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Polymer Nanoparticles: Newer Strategies towards Targeted Cancer Therapy

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Abstract

Encapsulation of therapeutic drugs inside nanoparticles has become the new norm in the field of drug delivery. Nanoparticles increase the therapeutic efficacy of the drugs by providing high loading efficiencies, shielding when in circulation, ability to target tumors, enhanced accumulations, and triggered release inside tumors. Polymeric nanoparticles have seen an unprecedented growth and usage in drug delivery and diagnostics in recent decades, and have emerged as extremely promising candidates for targeted delivery owing to their tunable properties, and the flexibility to design systems which respond to external stimuli such as pH, hyperthermia, redox, ultrasound, and magnetic field. This review summarizes recent exciting developments in the field of targeted polymeric nanoparticles for delivery of anti-cancer drugs, with a particular focus on functionalization with ligands, stimuli responsive and biodegradable systems. Further a critical overview of their design principles, drug release performance, and therapeutic advantages over conventional nanoparticles is discussed.

Keywords: Polymer nanocarrier; Polymeric nanocarrier; Polymer nanoparticle; Liposome; PEGylation; Drug accumulation; Drug delivery system; Drug release; Nanoencapsulation; Nanoengineering; Particle size; Surface property

Introduction

Cancer in its myriad forms affects millions of people worldwide and is growing at an alarming rate to become the world's deadliest disease of all times [1]. Till date, the most common methods of cancer treatment are the use of chemotherapy or invasive surgical procedures. Conventional chemotherapy however does not discriminate between the cancer cells and healthy cells thereby causing severe side-effects. Moreover, the systemic delivery of other novel biopharmaceutical anti-cancer agents such as antibodies, hormones, oligo-peptides, nucleic acids, growth factors etc. face significant obstacles from reticuloendothelial system (RES) and intracellular enzymatic degradation [2,3]. Recently, the use of nanoparticles as delivery vehicles for existing drugs aswell as novel cancer therapeutic agents has emerged to be highly effective and possible "game changers" in the field of targeted delivery. These developments are constantly striving to achieve enhanced care and quality of life for cancer patients [4,5]. Several strategies in the design such as nanometer sizes, (surface properties, and shape govern the biodistribution, uptake, drug loading capacities, and properties for sustained or controlled release making nanoparticle systems ideal and well suited for cancer therapy [6-8]. Lipid based nano-carriers are amongst the earliest nanoparticles investigated and utilized in variety of therapeutics including cancer. In fact liposomal doxorubicin used in the treatment of Kaposi's sarcoma, breast cancer, and ovarian cancer was the first nano-carrier to receive FDA approval [9]. Further a number of crucial design alterations are in progress to guarantee higher efficacy and effective tumor targeting using receptors such as folate or integrins which are highly expressed on variety of cancer cells [10-14]. Some other highly interesting reviews have very efficiently discussed these class of nanoparticles in great depth [8,12,15]. Polymer-mediated delivery systems along with lipid-nanoparticles have provided the foundations for the field of advanced nanotechnology based drug delivery. Polymericnanometer sized particles such as micelles, nanospheres, nanocapsules, polymerosomes, polyplexes, and hydrogels etc have been particularly in the limelight as nano-carriers [16]. Polymer carriers offer a large versatility in both structure and physiochemical properties due to awide variety of available monomers that may be used to form the polymer architectures. Drugs loading is accomplished by infusing the NPs with drugs in aqueous phase resulting in highly ordered cage like or capsule conformations along with more advanced methodologies include trapping drugs by chemical cross-linking, modifying surface properties of NPs etc [17,18]. A number of polymeric NPs are in the preclinical phase for the delivery of cancer therapeutics owing to the unlimited potential for targeted delivery. Recently, there has been significant interest in employing synthetic polymers like poly(ethyleneglycol) (PEG), [19] polylactide (PLA), [20] and poly(D,L-lactide–co-glycolide) (PLGA) [21]. Dhar et al. [22] have employed a platimum (pt(IV) based PLGA-PEG NP to deliver cisplatin in the form of a prodrug showing significantly improved efficacy in vivo. While these polyesters offer excellent biocompatibility and biodegradability, they have limitations with respect to drug release and stability owing to slow degradation of the polymers [23] (Figure 1).

Additionally, certain polymers contain chemical groups that interact with the surrounding environment and change their properties. These polymers are referred to as stimuli responsive or "smart polymers." Some common environmental stimuli such as pH, ionic strength, temperature, chemical agents, and electromagnetic radiation etc result into changes including degradation, phase separation, surface chemistry, shape, permeability, and mechanical properties to release the therapeutics. Such class of stimuli responsive polymers has been of considerable interest for targeted delivery of cancer therapeutics. Temperature responsive polymeric Nps have been developed based on the lower critical solution temperature (LCST) behavior of polymers like

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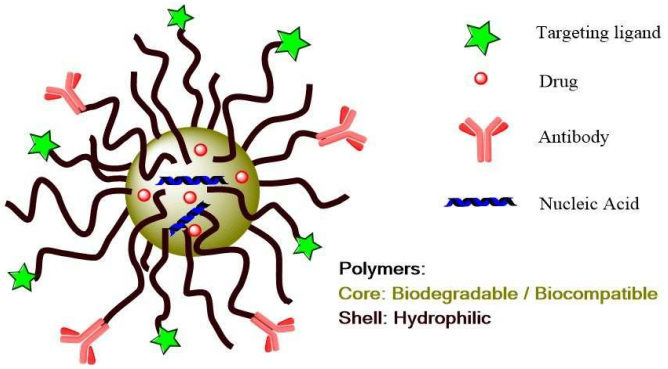

