

Polymeric micelles as a drug carrier for tumor targeting

Abstract

Polymeric micelle can be targeted to tumor site by passive and active mechanism. Some inherent properties of polymeric micelle such as size in nanorange, stability in plasma, longevity *in vivo*, and pathological characteristics of tumor make polymeric micelles to be targeted at the tumor site by passive mechanism called enhanced permeability and retention effect. Polymeric micelle formed from the amphiphilic block copolymer is suitable for encapsulation of poorly water soluble, hydrophobic anticancer drugs. Other characteristics of polymeric micelles such as separated functionality at the outer shell are useful for targeting the anticancer drug to tumor by active mechanisms. Polymeric micelles can be conjugated with many ligands such as antibodies fragments, epidermal growth factors, α_2 -glycoprotein, transferrine, and folate to target micelles to cancer cells. Application of heat and ultrasound are the alternative methods to enhance drug accumulation in tumoral cells. Targeting using micelles can also be done to tumor angiogenesis which is the potentially promising target for anticancer drugs. This review summarizes about recently available information regarding targeting the anticancer drug to the tumor site using polymeric micelles.

Key words:

Amphiphilic block copolymer, angiogenesis, drug carriers, polymeric micelles, tumor targeting

Introduction

Current chemotherapy of cancer is still facing a major problem of lack of selectivity of anticancer drugs toward neoplastic cells, thus cells of the bone marrow and gastrointestinal tract which are rapidly proliferating are getting affected by the cytotoxic action of these drugs. This results in a narrow therapeutic index of most anticancer drugs.^[1] Along with this, increasing resistant types of tumors require high dose of anticancer drugs which in turn enhances the toxicity of treatment.

By increasing the delivery of drug to the therapeutic sites and reducing delivery to the unwanted sites, an improved therapeutic index can be obtained with enhanced drug action at the therapeutic sites. Polymeric micelles possess several strong advantages because of their physicochemical properties for tumor targeting by passive targeting mechanism called enhanced permeability and retention (EPR) effect.^[2] In addition, polymeric micelles can be

engineered by means of ligand coupling or addition of pH-sensitive moieties according to the biological characteristics of the diseased site for active targeting. Various ligands such as different sugars, transferrine, folate residues, and peptides have been attached to polymeric micelles for active targeting. Thus, polymeric micelle acts as ideal drug carrier for targeting the cancerous cells. For targeting the tumor at the inaccessible sites, the drug should be administered by parenteral route. Pharmaceutical drug carriers carrying drug in plasma should possess properties such as biodegradability, small particle size, high loading capacity, prolonged circulation, and accumulation in required pathological site in the body.^[3] All these properties are mostly executed by polymeric micelles.

Poorly water soluble, hydrophobic agents are known to be associated with problems in therapeutic applications such as poor absorption and bioavailability, and drug

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aggregation-related complications such as embolism.^[4,5] On the other hand, poor solubility in water is associated with many drugs including anticancer drugs. Also, drugs should have hydrophobicity to penetrate a cell membrane and presence of hydrophobic group for sufficient affinity toward the target receptor.^[6,7] To overcome these problems, amphiphilic copolymers are used to encapsulate poorly water-soluble anticancer drugs in polymeric micelles which have inner core made up of hydrophobic block of copolymer in which drug gets entrapped and outer shell of hydrophilic block of copolymer which reduces the interactions of drug with the outer aqueous environment keeping them stable. Also, the hydrophilic micelle corona keeps the polymeric micelle stable in plasma for longer duration and also prevents their opsonization and capture by reticuloendothelial system.^[8] Polymeric micelles are very stable as having low critical micelle concentration (CMC) values comparative to surfactant micelles, as low as 10^{-6} M.^[9] All these issues related to polymeric micelles make them to be an ideal carrier for anticancer drugs and tumor targeting [Figure 1].

Drug Targeting Mechanisms of Polymeric Micelles

Passive targeting

Initially, it was thought that the receptor-mediated targeting was the only way for targeting the anticancer drugs to therapeutic sites, thus many researchers have developed engineered polymeric micelle conjugates in which various ligands have been attached to polymeric micelles.^[9,10] However, many recent studies have revealed that polymer-conjugated drugs and nanoparticulates show prolonged circulation in the blood followed by passive accumulation in tumors even in the absence of targeting ligands,^[11] showing existence of passive retention mechanism [Figure 2].

