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Review Article

Current Review on Nanoparticles Targeting Colorectal Cancer

Ijaz Sheik[1], Sri Naga Varun Mutte[2], Krishna Prasad Davarasingi[2], Ashok Thulluru[3]*

[1]*Department of Pharmaceutics, Shri Vishnu College of Pharmacy (Autonomous), Vishnupur, Bhimavaram, West Godavari Dist., Andhra Pradesh, India.*
[2]*Department of Ph. Quality Assurance, Shri Vishnu College of Pharmacy (Autonomous), Vishnupur, Bhimavaram, West Godavari Dist., Andhra Pradesh, India.*
[3]*Department of Pharmaceutics, Chhatrapati Shivaji Institute of Pharmacy, Balod Road, Shivaji Nagar, Durg, Chhattisgarh, India.*

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Abstract *- Despite great advancements in therapy, colorectal cancer (CRC) still causes major morbidity and death and is incredibly common around the world. One of the most promising approaches to treating cancer now involves using nanoparticles as a medication delivery mechanism. Targeted nanoparticles may use chemicals differently expressed on tumour cell surfaces to deliver cytotoxic medications to the tumour effectively. In a number of recent studies, different compounds have been used as ligands on the surfaces of nanoparticles to engage with tumour cells and facilitate the delivery of anticancer medicines. We address the prospective use of ligands and cellular targets in possible techniques for the treatment of CRCs and describe new developments in targeted nanoparticles against CRC in this article.*

Keywords *- Chemotherapy, Colorectal cancer, Ligands, stimulation, Targeted nanoparticles.*

1. Introduction

Yearly, 900,000 deaths and 1.80 million new cases of colorectal cancer (CRC) are heading the widespread of cancer and are the second reason for the cancer-connected death rate [1]. Nearly 26% of CRC occurs in the rectum, and 74% of CRC cases are present in the colon [2]. By the epithelial cells, glandular cells existing in the colon, CRC is a type of malignant tumour usually developed [3-5]. Chemotherapy is one of the most obvious treatments utilised for CRC. Coming to the delivery of active chemicals in pharmaceuticals, nanoparticles (NPs) specifically are successful [6].

Compared to the free medication dose, this approach has low side effects and more intra-tumoral delivery [7, 8]. In various cancer treatments, NPs have ranked as the most effective. Targeted nanoparticles have the advantage of expressing the molecules present on the upper layer of tumour cells, imparting an efficacious release of cytotoxic drugs. Numerous works have newly claimed the applications of various moieties as ligands on the upper layer of NPs to link with the tumour cells. Here, we present new progress in targeted approaches to treat CRC [9].

2. Etiology of Colorectal Cancer

Relating to cancer-linked mortality, CRC is obvious and one of the leading causes of cancer. Drastic variation in the lifestyle of the people is also a cause of cancer [10]. Developed countries have made great advancements in the treatment approaches related to CRC and in minimising the deaths associated with CRC. Adding population-dependent evaluation programmes can greatly reduce CRC-related casualties [11]. Even though developed countries have made advancements in the therapy of CRC, the mortality rate due to CRC continues to rise because of western country living style, intake of minimal-fibre content and diet having high-fat values, excessive tobacco smoking, and also lessened physical activity among the population [12,13]. Because of high metastasis and resistance to chemo CRC is identified by poor diagnosis and treatment. Digestion and intake of water, minerals, nutrients and collection of waste are the vital duties of the rectum and colon.

CRC grows gradually. Cells in neoplastic cells have handover on basic epithelial cells due to mutations in critical genes [14]. These mutations start with adenomas and then transform into carcinomas. Tumour development and histopathology are connected by these mutations, which take place step-by-step [15]. Importantly the biggest risk factor in CRC is intestinal inflammation. The relationship between inflammation and CRC is explained in (Figure 1) [16]. In the evolution of CRC, inflammation has many resisting effects. The dendritic cells, which can identify and express antigens, B cells and T cells mediated by the various immune cells, are induced by the antitumour effect in the intestines due to inflammation. Besides innate immunity provided by natural killer cells, neutrophils, Treg γ, δ, T cells also have antitumour effects of inflammation. Eventually, inflammation enhances tumour development enhancement of the tumour-linked immune cells in the tumour microenvironment leading to the production of various inflammatory factors, which increases the proliferation, attack, epithelial-mesenchymal change,

metastasis, angiogenesis and other procedures in tumour cells hence increasing the growth of tumours. The tumour microenvironment and gut microbia play a vital part in the progress of CRC [17]. Poisonous and side effects occur because of low drug availability and are disadvantages of conventional chemotherapy [18]. Effective and safe novel treatments are required for CRC treatment. Improvement of the drug efficacy and lessen adverse effects of the unrestricted drug forms can be achieved by NP-mediated targeted systems [19].

2.1. Various Advantages of NPs as Drug Delivery Systems

1. NP entrapment enhances drug solubility and stability under severe Gastro-intestinal environment;
2. Drug content and half-life in the blood can be improved by formulating into NPs.
3. Formulating into NPs can increase tumour cells' retention effect and permeability [20].
4. Few NP approaches have been studied to minimise the concentration of drugs needed for treatment [21].

