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Novel Composite Nanocarriers

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ABSTRACT

Need for materials with high biocompatible properties have led to the development of prodrug-decorated nanoparticles. The structure of present nanostructures consists of the hydrophobic core and hydrophilic shell. The shell acts as an external envelop which enhances the colloidal stability of dispersion which protects the prodrug of the nanoparticles from photo- and thermal-initiated degradation. The composite nanoparticles coated by organic shells with functional groups were considered to govern the covalent immobilization of therapeutics/biomolecules. The nanoparticles with unique physiochemical properties may be useful as biosensors in living whole cells. The enhanced cellular drug delivery to cancer cell lines via nanoconjugates revealed that smart nanoparticles are an effective tool for transporting and delivering drugs.

A predisposition to cancer can be inherited, but it often occurs spontaneously due to exposure to environmental risk factors such as smoking, high-energy radiation, or carcinogenic chemical substances. Cancer can also be caused by infections with certain bacteria, e.g., *Helicobacter pylori* [1]. More often, cancer can be caused by viruses, the major cause of cervical cancer, and presumably Epstein-Barr virus (EBV), which is linked to Burkitt's lymphoma [2, 3]. Ultimately, all triggers result in mutations and/or epigenetic changes in DNA structure that inactivate tumor-suppressor genes such as TP53 or activate proto-oncogenes such as HER-2 [4]. The trigger may in some cases be directly mutagenic, e.g., (1) the induction of point mutations by alkylating agents, nucleoside analogs, or intercalating chemicals; (2) the incorrect repair of DNA double-strand breaks induced predominantly by radiation; or (3) the integration of foreign DNA, disrupting the original genetic context and causing aberrant gene expression as observed for some viruses. The effects can also be indirect, e.g., the induction of chronic inflammation or infections that promote the proliferation of a subset of cells, e.g., B-lymphocytes, increasing the likelihood of uncontrolled growth as assumed for EBV in Burkitt's lymphoma.

Chemotherapy is the treatment of cancer with drugs. This approach is advantageous because it can kill residual cancer cells and small, undetectable secondary tumors [5]. Chemotherapy can also be combined with radiotherapy to increase the therapeutic efficacy [6]. One drawback is that the efficacy of chemotherapy depends on the way drugs are distributed in tissues, and poor results are often observed with larger solid tumors due to the limited vascularization, which prevents effective tumor penetration [7]. The active pharmaceutical ingredients (APIs) used for chemotherapy are often small molecules, such as paclitaxel [8]. Such molecules can circulate relatively freely and reach the tumor site(s) even if their precise location is unknown. The first generation of chemotherapeutics were developed to disrupt the metabolism and/or mitotic activity of rapidly dividing cells, whereas the second generation instead targeted signaling components, such as protein kinases or growth factor receptors [8]. For example, paclitaxel is a first-generation drug that disrupts mitosis by preventing tubulin depolymerization, whereas gefitinib is a second-generation drug that inhibits signaling via the epidermal growth factor receptor. Whereas some cancer drugs have a simple structure suitable for total chemical synthesis, most are complex molecules that must be produced using biotechnology [9]. Paclitaxel provides a useful example of the latter scenario. This compound was originally isolated from the bark of the Pacific yew tree (*Taxus brevifolia*) but is now produced in transgenic plant cell suspension cultures at the 75,000-L scale [10]. Some cancer drugs demonstrate limited selectivity, but most also affect rapidly dividing healthy cells, such as hair follicle cells and B-lymphocytes, resulting in the common

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side effects of chemotherapy: hair loss and a compromised immune system [11].

Monoclonal antibodies (mAbs) are directed against cancer-specific cell surface structures including receptors and other surface proteins that are overexpressed in tumors, or glycan structures that are more common in cancer cells – these tumor-selective targets are collectively described as tumor markers [12]. After binding to cancer cells, the mAbs can elicit antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) through their constant domains, causing natural killer (NK) cells to force the cancer cells into apoptosis [13]. Alternatively, the antibodies may block the binding of growth factors or carry a toxic conjugate such as monomethyl auristatin E, which is taken up into the tumors [14]. Such antibody-drug conjugates (ADCs) can combine the ADCC of regular antibodies with the additional toxic effect of a conjugated cytotoxic effector [15]. Lectins are another class of molecules that can be used for immunotherapy or chemotherapy [16]. These plant-derived proteins bind to various carbohydrate structures on the cell surface and can induce immunomodulatory effects or apoptosis.

