Nanoparticle and Targeted Systems for Colon Cancer Therapy

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1 Overview

Cancer is a state where the cells in the body divide without control and are able to invade the adjacent tissues. There are more than 100 types of cancer, including breast cancer, lymphoma, skin cancer, lung cancer, prostate cancer, and colon cancer (Jemal et al., 2011). Colon cancer occurs when malignant tumors arise in the colon, which constitute the last portion of the digestive tract and is nearly 5 ft. long (approximately one-fifth of the whole length of the intestine) (Allman, 2012). The colon participates in water reabsorption that results in the formation of solid feces. Additionally, it serves as a storage site for fecal materials prior to defecation (Tainter, 1954). The development of colon cancer occurs over a period of time. Prior to cancer development, cell overgrowth occurs in the inner lining of the colon, and are called polyps. The chance of cancer development depends on the type of polyp. Adenomatous polyps (adenomas) often develop into cancer (Drew et al., 2016). Hyperplastic polyps and inflammatory polyps are noncancerous (Lal and Gallinger, 2000). The growth of cancer cells begins in the wall of the colon, then spread to the adjacent blood and lymph vessels. The cells then reach the nearby lymph nodes which then metastasize to the distant organs. Colon cancer is the third most common cancer in the world. There are approximately 1.36 million cases worldwide which account for it being the fourth leading cause of cancer-related death (Ng and Yu, 2015). A high incidence of colon cancer has been reported in the west, including North America, Europe, and Australasia, but it is relatively uncommon in Central and South America, Asia, and Africa (Torre et al., 2015). The signs and symptoms related to colon cancer include changes in bowel habits, diarrhea, decreased stool caliber, bloating and abdominal cramps. The more general symptoms include weight loss and loss of appetite (Stokes, 2006).

Several lifestyle factors have been linked to colon cancer including diet, physical inactivity, obesity, smoking, and heavy alcohol consumption. Type 2 diabetes also contributes towards an increased risk of developing colon cancer (Hu et al., 1999). Some factors, such as working night shifts and previous treatment for other cancers, have less clear associations with developing colon cancer (Schernhammer et al., 2003). Age is one
of the important risk factors since more than 90% of colon cancer cases occur in people above 50 years. In addition to these, inflammatory bowel diseases, such as ulcerative colitis and Crohn’s disease, are also important risk factors for colon cancer (Ananthakrishnan et al., 2016). Ulcerative colitis causes chronic inflammation of the mucosal lining of the colon and rectum. Crohn’s disease causes full thickness inflammation of the bowel wall which may involve any part of the digestive tract (Rani et al., 2016). Inflammatory bowel disease contributes to 2% of colon cancer cases every year (Mattar et al., 2011). Patients with Crohn’s disease have 2% chance of developing colon cancer after 10 years, 8% after 20 years and 18% after 30 years; patients with ulcerative colitis have 16% chance of developing colon cancer after 30 years (Munkholm, 2003). Nearly 5% of colon cancer cases are hereditary (Jasperson et al., 2010). Genetic syndrome is accompanied with a high rate of cancer incidence. Hereditary nonpolyposis colorectal cancer (HNPPC or Lynch syndrome) contributes to approximately 3% of all cases of colon cancer in which 1% of the cases has a strong association with Gardner syndrome and familial adenomatous polyposis (FAP) (Piñol et al., 2005). Most colon cancer-related deaths are associated with metastasis. A MACC1 gene appears in metastatic colon cancer. Colon cancers can be prevented by lifestyle modifications. Several lifestyle factors including high consumption of fruits, whole grains, and vegetables and a reduced intake of red meat can prevent development of colon cancer (McCullough et al., 2003). Regular exercise and maintaining normal body mass index (BMI) could also help to reduce the risk of colon cancer.

