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Invited Review

Recent developments on titania nanoparticle as photocatalytic cancer cells treatment

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ABSTRACT

This review provides a background, fundamental and advanced application of titania nanoparticles (TiO_2) on the disinfection and killing of cancer cell through photocatalytic chemistry. It starts with the characteristic properties focused on the surface, light sensitivity, crystallinity and toxicology of TiO_2 as a photocatalyst. Consequently, outline and design of photocatalytic reactor has been figured out based on the target organisms, including bacteria, viruses, fungi and cancer cells. Despite a large number of studies undertaken, limited selectivity and efficacy of TiO_2 photocatalyst are still widely accepted problems. An ideal TiO_2 photocatalyst should have the combined properties of highly stable reactive oxygen species yield and a greater degree of selectivity towards cancerous cell without damaging the healthy tissues. Hybridization of TiO_2 with metal, metal oxide and carbon nano materials significantly improved both of stability and selectivity of TiO_2, whilst maintaining its high Photodynamic reactivity.

1. Introduction: Nanotechnology in Biomedical Applications

With the development of nanotechnology, nanoparticles are playing significant role in medical applications (Table 1). Application of various types of nanoparticles, including micelles, dendrimers, nano shells, liposomes, polymer-drug conjugates, hydroxyl apatite, calcium phosphate, metallic, porous ceramic and nano polymer with size in the range of 10 to 500 nm allow overcoming some traditional therapeutic method limitation in cell killing treatments [39]. In general, it is assumed that the ideal particle size for the purpose of cell killing treatment applications that ensures vascular permeability and maximizes the accumulation in cell cancer is 100 to 150 nm. Nanoparticles > 200 nm is isolated in the liver, spleen and kidneys, whereas those smaller than 100 nm might leave the blood vessels through fenestration [7,46].

With concern to cancer therapy, nanoparticles, including gold, 1–5 eV semiconductor quantum dots, including CdSe, CdS and ZnS, composed of lipids or polymers, platinum and liposomes have gained great attention. Compared with organic nanoparticles, including liposomes or Chitosan, metal nanoparticles have the advantages as a respect to their Photodynamic characteristics, therapeutic effect and do not need encapsulation of therapeutic agents [3,18]. Among various metal nanoparticles, TiO_2 has great generation property of reactive oxygen species when exposed to ultraviolet light based on particle sizes and morphology.

Recently, photo-therapy has been applied to several treatment approaches of different cancers and other diseases. This application contains the utilization of a photosensitizer, either by systemic or topical application and successive initiation of its exposure to light for production of reactive oxygen species (Fig. 1). This consequently kills the cancer cells via the mechanism of apoptosis or necrosis [86]. This concept is much more beneficial as compared to conventional cancer treatment methods. The photo therapy concept is a low toxicity to normal tissue/cells in the darks and activation by light alone leads to minimize damage to these cells [36]. The combined effect of light makes the photo therapy concept as a selector to be used against cancerous or diseased tissues.

2. TiO_2 Nano Photo Catalyst

The photo catalysis technique of TiO_2 is an emerging treatment for a variety of cancers due to its high therapeutic efficacy and less side effect for healthy tissues. TiO_2 has two crystalline forms which are anatase and rutile [54,63,64]. Anatase with a band gap of 3.2 eV has been considered as the most active form with the action spectrum. This crystalline form demonstrates a drastic decrease in the activity above about 385 nm [5]. Once the energy of the absorbed light is greater than TiO_2 band gap, electrons in the valence band are transferred to the conduction band, creating electron-hole pairs [4]. Such photo generated hole has strong oxidation and can cause various chemical reactions, including photo reduction, photo catalyst and photo organic synthesis [72].

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Table 1
Application of nanotechnology for cancer treatment.

Treatment/methods	Advantages	References
Nanoparticles drug delivery system	Provide intracellular release of the drug in order to obtain the higher intracellular concentration Minimum drug leakage Successfully penetrate inside cancer cells via endocytosis mechanism.	[85]
Surgery	Overcome biological barrier (e.g. blood barrier)	[63,64]
Photodynamic therapy	Excellent intraoperative adjuvant therapy Synergistic combination of advanced physical properties Promising targeting abilities of biomolecules Multiple function of drugs and imaging payloads in one system	[15]
Chemotherapy	• Unique recognition capability of molecules to achieve active transport • Specific elimination	[83]

Table 2
Series of TiO_2 nanoparticles with killing cancer cell properties.