Passive targeting of polymeric micelles to solid tumor can be achieved through the EPR effect, first identified by Maeda *et al.*^[12,13] In the solid tumor tissues, the pathological, pharmacological, and biochemical studies show that solid tumor generally possesses the pathophysiological characteristics such as hypervascularity, incomplete vasculature architecture, secretion of vascular permeability factors stimulating extravasation, and immature lymphatic capillaries.^[14] Tumor vasculature has characteristics such as high proportion of proliferative endothelial cells, increased tortuosity, pericyte deficiency, and aberrant basement membrane formation, which result from rapid vascularization necessary to provide oxygen and nutrients to proliferating tumors. These characteristics render blood vessels permeable to macromolecules due to increased vascular permeability. Furthermore, lymphatic drainage system does not operate effectively due to immature lymphatic capillaries, thus macromolecules

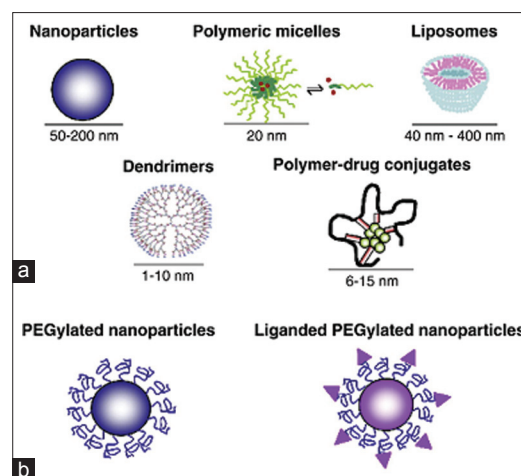


Figure 1: Nanomedicine in drug delivery. (a) Types of nanocarriers currently described in preclinical and clinical studies. (b) Schematic representation of PEGylation and ligand grafting

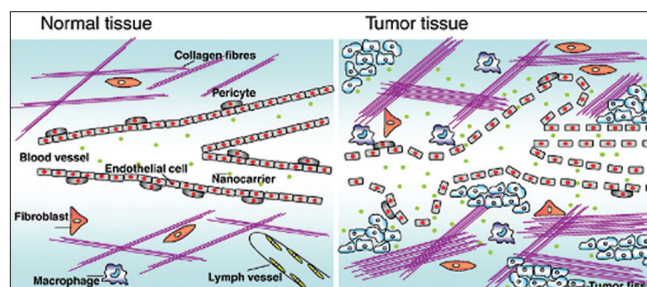


Figure 2: Differences between normal and tumor tissues that explain the passive targeting of nanocarriers by the enhanced permeability and retention effect

get selectively retained for prolonged time period in the tumor interstitium.^[12,13,15] Thus, numerous studies have shown that EPR effect causes passive accumulation of macromolecules and nanoparticulates in solid tumor, enhancing therapeutic index while decreasing side effects. Also, it has been found that in most human tumors, the effective pore size in the vasculature ranges from 200 to 600 nm, in diameter which allows for passive targeting to tumors.^[16] It has been noted that secretion of various factors such as nitric oxide, prostaglandins, bradykinin, basic fibroblast growth factor in tumor tissues, and overexpression of genes such as vascular permeability factor or vascular endothelial growth factor^[17,18] cause hyperpermeability of tumor microvasculature. However, it should be noted that permeability of vessels in tumor varies during progression, tumor type, and anatomical location of tumor while physicochemical properties of polymer used affect the extravasations of polymeric nanoparticulates.^[19]

Active targeting

Active targeting aims to increase the drug delivery to the target utilizing biologically specific interactions such as antigen antibody binding or locally applied signals such as sonication or heating.^[2] Here, carrier can be engineered by

means of ligand coupling or addition of pH sensitive moiety according to the biological characteristics of the tumor tissue.^[20,21] Active targeting makes use of the characteristics shown by the tumor cells such as overexpression of cell surface tumor-associated antigens that are at low level in normal tissue cells as well as of the tumor-specific antigens^[19] and relatively more acidic nature of tumor (pH 7.0) than normal tissue (pH 7.4). Specific interactions between the targeting components with antigen displayed on target tissues cause the selective accumulation of drug in the target tissue. Active targeting decreases adverse side effects as the drug gets accumulated only in the tumor sites and it allows the drugs' cellular uptake through endocytosis.