The evolution of nanomedicine for its production have been a great boon and have shifted paradigms in therapy and tissue engineering, owing to the advantages of nanocarriers (nanoparticles, micelles, dendrimers, etc.) such as a high surface area to volume ratio, unique features of surface modification and engineering to obtain particles of various sizes, shapes and different chemical characteristics. These have proven to be biocompatible, biodegradable and non-toxic which adds to its advantages [17]. Major challenges for the preparation of prodrug-loaded nanoparticles are to design and prepare desired structures with low toxicity, high stability, favorable drug release profiles and acceptable cellular uptake. Although the potential of bare inorganic/polymer nanoparticles (NPs) has already been shown in the field of drug delivery, the researchers have functionalized their surface to further improve the biological and physicochemical properties of the NPs for efficient intracellular drug delivery [18]. The presence of covalently-bound polymer(s) on the surface of the NPs not only improved the hydrophilicity of the particles, but also played a crucial role in augmenting the aqueous dispersibility of the NPs as a result of the electrostatic or steric repulsion forces and thus, preventing the NP's aggregation [19]. Furthermore, the increase in the zeta-potential also indicated a further improvement of the stability by enhancing the repulsion force between the particles [20].

These nanostructures can be synthesized by several methods such as oil-in-water microemulsion, miniemulsion, surfactant-mediated hydrothermal synthesis, hydrothermal synthesis, nanoprecipitation, etc. [21]. Suitable manufacturing methods are selected based on the aqueous solubility of the amphiphilic block copolymer, the molecular weight of each block constituent, and the proportion of each block constituent. In the solid dispersion method, an amphiphilic polymer and a hydrophobic drug are dissolved in an organic solvent. The solvent is evaporated under reduced pressure to form a gel-like polymeric matrix. In the emulsion-based method, a polymeric dispersed phase is emulsified in an aqueous phase. Solvent removal by evaporation and/or extraction causes the rearrangement of polymeric chains to form micelles. Nanoprecipitation involves the use of a water-miscible solvent (e.g., tetrahydrofuran, acetonitrile, acetone, and dimethyl formamide) as a dispersed solvent. Addition of the dispersed phase to an aqueous phase triggers instant solvent diffusion, leading to spontaneous formation of polymeric micelles. The crosslinking agent provides the polymer network structure by connecting the long, linear chains in these polymerizations. Hydrogel networks formed from poly(acrylic acid) (PAA) have the ability to absorb many times their weight in water and are the basis of a class of materials called super absorbents [22].

Ultrasonication is an effective method to fabricate small size nanoparticles following double emulsion solvent vaporization protocol, since the low ultrasonic vibrational energy used for atomization during this process produce high energy which is transmitted directly from the tip of the ultrasonic probe into the emulsion, the shear forces generated by the alternate expansion and compression of these ultrasonic vibrations result in the dispersion of emulsion into nanodroplets, and subsequently into nanoparticles upon solvent vaporization [23]. The sol-gel synthesis of monodisperse silica nanoparticles ranging in size from 50 nm to 2 µm was reported by Stöber and co-workers [24]. Sol-gel chemistry is a widely explored process for the synthesis of many inorganic materials. Lin and collaborators proposed a new technique for the synthesis of porous silica (PSi) NPs using water-in-oil microemulsion as a template. The advantages of this method were the uniformly sized particles obtained compared to other methods [25]. The imaging or therapeutic cargoes can be either directly incorporated in the silica matrix or grafted to the outer surface of the solid silica particles. PSiNPs can be functionalized with imaging or therapeutic agents in several ways, including loading of cargo into the pores, covalent grafting, and co-condensation of siloxy-derived cargoes [26].

The particle size can be effectively controlled by adding suitable additive agents like surfactants, alcohols, amine, inorganic bases, hydrophobes and inorganic salts. Ultrasound (sonication) can also vary the particle size and particle distribution. Along with this, the addition of alcohols also influenced the particle size of the polymer NPs. Polyethylene glycol (PEG)-silane capping on the surface of nanoparticles was also found to effectively attenuate the particle growth process by steric stabilization. An increase of particle sizes up to 300 nm was reported with an increase in the triblock copolymer Pluronic F127 concentration [27]. The encapsulation of such a payload by various nano formulations has been proven successful in enhancing its efficacy in treating cancers, cardiovascular disease, Alzheimer's disease, inflammatory disorders, and neurological disorders [28]. These nano formulations include synthetic amphiphilic copolymers, micelles, polymer nanoparticles, core@shell nanoparticles, liposomes, polymers, dendrimers, nanogels, etc., and these could be translated after preclinical and human clinical trials [29].