Regular screening can easily be used to detect colon cancer which, if detected early, is mostly curable. Some polyps or growths can be removed before they turn malignant. Guaiac-based fecal occult blood test (gFOBT), fecal immunochemical test (FIT), stool DNA test, sigmoidoscopy, colonoscopy, double contrast barium enema, and CT colonography are screening tests for colon cancer or polyps (Burt et al., 2010). Screening tests can help to identify the presence of polyps. In many cases, colon cancer is only found after the symptoms appear, as an early stage usually presents with no symptoms. Symptoms usually appear in more advanced stages. The test modalities that can be used to detect the presence of colon cancer include ultrasound, microsatellite instability (MSI) test, computed tomography (CT or CAT) scan, magnetic resonance imaging (MRI) scans, positron emission tomography (PET) scans, and angiography (El Zoghbi and Cummings, 2016). Colon cancer can also be detected by fecal occult blood test (Hemoccult FOBT) and analysis of urinary volatile organic compound (Kershenbaum et al., 2013). A diagnosis of colon cancer can be made by identifying the specific markers, for example, carcinoembryonic antigen (CEA) and cancer antigen (CA 19-9) (Wang et al., 2014). The extent of cancer metastasis can be determined by a computed tomography (CT) scan. Meanwhile, a tumor node metastasis (TNM) system can be used to predict the cancer-spread area and the area of lymph node involvement. Colon cancer is usually confirmed by colonoscopy which depends on the location of the lesion. Colonoscopy is a safe procedure but has a risk of perforation (Sung et al., 2003). The biopsied samples will be taken and analyzed for the histopathological changes which include cell types and grades. The tumor lesion usually has an irregular tubular structure with multiple lumens and reduced stroma. Occasionally, a tumor secretes
mucus. Immunostaining can be used to confirm colon cancer cells by detecting the presence of specific antigens (Van Rossum et al., 2008).

Surgery can be curative when colon cancer is detected at an early stage. The type of surgery depends on the type of tumor. Early screening of colon cancer can be made by colonoscopy, which can also be used to remove early cancer lesions (Robertson et al., 2014). Polypectomy is a procedure which is performed to remove the small polyps in the inner lining of the colon (Raju and Pasricha, 2005). In local excision, a portion of the colon can be removed. In total colectomy, the whole colon is removed. The common complications of colon surgery include changes in bowel habit, bleeding, and infection. Cancer may not be completely cured even after surgery. In these cases, treatments such as radiation therapy, chemotherapy, and so on can be used to reduce cancer progression. Radiation therapy uses high-energy X-rays, electron beams, or radioactive isotopes that destroy the cancer cells and is mainly used when the cancer cells are attached to visceral organs or in the lining of the abdomen or when cancer cells spread to bones or brain. The radiation therapy for colon cancer produces side effects which include skin irritation, nausea, rectal irritation, hair loss, fatigue, and sexual dysfunction. Chemotherapy is another modality for treatment where anticancer drugs could be used to inhibit or slow the growth of dividing cancer cells. Chemotherapy may be used at different times during the treatment of colon cancers (Chabner and Roberts, 2005). Adjuvant chemotherapy is used postsurgery to remove the cancer. In neoadjuvant therapy, treatment is given before surgery to shrink the cancer in order to make surgery easier. Several drugs can be used to treat colon cancer which includes capecitabine, fluorouracil, irinotecan, oxaliplatin, and 5-fluorouracil (5-FU) (Grothey et al., 2004). The common complications of chemotherapy include hair loss, mouth sores, loss of appetite, nausea, vomiting, and low blood cell counts (Almeida et al., 2004). Targeted cancer therapies or molecular-targeted drugs that impede the growth and spread of cancer interfere with specific molecules that are involved in cancer’s growth, progression, and spread (Nelson and Benson, 2013). The targeted drugs work differently from chemotherapeutic drugs. Nowadays, numerous targeted cancer therapies (Fig. 25.1) such as nanotechnologies can be used.