3. Molecular Mechanism of Colorectal Cancer

The development of adenoma in the profession of metastatic cancer contains numerous steps. Before the action starts, the generation of dysplastic epithelium causes to disable of adenomatous polyposis coli, a tumour suppressor gene. It accompanies by an alteration of the KRAS gene, which results in forming of adenomas, which finally concludes in the progression of carcinoma due to the sudden change in (PIK3CA) and P53 genes, etc., as presented in (Figure 2) [22]. Most CRCs are adenocarcinomas, cancerous tumours that begin to multiply and discharge mucus and other fluids. Colon cancer is divided into four stages, ranging from 0 to IV, based on histological characteristics. Numerous polyps in the mucosal surface of the colon increase in early levels. After developing, some polyps may become malignant, but in the initial process, polyps transform into tumours and infiltrate the deeper surface of the colon mucosa. In the secondary level, metastases are spread to the outer surface and not to lymph nodes, which is a characteristic of the secondary level. The third level is characterised by the spread of cancer all over the colon and adjacent lymph nodes. It entirely reaches other body organs in the fourth stage, including the lungs, gut, liver, kidney, ovary, and testis, and is thus classified as metastatic colon cancer. This step is exceedingly serious, with only a 3% chance of survival [22].

4. Genetics of Colorectal Cancer

Familiar adenomatous polyposis coli affect nearly 0.5 % of CRC cases. In this case, the adenomo polyposis coli gene (a tumour-suppressing gene) has undergone mutation, which prevents β-catenin breakdown. β-catenin is a transcription factor that has a place in the transmission of signals from E cadherin on cell lining to downstream targets like C-myc, cyclin D1, and PPAR-7 (peroxisome proliferator-activated receptor-7), among others, in the Wingless-Wnt pathway. After transcription, these target genes lead to cell augmentation and transformation. TGF-β (transforming growth factor-beta) is a cytokine superfamily polypeptide. It serves a variety of cellular tasks, including cell proliferation, differentiation, growth regulation, and apoptosis [23]. TGF- β binds to its membrane-bound receptor and phosphorylates it, causing R-SMAD2 and 3 to phosphorylate. While SMAD6 and SMAD7 serve as inhibitors, this group attaches to SMAD4 and changes its location to the nucleus, where the responsive genes are duplicated. TGF-RII mutations are the most obvious modifications in TGF-expressing in CRC cells, and NSAIDs effectively reduce CRC by 40–50% through COX-2 inhibition [24]. Galectin-3 (molecular weight 29 to 34 kDa) and other carbohydrate-binding proteins appear to play a vital role in tumour growth and development, according to mounting data. It is widely expressed in neoplasms, and through contact with particular ligands, it is engaged in various biological steps, including cell proliferation, differentiation, and inflammation. It increases chemotaxis in macrophages, reducing their mobility during the early stages of tube formation. It induces integrin overexpression after binding to its receptor, resulting in endothelial cell movement and adhesion. Galectin-3 is an attribute in pre-mRNA splitting that regulates the cell cycle and prevents apoptosis, possibly through interactions with Bcl-2 group members [25, 26].

5. Approaches for Targeting Colorectal Cancer

Researchers are experimenting with a variety of methods to improve drug penetration across the epithelial membrane of the colon. It could result in medicines being delivered both locally and systemically for the therapy of CRC. Administering chemotherapeutic drugs to the colonic region is beneficial in treating diseases related to the colon because it allows for a high concentration of drugs to be obtained locally while minimising side effects caused by therapeutic release in the upper region of the GIT or systemic absorption. Several formulations and preclinical studies were created for target medications to the colon by oral delivery. It has been grouped into four main methods:

- Drug delivery depends on pH (activated by a change in the local pH).
- Drug delivery depends on enzymes.
- Controlling of distribution of drugs in terms of timing.
- Systems based on pressure (pressure alters through the GIT lumen activates the drug release). Prodrug-based systems, osmotic controlled drug delivery and hydrogel-based systems are some other options. The presented approaches have merits of their own and a few drawbacks. And to overcome these limitations and obtain successful drug delivery to the colon, a combination of more than two approaches is used [27].

6. Therapy of Colorectal Cancer by NPs

Developing nanoparticle-based treatment approaches for cancer therapy has resulted in significant advancements

in pharmacology, reducing cytotoxic drug adverse effects and enhancing effectiveness, solubility, pharmacokinetics, and biodistribution. Various NPs of various forms, dimensions, and chemical moieties have demonstrated significant results in the entrapment of different forms of anticancer drug load involving siRNA throughout the last 50 years [28]. These primary-generation anticancer NPs enter tumour tissue easily, having the advantage of the tumour's vascular and lymphatic drainage's improved penetration and retention impact; this causes NPs to extravagate and accumulate within cancer cells, improving therapeutic efficacy [29]. Platforms based on liposome drug delivery are the most popular, and they were the primary nanocarriers licensed for use in humans by the US FDA [30]. The inner phospholipid bilayer and exterior aqueous phase make up the vesicles capable of encapsulating hydrophilic and hydrophobic medicines. Thermodox, CPX1, and LE-SN38 are liposome-based nanoproducts now in clinical studies for the therapy of CRC; CPX-1 (Irinotecan HCl: Floxuridine) has finished Phase II clinical trials [31].