Figure 1: Schematic representation of a polymeric nanoparticle for targeted drug delivery.

poly (N-isopropylacrylamide) (poly(NIPAAm)) and their copolymers [24-26]. Poly(NIPAAm) and its copolymers can be used to form core-shell micellar structures consisting of an inner hydrophobic core surrounded by an outer hydrophilic shell below its LCST. Hydrophobic drugs can then be loaded inside the inner core safely protected from leakage from the exterior hydrophilic shell. The drugs can then be easily released by localized heating which causes the exterior shell to become increasingly hydrophilic. Taillefer et al. [27] have shown that by using poly(*N*-isopropylacryamide-*co*-methacrylic acid-*co*-octadecyl acrylate) (Poly(NIPAAm-*co*-MAA-*co*-ODA)*)* copolymer, aluminum chloride phthalocyanine (AlClPc), a photoactiveanticancer payload was delivered to inhibit the growth of EMT-6 mouse mammary cells. In another study, Cheng et al. [28] used biotin-PEG-*b*-P(NIPAAm-*co*-HMAAm) diblock copolymer to bind HeLa cells pretreated with transferrin, indicating that drug loaded polymeric micelles can be manipulated to release their cargo by thermally induced structural changes to the micellar core. Temperature responsive polymeric NPs or micelles have been mainly employed as drug delivery vehicles in vitro experiments. The next big step will be to design systems to respond to subtle changes in temperatures targeted at the local tissue sites with greater control over drug release. On the other hand, pH responsive polymers have also emerged as novel stimuli-responsive nanocarriers. For example, Devalapally et al. demonstrated that pH-sensitive poly(ethylene oxide) (PEO)-modified poly(beta-amino ester) (PbAE) nanoparticles lack systemic toxicity and efficiently delivered paclitaxel [29], whereas Du et al. designed dual pH-sensitive polymer containing monomethoxyl poly(ethylene glycol)-b-poly(allyl ethylene phosphate) (mPEG-b-PAEP)-Hydrozone-Doxorubicin-Dimethymaleic anhydride for extracellular cationization and uptake to follow by endosomal/lysosomal release of the drug [30]. While a number of thermal and pH responsive co-polymers with pNIPAAm have been discussed [31], many of them can also be categorized into a novel class of hydrogels for drug delivery [17,32].

All nanoparticles in general benefit from enhanced permeation and retention (EPR) effect and result into an increased extravasation into the tumour interstitium, however a thorough careful engineering of polymer nanoparticles including functionalization with targeting ligands is needed to promote receptor mediated uptake into the cancer cells. On the contrary, targeting to tumor vasculature endothelia occurs relatively quickly and does not require extravasation of the nanocarriers [33]. A variety of ligands including folate, transferrin, antibodies or their fragments, and peptides can be conjugated to polymeric nanoparticles to target plethora of receptors commonly overexpressed on a number of cancer types [23,34-36]. Targeted polyester based nanocarriers including Poly(lactic acid) and poly(lactic-co-glycolic acid), Poly(ε-caprolactone) functionalized with folate ligands [37]. RGD peptide [38,39] and several other ligands [40] are discussed. Several polysaccharides such as chitosan and cyclodextrins are used to prepare nanocarriers for drug delivery because they offer outstanding physical and biological properties and plenty of reactive groups for functionalizing ligands or reacting drugs [40]. Chitosan nanoparticles has been extensively studied for targeted drug delivery using folate [41], RGD [42] and several other ligands [40]. Additionally, a wide variety of poly amino acids, peptides, and proteins are often coupled with variety of ligands to design targeted biopolymer nanocarriers [40]. In a different approach, epidermal growth factor (EGF) receptor targeted cancer nano-carriers have gained considerable attention as these receptors are overexpressed on cancer cells [43]. Milane et al. have recently targeted clinically challenging multi-drug resistant tumors with polymer nanoparticle constructs made of poly(oxlactide-co-glycohde)/poly(ethylene glycol)/epidermal growth factor receptor targeting peptide (PLGA/PEG/ EGFR-peptide) and poly(epsilon-caprolactone) (PCL) [44]. In summary, combining active targeting with polymeric drug delivery carriers have resulted in huge improvements in delivery and efficacy of otherwise poorly effective drugs.

Conclusion

Cancer therapy has seen extraordinary growth in the past two decades due to the advent of variety of strategies to design and functionalize nanocarriers, and a huge selection of therapeutics including drugs, nucleic acids, antibodies etc. Compared to free drugs, nanocarrier-encapsulated drugs preferentially accumulate in the tumour sites through the EPR effects, thereby improving therapeutic outcomes and reducing side-effects. Targeting of nanocarrier can further improve the efficiency and specificity of drug delivery. A wide variety of targeted nanocarriers have been developed and demonstrated efficacy in vivo. Incorporation of active targeting agents will continue to play a crucial role in the delivery of therapeutic agents. Polymer systems offer immense flexibility in customization and optimization of nanocarriers to efficiently deliver new therapeutics and provide an integral step in aiding their progression to clinical practice. Although the current investigations on targeted, multifunctional and stimuli-responsive polymeric nanoparticles are encouraging, there is a pressing need for careful evaluation in terms of physicochemical properties in vivo, pharmacokinetics, bio-distribution, and biodegradability. These challenges can be successfully addressed with increased cooperation between polymer scientists, pharmaceutical, chemical and biomedical engineers, and medical scientists.

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