2 Cancer Nanotechnology

Nanotechnology is a new revolution in cancer therapy, “nano” refers to nanometer, which is a billionth of a meter. In a single nanometer, ten hydrogen atoms can be laid side by side. Nanotechnology is a technology that is engineered to create useful materials, devices, and systems through the manipulation of atomic, molecular, and supramolecular materials (Calixto et al., 2016). Nanotechnology is a very broad area which involves scientists from different fields, including physicists, chemists, engineers, and biologists. Cancer nanotechnology is an emerging new field that has the potential to improve cancer imaging, early diagnosis, treatment, and prevention. A wide variety of nanomaterials is currently under investigation that contribute towards the development of cancer nanotechnology, such as polymers, dendrimers, lipids, organometallic, and carbon-based materials
(Tan and Wu, 2016). Nanomaterials for various cancers types have wide applications depending on their biocompatibility, toxicity, size, and surface chemistry. Nanoparticles have unique properties as therapeutic or diagnostic tools. For example, iron core and gold shell nanoparticles carrying specific markers for cancer stem cells can bind specifically to the stem cells of cancer for early detection (Wu et al., 2011). Nanoparticles also have the ability to attach to multivalent targeting ligands with a high affinity and specificity for the target cells. Nanoparticles can be made to accommodate multiple drug molecules that simultaneously allow combinatorial cancer therapy. The nanoparticles are also able to pass the traditional drug-resistant mechanisms (Azhdarzadeh et al., 2016). Nanoparticles are created by two basic approaches: top-down or bottom-up. In the top-down approach, materials are molded and etched into smaller components while in the bottom-up approach, materials are assembled atom-by-atom or molecule-by-molecule (Choi et al., 2008).

### 3 Classes of Nanomaterials

Because the diameter of animal cells ranges between 10,000 and 20,000 nm, nanoscale devices (usually less than 100 nm) can easily enter the cells and organelles and interact with DNA and proteins (Cabeza et al., 2016). Due to this characteristic, nanomaterials can
be used for cancer detection, diagnosis, and treatment. Detection of early-stage cancer can help to improve prognosis and to decide on the best treatment modalities. Due to the advent of nanotechnologies (Fig. 25.2), cancer diagnosis has improved substantially. Among the nanocompounds used in the detection, diagnosis, and treatment of cancer are nanoshells, nanotubes, quantum dots, and dendrimers (Wang, 2016). Nanoshells are spherical-shaped nanoparticles consisting of a dielectric core and a metal shell (usually gold) to improve the biocompatibility and optical absorption. In nanoshells, the antibodies first attach to the polyethylene glycol (PEG) and antibody-PEG complex, then easily attach themselves to the nanoshells that specifically recognize and target the cancer cells (Liu et al., 2016). The nanoshells successfully kill the cancer cells while leaving the normal neighboring cells to generate the heat by absorbing the light. Nanotubes are long, thin cylinder layers made up of a distinct atomic arrangement of carbons in molecular form. Recently nanotubes have become popular tools due to their unique physiochemical properties and better drug delivery (Rastogi et al., 2014). Nanotubes can be used to overcome the physiological barriers, namely, the heterogeneous permeability of tumor vessels, interstitial compartment, and plasma membrane. Nanotubes have a high capacity for detecting cancers. Nowadays researchers pay much attention towards developing carbon nanotube devices which can detect a single cancer cell. In addition, nanotubes have various biomedical applications including acting as drug-delivery carriers for biological imaging, photothermal agents, neural prosthetics, and artificial muscles (Heister et al., 2013). Recently, single-walled carbon nanotubes (SWCNTs) have been designed as drug carriers due
to their salient properties, including high surface area, high aspect ratio, and unique cylindrical structure (Chen et al., 2008). Studies in human epithelial colorectal adenocarcinoma cells showed that paclitaxel, an anticancer drug formulation with SWCNTs, exhibited the extraordinary ability to envelop hydrophobic materials and enhance their water solubility. Carbon nanotubes can be used to modify cetuximab (C225), a chimeric monoclonal antibody (mAb) and epidermal growth factor receptor (EGFR) inhibitor which is used in the treatment for metastatic colorectal cancer (Ciardiello and Tortora, 2008). Carbon nanotubes with C225 can be an effective carrier for specific transport of anticancer drugs into the epidermal growth factor receptor (EGFR)-expressing colon cancer cells. Multiwalled carbon nanotubes (MWCNTs) can also act with ATP-binding cassette (ABC) transporters, which are an integral membrane family of proteins in which overexpression can cause cancer-drug resistance (MDR) that frequently leads to the failure of chemotherapy (Wang et al., 2015). MWCNTs reduce the transport activity and expression of ABC transporters including ABCB1/Pgp and ABCC4/MRP4 in human colon adenocarcinoma Caco-2 cells. Meanwhile, single-walled carbon nanotubes (SWCNT) can be used to attach to anticancer drug cisplatin which could help to increase their therapeutic activity. This could also serve as a highly promising drug-delivery platform that targets C26 colon carcinoma, as shown in a BALB/c mice model (Kazemi-Beydokhti et al., 2014).