Types of TiO_2	Killing cell properties	References
TiO_2-Pt	The existence of TiO_2-Pt catalyst caused by illumination with near UV light for 1–2 h can result in death of Microbial cells in water	[68]
TiO_2-acetylcellulose membrane	*E-coli* suspension flowing through was completely killed Create new avenues for sterilization, disinfecting drinking water and eliminating bio aerosols from indoor environments	[10]
TiO_2	Killing of polyunsaturated phospholipids as integral component of the bacterial cell membrane	[78]
TiO_2 nanoparticle	Lipid peroxidation reaction	[43]
TiO_2	The surviving fraction of *S. mutans* cells up to 58% under white fluorescent light The analysis based on second order kinetics with respect to the concentrations of microbial cell and oxidative radicals	[105]
Ultra-fine TiO_2	Can cause plasmid DNA breakage at the concentration range of 0.05 to 0.15 mg/mL after incubation for 8 h at 37 °C	[109]

2.1. TiO_2 Nano Photocatalyst: Photocatalytic Properties

Once the TiO_2 illuminated by UV light with wavelength of <385 nm, photo-induced electron and hole is subsequently created. These photo-induced electron and holes could further react with hydroxyl ions or H_2O to form powerful oxidative radicals, which capable of destroying the structure and components of cancer cells [16]. The cell killing properties of TiO_2 photo catalyst have been reported (Table 2). The reactive oxygen species may disrupt or damage various cells or viral structure (Fig. 2). The photocatalytic chemistry studies revealed that the hydroxyl radical created by holes transfer does not diffuse from the surface of TiO_2 [8]. For the cell or virus which are located on TiO_2 surface, there could exist direct electron/hole transfer to the organism or one of its components. In nano sized, TiO_2 may penetrate into the cell and this process may take place in the interior [65]. Orientation and distance are highly influenced by microbes which have similar size with aggregates of TiO_2 nanoparticles.

TiO_2 nanoparticles have been applied in the phototherapy of malignant cell and have potential for the photo degradation of cell cancer treatment because of its high stability and irradiation-induced photo toxicity [115]. Indeed, the series of cellular cells, including carbohydrates. Lipids, proteins and nucleic acids can be damaged and afterward cause cell death under irradiated TiO_2. TiO_2 also demonstrated a noticeable activity in the adsorption of basic L-amino acids, including L-lysine and L-arginine in an aqueous solution [91]. TiO_2 is capable of absorbing and inactivating various bacteriocin from culture supernatant. TiO_2 photo degradation of DNA and RNA bases has been proved by the formation of nitrite, carbon dioxide and ammonia. Synthetic supercoiled

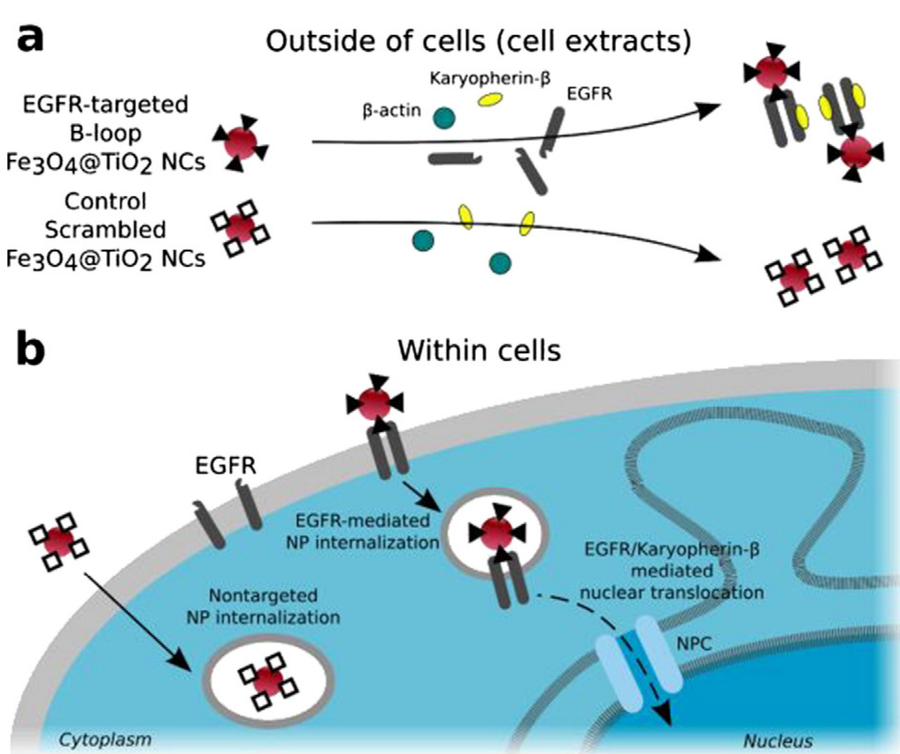

Fig. 1. Photoactivation of targeted nanoparticles in cell nuclei [112,113].