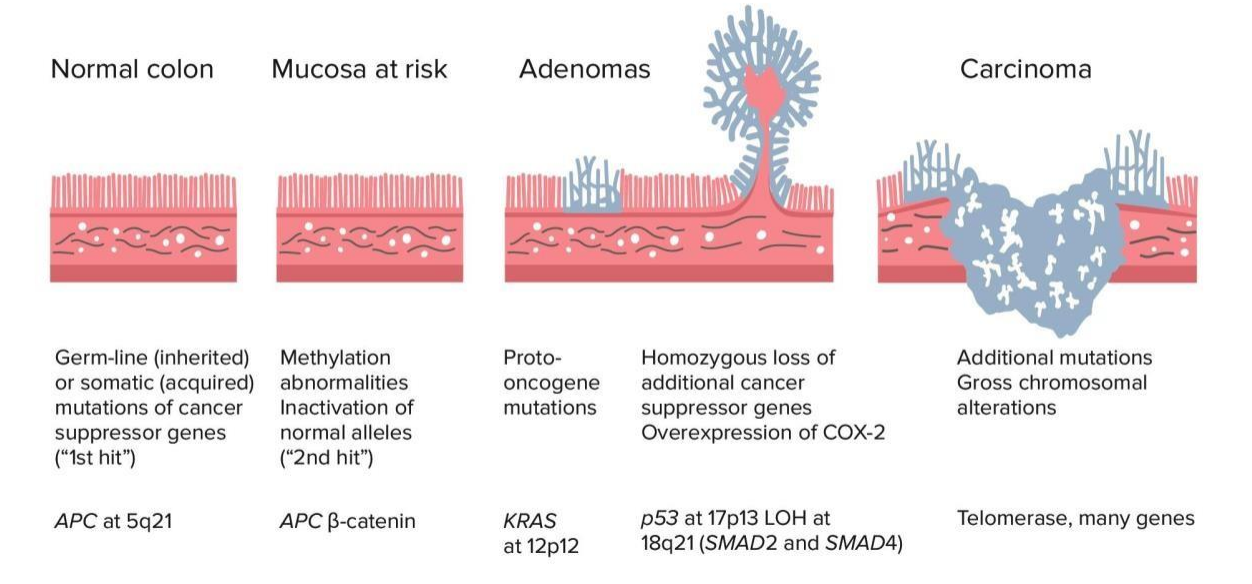


Fig 1: Molecular model explaining how colorectal cancer developed via the adenoma-carcinoma process.

2.1 Colon Cancer

Colon cancer (CRC) ranks third in the world among males (746, 000 cases year) and second most prevalent in women (614, 000 cases annually) worldwide. Compared to less developed nations (624, 000 cases annually), developed nations have far higher incidence rates (737,000 cases annually). Men are far more likely than women to have it. Furthermore, incidence rises noticeably with age; in affluent nations, the median age of diagnosis is roughly 70 years old[18]. The third most prevalent cancer type globally and a major cause of cancer-related mortality is colorectal cancer (CRC). Sequential genetic and epigenetic alterations in certain oncogenes[19'20]. in intestinal tract epithelial cells occur throughout the development of colorectal adenocarcinomas, which causes the initiation, progression, and metastasis of CRC[21]. Treatment for colorectal cancer (CRC) heavily relies on early diagnosis and improved understanding of the molecular causes of the disease's origin and progression.[22] An overview of CRC diagnosis and management is provided by this review according to Fearon[23'24], a combination of processes, including as microsatellite instability

(MSI), chromosomal instability (CIN), and CpG island methylator phenotype (CIMP), generate CRCs.The promoter

hypermethylation of several tumor suppressor genes, including MGMT and MLH1, is indicative of the CIMP pathway. The BRAF mutation and unstable microsatellite are examples of this hypermethylation.[27] Deactivation of genetic alterations in sparsely repeated sequences is part of the MSI Pathway. This initiation occurs in CRCs involving the MMR (DNA mismatch repair) gene. Additionally, MSI may be brought on by the hypermethylation of the MMR genes. The CIMP pathway is connected to this mechanism.[26] MSI tumors have a good prognosis but are associated with weak differentiation in the proximal colon.[27] In CRC, three processes frequently overlap.[27'28'29]

2.1.1 Molecular basis of CRC

After forming the hyperproliferative mucosa, the normal epithelium will eventually develop a benign adenoma that, in about ten years, would develop into a carcinoma and spread.[21] Roughly 70% of all colorectal cancers (CRCs) are sporadic, caused by somatic mutations. About 10–30% of instances of CRC are familial, compared to approximately 5–7% caused by genetic illnesses.[30]Hereditary colorectal cancer (CRC) is produced by inactivating mutations in the same genes, whereas single-nucleotide polymorphisms (SNPs) in oncogene are the cause for the family forms of the illness.[31'32]Adenomatous polyposis syndrome and hereditary nonpolyposis colorectal cancer (HNPCC) are two of the main hereditary CRC syndromes.[33]