Quantum dots are tiny, crystal semiconductors commonly made with cadmium selenide and capped with zinc sulfide (CdSe/ZnS) (Cingarapu et al., 2012). Upon stimulation by ultraviolet light, quantum dots glow with the wavelength and color of the light produced dependant upon the size of the crystal. Probes that are released have distinct colors and light intensities that can help to identify a particular region of DNA (Alibolandi et al., 2014). Probes can be created by using combinations of different quantum dots within a single bead. Quantum dots have been designed to bind the sequences of DNA that are associated with cancer. The use of near-infrared (NIR) quantum dots can maximize depth of tissue penetration, allowing accurate and sensitive detection of photons in vivo (Cheng, 2004). Quantum dots have advantages over conventional imaging which is usually limited due to absorption and light scattering. Quantum dots can also be used to detect and quantify biomarkers for colorectal cancer which are usually done by immunofluorescence. Fluorescence images can be clearly labeled with core–shell quantum dots made of a zinc oxide (ZnO) semiconductor and coated with titanium oxide (TiO₂) (Ali et al., 2014). Antibody-coated quantum dot (Ab-QDs) probes show rapid and accurate molecular fluorescence images of colon cancer tissues which subsequently excited (Park et al., 2014). These probes can detect not only cancerous cells, but also hyperplastic and adenomatous regions of cancer lesions. Meanwhile, circulating colorectal cancer cells in the body fluids can be distinguished by using antibody-specific molecules, for example, monoclonal cytokeratin 19 which is incorporated with cadmium selenide quantum dots. The detection signal is usually acquired from the fluorescence signal of the quantum dots (Gazouli et al., 2012).

Dendrimers are a class of novel polymers defined by core and branched units. Dendrimers are a new class of emerging therapeutic and diagnostic agents (Stanczyk
et al., 2012). A single dendrimer molecule can carry a diagnostic agent, a therapeutic drug, and an active targeting molecule. Dendrimers with a hydrophobic core and hydrophilic surface are able to form micelles through hydrophobic/hydrophilic self-assembly (Wolinsky and Grinstaff, 2008). In colon cancer, dendrimers can be used to transport drugs into specific areas and at the same time monitor the state of the organs attacked by the cancer cells. Dendrimers can also be used to monitor progress during the curing process. PEGylated dendrimers are a subclass of dendrimers that possess lower toxicity levels and have lower tissue accumulation; PEGylated dendrimers can also be designed to carry drugs through blood circulation. Due to its solubility, PEGylated dendrimers can release drugs through pH-sensitive hydrazone linkages (Guillaudeu et al., 2008). Dendrimers conjugated with the anticancer drug doxorubicin (DOX) can be used to modulate the pharmacokinetics of this drug and has been reported able to cure mice bearing C-26 colon carcinomas (Lee et al., 2006). Polyamidoamine (PAMAM) dendrimers contain tertiary amines and amide linkages. This structure allows it to bind to numerous target and guest molecules. PAMAM dendrimers can act as carriers for anti-EGFR and c-Src specific antisense oligodeoxynucleotides in a single formulation (Nourazarian et al., 2012). This formulation shows considerable effect in halting the growth of colon cancer via down regulating EGFR and its downstream genes. Liposomes are another example of a nanocompound. An example is a liposome-modified PAMAM which is synthesized from liposome and polyamidoamine dendrimers. Liposome-modified PAMAM mixed with plasmid PEGFP-N1 can form nanoparticle complexes that can be used to target colon cancer cells (Nourazarian et al., 2012).

