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Editorial

Role of Nanoparticles in Drug Delivery Encompassing Cancer Therapeutics

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Introduction

Myriad challenges are encountered while designing drug delivery strategies to tackle cancer delivery. Cancer still remains one of the prime causes of mortality world-wide. The major limiting factor is the impediment to deliver these chemotherapeutics in required optimal concentrations at affected tissues, without exhibiting severe side effects on healthy tissues [1]. Current anti-cancer therapies involve a combination of carefully monitored chemotherapeutic regimens, surgical excisions as well as radiation therapy in certain cases. The most efficacious of these therapies generally involves the selective delivery to the affected, malignant, heavily proliferating tissue and bypassing the healthy, non-affected tissue in the process [2-4]. Nanotechnology, in combination with these above-mentioned therapies, can offer the most promising solution to address the insurmountable hurdles encountered while developing an appropriate delivery system [5]. Recent advances in nanoparticulate technology has led to the development of several nano-vehicles such as polymeric micelles, nanoparticles, liposomes, dendrimers, solid-lipid nanoparticles to deliver these highly hydrophobic chemotherapeutic drugs to the target tumor sites [6,7]. These delivery strategies have led to a massive improvement in the efficacy of these chemotherapeutic drugs by increasing the mean residence time of exposure of these drugs at the site of action, coupled with a favorable distribution profile, which encompasses the minimal distribution of these toxic drugs at the peripheral sites of elimination [8,9].

Limitations of Chemotherapeutic Agents

Conventional chemotherapeutic agents are small molecules that act on tumor cells via multiple mechanisms. They inhibit the normal functioning of tumorigenic cells through mechanisms such as induction of programmed cell death (apoptosis) or prevent their replication by exerting their effects on cellular DNA. Various chemotherapeutic agents that belong to the group of Taxanes such as Paclitaxel, demonstrate their effects by stabilization of microtubules and preventing further mitotic processing from metaphase to anaphase [10]. Chemotherapeutic agents belonging to the class of anthracyclines such as Doxorubicin and daunorubicin exert their efficacious effects on the tumor cells by acting upon the topoisomerase II-DNA complex, thus preventing the replication at the cellular level [11]. However, the greatest barrier with these chemotherapeutic agents is their lack of ability to differentiate between healthy tissue and a tumorigenic tissue, thus leading to a cascade of potential toxicity problems. These agents will target any rapidly proliferating cellular mass, whether it is malignant or benign [12]. This is the root cause of major toxicity symptoms that are manifested during a regimen of chemotherapeutic treatment. Doxorubicin, which is included in most of first-line therapies and is generally considered as a very efficacious chemotherapeutic agent suffers from many dose-limiting limitations such as nausea, drowsiness, vomiting, fatigue and cardiotoxicity [13]. In wake of such instances, an effective balance must be sought between the toxicity exerted by the drug and its overall efficacy to attack and kill tumor cells, thus prolonging a patient's survival. Nanotherapeutics can be used effectively to ameliorate these toxic effects by minimizing or preventing the distribution of chemotherapeutic agent to the healthy tissues [14].

Nanoparticulate Therapy

Different types of nanoparticles exhibit different variations in their composition, structure and surface morphologies thus making them ideal candidates for drug delivery with their own specific advantages and accompanying limitations. Optimizing the surface composition of these nanoparticles and making them more specific towards the characteristics of the tumor makes them more suited towards different tumor subtypes. Some of the nanoparticles, which have been researched for a long time, and are witnessing major progress in clinical development, include liposomes, polymeric micelles, dendrimers, and solid-lipid nanoparticles. Liposomes are promising candidates for drug delivery due to a number of reasons. Primarily, they are composed of non-toxic, non-immunogenic and natural amphiphilic molecules. They are biomimetic that is they closely resemble the structure of cellular membranes. To impart sustained release attributes to the liposomal drug delivery system, they can be surface-tailored with Polyethylene glycol (PEG) molecules to afford steric stabilization to the molecule. These characteristics make them ideal candidates for drug delivery. A promising example is that of Doxil, which was approved for the treatment of cancer, encapsulated Doxorubicin in a PEGylated biodegradable liposome [15]. Similar to liposomes, micelles are also composed of amphiphilic moieties that are capable of self-assembly into roughly spherical structures with a hydrophobic core and hydrophilic corona (external area) [16,17]. The hydrophobic core serves as an ideal loading place for poorly water-soluble drugs. The hydrophilic corona can be composed of Polyethylene Glycol moieties, which can confer abilities to possess a sustained release profile for the delivery system *in vivo*. These micelles are formed above a specific polymeric concentration, also known as critical micellar concentration (CMC) and above a particular temperature, also known as critical micellar temperature (CMT). Due to their smaller size (typically less than 100 nm), these micelles can evade uptake and sequestration by the Reticulo-endothelial system (RES), thus enabling prolonged circulation in the blood. These micelles find great applications in delivering extremely hydrophobic chemotherapeutic agents, either by physical loading or chemical conjugation of these drugs to the backbone of the polymeric micelle. Apart from these, other systems which can be successfully utilized are Dendrimers (highly branched structures that are stable and can be optimally surface-functionalized to include targeting ligands that can enable successful delivery at the target site) [18] and nanospheres/nanocapsules (hydrophobic drugs are suspended evenly throughout the matrix and released via diffusion related mechanisms). For all these nanosystems, the composition of the polymer, surface morphologies, size and shape of the nanoparticles govern an all-important role in

determining the delivery characteristics as well as the eventual fate of these nanoparticles within the body.

Conclusion

Nanoparticles have shown tremendous potential in changing the landscape for the delivery of promising chemotherapeutic drugs, which have suffered from inherent limitations all along. Targeted as well as passive delivery of these drug loaded nanoparticles have the capability to overcome these problems and with successful ongoing research, their potential can be maximized manifold with steps taken to systematically eliminate any pending toxicity or delivery issues [19]. Some of the imminent tasks in improving these delivery systems are increasing the extent of drug loading, fine-tuning the release characteristics as well as optimal surface-functionalization of these nanoparticles to improve the overall delivery profile of these nanoparticles to the target tumor tissue.

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