2.1.2. Hereditary CRC and molecular diagnosis

Hereditary CRCs accounts for around 7-10% of CRC and it Comprises of HNPCC, adenomatous which includes FAP and MAP and hamartomatous which comprises of PJS, JPS, PHTS Polyposissyndromes.[31]

3.1 Cancer Therapy

Although there are palliative treatments for cancer, there is no cure. Numerous medications are available on the market that may be able to combat cancer. The majority of the chemicals have several adverse effects in addition to their anticancer properties. Treatment options for cancer include:

a) Surgery
b) Chemotherapy
c) Radiation therapy
d) Immunotherapy
e) Monoclonal antibody

3.1.1 Chemotherapy:

Chemotherapy refers to the wide range of medications used in the treatment of cancer. Usually, the way these treatments work is by either destroying cells that are dividing or altering their growth. As more and more cells are created, they begin to take up large amounts of space and eventually occupy the area where functional cells once stood. Chemotherapy medications prevent cancer cells from dividing and proliferating. One may use a medication by itself or in combination with other medications. They can be administered directly into the bloodstream, directed against specific cancerous areas, or used to combat cancer cells already existing in the body.

Chemotherapy medications can:

- Cause cell division to cease or disrupt the mitotic process.
- Concentrate on the elements required for the development of cancer cells.
- The cell's death process.
- Starve a tumor by stopping the development of new blood vessels that supply it.

3.1.1.2. Cell cycle-specific and non-specific agents:

Nonspecific substances exhibit a linear dose response curve, meaning that the greater the drug dose, the greater the number of cells that are destroyed. However, the ability of a medication specific to a particular cell cycle phase to damage cells reaches a plateau; further increases in dosage will not cause more cell damage.

3.1.1.2.1 Cell cycle-specific agents:

- **S phase-dependent:** Antimetabolites: Hydroxyurea, Mercaptopurine, Methotrexate, Cytarabine, Doxorubicin, Fluorouracil, Floxuridine, Cytarabine, Prednisone.
- **M phase:** Vinca alkaloids: vincristine, vinblastine, and vinorelbine. Teniposide and Etoposide are podophyllotoxin. Docetaxel and Paclitaxel are taxanes.
- **G2 phase-dependent:** Bleomycin, Irinotecan, Mitoxantrone, and Totecan
- **G1 phase-dependent:** corticosteroids, aspariginase.

3.1.1.2.2. Cell cycle non-specific agents:

- Alkylating agents
- Antibiotics
- Cisplatin
- Nitrosoureas

3.1.2 Combination Chemotherapy:

Combination chemotherapy refers to the use of multiple chemotherapy drugs concurrently for the treatment of cancer. A single medication was once frequently used to treat cancer, but modern cancer treatments use a combination of two or more different drugs at the same time to treat a wide range of cancer types. As it is a logical tactic to boost response and tolerability and to reduce resistance, it is currently regarded as the standard of care, particularly in cancer treatment.

3.1.2.1 Selection of drug for combination chemotherapy:

It has been established that the following guidelines should be followed when choosing medications for combination regimens:

- Drugs with high single-agent activity should be chosen for combinations. It is preferable to use a medication that induces remissions.
- Combining medications with different modes of action will allow for synergistic or additional effects on the tumor.
- It is best to combine medications with different dose-limiting toxicities so that each medication can be administered at its full or almost full therapeutic dose.
- Medication needs to be taken on a regular basis.
- Chemotherapy can result in complete treatment if administered early, which makes the side effects bearable

for a large number of patients. A plan is created outlining the course of treatment.

The patient may receive chemotherapy orally, intravenously, by injection into a vein, or at another location, depending on the type of cancer.

Orally: Tablets can be taken. The drug may also be in capsule or liquid form.

Intravenous chemotherapy: This can be administered via intravenous infusion or by inserting a needle straight into a vein. The medications can also be administered intrathecally, which involves injecting them into the tissue layers covering the brain and spinal cord, or as an injection into a muscle.

• intra-arterially (IA), injected into the artery that leads to cancer; or as an intraperitoneal (IP) injection, administered directly where the intestines, stomach, and liver are present.