7. Polymeric NPs

Colloidal systems made up of biodegradable polymers are known as polymeric NPs. These NPs have a number of pros against conventional nanocarrier systems, including good biodegradability and biocompatibility, sustained release, the increased half-life of the drug, and greater drug incorporation [32]. Synthetic polymers such as polycaprolactone (PCL), poly lactic acid (PLA), polyethylene glycol (PEG), poly (caprolactone) / poly (ethylene glycol) and poly (D, L-lactide-co-glycolic) acid (PLGA) are used to make polymeric NPs for cancer treatment [33]. Conventional chemotherapy has a number of flaws, including a lack of specificity for cancer cells, which can cause side effects in healthy cells. As a result, TNF-related apoptosis-making ligand (TRAIL) covalently linked SLN loaded with oxaliplatin were generated (CD-253) Antibody that is monoclonal. Compared to free oxaliplatin, the formulation showed a 1.5-fold increase in immuno-nanoparticle cytotoxicity (4.9μm).In relation to the free medication, the IC50 value of immuno-NPs (4.6 μm) showed an 8-fold decrease in IC50 value. PLGA [poly (lactic-co-glycolic acid)] NPs In mice containing 5-FU for colon cancer targeting, the anticancer impact was improved, as were the survival rates.5-FU-loaded PLGA showed anticancer efficacy and increased apoptosis in HCT-116 and HT-29 colon cancer cell lines on comparing the free 5-FU. The findings revealed that the created technology had a huge amount of potential for cancer targeting [34]. The NPs showed increased absorption in HT-29 cells, indicating to design of a CRC-targeted approach [35]. For CRC treatment, folic acid-altered NPs containing 5-FU synthesised by (Zhang et al.) produced similar results [36]. Using mucoadhesive polymers is another method for improving nanoparticle adhesion to colorectal cells. (Anitha et al.) produced nanocarriers encapsulated with 5-FU and curcumin for colon cancer treatment [37].

8. Lipid-based NPs

Because of their biodegradability, biocompatibility, structural flexibility, and tailorable capability, lipid NPs (LNPs), particularly liposomes, are potential candidates in cancer therapy [38]. Liposomes, core-shell NPs, micelles, solid lipid NPs (SLN), nanodiscs, and cubosomes are the six different types of LNPs. Liposome surfaces are altered by integrating numerous functional subjects. LNPs are frequently employed not only because of their diversity but also because chemotherapeutics, peptides, proteins, DNA, and RNA, can be loaded [39]. The recent advancements and uses of SNPs and liposomes were the emphases of this section. Solid lipid NPs comprise low-melting-point lipids, surface active agents, and co-surfactants [40]. The lipid and surfactant ratios used determine the drug release, magnitude, potential stability, and drug loading of lipid NPs. Drugs having less water solubility are encapsulated as solid lipid NPs. For example, quercetin, an antioxidant present in onions, has powerful antitumour properties over CRC but is poorly soluble in water. (Li et al. 2009) used emulsification and a low-temperature solidification process to create quercetin-loaded solid lipid NPs (QT-SLNs) [41]. The QT-SLNs (hydrophobic drugs) had a longer T_{max} and MRT and better relative bioavailability, showing SLNs are good oral delivery carriers. The ability of these SLNs to target tumour cells was improved, and cellular absorption was enhanced. In vivo tests revealed that SLNs efficiently suppressed primary tumour and metastatic loads while causing less systemic damage. Liposomes are divided into three categories depending on size and lamellarity. These groups include large unilamellar vesicles (LUVs), multilamellar vesicles (MLVs), and small unilamellar vesicles (SUVs) [42, 43]. SUVs have particle sizes ranging from 25 to 50 nm, LUVs have particle sizes of more than 100 nm, and MLVs have particle sizes ranging from 0.05 to 10 m and are made up of multiple-layer phospholipid bilayers. Hydrophilic medications are non-covalently entrapped in liposome core, whereas hydrophobic drugs are contained in the phospholipid bilayer of the liposomes. (Batist et al. 2009) created CPX-1, a new liposome-entrapped formulation of irinotecan with floxuridine that was tuned for therapeutic synergy [44]. The co-delivery device not only successfully contained high drug levels in blood circulation next to systemic administration; it also demonstrated higher antitumour action in suffering patients by CRC. Phase II trials are now underway to assess the efficacy and safety of CPX-1 for the treatment of CRC.

