Review Article

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NanoParticle (Np) Delivery of Chemotherapy Drugs To Prostate Cancer Patients

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Abstract

The use of nanoparticles (NPs) for enhanced drug delivery in prostate cancer treatment has been extensively exploredin many studies. However, there are serious limitations to nanoparticle delivery of drugs to prostate cancer. It has become increasingly obvious that the physicochemical properties of the nanoparticles dictate the volume of the nanoparticles needed for the drug delivery. The volume of nanoparticle used in turn determines therapeutic efficacy of the drug and the nanoparticle delivery system. In this review, we reflect on the physical chemistry of NP-mediated drug delivery to the target cell/tissue during prostate cancer treatment.

Keywords: Prostate cancer; Patients; NanoParticles; Delivery System; Therapeutic Efficiency; Drug;NP-Mediated Drug; Biodegradable Copolymers; Physicochemical Properties; Moieties; Peptides; OligoNucleotides; P-Glycoprotein; Bio-Compatibilities; 3-Bromopyruvate; prostate-specific membrane antigen (PSMA);

Abbreviations:NP: Nanoparticles;3-BPA:3-Bromopyruvate; PLGA: Poly lactic-co-glycolic acid; FDA:Food and Drug Administration; EMA:European Medicine Agency;OVA: Ovalbumin;TLR 4:Toll like Receptor-4; TAA:Tumor Associated Antigen; RNA:Ribonucleic Acid;CPs:Control Nanoparticles;

Review

Controlled drug delivery systems have attracted diverse research interests over the years[1–5].This system is a useful mechanism in prostate cancer treatment. Designing nanoparticles that selectively recognize and killprostate cancer cells in the body, remains an innovative concept[6–8]. The knowledgehas motivated researchers to buildnanoparticles with unique physicochemical properties such as, size, shape and surface chemistry. These nanoparticles are programmed with a multitude of biological and medical functions[9,10] that are vital for effective treatment of prostate cancer.Nanoparticles of biodegradable copolymers are emerging as a promising drug delivery vehicle for prostate cancer treatment. These nano-carrier systems possess diverse range of beneficial features including the significant reduction in volume of drug. These particles also have the ability to develop better pharmacokinetics[11]. Nanoparticles are therapeutic enhancers of anticancer drugs through passive or active targeting while reducing the lethal effects of drugsto healthy cells and tissues[12].

The use of nanoparticles (NP) for prostate cancer treatment has made a revolutionary impact in the area of the rapetics[13]. These release systems have been shown to enhance the stability of various therapeutic agents such as tiny hydrophobic moieties, peptides, and oligonucleotides[14].Due to the small size of nanoparticles, the surface area to volume ratio is very large and can lead to the release of drugs at concentrations high enough to kill prostate and other cancer cells[15].The drug release mechanisms are mainly effected by pH, temperature, light, and hydrophobicity, among other factors[16].The non-covalently bonded drugs have been released through hydrophobicity-induced phenomena via applying hydrophobic/hydrophilic forces to the nanocarriers[17,18]. The high surface area of the nanoparticles allows enhanced drug loading efficiency and targeted drug delivery with minimum leakage and toxicity[19].

Nanoparticles present prolonged distribution of bioactive particles with higher body retention and permeability[20]. These are different types of nanoparticles,including organic nanoparticles(polymers, dendrimers, solid lipid), inorganic nanoparticles (magnetic iron oxide, quantum dots of various mineral compositions of silica), and protein-based nanoparticles (viruses and albumin)[16]. Each type couldallow distribution of bioactive molecules to the target organsof interest[20].In this article, the focus is on polymeric nanoparticles.Polymeric nanoparticles (NP) show some advantages with respect to other drug delivery systems; such as more stability during storage[21]. Polymeric nanoparticles could reduce the multi-drug resistance that characterizes many anti-cancer drugs, by a mechanism of internalization of the drug[22]thereby reducing efflux from cells mediated by the P-glycoprotein[23]. It has been reported that

gold NP attached to 3-Bromopyruvate (3-BPA) could target the mitochondrial membrane potential more selectively and precisely than treatment with 3-BPA alone [24,25].

Interestingly, gold NP preferentially kill cancer cells more than normal mesenchymal stem cells due to higher mitochondrial membrane potential in cancer cells compared to normal cells [24,25]. Furthermore, oral administration of surface modified Poly (lactic-co-glycolic acid) (PLGA) NP containing capecitabine delivers the drug to the prostate effectivelyand precisely than conventional treatment approach[26]. This drug formulation significantly improves patient condition by reducing dosing frequency of conventional treatment modality. This delivery method helps in better management of prostate cancer [26]. Additionally, PLGA adjuvant NP systems are reported to elicit a strong T cell immune response, using 100-fold lower doses (0.05μg) of CpGoligodeoxynucleotide antigen. In previous studies, PLGA NP systems showed significantly higher cytokine secretion (up to 10-fold), as well as a comparative antibody response to abnormal body physiology [27]. Inevitably, PLGA systems may be further developed for tailored drug delivery in both chemo- and immunotherapy in prostate cancer treatment regimen.