Ligand coupling

It involves coupling of polymeric micelle or other nanoparticulates with monoclonal antibodies, folate, transferrin, luteinizing hormone releasing hormone, epidermal growth factor (EGF), and α_2 glycoprotein [Figure 3].

Polymeric immunomicelles

Micelles with surface-attached specific antibodies also called as immunomicelles provide an opportunity for targeting in term of diversity of targets and specificity of interactions. Micelles attached antibodies retain their ability to specifically interact with their antigens.^[22] Recently, it has been shown that certain non-pathogenic monoclonal antinuclear autoantibodies with the nucleosome-restricted specificity (monoclonal antibody 2C5, mAb 2C5 being among them) recognize the surface of numerous tumors, but not normal cells via tumor cells surface-bound nucleosomes.^[23,24] As these antibodies bind to broad variety of cancer cells, they serve as specific ligands for the delivery of drugs and drug carriers into tumors. Intravenous administration of tumor-specific 2C5 immunomicelles loaded with a sparingly soluble anticancer drug paclitaxel into experimental mice bearing murine Lewis lung carcinoma resulted in an increased accumulation of paclitaxel in the tumor compared with free drug or drug in non-targeted micelles and in an enhanced tumor growth inhibition *in vivo*.^[22]

As shown in Figure 4, for attachment of monoclonal antibody to the poly (ethyleneglycol)-poly (ethylene) (PEG-PE)-based micelles, a technique has been adapted which utilizes PEG-PE with the free PEG terminus activated with p-nitrophenylcarboxyl (pNP) group^[25] which remains stable at pH values below 6 and interacts with amino groups of various peptides and proteins including monoclonal antibodies yielding stable urathan (carbamate bond) when pH value is increased above 7.5. These immunomicelles are quantified using fluorescent labelled antibody or by SDS-PAGE.^[26,27] Characterization of immunomicelles by analysis of micelle size distribution before and after attachment of various antibodies was performed by dynamic light-scattering and freeze-surface electron microscopy and

