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Editorial

Titanium Dioxide (Tio2) Nanostructures as an Ideal Tumor-Targeted Drug Delivery System

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Editorial

Despite recent advances in the field of medicine, cancer still remains one of the leading causes of death with increasing incidence in the world [1]. Chemotherapy, as the most widely used treatment strategy in cancer patients, is usually faced with drug resistance, non-specificity and insufficient efficacy of drug delivery into the malignant cells, thus results in failure in eradicating cancer [1,2]. One strategy to tackle these problems is to design controlled drug delivery devices, also so-called tumor-targeted drug delivery systems, with properties of biocompatibility, biodegradability, selectivity, non-toxicity, and non-immunogenicity to assist in localizing therapeutic drugs for a prolonged period of time to a targeted tumor area, thereby preventing drug-mediated damage to the healthy cells and surrounding tissue [2-4]. This is where the nanomedicine, in particular Nanoparticles (NPs), becomes extremely useful. That is because nanoscale sizes, dimensions of less than 100 nm, can affect physico-chemical properties of a material and modify its behavior in comparison with the bulk form [2-4]. In the other word, nanoscale sizes not only can permit modulation and maximum quantity loading of the drug due to their high surface energy, but also can increase capability of attaching to cell surface markers and efficacy of transporting into the cells [2-4].

To date, a variety of nanostructures, including polymer-based lipids, polymeric-based micelles liposomes, dendrimers and lipoprotein-based drug carriers have been successfully developed [3,4]. As a suitable candidate for drug delivery system, Titanium Dioxide (TiO2) or titania, a metal oxide semiconductor, attracted emerging attention, mostly due to its photo catalytic activity and chemical stability as well as low-cost and low-toxicity [4,5]. Many TiO2 nanostructures, including TiO2 NPs, TiO2 nanotubes, TiO2 matrices, as well as TiO2 capsules and TiO2 whiskers (TiO2 Ws), have been used as drug delivery systems for different anti-cancer drugs, such as Daunorubicin (DNR), Temozolomide (TMZ), Gambogic Acid (GA), Doxorubicin (DOX), cisplatin and valproic acid [4,6-14]. For instance, one-dimensional TiO2 Ws could obviously enhance cytotoxic effects of DNR by increasing its dose inside human SMMC-7721 hepatocarcinoma cells [6]. TMZ, a therapeutic drug for brain gliomas, is another example that its anti-tumor efficiency could be improved by TiO2 nanostructures [7]. Also, encapsulation into TiO2 matrices led to gradual but long lasting release of valproic acid in several diseases [8]. Moreover, DNR and GA from DNR-TiO2 andGA-TiO2 nanocomposits represented more potential anti-tumor efficiency in human leukemia K562 cells, when compared with either drug alone [9,10].

A desirable characteristic of TiO2 nanostructures as a unique drug delivery system is that they can release drug in a pH-dependent manner into the cells [9,10]. Since the niche (extracellular microenvironment) of tumors is slightly more acidic than that of normal tissue, designing new class of tumor-targeted drug delivery systems with capability of retaining the drug during transportation in blood circulation (pH 7.4) but releasing it upon internalization into tumor cells (pH<7.4) are of particular interest [9]. In that line, Zhange et al., demonstrated that DNR could be released from TiO2-baseddrug delivery system much more rapidly at acidic condition (pH 5 and 6) than at pH 7.4 [10]. Therefore, DNR-TiO2 nanocomposites were able to intelligently control release of DNR and augment its chemotherapeutic efficiency by inducing caspase-dependent apoptosis in leukemia cells [10,11]. In parallel, Qin et al., found that modulation of loading mode between drugs and TiO2 could prepare a platform for "smart" drug delivery into cancerous cells [11]. When DOX was loaded on the TiO2NPs by non-covalent complexation (TiO2/DOX), the main portion of DOX is found inside the nuclei while covalent conjugation (TiO2-DOX) led to accumulation of the drug in cytoplasm of glioma cells [11]. Notably, the pH-responsive release of DOX from TiO2/DOX exhibited a significantly higher cytotoxicity in glioma cells than either free DOX or DOX-TiO2 [11]. This "smart" delivery system has been recently improved to utilize modified TiO2 carriers (eg. core–shell nanocomposites) for combating drug resistance in cancerous cells [12]. These findings are therapeutically noteworthy because DOX is currently used for treatment of variety of cancers but drug resistance and cardio toxicity are among serious side effects that limit its use as a single chemotherapeutic drug [11,12].

The specificity and selectivity of drug's action can be also optimized by drug delivery systems based on TiO2 [13,14]. In this scenario, TiO2 is conjugated with the specific molecules to obtain the capability of selective binding to cancerous cells [13,14]. For example, conjugating TiO2 with monoclonal antibodies against Her2 could selectively release entire load of camptothecin into breast cancer cells [4,13]. Also, functionalizing TiO2 NPs with Hyaluronic Acid (HA), and then loading with cisplatin could improve neoadjuvant chemotherapy of ovarian cancer in a tumor-targeted delivery approach [14]. All these new drug delivery systems exhibited high selectivity for cancerous cells as well as high loading capacity for hydrophobic anti-cancer drug, thus offering a new therapeutic approach in cancer.

A recent breakthrough in the field is developing novel porous

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TiO2 NPs modified with Polyethylenimine (PEI) in order to utilize the photo catalytic property of TiO2 for triggering drug release [14]. Following UV illumination, PEI molecules are cut off by TiO2-produced Reactive Oxygen Products (ROS) which subsequently result in releasing the drug loaded in the carrier into the cells. Intriguingly, the amount of drug released from porous TiO2 NPs can be controlled by the irradiance of UV-light (light energy and duration times). More importantly, ROS produced by combination of UV and TiO2 has cytotoxic effects per send can reinforce anti-cancer activities of chemotherapeutic drugs [15].

Conclusion

TiO2-based drug delivery system can successfully improve efficiency of drug delivery by prolonging exposure time to drugs (i.e., days, weeks, or months), by enhancing local concentrations of chemotherapeutic drugs, and by reducing drug's toxicity in normal cells. Also, the photo catalytic activity of TiO2aids in reducing drug resistance, while providing a safer means of drug transport and cancer cell targeting. The human-safe properties of Titania go in harmony with the cytotoxic effects of important anti-cancer drugs such as DOX and DNR. However, more investigation needs to be done, as these are all preliminary studies in the grand scheme of treating and ultimately eradicating cancer.

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