4 Nanoparticle-Based Colon-Specific Drug Delivery

The delivery of drugs to the target site is a major problem in the treatment of cancer. A conventional application of drugs is considered limited due to their ineffectiveness, poor biodistribution, and lack of selectivity. The colon is the preferred absorption site for many oral protein and peptide drugs due to its relative low proteolytic enzyme activities. Insulin, calcitonin, and vasopressin were reported to be absorbed in the colon. However, the intrinsic permeability of peptide and protein drugs across the colon luminal epithelium is poor. Absorption enhancers have been utilized to facilitate the transport of peptide and protein drugs across the colonic epithelium (Wilczewska et al., 2012). Nanoparticles play an important role in enhancing drug absorption and specific drug delivery to the site of colon cancer. Nanoparticles can overcome the aforementioned limitations due to their small size, biocompatibility, nontoxicity, and unique physicochemical and biological properties (Cho et al., 2008). The cancer target therapy depends on the way drugs are conjugated to the nanocarrier either by adsorption or covalent attachment to the nanocarrier surface. Once a drug nanocarrier reaches the cancer site the therapeutic drugs will be released. The controlled release of drugs from the nanocarriers can be modified through alterations in the physiological environment such as temperature, pH, osmolality, or enzymatic activity.
Liposomes are the most common vehicle used for targeted drug delivery. Liposomes are lamellar phase phospholipid vesicles (50–100 nm) used for therapeutic and diagnostic applications. They are amphiphilic in nature and can carry both hydrophobic and hydrophilic drugs (Sercombe et al., 2015). Furthermore, liposomes show outstanding circulation, penetration, and diffusion properties and their surface can be changed with ligands to increase drug-delivery capacity (Allen and Cullis, 2013). Liposomes are also vehicles for antibodies in the targeted delivery and enhancement of target-specific drug therapies for cancer agents. Currently doxorubicin (Doxil) and daunorubicin (Daunoxome) are marketed as liposome-mediated drug systems (Chang and Yeh, 2012). Integrinβ6 (ITGB6), which is expressed in malignant colon epithelia, is also a target for immunoliposome (iL)-drugs. ITGB6-targeted iLs has ITGB6 monoclonal antibodies (mAbs) for targeting drug delivery to colon cancer (Liang et al., 2015). The liposomes are also entrapped within drugs with poor water solubility such as curcumin. Small quantum dots, liposomes, silica, and polystyrene nanoparticles can be incorporated into liposomes for various applications. These hybrids have increased survival time in the bloodstream and can easily detect a carcinomatous colon. pH-sensitive dPEGylated liposomes can act as drug carriers and show enhanced intracellular delivery to colon cancer cells (Dhule et al., 2012).

Hydrogels are a crosslinked network of polymer chains that easily disperse in an aqueous solution. Hydrogels have several characteristics which make them excellent drug-delivery carriers (Hoare and Kohane, 2008). Hydrogels are prepared by using many polymers including polyacrylic acid (PAA), polyhydroxyethylmethacrylate (PHEMA), polyethylene glycol (PEG), and polyvinyl alcohol (PVA). These polymers have mucoadhesive and bioadhesive characteristics that improve drug residence time and tissue permeability. Hydrogels have dual properties that support the material for cells during tissue regeneration as well as act as a drug-delivery payload (Hamidi et al., 2008). Superparamagnetic chitosan-dextran sulfate hydrogels release specific drugs into the colon, an environment rich in bacterial enzymes that degrade chitosan-dextran sulfate and allow the drugs to be released (Saboktakin et al., 2010). A novel pH-sensitive swelling and enzymatic degradable colon-specific hydrogel (Dex-MA-SA) which is produced by photo crosslinking can potentially be used as an oral treatment system for colonic cancer. Hydrogel nanoparticles can be synthesized from free radical polymerization using N,N-methylene-bis-acrylamide (MBA) as a crosslinker, potassium persulfate as reaction initiator, and therapeutic drug 5-fluorouracil (5-FU) that able to degrade in the colon (Ray et al., 2008).