Additionally, several natural lipid molecules have been utilised to synthesise lipid NPs and drug derivatisation. Utilising this technique (Kotelevets et al. 2017) used this approach to create squalene-dependent NPs loaded with cisplatin (SQ-CDDP NP) for oral delivery, significantly increasing cisplatin efficacy [45]. Cisplatin therapy for CRC is accompanied by significant toxicity and a substantial chance of drug resistance [46]. In a nutshell, this technique connected polyunsaturated fatty acids to chemical medications (PUFAs). Such a prodrug could assemble itself in an aqueous medium without needing external adjuvants, resulting in potent antitumour actions.

Finally, because of their biocompatibility, cytocompatibility, and extended functionality, LNPs are the most attractive drug delivery systems. They are suitable for cancer treatment because they enhance medication solubility, delivery effectiveness, and safety.

9. Inorganic NPs

Metal NPs and silica NPs, can be utilised as drugs, imaging agents, gene carriers, sensors and antiseptics [47]. Because inorganic NPs are used for several functions, advances in biomedicines offer a viable opportunity to formulate novel diagnostic and drug delivery systems [48]. Inorganic NPs can be divided into three categories based on the materials employed and their shapes: round gold, mesoporous silica NPs, gold nanocage, gold nanoshell, silver NPs, quantum dots, iron oxide, gold nanorods, carbon nanotubes. A basic inorganic NP is made up of three parts: an inorganic core, tailored protective coatings, and a layer of biological molecules that have been adsorbed. The following diagram depicts the destiny of typical inorganic NPs post-administration (Figure 3) [49]. A general inorganic nanoparticle consists of an inorganic core, an organised surface and biological molecules that are absorbed into the shell. In the degeneration proceeding, the NPs may crumble to separate constituents. Inorganic core would start degenerating early, modifying its physical and surface characteristics. Intracellular degeneration partly removes the modified organic coating. In brief, in the absence of a carbon-based layer, pure inorganic cores will collage in physiological settings. NPs consisting of carbon-based layers show finer biocompatibility and have better cell sticking and cellular intake properties. When incorporated, the physical and surface characteristics of NPs are modified, and their inorganic core has degenerated. The organic layer shall be removed through intracellular degeneration or protein corona alteration. Metal-dependent NPs are extensively utilised for treating CRC, as they are evaluated by great stability and chance of producing on a large scale, limiting organic solvents [50]. The metal-dependent NPs can be tweaked to enhance medication delivery efficiency. Lactoglobulin (-LG) NPs were designed by (Ghalandari et al. 2014) for the delivery systems of oxali-palladium as a metal-based therapy for colon cancer [51]. According to this study, LG NPs comprising oxali-palladium cross-linked to lower methoxyl pectin (LMP) are a viable possibility for improved oral medication transfer for colorectal cancer treatment.

10. Ligand-Conjugated NPs

Focusing NPs on CRC lesion areas is critical for their effective use. Various targeting ligands have been recognised and investigated to encourage the effective targeting of NPs, comprising small compounds, receptors, peptides, antibodies, polysaccharides, DNA, and RNA, as illustrated in (Figure 4) [52-54]. Higher binding and cellular ingestion are aided by improved ligand concentration. In practical NPs, a diversity of ligands are utilised, aptamers, proteins, polysaccharides, peptides, and small molecules. They can be chemically or physically attached to the NPs, or they would be confined to the NPs' constituents before production. These ligands could bind to specific receptors on the membrane of target cells, enhancing NPs consumption and, as a result, therapeutic efficacy is also enhanced [55]. We categorised NPs according to the sorts of changed ligands in this area. Hyaluronan (HA) is a polysaccharide of N-acetyl glucosamine and a -glucuronic acid, one of the external matrix's constituents [56]. Because its receptor, CD44, is upregulated in various cancers, it is a prime suspect for cancer-targeting NPs. HA-NPs-PTC209, a colon melanoma method to administer the BMI-1 inhibitor PTC209, was devised by (Xu et al. 2019). PTC209 distorts the pluripotency of CRC, reducing CRC relapse and metastasis [57]. These HA-modified NPs showed a greater attraction to CRC cells with high CD44/CD168 activity and offered excellent tumour location targeting. Microporous NPs (MSNs) were coupled with poly (ethylene glycol) (PEG), poly (ethylene imine) (PEI), and FA in various combinations[58] by (Desai et al. 2016). The resultant Microspheres were infused with Notch pathway-secretase antagonists for colon chemotherapy. These modified MSNs targeted the colon selectively and were easily internalised by enterocytes, preserving physical and organisational stability in the digestive region.