The drug loading is mainly based on the adsorptive properties of PSiNPs. Both hydrophilic and hydrophobic cargos can be incorporated into the pores of PSiNPs. Owing to their large pore volume, PSiNPs inherently possess greater loading capacity compared to other carriers. The drug loading is mainly based on the adsorptive properties of PSiNPs. The loading capacity of PSiNPs could be further enhanced by utilizing polymer gatekeeping for the entrapment of hydrophobic drugs [30]. Consecutive drug loading process which increases the intermolecular interactions can also lead to improved loading of the drugs [31]. An increase in the drug feeding ratio was also found to have a profound

influence on the loading capacity of PSiNPs [32]. The pore volume of PSiNPs is the major factor which dictates the loading of the drug.

The strong cellular association of the functional polymers (such as polyethyleneimine (PEI), poly(methyl vinyl ether-alt-maleic acid) (PMVE-MA), etc.)-functionalized porous silicon nanoparticles can be attributed to the high dispersibility of these NPs as well as bio adhesive properties of the polymers [33]. The unique property of some drugs can enhance the probability of their interaction with the functional (amine, carboxyl, etc.) groups of the polymers conjugated to the SiNPs and, consequently, increase their loading degree in the PSiNPs. For example, the loading degree of methotrexate (MTX) in the bare PSiNPs was ~6.4%, whereas PEI and PMVE-MA conjugation improved the MTX loading degree to ~12.6 and ~14.0%, respectively [34]. This suggests that the polymer conjugation increase the loading of the drug due to the more interactions of the drug's functional groups with the free amine and carboxyl groups of the polymer conjugated PSiNPs.

Curcumin-loaded chitosan-coated nanoparticles (Cur-CSCNP) was reported to decrease the survival and the ability of B16F10 cells to generate colonies. Cell migration is an essential component of the invasive phenotype of cancer cells [35]. Cur-CSCNP significantly slowed the migration rate of the cells into the wounded area compared with control group. Treatment with Cur-CSCNP prevented cellular growth in the scratched area. Thus, the reduction of cells that have migrated or invaded after Cur treatment might be partially due to the inhibition of cell proliferation and induction of apoptosis.

Biodegradable methoxy poly(ethylene glycol)-poly(lactic acid) copolymer (mPEG-PLA) was conjugated with curcumin via a disulfide bond or ester bond (control), respectively. The selfassembled redox-sensitive micelles exhibited a hydrodynamic size of ~116 nm with a zeta potential of −10.6 mV. The critical micelle concentration was determined at ~ 6.7 μg mL^{-1}. Under sink conditions with a mimicked redox environment (10 mM dithiothreitol), the extent of curcumin release at 48 h from disulfide bond-linked micelles was nearly three times higher compared to the control micelles. Such rapid release led to a lower half maximal inhibitory concentration (IC_{50}) in HeLa cells at ~ 18.5 μg mL^{-1}, whereas the IC_{50} of control micelles was ~ 41.0 μg mL^{-1}. The cellular uptake study also revealed higher fluorescence intensity for redox-sensitive micelles. In conclusion, the redox-sensitive polymeric conjugate micelles could enhance curcumin delivery while avoiding premature release and achieving on-demand release under the high glutathione concentration in the cell cytoplasm. This strategy opens new avenues for on-demand drug release of nanoscale intracellular delivery [36].

Conclusion

Prodrug decorated nanomaterials are prepared and broadly used for imaging and therapeutic applications. The functionalized NPs can be decorated with some agents in several ways, including loading of cargo into the pores, covalent grafting, and co-condensation of carboxy-derived cargoes. Polymer and mesoporous silica nanoparticles belong among functional nanostructures with a high surface area and tunable pore structures exhibiting high delivery activities for various therapeutics**.** The polymeric conjugate micelles could enhance prodrug delivery while avoiding premature release and achieving on-demand release under the high reducing agent concentration in the cell cytoplasm.

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