4.1 Targeted Drug Delivery:

Ehrlich first proposed the concept of the "magic bullet" in 1906, which is where the entire drug- focused idea originated. Although the idea's persistence is a significant indication of its attractiveness, finding the "magic bullet" for the clinic remains a difficulty. The three main issues are identifying the target for a particular disease state, locating a medication that effectively treats the condition, and coming up with a plan to take the stable form of the medication while avoiding immunogenic and nonspecific interactions that effectively remove foreign material from the body

[34].Giving a patient medication in a way that increases the amount of that medication in specific body regions relative to other sections of the body is known as targeted drug delivery. In targeted drug delivery, the medication is concentrated in the target tissues while its relative concentration in the other tissues is lowered. The medication is given so that it is only active in the designated location of the body and is then released gradually throughout the body (e.g., colon focused medication). This reduces negative effects and increases efficacy. A medication molecule finds it extremely difficult to navigate the intricate cellular network of an individual to reach its endpoint. Drugs with targeted delivery are more likely to reach the desired area for the medication molecule. Reduction of pharmacological side effects and dosage are two benefits of this approach. In the pharmaceutical industry, research related to the development of tailored drug delivery systems is currently highly valued.[37]

4.1.1 Types of Targeted Drug Delivery System:

Targeting a specific area with a medicine not only increases its therapeutic efficacy but also attempts to lessen its associated toxicity, allowing for the use of lower dosages. For medication

targeting, two methods are frequently employed.[36’37’38].Figure 2 illustrates both active and passive targeted medication delivery diagrammatically.

4.1.1.1 Passive targeting

It refers to medication or a drug delivery system concentrated in a specific area, such as an anti- cancer medication whose cause may be attributed to pharmacological or physicochemical aspectsof the illness.[39]

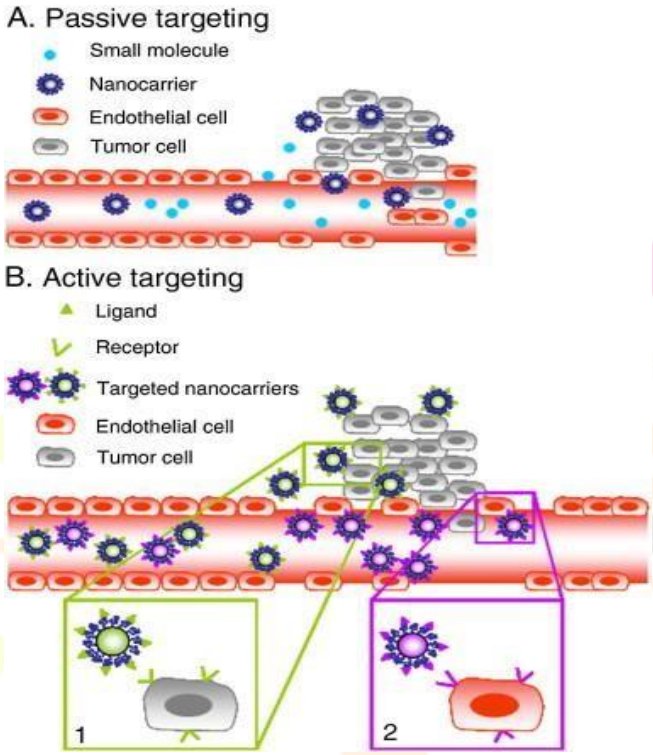
4.1.1.2 Active Targeting

1) The restricted distribution of drug carrier systems to the capillary bed of a fixed organ ortissue

2) Second-order targeting refers to the deliberate administration of medications to certain cell types, such as tumor cells, rather than to healthy cells.

3) Third-order targeting encompasses the delivery of drugs. especially to the targeted cells'intracellular area.[40]

Fig 2: Active and passive targeted drug delivery.



5.1 Targeted Dosage Form Benefits against Conventional Dosage Form

- One sort of treatment that has side effects as well is chemotherapy.
- Consistent use of costly medications and their excipients as well as a drop in productioncosts.
- To achieve a precise medication release.
- Targeted therapy decreases toxicity to healthy cells while being specifically targeted towards cancer cells.
- Medical oncologists now have a better way to customize cancer treatment with targetedtreatments.

6.1 Colon Targeting:

The colon is a location where drugs can be delivered locally or systemically. Local distribution aids in the topical treatment of IBD. If the medications are able to reduce the systemic adverse effects by specifically targeting the colon, the treatment can be rendered more effective.For the local therapy of many intestinal illnesses, targeted

medication delivery is required.[41'42]The medication should be protected by the colon-specific drug delivery system (CDDS), meaning thatit should only release and absorb the medicine once the system enters the colon.