11. Stimuli-Responsive NPs

Extracellular matrix (ECM), cancer immune cells, neuroendocrine (NE) cells, adipose cells, blood and lymphatic vascular networks, cytokines, stroma, and other signalling moieties are found in the tumour microenvironment [59, 60]. Certain bone marrow-obtained precursor cells migrate to the TME and transform into endothelial cells, pericytes, fibroblasts, and some other stromal cells, accelerating tumour malignancy [61, 62]. TME also plays a chief function in regulating cancer cell metabolism [63]. As a result, in tumour therapy, a deeper comprehension of the interplay between TME, cancer cells, and medicines is critical. Acidity, hypoxia and thermal stability features of the tumour microenvironment are all conducive to developing stimuli-responsive NPs. Because these NPs are ineffective in the bloodstream and under basal conditions, they assure tumour-targeted delivery [64-68]; once they arrive at the tumour location via active or passive targeting, they are engaged, distributing therapeutics in response to TME features, resulting in targeted medication production and less adverse effects. (Figure 5) [69] depicts interactions across stimuli-responsive nanocarriers and TME. NPs will clump together in tumours as a result of both internal and external stimulation. ATP, enzyme, pH, redox and hypoxia are examples of internal stimuli, whereas external factors embrace electronic field, magnetic field, heat, ultrasound and light. The stimuli-responsive increases increased medication flow at tumour-specific locations, allowing for more exact diagnostics and tumour treatment. Drug delivery systems, and imaging, theragnostics can all benefit from stimuli-responsive NPs. They have the ability to modulate the release of drugs, drug and device engagement, ligand availability, shape and size compliance, charge translation, and reactivity to specific

biological molecules due to these features, resulting in increased site-targeted delivery [69]. Basic forms of stimuli-responsive NPs are reactive oxygen species (ROS)-responsive NPs. Self-assembly of MeO-PEGb-PMOT optimised an oral nanotherapy utilising a redox nanoparticle RNP(O) (Vong et al. 2015) [70]. Nitroxide radicals operate as ROS scavengers and are at the heart of RNP(O). In mice, orally directed RNP(O) in conjunction with irinotecan increased therapeutic effects for CAC. Furthermore, RNP(O) given orally was successfully assimilated in cancer cells compared to normal cells, eliminating unwanted adverse and cytotoxicity. For such therapy of CRC, various additional redox NPs have indeed been produced. (Vong et al. 2017) created a silica-based redox nanoparticle (siRNP) capable of scavenging ROS [71]. BNS-22, a hydrophobic anticancer chemical, was also utilised as a new nanocarrier for treating CRC.

12. Targeted NPs for CRC Therapy

Incorporating ligands like aptamers, antibodies, portions of antibodies, peptides, and some other mini molecules on the upper layer of nanoparticles for cell signalling has resulted in a new type of cancer therapeutic nanoparticles with better in vivo accuracy (Figure 6) [72, 73]. These ligands are ingested through chemical fictionalisation during nanoparticle formation or chemical interaction involving ligands and polymers before synthesis. Targeted nanoparticles are ones with ligands on coated surfaces and the ability to detect cells appropriately. Tumours have a small number of biomarkers that act as targets for the nanoparticles. (Graf et al.), for example, produced cisplatin prodrug-loaded poly (d, l-lactic-co-glycolic acid)-block-polyethylene glycol NPs that adhere to the integrin receptor, which is driven largely in tumour-linked endothelial cells during angiogenesis [74].

13. NPs in Imaging and Detection of Colorectal Cancer

NPs can also be utilised in the pre-diagnosis and monitoring of clinical effectiveness. Multiple agents (e.g., radioactive, superparamagnetic), targeting groups, and biocompatible coatings could be used to synthesise NPs [75]. Due to constraints of low molecular-weight gadolinium and metal chelate-based dissimilarity agents, like relatively low selectivity, rapid clearance, and circulation, which is not specific to the extracellular medium, nanotechnology is being used to enhance the high specificity of CRC diagnostics [76]. (He et al.) recently reported lectin core/shell NPs made of iron oxide magnetite and gold (lectinFe_2O_3#Au NP), which may be used for double-modality imaging (T2-weighted MR and x-ray CT) in nude mice with CRC tumours (SW620) [77]. NPs constituted with a core of superparamagnetic iron oxide nanocrystals, connected by quantum dots, and directed with monoclonal antibody attached to CEA-linked cell-adhesion molecules are yet additional approach that had excellent in-vivo potency by MRI, minimal cytotoxicity, and magnificent fluorescence constancy [78]. A new technique that uses near-infrared fluorescence (NIRF) endoscopic detection improves the high specificity of colonoscopy in CRC patients. In research employing a mouse model of coli tis-linked cancer examined using NIRF endoscopy [79], high effectiveness was reported in recognising dysplastic foci with chronically swollen colons. In NIRF endoscopy for CRC cells, (Yang et al.) used folic acid-conjugated chitosan NPs infused with 5-aminolaevulinic acid. In healthy cells, 5-aminolaevulinic acid is a precursor in forming heme groups and quickly transforms into fluorophore protoporphyrin IX. So because breakdown metabolism in cancer cells is longer than in normal cells, protoporphyrin IX accumulates intracellularly, allowing it to be used in NIRF endoscopy and especially on CRC cells that contain the folate receptor [80]. NPs in imaging of colorectal cancer have shown promising results and aided in the early findings of CRC.