Polymeric micelles are very useful to overcome the problem of bioavailability following oral administration of anticancer drugs due to reduced absorption. They are also useful to counter the challenging concern of intravenous administration of these drugs (Oerlemans et al., 2010). Polymeric micelles are nanoscopic core/shell structures formed by amphiphilic block copolymers; they are the best alternative drug carriers and have several advantages over other nanosized drug-delivery systems. Polymeric micelles are important for carrying insoluble drugs and delivering the drugs via percutaneous lymphatic delivery or extravasation from blood vessels into the tumor tissue (Xu et al., 2013). Curcumin encapsulated in monomethoxy poly (ethylene glycol)-poly(ε-caprolactone) (MPEG-PCL)
micelles through a single-step nanoprecipitation method, which create curcumin-loaded MPEG-PCL (Cur/MPEG-PCL) micelles is an example of an excellent intravenous injectable aqueous formulation that improves the water solubility of hydrophobic drugs (Yang et al., 2015). Cur/MPEG-PCL micelles formulation can inhibit the growth of colon cancer via inhibiting angiogenesis and directly killing the cancer cells (Gou et al., 2011). Natural flavonoid fisetin (3,3′,4′,7-tetrahydroxyflavone) has been discovered to possess antitumor activity. Due to its poor water solubility, intravenous administration seems to be difficult. In order to overcome this problem, nanoassemblies of fisetin via a self-assembly procedure involving the monomethyl poly(ethylene glycol)-poly(ε-caprolactone) (MPEG-PCL) copolymer which form fisetin micelles has been shown to enhance cancer apoptosis as well as act as an antiangiogenesis agent in the treatment of colon cancer (Chen et al., 2015). Polymeric micelles also allow the intracellular delivery of hydrophobic compounds (prednisone, retinoic acid, and doxorubicin) without causing cellular toxicity. Micelles can also act as a novel gene carrier which delivers the S-T34A gene in the treatment of colon cancer (Duan et al., 2012).

5 Nanotherapies for Colon Cancer

Nanotherapies are targeted approaches for colon cancer treatment. Several molecules can be directly targeted by nanodrugs which include angiogenesis molecules. Tumor angiogenesis is an important process that delivers blood, oxygen, and nutrients to the rapidly proliferating cells. This process is controlled by proangiogenic and antiangiogenic factors. The regulatory factors include vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), angiogenin, transforming growth factor (TGF)-α, TGF-β, tumor necrosis factor (TNF)-α, platelet-derived endothelial growth factor, granulocyte colony-stimulating factor, placental growth factor, interleukin-8, hepatocyte growth factor and epidermal growth factor (EGF) (Geng et al., 2013; Jary et al., 2015; Pardali and Moustakas, 2007).

Binding of VEGF-A to a VEGF receptor (VEGFR)-2 is believed to be the key signaling pathway in mediating angiogenesis. An angiogenesis inhibitor (antiangiogenesis) is a substance that inhibits angiogenesis. Angiogenesis inhibitors have been used to treat cancer effectively. For example, bevacizumab (Avastin) is the most widely used angiogenesis inhibitor as it is an antivasculare endothelial growth factor monoclonal antibody that specifically recognizes and binds to VEGF (Pavlidis and Pavlidis, 2013). When VEGF attaches to bevacizumab, VEGF is not able to activate the VEGF receptor. Human colorectal tumors produce VEGF and its expression is upregulated by cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2), and directly correlates with neoangiogenesis (Huang et al., 2005). Oxaliplatin, fluoropyrimidines, and VEGF drugs work in synergy and are very effective in the treatment of advanced colon cancer (Bonetti et al., 2014). Other angiogenesis inhibitor examples are sorafenib and sunitinib, which bind to receptors on the surface of endothelial cells or other proteins in the downstream signaling pathways while blocking their activities (Choueiri et al., 2010). Nanoparticles can be designed to target VEGFR. Gold
nanoparticles specifically bind to VEGF and cause inhibition of endothelial cell proliferation. Silver nanoparticles (Ag-NPs) also inhibit VEGF-induced cell proliferation, migration, and capillary-like tube formation in bovine retinal endothelial cells; for example, pigment epithelium-derived factor (PEDF) through PI3K/Akt signalling pathways (Gurunathan et al., 2009).

Epidermal growth factor receptor (EGFR) is a cell surface tyrosine kinase transmembrane receptor family, which includes Her-2/new, EGFR3, and EGFR4. Impairment of the physiological regulatory mechanism of EGFR occurs in many ways including genetic mutation, gene amplification, protein overexpression, structural rearrangement, and autocrine ligand production that leads to constant activation and results in tumors (Roskoski, 2014). The presence of EGFR on cancer cells has led to the development of anticancer therapeutics called EGFR inhibitors, which are effective orally. Cetuximab and panitumumab are both IgG1 monoclonal antibodies (moAb) that specifically attack EGFR (Kim and Grothey, 2008). Therefore, binding leads to inhibition of the downstream effect, including k-ras and interfering with tumor cell proliferation and drug resistance.