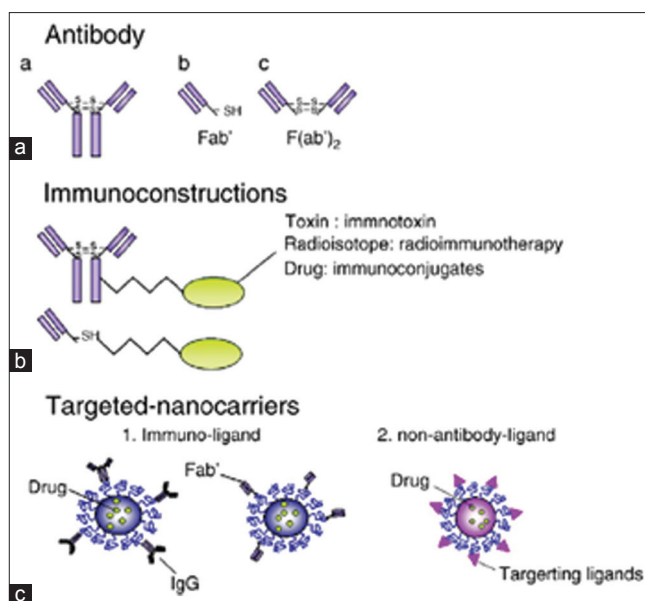


Figure 3: Main classes of ligand-targeted therapeutics

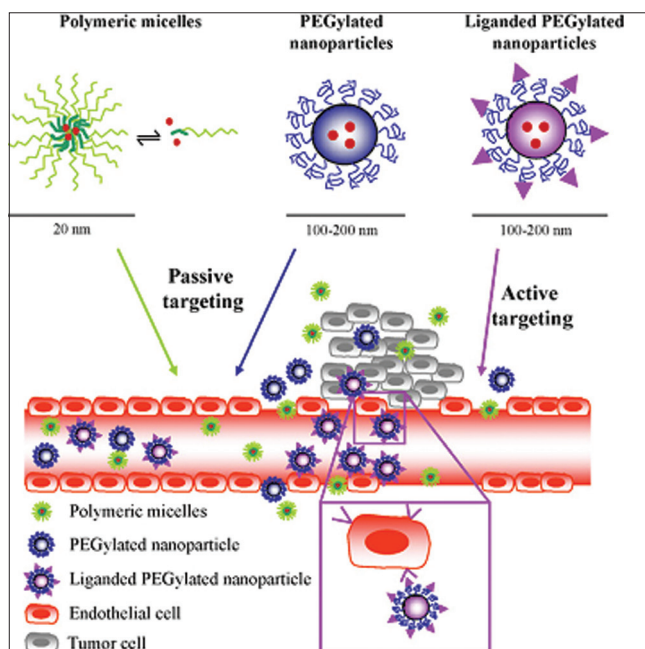


Figure 4: Schematic representation of polymeric micelles, PEGylated nanoparticles, and liganded nanoparticles

shows that protein attachment did not affect the size of the micelles substantially.^[28-30]

Folate-mediated drug delivery

Micelles equipped with folate ligands are mainly used for the intracellular transport of the drug. After intracellular transport of folate equipped micelles, the drug carried by micelles should also be released intracellularly; this problem is solved by the pH sensitivity of polymeric micelles that enable selective drug release in intracellular acidic compartment of endosomes with pH 5–6.^[20,21] Such

micelles are partially crucial to the carriers for delivery of materials that should become pharmaceutically effective after entering the cell. Folate behaves as a ligand having high affinity for its receptors, folate binding proteins, that are selectively overexpressed on the surface of the cancer cells.^[31,32] Elevated levels of folate receptors are expressed on epithelial tumors of various organs such as colon, lung, prostate, ovaries, mammary glands, and brain.^[33] Thus, the folate conjugates with an appropriate design can be directed to the tumor cells in the body and internalized in the target cells via receptor-mediated endocytosis. Furthermore, the use of folate conjugates has shown to escape cancer cell's multidrug efflux pumps^[34] and remain in recycling endosomes (pH 5–6) or escapes into the cytoplasm. Such characteristics play an important role for enhancing intracellular uptake of drug by the cell and avoid possible side effects of lysosomal enzymes action.^[35] In order to confirm that folate installation enhances the cellular uptake to the micelles, flow cytometric analysis was carried out by changing sample exposure time to cells. In an experiment based on *in vitro* cytotoxicity results, samples of adriamycin (ADR), folate-bound Ph-sensitive micelles with ADR (FMA), and folate-unbound pH-sensitive micelles with ADR (MA) were exposed to human pharyngeal cancer cells, for 3 and 24 h and increasing fluorescence of the cell was monitored. The experimental result clearly demonstrated that cellular uptake of FMA drastically increased even with short exposure time (3 h) and it was also similar to that of ADR uptake after 24 h. This time-dependent increase in fluorescence intensity was also observed for MA, but cellular uptake was low compared with FMA and ADR. This proved that folate installation greatly enhances cellular uptake of micelles.^[21]

In another research, the pH-sensitive and folate-conjugated polymeric mixed micelles using folate-PEG-b-poly (L-histidine) and poly (ethyleneoxide)-b-poly (L-lactic acid) block copolymer were prepared and loaded with doxorubicin.^[20] These polymeric micelles showed efficient drug delivery of doxorubicin to tumor cells *in vitro* demonstrating efficient treatment of solid tumor using combination of targetability and pH sensitivity.

Transferrine

Transferrine also acts as a suitable ligand for targeting tumor tissue as the receptors for transferrine are overexpressed on the cancer cells which correlate to the degree of malignancy.^[36] Transferrine is an 80-kDa glycoprotein, synthesized by liver, which binds to endogenous iron in plasma. Transferrine after interaction with its surface receptors undergoes endocytosis into acidic compartment. In acidic environment, iron dissociates from transferrine and dissociated transferrine recycles after getting released from cells. Enhanced cellular uptake and reduced exocytosis were shown by the transferrine-conjugated nanoparticles loaded with paclitaxel. Nanoparticles consisted of shell of

biodegradable polymer poly-(lactic-co-glycolic acid) (PLGA). Nanoparticles showed greater anticancer activity and more sustained effect compared with free drug or conjugated nanoparticles.^[37]

Luteinizing hormone releasing hormone

It is also used as a ligand for conjugation to micelle. Luteinizing hormone releasing hormone (LHRH) receptors are present on the surface of most of healthy human cells, but are overexpressed in ovarian and also some other cancer cells. Dharap *et al.*^[38] carried out an experiment to show the significantly higher cytotoxicity against cancer cells by the LHRH-PEG-camptothecin-targeted anticancer drug delivery system.

