The Applications of Nanomaterials in Phototherapy Against Cancer

Lin Zhu*

Department of Chemistry and Materials Science, Shanghai Normal University, Shanghai, China

* Corresponding Author Email: 1000500297@smail.shnu.edu.cn

Abstract. Since nowadays cancers have caused a high death rate among human, it is quite important to find some new therapies against cancer. Phototherapy is a promising therapy against the cancer due to its better effect than other traditional methods, but still needs some improvements. With the combinations of the nanomaterials, some of the disadvantages of phototherapy have been solved, because of the properties of nanomaterials such as low toxicity, good biocompatibility, high selectivity and so on. However, some shortcomings still exist. This paper will be first divided into two parts to introduce the applications of nanomaterials in photothermal therapy (PTT) and photodynamic therapy (PDT) and their current problems and solutions, respectively. Then the effects brought by the cooperation of PTT and PDT are mentioned. The final part is about the directions of future developments of them. With the development of the nanotechnology, the nanomaterials can overcome more and more weaknesses in the phototherapy and get better effects.

Keywords: Cancer, Nanomaterials, Phototherapy.

1. Introduction

At present, the cancer can be a serious threat for people's health, which caused more than 4 million people to die in 2020 [1]. Although there have already been many therapies to deal with this disease, such as surgical treatment, chemotherapy and radiotherapy, all of them still have some disadvantages like recurrence of illness, the high side effect, insufficient treating depth and so on. As a result, it is quite important to find some other treatments to make up the vacancy. The phototherapy can be a good choice. Besides, with the help of nanomaterials, the phototherapy can solve more problems from the traditional methods, due to the properties of nanomaterials, like small size, good biocompatibility, easy combinations with other materials and so on. The current technology of phototherapy with nanomaterials can be used in the labs or the clinic treatments. This paper begins with the introductions of the theories of the two types of phototherapy including PTT and PDT and then talks about the common nanomaterials used in them for better effects like low accurate targeting, low toxicity and high efficiency. This paper also mentions the current problems of PTT and PDT and solutions to each problem to show the latest process of development. Finally, there are the combined effects of these two therapies and the directions of the future development of phototherapy. The nanomaterials have done quite a lot of contributions in the phototherapy, while it still has quite a long way to go. The phototherapy can have a better effect in a wider range of clinic treatments with the consisting developments of nanotechnology.

2. PTT

2.1. Theory

With the use of photothermal transforming agents (PTAs), the mechanism of PTT entails converting light energy to heat energy, which is then used to raise the temperature of the tumor tissues. Finally, the heat causes the tumor cells to degenerate and necrotize, which satisfies the needs of therapy.

2.2. The main nanomaterials used in the PTT

Nowadays, photothermal agents include various materials, such as noble metal like gold, two-dimensional materials like black phosphorus (BP), and some tiny organic molecule photothermal agents such as porphyrin.

2.2.1 Gold

Gold has the advantages of bacteriostatic, anticorrosive, and antioxidative properties. Besides, gold can be produced at the nanoscale and functionalized with amine groups and thiol, which allows the gold to combine with diverse functional groups like medicinal products or targeted antibodies [2]. Then gold nanoparticles can absorb light and then transform it into heat through a number of nonradiative processes. Wang et.al. showed that gold nanostars (GNSs) can produce heat under NIR light irradiation efficiently [3]. It also has the benefits of excellent photothermal stability and biocompatibility [4]. In this way, GNSs are one of the promising photothermal agent in the biomedical field recently.

2.2.2 Black phosphorus (BP)

BP, which is a kind of double dimensional material, owns lots of advantages like the huge specific surface area, excellent NIR photothermal conversion efficiency (PCE) and quantum confinements for quantum dot derivatives of BP which is vertical to the basic plane [5]. Jundong Shao et.al. demonstrated that biodegradable black phosphorus quantum dots (BPQDs)/poly (lactic-co-glycolic acid) (PLGA) nanospheres are produced through the processing of PLGA and BPQDs using an emulsion method. The hydrophobic PLGA both takes the inner BPQDs out of oxygen and water in order to enhance its photothermal stability, and controls the BPQDs' degradation rate. The experiments, which have been done both inside and outside the body, prove that the BPQDs/PLGA nanospheres are capable with good biocompatibility and mild toxicity, and also have high PTT efficiency and brilliant tumour targeting ability, which are demonstrated according to the nanospheres' remarkably effective tumor ablation with the laser illumination from near-infrared (NIR) [6].