EGF can also be used in cancer detection. EGF can be labeled with an infrared (NIR) fluorophore to produce a fluorescently quenched EGF-based nanoprobe (EGF-NP) (Ryu et al., 2013). An EGFR-specific antibody molecule (Eaff) labeled with near-infrared (NIR) dye IRDye800CW maleimide can be used as a molecular imaging agent for EGFR-overexpressing tumors (Gong et al., 2010). Cetuximab-conjugated with magneto-fluorescent nanoparticles (MFSN-Ctx) can specifically target EGFR-expressed colon cancer. The near-infrared fluorescent molecule indocyanine green (ICG) and cetuximab monoclonal antibody for EGFR, which attach to liposomes and show specific tumor cell-recognizing ability, is useful for imaging, evaluation, and diagnostic purposes. EGF can be conjugated to carboxymethylidextran (CMDx)-coated iron oxide magnetic nanoparticles to obtain magnetic nanoparticles that target EGFR. Another nanoparticle, O-carboxymethyl chitosan (O-CMC), conjugates with cetuximab and exhibits better selectivity for targeting cancer cells and contributes to enhanced cancer cell death in EGFR overexpressing cancer cells (Fig. 25.3).

Monoclonal antibody therapies (mAbs) are a relatively new revolution in cancer treatment. A monoclonal antibody specifically binds to a target protein in cancer cells (Adams and Weiner, 2005). Anticancer monoclonal antibodies are targeted against cancer cells via several mechanisms (Scott et al., 2012). A naked mAbs—for example, trastuzumab—is an antibody with no drug or radioactive materials attached to human HER2 proteins in colon cancer. This prevents expression of HER2 proteins on the surface of cancer cells and prevents cancer growth (Seo et al., 2014). Trastuzumab binds to HER2 proteins and inhibits the cells from becoming active (Blok et al., 2013). Afatinib (BIBW 2992), an irreversible EGFR/HER2 inhibitor, has been shown to be effective in eliminating cancer cells (Solca et al., 2012). The afatinib-encapsulated micelles displayed higher cytotoxic activity and are effective in suppressing colon cancer cell growth. mAbs can be combined with chemotherapy drugs or radioactive particles to produce conjugated monoclonal antibodies which circulate in the body and bind to the target antigen. Radiolabeled antibodies have
small radioactive particles that are conjugated to mAbs. Carcinoembryonic antigen (CEA) and B72.3 murine antibodies labeled with 131I have been found to exhibit antitumor effects in the colon (Buchegger et al., 1989). Chemos-labeled antibodies are powerful chemotherapy drugs that are attached to mAbs, and are also called antibody–drug conjugates (ADCs). ADCs have the ability to harness mAb specificity and target the delivery of cytotoxic agents to the tumor that may significantly enhance both mAb and drug activities.

The CD105 antigen (endoglin) is a transmembrane glycoprotein and coreceptor for transforming growth factor β (TGF-β). TGF-β and CD105 antigen are overexpressed in cancer cells (Nassiri et al., 2011). The anti-CD105 mAbs can inhibit angiogenesis and prevent the growth of cancer cells. TRC105 is a human/mouse chimeric anti-CD105 mAb used for the treatment of cancer (Fonsatti et al., 2003). 64Cu-labeled PEGylated nano-graphene oxide (GO) covalently linked to a chimeric monoclonal antibody TRC105 is a suitable agent to detect cancer cells. Meanwhile, iodine 131-labeled mAbs A33 (131I-mAb A33) which can
be administered intravenously to colon cancer patients has been found to show modest antitumor activity (Welt et al., 1994). Tyrosine-kinase (TK) inhibitor is a pharmaceutical drug that blocks tyrosine kinases. Tyrosine kinase has a role in modulating growth-factor cell signaling via catalyzing the transfer of the phosphate group from adenosine triphosphate to target proteins (Arora and Scholar, 2005). Tyrosine kinase plays important role in diverse regulatory process in cells. The TK inhibitor, a small molecule, is orally active that can easily combine with other forms of chemotherapy or radiation therapy and competes with the ATP binding site of the catalytic domain of several oncogenic tyrosine kinases (Morabito et al., 2006). Numerous TK inhibitors have been reported to have antitumor activity and are an important class of new, targeted therapies to interfere with specific cell-signaling pathways. Oral treatment with the TK inhibitor AEE788 effectively reduces the number of peritumoral lymphatic vessels and the incidence of lymph node metastasis in nude mice with human HT29 colon cancer cells growing in cecum by direct inhibition of lymphatic endothelial cell signaling (Goudar et al., 2005). The multi-TK inhibitor E7080 (Lenvatinib) showed antitumor activity against colon cancer. Regorafenib is an orally administered multikinase inhibitor that is also useful in the treatment of colon cancer by nonspecific binding to several intracellular kinases, with potent inhibitory activity against VEGFR 1-3 and mutant oncogenic kinases KIT, RET, and BRAF (Takigawa et al., 2016).