Epidermal growth factors

EGF coupled polymeric micelle is another approach for targeting tumors. EGFs are the ligand having nuclear translocation properties. Zeng *et al.*^[39] reported an EGF-conjugated PEG-b-poly (D-valerolactone) (PGG-b-PVL) micelle system that targets the EGF receptors overexpressed by the breast cancer cells. These micelles were shown to localize in the nucleus of the MDA-MB-468 breast cancer cells and perinuclear region. Thus, EGF conjugates are useful for nuclear targeting which is critical for the delivery of anticancer drug whose site of action is located in the nucleus.

α_2 -Glycoprotein

The α_2 -glycoprotein-conjugated micelles are used to target cancerous cells especially brain glial cells. α_2 -Glycoprotein conjugation to fluorescein isothiocyanate (FITC) containing Pluronic[®] micelles has shown the accumulation of FITC in brain tissues and decreased clearance of FITC by the lung in comparison to delivery using conventional Pluronic[®] micelles.^[40]

pH-sensitive polymeric micelles

The tumor extracellular pH which is slightly lower than normal tissue pH is the distinguishing characteristic of most solid tumors. The tumor extracellular pH ranges from pH 5.7 to 7.8 measured with invasive microelectrodes with a mean value of 7.0, but most of the pH values are below pH 7.2, with normal blood pH remaining constant at pH 7.4.^[41,42] Such acidic environment of tumor is the basis of development of the pH-sensitive anticancer drug delivery systems such as pH-sensitive polymeric micelles. Such systems developed by using pH-sensitive polybase (poly (L-histidine)),^[43] pH-sensitive linkages (hydrazone linkage),^[44] or by introducing titrable groups (methacrylic acid)^[45,46] into the copolymer at the hydrophilic end while modifying polymeric micelles for pH-sensitive targeting. Micelles with a phase transition of approximately pH 7.0 are useful for tumor targeting, as solid tumors have pH of approximately 7.0, but for subcellular targeting, micelles that are responsive to pH values ranging from 5.0 to 6.0 (endosomal/lysosomal pH) are beneficial.

Lee and co-workers^[47] have developed such system in which CMC of the PEG-b-poly-His copolymer was found to increase, thus reducing thermodynamic stability as the pH of the media was reduced. An abrupt increase in the CMC occurs at pH 7.2, resulting in unstable polymeric micelles which release their content. Doxorubicin-loaded PEG-b-poly-His micelles were shown a significant increase in the *in vitro* intracellular accumulation of drug, *in vivo* tumor localization, and tumor growth inhibition in the A2780 ovarian tumor model^[48] via extracellular pH-dependent targeting of the tumor.

pH sensitivity was also obtained by linking a pH-sensitive moiety between the drug and copolymer. A hydrazone linkage between doxorubicin and PEG-b-(Aspartate) copolymer had been used. Such micelles showed selective release of doxorubicin in the endosomes where pH ranges from 5.0 to 6.0. Released drug was found to get localized in cytoplasm and eventually in the nucleus.^[44]

Introduction of titrable group is another approach to disrupt micelles in the acidic environment.^[45] Leroux *et al.*^[46] introduced a hydrophilic titrable monomer methacrylic acid at the hydrophilic end of poly(N-isopropylacrylamine)-b-poly(O-octadecyl acrylate), i.e., p(NIPA)-b-p(O-ODA) copolymer. These micelles undergo pH phase transition and structural changes in the micelle core at pH of approximately 5.8. These micelles can be further modified by ligand coupling (folate, biotin) to achieve a double targeting. Lee *et al.*^[49] developed poly His-b-PEG-b-PDLLA (poly-Histidine-b-polyethylene glycol-b-poly-DL-lactic acid) mixed micelle with biotin as the targeting ligand. Biotin is protected at pH above 7 by PEG and exposed on the surface at pH 6.5–7.0 (extracellular tumor pH). As pH further reduces to less than 6.5, micelles destabilize and trigger drug release disrupting endosomal membrane via the proton sponge effect.