PLGA is a biocompatible member of the aliphatic polyester polymer family of biodegradable polymers. It has long been a popular choice for drug delivery applications since its approval by the Food and Drug Administration (FDA)for use in humans [28]. PLGA nanoparticle can transport hydrophobic drugs such as SC-514 in an aqueous environment for delivery within minutes. The drug enters the cell just by ''slight contact'' with the phospholipid layer of the cell[29].Biodegradable NP constructed from PLGA polymers are widely used as antigen carriers/adjuvant due to its biocompatible and biodegradable characteristics. Safety profile and use has been approved by boththe US FDA and the European Medicine Agency (EMA)[30].PLGA offers unique advantages and properties for drug delivery purposes, like the world-wide approval for medical use, biodegradability, biocompatibility, and controlled release[26].However, there are considerable challenges that must be overcome in developing PLGA-based NP systems for drug delivery application. The challenges:targeting the diseased tissue, cellular uptake together with pre-programmed intracellular trafficking, and escaping the reticuloendothelial system are not manageable by a single polymer [26]. The contact of PLGAnanoparticle with the body and the impact are mediated via the surface of the PLGA nanoparticles.PLGA-based NPs have poor loading capacity, and display sudden release of drugs to unwanted tissues and/or cells.Surface modification of PLGA-particles by grafting with selected bio mimetic ligands can meet some of these challenges. Surface modification can lead toa more efficacious medication. Effective medications can reduced side effects and improve patient's treatment outcome[26].Surface modification of PLGA nanoparticles can deliver the drug in a controlled manner throughout the prostate by using a much reduced dosing schedule to increase the therapeutic efficiency[26].

Several modifications have been utilized to overcome these problems. A pH sensitive PLGA NP system was developed for rapid release of ovalbumin (OVA) antigen in acidic environments to improve immune response[31]. The pH based drug release has been used for tumor targeting drug release. This release mechanism is effective because tumor tissues possess lower pH than normal tissues [32–34].Another modification to improve the drug release is the bio-molecular supported process[35].This method is commonly grouped into three parts: ligand exchange mediated release[36], enzymatic release[37,38], and chemical reduction-based release[39].Delivery of dual or triple antigens in PLGA-NPs, co-delivery of Toll like Receptor-4 (TLR 4) ligand and Tumor Associated Antigen (TAA) using PLGA-based NPs [40], may occur through ligand exchange mediated release mechanism. Hydrophilic or hydrophobic interactions by heating, may occur through chemical reduction mechanism.This latter interaction permits encapsulated drugs to diffuse out of the matrix and into the target cell or organ [16].

The major considerations in determining the method for drug delivery are the parameters that influence bio-compatibilities and bioactivities of nanoparticles. Particle size is one of the most important parameters that determine bio-compatibilities and bioactivities of nanoparticles. Particle size has a direct relevance to the stability ofdrug formulations[26]. The delivery efficiency of PLGA nanoparticle is impacted by all the drug releasing factors aforementioned.Recommendations to augment delivery efficiency of PLGA nanoparticles to prostate cancer include; surface fictionalization ofPLGANPs with the A10 2'-fluoropyrimidine ribonucleic acid (RNA) aptamers (that recognize the prostate-specific membrane antigen (PSMA) on prostate cancer cells) and biotin to modify the surface of PLGA nanoparticle[41].Biotin is a small molecule that can induce efficient receptor-mediated endocytosis[42]. Growing evidence suggests a role for biotin in cell signalling, gene expression and chromatin remodeling, together with its potential involvement in inhibiting prostate cancer cell proliferation[43].

Previous work indicated that molecular modification of PLGA nanoparticles with biotin did not change the process of nanoparticle nucleation and growth in solution. There was no evidence of change in shape, size or aggregation of biotinylated nanoparticle compared to the control nanoparticles (CPs)[44]. This observation further justifies the suggested use of biotin to functionalize PLGA nanoparticle.In conclusion, clinical effectiveness of nanoparticles has many limitations[45]. A central strategy for addressing all of these issues is to increase the delivery efficiency and specificity of the drug on the targeted tumor. If delivery efficiencies increase from 1%to 10%, the volume of nanoparticles needed to release the same concentration of drug decrease from 90ml to 9ml[45]. The lower the volume of nanoparticles used in prostate cancer treatment the lesser the chances that healthy tissues and cells will be impacted with toxicities. The reduction in the volume of nanoparticles in contact with healthy cells and tissues implies increase therapeutic efficiency of the drug and the nanoparticle delivery system.

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