14. Conclusion

Although novel diagnostic and treatment approaches are being developed, the prevalence of CRC is rising due to changes in industrial society's lifestyle. Despite this, cancer's poor survival rate may get worse as the disease becomes more common. Promising preliminary findings have come from new research focusing on building functionalised NPs to provide more precise diagnostics and create tailored medicines. NPs are now being used in several clinical studies for CRC. But before they can be sold, the majority of these techniques still need to get through many clinical stages. It follows that more research is required in the preclinical and clinical stages regarding toxicity, bioavailability, biocompatibility, side effects, and cost-effectiveness.

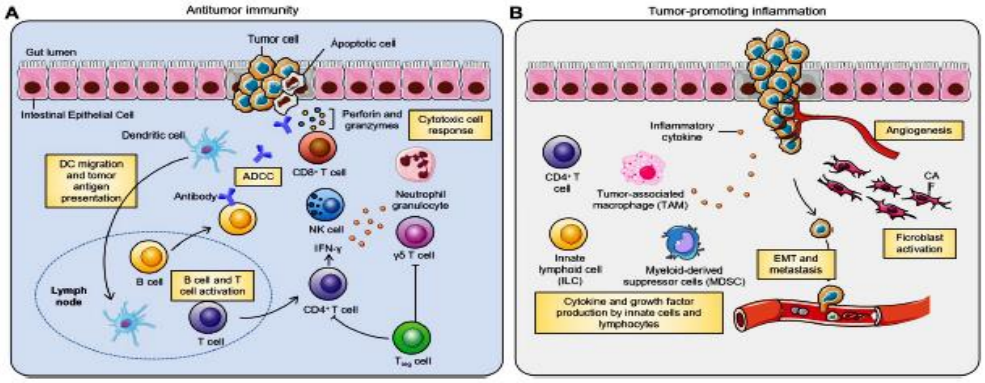

Fig. 1 Role of inflammation in the development of CRC; A. Antitumor immunity and B. Tumor-promoting inflammation