2.2.3 Porphyrin

Since many biological organs in living systems are made of peptides and porphyrins, utilizing comparable structures in the PTT can partially address the drawbacks of the conventional inorganic photothermal materials. For instance, Qianli Zou et al. presented a supramolecular approach that uses peptide-modulated self-assembly of photoactive porphyrins to make photothermal nanodots. Porphyrins' ability to self-assemble can lead to the development of nanodots that totally suppress singlet oxygen generation and fluorescence emission because their substructures are J-aggregates. This will enable the high photothermal conversion efficiency, which is essential for PTT operations [7].

2.3. Current problems with PTT and their solutions

The two main concerns with PTT today are that (1) it has poor targeting capabilities, which will harm nearby normal tissues, and (2) cancer cells' thermal defense mechanisms can lessen the impact of PTT. The two techniques listed below are the primary remedies for them.

2.3.1 Improve the targeting ability

In order to increase the reaction yield, Li Liang et al. created CuS@BSA, which consisted of copper (II) sulfide (CuS) nanoparticles covered by bovine serum albumin (BSA). After additional conjugation of the ligand cyclic RGD which can target tumors and the NIR fluorescent probe MBA on the top of CuS@BSA, then the CuS@BSA-MBA-cRGD was produced. They found that the CuS@BSA-MBA-cRGD is capable of targeting thanks to acceptor-ligand affinity in their tests of the recovery of the entire body of the mice which are bearing tumors. This ability is attributed to the NPS's potential to specifically activate integrin-mediated active transport by cRGD ligands. The nanocomposite CuS@BSA-MBA-cRGD is able to be considered a potential PTT agent which is used to target tumors for photothermal treatment as a result [8].

2.3.2 Overcome the thermal protection mechanism of cancer cells

Low-temperature photothermal therapy is becoming more and more popular since high temperatures cause cancer cells' thermal defense system to activate. The Bi@ZIF-8 (BZ) nanomaterial was created by Jinghua Li et al. using a reduction technique which only require one step. After that, gambogic acid which is a natural suppressant of Hsp90, was put onto the BZ nanomaterial through physical blending with high efficiency. In acidic circumstances, this nanomaterial presented an obviously better drug release rate with higher temperature and in nice light stability due to the appearance of the laser irradiation. Additionally, it exhibited an about 24.4% photothermal conversion efficiency. In light of its excellent biocompatibility, this new nanomaterial had the potential to be used in low-temperature PTT and achieve brilliant therapeutic efficacy [9].

3. PDT

3.1. Theory

PDT largely depends on PSs to generate $^1O_2$ from O_2 with the induction of specific wavelengths of light, leading to oxidative damage to cancer cells and killing them, and even causing immunogenic cell death (ICD).

3.2. The main nanomaterials used in the PDT

There are also various nanoparticles used as photosensitizers PDT, like carbon nanomaterials, upconversion nanoparticles (UCNPs), and quantum dots (QDs).

3.2.1 Carbon nanomaterials

An excellent biocompatibility and distinctive photophysical characteristics of carbon-based materials make them suitable for PDT applications. In addition to the benefits for all, graphitic carbon nitride (g-C_3N_4) is part of them and is a low-cost, nontoxic, and environmentally benign material. Additionally, it is highly resistant to heat, powerful acids, and powerful alkaline solutions and also has good water solubility. It was shown by Gabriela N. Bosio et al. that g-C_3N_4 can be used to treat the hypoxia in tumor tissues. The g-CN_4-based nanomaterials' band gap should be around 1.23 - 3.0 eV is required for the production of oxygen from water splitting under irradiation. As a result, the hypoxia in the tumor tissues can be reduced [10].

3.2.2 Upconversion nanoparticles (UCNPs)

UCNPs can emit NIR or visible light which is in narrow spectrum bandwidth, having some characteristic optical qualities especially the ability to increase the penetration depth of light inside biological tissues [11]. UCNPs also exhibit nice biocompatibility. The property has already been discovered that functionalized ultra-small UCNPs can inch by inch leave reticuloendothelial systems (RES) and have no appreciable deleterious effects on the animals who receive treatment [12]. Hou et al. constructed a titanium dioxide-coated UCNP nano-carrier. With NIR excitation, UCNPs were transformed into ultraviolet light that was compatible with titanium dioxide's absorption, promoting $^1O_2$ production and efficiently eliminating malignancies. In this way, the UCNPs can have a brilliant application in PDT[13].