Thermo-responsive polymeric micelles

Anticancer drugs targeting tumors can also be triggered by hyperthermia. It has significant advantages in clinical applications since it is easy to implement and side effects of chemotherapy are also reduced. For such type of targeting, drugs are loaded into thermo-sensitive polymer matrix with a low critical solution temperature (LCST) between 37° and 42°C to release drugs site specifically upon local heating.^[50] However, as the LCST of most thermo-responsive materials was below 37°C, the polymeric micelles with such materials would precipitate once injected into human body with normal body temperature of 37°C and loses thermal targeting function.

A temperature-sensitive polymeric micelle had been prepared using the block copolymer of poly(N-isopropylacrylamide-b-butylmethacrylate) (PIPAA-PBMA). Here, PIPAAm in aqueous solution is known to exhibit a reversible thermo-responsive phase transition at

a lower critical solution temperature of 32°C to insoluble and hydrophobic aggregates and above the LCST showing an extended chain conformation.^[51] Core-cross-linked (CCL) biodegradable thermo-sensitive micelles based on mPEG 5000 and N-(2-hydroxyethyl) methacrylamide-oligolactates (mPEG-b-pCHEMAM-LaCn) were synthesized and their properties were investigated, which have shown to maintain their integrity and stability below the critical micelle temperature. The circulation kinetics and biodistribution of CCL micelles were considerably better than those of non-cross-linked micelles.^[52]

A thermo-responsive doxorubicin-loaded micelles having LCST of 32°C were developed.^[51] In such micelles, the release of doxorubicin may be switched on or off reversibly by toggling temperature below and above the LCST. By increasing a temperature above the LCST, drug release is accelerated, while decreasing the temperature below LCST, drug release is reduced. Release of drug from such micelles is also influenced by the state of the micelles core in addition to the thermosensitivity of the PIPAAm at outer shell. Micelles formed from copolymers having liquid state core (e.g., Tg = 20°C for PBMA) are more sensitive to thermally triggered drug release than the micelles with solid state core. Doxorubicin-loaded PPIAAm-b-PBMA micelles showed three times enhanced cytotoxic effect than the PPIAA-b-PS micelles above the LCST of micelles. At temperature below the LCST, both systems exhibited almost no cytotoxicity.^[53]

Sonication

A new method of drug targeting to tumor is based on localized release of drug at tumor site by ultrasound focusing in which ultrasound is focused through the skin to irradiate tumor only. In this approach, transducer is placed in contact with a water-based gel or water layer on the skin and no insertion or surgery is required. Ultrasound application above the cavitation threshold causes cell sonolysis but ultrasound-induced drug release from micelles proceeds without power density threshold, thus this process does not require transient cavitation. This difference provides the window of power densities, in which effective drug release from micelles by focusing ultrasound can be achieved without any mechanical damage to cells. Hence, this window could be useful in clinical application of ultrasound for targeting anticancer drugs.^[1]

Ultrasound irradiation may play multiple roles in tumor therapy. Ultrasound may induce thermal effects, enhance extravasation of drugs encapsulated micelles into tumor, enhance drug diffusion through tumor interstitium, release drug from micelles in the tumor volume, and also enhance the intracellular uptake of both released and encapsulated drug at irradiation site; all these effects result in an enhanced drug accumulation in the tumor cells. Combination of drug-loaded polymeric micelles and ultrasound irradiation of tumor result in effective tumor

targeting and suppression of tumor growth. However, the *in vivo* study revealed that ultrasound does not target polymeric micelles to solid tumors, rather the enhanced drug accumulation in tumor after ultrasound application requires initial accumulation of drug-loaded micelles in the tumor via passive mechanism.^[54]

The application of ultrasound irradiation for enhancing the drug accumulation in tumor can be optimized by varying many factors such as types of waves applied, sonication frequency, time period between drug injection, and application of ultrasound and micelle physiochemical properties.^[54,55] Micelle physiochemical properties such as hydrophobicity and state of inner core were found to influence drug accumulation in tumor.^[56,57] The main advantage of ultrasound is its non-invasive nature. There are no side effects of chemotherapy and ultrasound is painless.