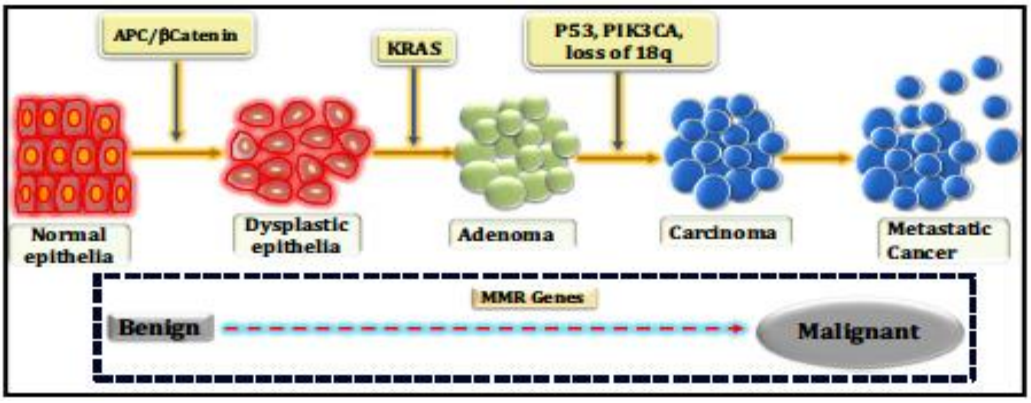

Fig. 2 Gradual transformation of adenoma-carcinoma to CRC

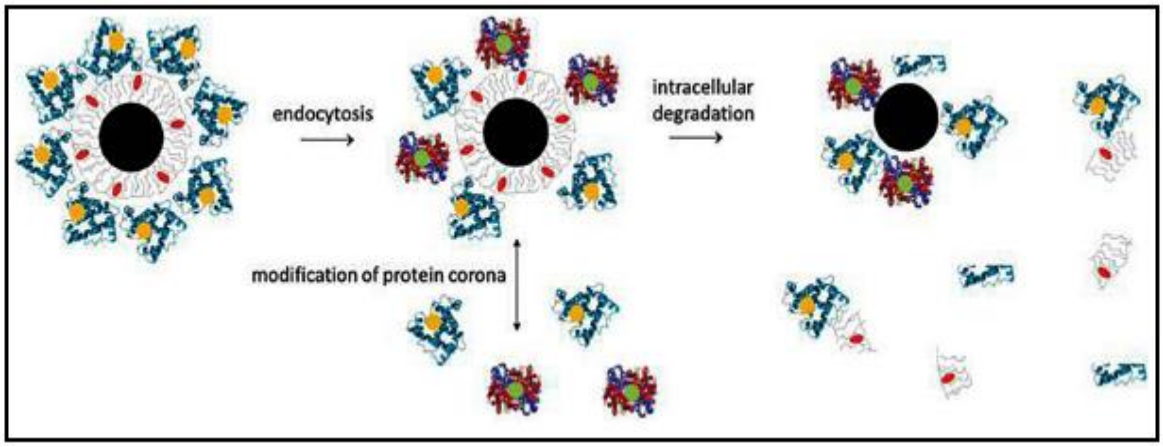

Fig. 3 Formation and *in vivo* degeneration of inorganic NPs

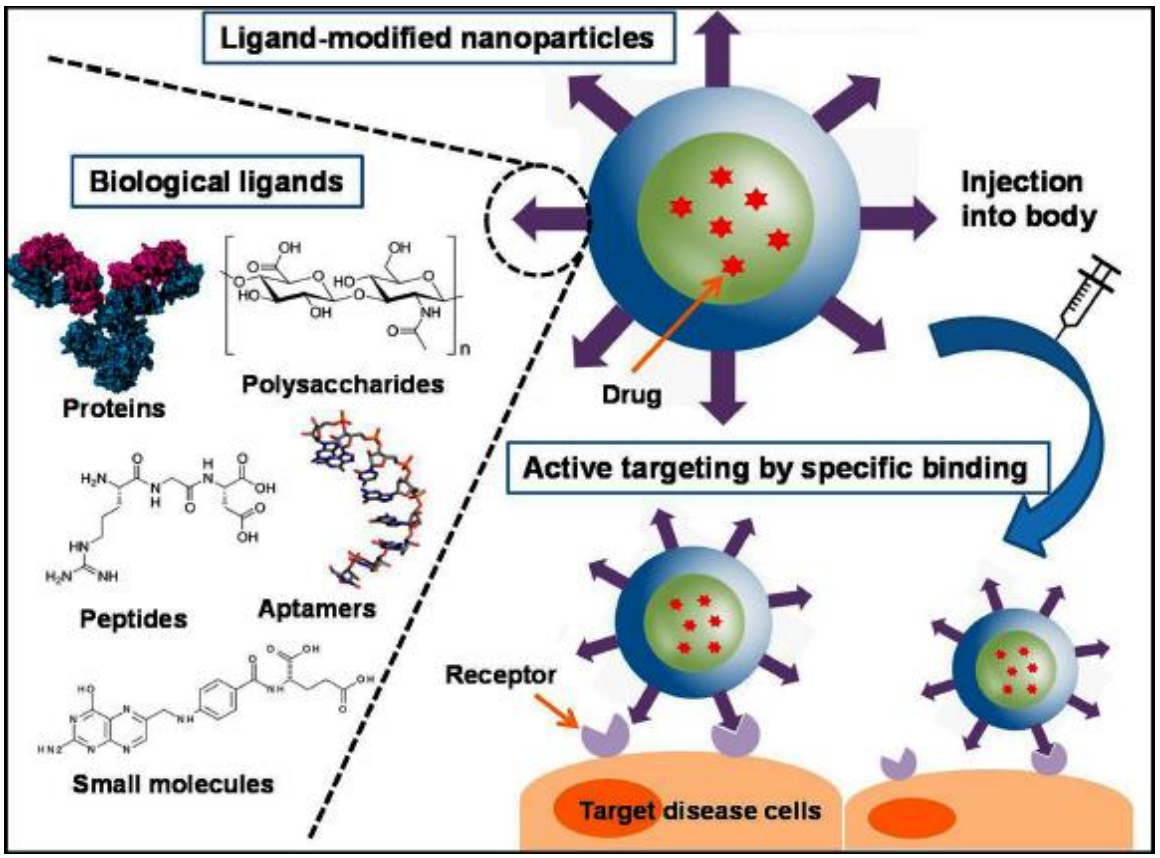

Fig. 4 Numerous forms of ligand-bounded nanoparticles containing various active compounds, as well as their targeting methods (Yoo et al., 2019)