3.2.3 Quantum dots

Take ZnO QDs on the SW480 tumor cells as an example, the results demonstrate that when exposed to the ultraviolet light, the ZnO QDs can produce ROS, like the singlet oxygen, hydroxyl radical and so on. These substances will lead to the integrity of cell membrane and the organelles with important physiological functions like the lysosomes and mitochondria, which finally leads to the cell apoptosis. In this way, the ZnO QDs can have a good effect in the tumor treatments [14].

3.3. Current problems with PDT and their solutions

The current basic problems with PDT are that (1) The lack of ideal photosensitizers. (2) The depth which light sources can penetrate is not enough. (3) The anaerobic environment in the cancer cells will decrease the impact of the PDT. Here are three methods to relief the problems respectively.

3.3.1 Improving the properties of PS

Hypericin (Hyp) has a lot of advantages like low dark toxicity, the absorption from 400 to 600 nm, excellent singlet oxygen yield, so it was regarded as a promising PS for PDT. However, the application was hindered due to the poor solubility. Then the Hypericin thermosensitive liposomes (Hyp-TSL) can solve this problem. Hyp-TSL can be accumulated inside the body especially in the tumor site. It is also quite safe to be used in intravenous applications. Besides, since the Hyp-TSL is sensitive to heat, it can be easily absorbed by tumor and then the heat will destroy the structure of TSL and release Hyp. In this way, the property of the Hyp was improved and this method does no harm to the real effects of Hyp [15].

3.3.2 Increasing the penetration depth which light sources can penetrate

UCNPs are capable with the excellent ability to turn NIR light into shortwavelength photons and also because of its brilliant biocompatibility, high safety and other benefits, it is always used as energy donors or the carriers of PS in PDT therapy. In the study of Yi Jin, et al., they proposed a upconversion nanoplatform with many functions, a long single-stranded DNA (ssDNA) which has a survivin-targeted DNAzyme and repetitive aptamer (AS1411) was attached to the UCNPs through electrostatic attraction. When the nanoplatform gets into the targeted cancer cells, NIR light is able to trigger PDT to produce reactive oxygen species (ROS) to cause the death of cancer cells [16]. In this way, the penetration depth can be improved.

3.3.3 Improving the oxygenation in the cancer site

Jin Zhang et al. showed an apoptosis and tumor responsive photoactivity conversion nanocomposite (MPPa-DP) which was used to keep the oxygenation of tumor both before and after PDT. This nanocomposite exhibits a modest photoactivity under physiological circumstances. Given the high concentration of H_2O_2 in the tumor microenvironment, this nanocomposite might utilize the H_2O_2 to create oxygen and free the chimeric peptide PPa-DP with high photoactivity, which would oxygenate the tumor and PDT. Additionally, because cell apoptosis is induced by PDT, the photoactivity of PPa-DP could be effectually quenched and then the use of oxygen started to slow down, which stopped apoptotic cells from consuming any more residual oxygen. The tests which have been done both inside body and outside the body showed that the photoactivity of this nanocomposite was able to be effectively modified and the consumption of oxygen could also be reasonably controlled, which caused the increase of the remaining amount of oxygen in the tumor site after PDT [17].

4. Discussion

According to the theory, the contrast between PTT and PDT is that PTT mainly depends on the heat energy to kill the cancer cells, while PDT uses the singlet oxygen to cause the oxidative damage to cancer cells to meet the demands of therapy. From the examples above, PTT and PDT do have their own advantages, while using the combination of them can have a better effect. This combination can maintain their own benefits and make up the shortcomings of each other at the same time.

4.1. The effect of the combination of PTT and PDT

Under the circumstance of low duration levels and laser power, the combination of the irradiation conditions of PDT and PTT triggered a synergistic reaction which result in the whole cell population's death. The effectiveness of drug delivery that targets tumors was also enhanced by this combination.