Miscellaneous tumor targeting

Photodynamic therapy (PDT) is another approach used for treating the superficial tumors. In this therapy, photosensitizing agents are used for photochemical irradiation of malignant cells.

Polymeric micelles are nanosized water dispersible clusters of polymeric molecules and thus are excellent nanocarriers for PDT drugs. Along with photosensitizing agents, iron oxide nanoparticles were encapsulated inside the nanocarrier, which allowed them to respond to externally applied magnetic field. This magnetically guided drug delivery would allow for the use of lower concentration of drug to deliver a therapeutic dose, significantly reducing the amount of PDT drugs that accumulate in normal tissue.^[58,59] In another approach, a poorly water-soluble photosensitizing agent, mesotetraphenylporphine, solubilized in polymeric micelles modified with a cancer specific antibody was found to produce more efficient cytotoxicity to cancer cells under the conditions of PDT.^[60]

Angiogenesis

Another potentially promising target for cancer chemotherapy is tumor angiogenesis, in which tumor undergoes regeneration of vascular capillaries. In almost all tissues, the vascular network is a stable system with no significant regeneration of vasculature, exception are the cases of ovulation, embryonic development, and wound healing. But in cancer, tumor after growing in size with greater than critical volume of 2 mm³ undergoes tumoral angiogenesis. Tumor does not undergo angiogenesis when they are small and surrounded by healthy tissue, as nutrients and oxygen can diffuse in them. But after a certain point in growth when nutrients, oxygen, and growth factors cannot reach them, the tumor cells require blood

flow for further growth of the tumor, thus tumor induces angiogenesis.^[61] Angiogenesis in tumor is an important control point in cancer therapy, as many researchers have revealed that tumor cannot grow effectively past a critical size of tumor without angiogenesis.^[62]

Angiogenesis is regulated by a critical balance between factors influencing stimulation and inhibition of blood vessel formation, but when hypoxia induces cancerous cells to release preangiogenic agents such as growth factors, the balance gets in side of angiogenesis.^[63] Then the endothelial cells of pre-existing blood capillaries undergo differentiation, migration, and proliferation in response to angiogenic agents such as vascular endothelial growth factors, epidermal growth factor, and angiogenin. Angiogenesis is a complex process involving many components, cell types, cytokines, growth factors, receptors, proteases, and adhesion molecules.^[64] Tumor angiogenesis is a potentially promising target of cancer chemotherapy and also gene nanoparticle therapy. The drugs used in chemotherapy of cancer pointing angiogenesis are based on the concept of removal of or inhibition of growth of angiogenic blood vessels, which will stop the supply of oxygen and nutrients to cancer cells. The various approaches used are inhibition of endogenous angiogenic factors, endothelial cell process such as differentiation, migration, and proliferation. The regenerated blood vessels overexpress receptors for vascular endothelial growth factors; thus by using monoclonal antibodies against vascular endothelial growth factor receptors, the cancer can be treated.^[65] Many researchers have studied targeted therapy of chemotherapeutic agents to site of tumor neovascularisation or targeting angiogenesis-inhibiting drugs to tumor for inhibition of proliferating capillaries in tumor.

Conclusion

Over the past few decades, scientists have made many attempts to develop an ideal drug delivery system that selectively targets drug to diseased cells but is not harmful to healthy cells. Polymeric micelles are one of the nanocarriers that can selectively target drug to cancerous cells. Also, as most of the anticancer drugs are poorly water soluble, polymeric micelles are the convenient drug carriers for carrying and targeting such drugs to tumors. Collectively, all these studies suggested that drug encapsulated in micelles showed enhanced therapeutic index in solid tumors, correlating to their passive targeting taking advantage of tumor characteristics and active targeting using various mechanisms and decreased side effects compared with conventional drug formulations. But there is a need to translate these proven experimental advantageous concepts into clinical practice for diminishing death rate from cancers and increasing hope in cancer chemotherapy.

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