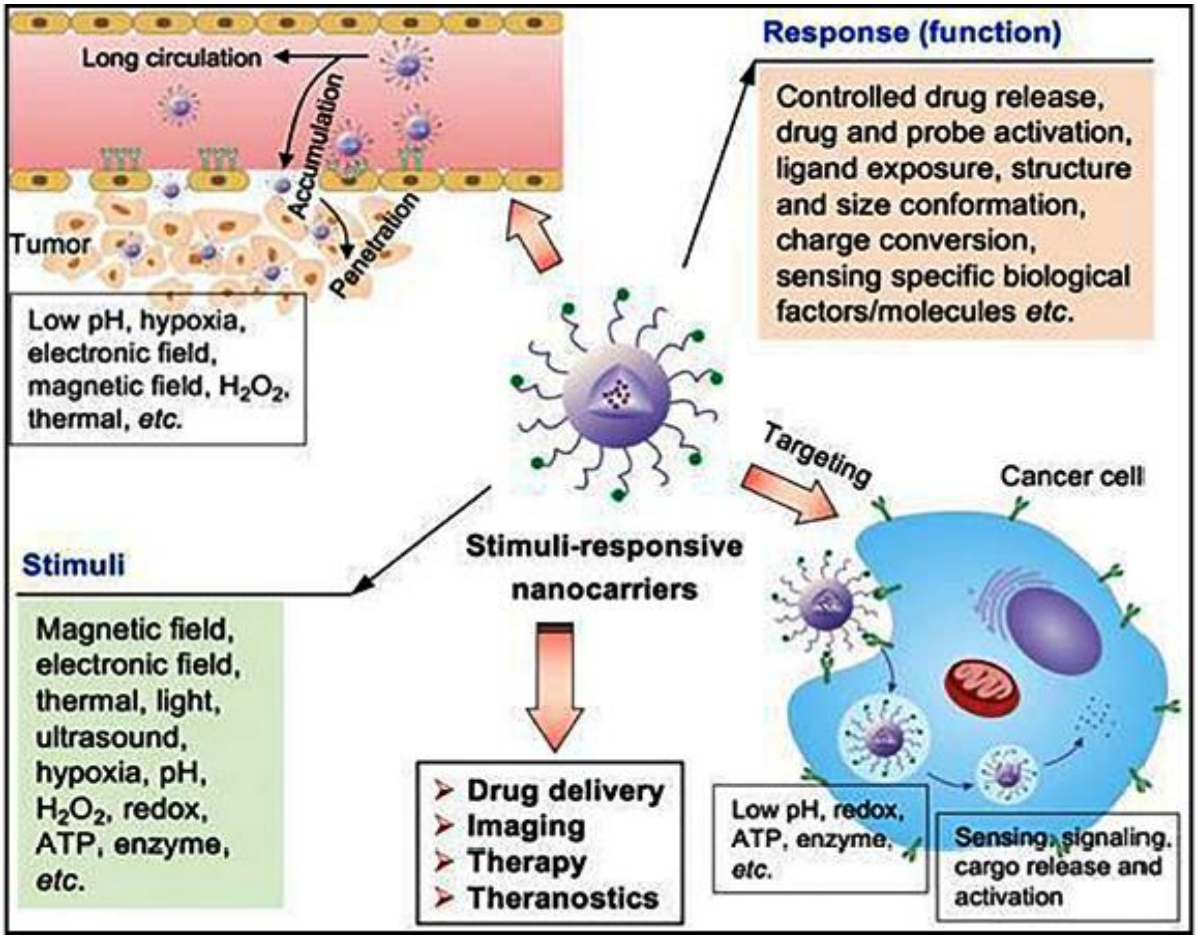

Fig. 5 Different functions of stimuli-responsive NPs

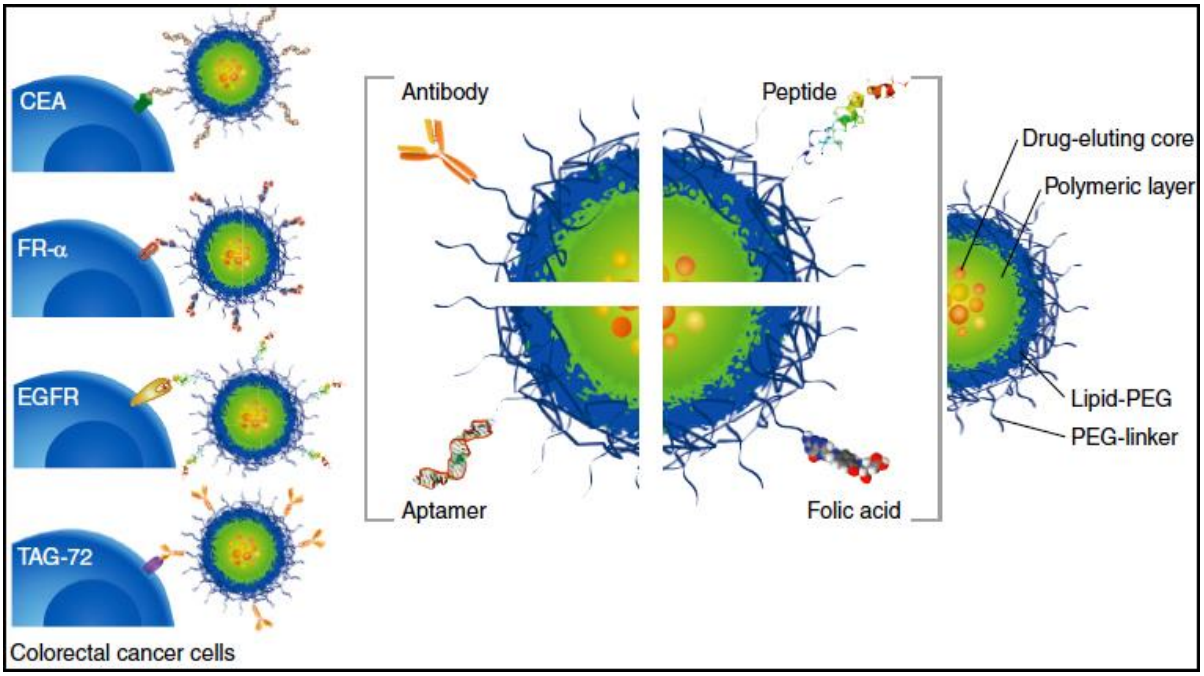

Fig. 6 The usual CRC biomarkers presented on the cellular membrane and the typical molecules/ligands utilised on the upper layer of NPs in targeting approaches

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