One of the major therapeutic issues when employing a single photodynamic therapy is the depletion of tissue oxygen caused by a lack of molecular oxygen, which would worsen local hypoxia and reduce the effectiveness of ROS formation. PDT and PTT could combine their efforts to enhance oxygen transport in order to combat the hypoxic effect. Since localized heat might increase blood flow to the tumor location, the oxygen content will increase [18]. For the PTT, a very powerful laser is typically required to produce a lot of hyperthermia. However, exposure to bright light may have negative effects on healthy tissues that it penetrates. PDT and PTT work together to enable PTT to use a lower laser power. Milder hyperthermia can improve cellular medication absorption and decrease tissue hypoxia, making the cells more responsive to the effects of other therapies [19–21]. In this way, the PDT and PTT combination is able to provide greater treatment effectiveness with fewer adverse effects.

Wu et al. Synthesized AAM HNSs nanoparticles by trapping Ce6 in hollow, mesoporous MnO2 that has been altered to absorb in the NIR II region. In this setup, MnO2 not only generated ROS for PDT but also used acid sensitivity to regulate the release of Ce6. ROS greatly increased the laser absorption of the system (630 nm and 1 064 nm), showing that PDT had a photothermal effect that encouraged PTT [22].

4.2. The direction of the future developments of PTT and PDT

Even though there have been numerous experiments on how to improve the PTT and PDT, there is still room for improvement.

The PTT metals may have toxicity issues, extreme hot effects, metabolization issues, and some other issues. Future researches should concentrate on creating photothermal reagents that have high levels of biological security, conversion efficiency, and targeting precision. Future photothermal materials must also be compatible with biological imaging, medication therapy, and other techniques in order to attain outstanding anticancer efficacy [23]. In this way, the PTT can have a better effect with high security.

Then, with regard to PDT, issues could arise in the areas of in vivo biodistribution, general toxicity, cumulative effects on the human body, unclear pharmacokinetic features, and more [24]. Those problems are needed to be solved before put into use for quite a lot of people. Then, as nanotechnology continues to advance, it will be necessary to solve all of those issues.

5. Conclusion

With the help of the nanomaterials, the drugs can have better biocompatibility, more accurate targeting and other good properties, and the PTAs and the PSs can also have improvements of their effects. Besides, the nanomaterials can also improve the environment in vivo to make it more suitable for the PTAs and PSs to work. PTT and PDT working together can also bring a better result. In this way, the phototherapy can have better effects. This article provides detailed understanding on the contributions brought by the nanomaterials in phototherapy. However, phototherapy still needs some improvements. In the future, researchers can pay more attention to the long-term effects brought by the nanomaterials inside human body and the absorption and metabolism of drugs in vivo to have better securities. Along with the development of nanotechnology, more detailed problems about phototherapy can be solved. Thus, the phototherapy can be applied in a larger range of clinic treatments.

References

[1] Yaorongyun, the latest cancer data in China in 2020 The number of cases and deaths ranked first in the world, 2022-08-30, 2022-11-8.

[2] Jeremy B. Vines, Jee-Hyun Yoon, Na-Eun Ryu, et al, Gold Nanoparticles for Photothermal Cancer Therapy. Frontiers in Chemsitry, 2019, 7: 167-167.

[3] Wang, L., Meng, D., Hao, Y., et al., Gold nanostars mediated combined photothermal and photodynamic therapy and X-ray imaging for cancer theranostic applications. J. Biomater. Appl, 2015, 30(5): 547–557.

[4] Pervin Deveci, Synthesis, optical properties and photherapy applications of gold nanostars. Journal of Inclusion Phenomena and Amcrocyclic Chemistry, 2021, 99(1):23-31.

[5] Xiaoyan Yang, Gongyuan Liu, Yunhao Shi, et al., Nano-Black Phosphorus for Combined Cancer Phototherapy: Recent Advances and Prospects. Nanotechnology, 2018, 29(22), 222001.

[6] Shao, J.; Xie, H.; Huang, H. et al., Biodegradable black phosphorus-based nanospheres for in vivo photothermal cancer therapy, Nature Communication, 2016, 7(1): 1-13.

[7] Qianli Zou, Manzar Abbas, Luyang Zhao, et al., Biological Photothermal Nanodots Based on Self-Assembly of Peptide−Porphyrin Conjugates for Antitumor Therapy. Journal of the American Chemical Society, 2017, 139: 1921-1927.