Phosphatidyl-inositol 3-kinase is a phosphorylated lipid produced on cellular membranes through signaling events and contributes towards the recruitment and activation of various signaling compounds (Carpenter and Jiang, 2013). Phosphoinositide 3-kinase (PI3K) enzymes are involved in cellular functions including cell growth, proliferation, differentiation, motility, survival, and intracellular trafficking, which in turn are involved in cancer. The mutations in the PI3K enzyme cause cancer in different organs. Tissue analysis of colon polyps demonstrate that mutations in the PI3K enzyme isoform, PIK3CA gene (encoding for the p110 subunit), were found in 6% of nonmalignant lesions indicating that the genetic changes are possible primary events in colon cancer (Liu et al., 2009). Human colon cancer has been shown to possess mutations in PIK3CA, KRAS, and the overexpressing protein kinase B (AKT). Meanwhile, PI3Kalpha and PI3Kbeta play important roles in human colon-cancer cell growth where PI3Kbeta specifically functions in de novo DNA synthesis while PI3Kalpha functions in cell survival. PI3K isoforms, AKT, and mammalian targets of rapamycin (mTOR) can be targeted in cancer therapy (Vara et al., 2004). PI3Ks have been developed as possible targets for novel anticancer therapies. A successful drug design for PI3Ks inhibitors is small molecules which inhibit the different stages of cancer. The anticancer drug LY294002 inhibits PI3Ks by decreasing aminoacyl-tRNA synthetises in human HT-29 colorectal cancer cells (Mallawaaratchy et al., 2012).

In conclusion, targeted cancer therapies that use nanoparticles are useful in interfering with specific molecules that are involved in cancer’s growth, progression, and spread. Nanotechnology improves selectivity and enhances the apoptosis of cancer cells, making it a better choice to treat colon cancer.
Abbreviations

ABC  ATP-binding cassette
Ab-QDs  Antibody-coated quantum dots
ADCs  Antibody-drug conjugates
Ag-NPs  Silver nanoparticles
bFGF  Basic fibroblast growth factor
CA  Cancer antigen
CBC  Complete blood count
CEA  Carcinoembryonic antigen
COX-2  Cyclooxygenase-2
CT  Computed tomography
DOX  Drug doxorubicin
EGF  Epidermal growth factor
EGFR  Epidermal growth factor receptor
FAP  Familial adenomatous polyposis
FIT  Fecal immunochemical test
FOBT  Fecal occult blood testing
5-FU  5-Fluorouracil
gFOBT  Guaiac-based fecal occult blood test
IHC  Immunohistochemistry
ILs  Immunoliposomes
ITGB6  Integrin β6
mAb  Monoclonal antibody
MACC1  Metastasis associated in colon cancer
MBA  Methylene-bis-acrylamide
MPEG-PCL  Monomethyl poly (ethylene glycol)-poly(ε-caprolactone)
MRI  Magnetic resonance imaging
MSI  Microsatellite instability
mTOR  Mammalian target of rapamycin
MWCNTs  Multiwalled carbon nanotubes
Nm  Nanometer
O-CMC  Nanoparticle O-carboxymethyl chitosan
PAA  Polyacrylic acid
PEDF  Pigment epithelium-derived factor
PEG  Polyethylene glycol
PET  Positron emission tomography
PGE2  Prostaglandin E2
PHEA  α, β-poly (N-2-hydroxyethyl)-DL-aspartamide
PHEMA  Polyhydroxyethylmethacrylate
PI3K  Phosphoinositide 3-kinase
PVA  polyvinyl alcohol
SWCNT  Single-walled carbon nanotubes
TGF  Transforming growth factor
TNM  Tumor node metastasis
VEGF  Vascular endothelial growth factor
ZNPs  Zinc oxide nanoparticles
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