As a result, CDDS protect peptide drugs from hydrolysis and enzymatic degradation in the duodenum and jejunum, releasing the drug into the ileum or colon and increasing systemic bioavailability[43'44]. Moreover, the colon has a lengthy residence time of approximately five days and is highly responsive to absorption enhancers.

Possible routes for colon targeting:

1. Oral route
2. Rectal route

6.1.1 Criteria for Selection of Drug for CDDS:

The best candidates for CDDS are medications, particularly peptides, that exhibit limited absorption from the stomach or intestine. The medications used to treat diarrhea, ulcerative colitis, colon cancer, and IBD are effective when administered locally.[47]

6.1.2 Factors affecting colon targeted drug delivery:

6.1.2.1 Physiological factors

6.1.2.1.1 Gastric emptying:

When taking drugs orally, the colon receives them mostly through the effects of stomach emptying and intestinal transit time. The dose form's transit time within the colon is contingent upon the particle size. In comparison to bigger particles, smaller particles have a longer transit time. Patients with diarrhea had shorter transit times, while those with constipation experience longer transit times

6.1.2.1.2 pH of the colon:

The GIT's various sections have considerably varying pH values. For instance, the pH of the gastrointestinal tract's contents can vary greatly, from the stomach's 1 to 2 to the small intestine's distal 7.5. [43]The pH then gradually rises again in the colon after declining from the end of the small intestine. The creation of colon-targeted medication delivery devices is based on this variation in pH in various GIT regions. To target the medicine to the location, coatings made of various polymers are applied.

6.1.2.1.3 Colonic microflora and enzymes:

Peristalstic motions and the contents of the GIT regulate the growth of this microflora. Relation between the colon's various bacteria and enzymes

6.1.2.2 Pharmaceutical factors

6.1.2.2.1 Drug candidates:

Drugs that are poorly absorbed, such as peptides and medications used to treat inflammatory bowel illnesses, are suitable for use in colon targeted drug delivery systems because of the colon's longerretention period.[46]

6.1.2.2.2 Drug carriers:

The drug's characteristics and the illness it is intended to treat are taken into consideration when choosing a carrier.[46]A few of the several variables that influence the choice of carrier are stability, partition coefficient, and chemical nature.

7.1 Approaches used for Targeted Drug Delivery to Colon:

7.1.1 Liposomes: These are spherically shaped vesicles composed of bilayers of phospholipid. They are regarded as an effective drug delivery method for a range of physicochemical characteristics[47].Liposomes have several advantages as drug delivery vehicles, including the ability to encapsulate hydrophilic and lipophilic medicines as well as their biodegradability, biocompatibility, and other harmless qualities[48].Targeting strategies including the conjugation of ligands to the liposome surface have been thoroughly investigated in an effort to enhance liposomal medication delivery to the tumor location. When anticancer medications are administered to cells, several types of cell death occur. Mitochondria have a key role in many transduction pathways associated with cell death[47].

Apoptosis is essential for responding to regulatory signals, which might come from several sources or be induced by stress. Apoptosis is caused by two main pathways: the extrinsic (death receptor) pathway and the intrinsic (mitochondrial) mechanism. Numerous events, including as intracellular cues like DNA damage, oxidative stress, and growth factor deprivation, can activate the mitochondrial pathway. The binding of death ligands, including as TNF-α and Fas ligand, to death receptors of the TNF receptor super family initiates the extrinsic cascade of apoptosis[46].

7.1.2 Nanoparticles:

The process of creating nanoparticles is straightforward, and these are helpful in protecting protein and peptide medications from enzymatic and chemical destruction in the gastrointestinal tract, which enhances their stability and absorption via the intestinal epithelium. Heat, agitation, and organic solvents are some of the techniques used. One drawback of these techniques is that the heat is damaging the peptide and protein medications[46]. Proteins and peptide medications are treated using the ionic gelation process. The EPR Effect on tumor tissues is the basis for the application of nanoparticles (NPs) in cancer treatment[47].

7.1.3 Monoclonal antibodies:

The atypical cadherin FAT1 has been shown to be a specific marker of colorectal cancer (CRC), and mAb198.3, a monoclonal antibody that specifically targets FAT1, may offer a novel therapeutic approach for CRC. It internalizes well into cancer cells and inhibits the growth of cancer in colon cancer xenograft models. In order to improve the targeted management of colorectal cancer (CRC), we examined the therapeutic efficacy of mAb198.3 in this study using the two drug delivery systems (DDS).[48]

7.1.4 Prodrug:

To release the active drug, the inactive form of an active parent drug undergoes a mostly enzymatic change. A set of procedures were followed in order to synthesize Gal-Dox in a good to exceptionalyield[43].

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