[8] Li Liang, Shuwen Peng, Zhenwei Yuan, et al., Biocompatible tumor-targeting nanocomposites based on CuS for tumor imaging and photothermal therapy.RSC Advances, 2018, 8: 6013-6026.

[9] Jinghua Li, Daoming Zhu, Weijie Ma, et al., Rapid synthesis of a Bi@ZIF-8 composite nanomaterial as a near-infrared-II (NIR-II) photothermal agent for the low-temperature photothermal therapy of hepatocellular carcinoma, Nanoscale, 2020, 12(32):17064-17073.

[10] K. Su, S. Deng, L. Li, et al., G-C3N4 derived materials for photocatalytic hydrogen production: a mini review on design strategies, Journal of Renewable Materials, 2022, 10 (3): 653–663.

[11] Wang C, Tao HQ, Cheng L, et al., Near-infrared light induced in vivo photodynamic therapy of cancer based on upconversion nanoparticles, Biomaterials, 2011, 32: 6145-54

[12] Xiong LQ, Yang TS, Yang Y, et al., Long-term in vivo biodistribution imaging and toxicity of polyacrylic acid-coated upconversionnanophosphors, Biomaterials, 2010, 31: 7078-85.

[13] Hou Z,Zhang Y, Deng K,et al., UV-Emitting up conver- sion-based TiO2 photosensitizing nanoplatform: near-in- frared light mediated in vivo photodynamic therapy via mi- tochondria- involved apoptosis pathway. ACS Nano, 2015, 9(3): 2584-2599．

[14] Tianming Song, Yawei Qu, Zhe Ren, et al., Synthesis and Characterization of Polyvinylpyrrolidone Modified ZnO Quantum Dots and Their In Vitro Photodynamic Tumor Suppressive Action, International Journal of Molecular Sciences, 2021, 22(15): 8106.

[15] Alice Abu Dayyih, Mohamad Alawak a, Abdallah M. Ayoub, et al., Thermosensitive liposomes encapsulating hypericin: Characterization and photodynamic efficiency, International Journal of Pharmaceutics, 2021, 609: 121195．

[16] Yi Jin, Hao Wang, Xiaona Li, et al., Multifunctional DNA Polymer-Assisted Upconversion Therapeutic Nanoplatform for Enhanced Photodynamic Therapy, ACS Appl. Mater. Interfaces, 2020, 12: 26832−26841.

[17] Jin Zhang, Mengqing Xu, Yongli Mu, et al., Reasonably retard O2 consumption through a photoactivity conversion nanocomposite for oxygenated photodynamic therapy, Biomaterials, 2019, 218: 119312.

[18] Liu, P.; Zheng, H.; Yang, Z.; et al., Facile preparation of versatile gadolinium-chelated protein nanocomposite for T1 magnetic resonance imaging-guided photodynamic and photothermal synergetic therapy, Journal of Materials Chemistry, 2018, B 6(11): 1688–1698.

[19] Gao, D.; Guo, X.; Zhang, X.; Chen, S.; Wang, Y.; et al., Multifunctional phototheranostic nanomedicine for cancer imaging and treatment, Materials Today Bio, 2020, 5: 100035.

[20] Ji, D.K.; Ménard-Moyon, C.; Bianco, A., Physically-triggered nanosystems based on two-dimensional materials for cancer theranostics, Advanced Drug Delivery Reviews, 2019, 138: 211–232.

[21] Zeng, D.; Wang, L.; Tian, L.; et al., Synergistic photothermal/photodynamic suppression of prostatic carcinoma by targeted biodegradable MnO2 nanosheets. Drug Deliv., 2019, 26: 661–672.

[22] WU K, ZHAO H, SUN Z, et al., Endogenous oxygen gen-erating multifunctional theranosticnano platform for enhanced photodynamic-photothermal therapy and multi-modal imaging, Theranostics, 2019, 9(25): 7697- 7713 .

[23] Haohao Zhang, Guihuan Chen, Bing Yu, et al. Emerging Advanced Nanomaterials for Cancer Photothermal Therapy, Reviews on Advanced Materials Science, 2019, 53: 131-146.

[24] ZHOU Jie, CHEN Yu, CHEN Daozhen, et al., Application of nanoparticles in photodynamic therapy of tumor. Journal of Practical Oncology, 2018, (03):245-249.