Ecomaterials 2023; 3(1): 7 pages
Original Research Article

Research Progress of Photothermal Nanomaterials and Bioreaction Degradation Mechanism in Cancer Therapy

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ARTICLE INFO

Received: 2 January 2023
Accepted: 17 February 2023
Available online: 13 March 2023

http://doi.org/10.59400/eco.v3i1.25

ABSTRACT: Photothermal therapy (PTT) is an alternative new cancer treatment after surgery, radiotherapy and chemotherapy. Thinking about the characteristics of tumor photothermal therapy, the key factors of photothermal nanomaterials in clinical applications include theire photothermal conversion efficiency, surface modification activity, biocompatibility, biodegradability and low toxicity. With the development of photothermal nanomaterials, PTT holds immense potential in clinical translation. Up to now, four generation of photothermal nanomaterials have been developed, including noble metal nanoparticles, carbon based nanomaterials, metal and non-metallic compound nanomaterials and organic dyes.

KEYWORDS: Photothermal therapy; Photothermal nanomaterials; Biodegradation; Biological metabolism

Photothermal therapy (PTT) is another promising new tumor treatment method after surgery, radiotherapy and chemotherapy in clinical practice. Photothermal therapy is mainly based on gathering nano-photothermal materials at tumor tissues with various targeting technologies, and then using external light sources with strong tissue penetration (currently, the most studied ones are near-infrared light) to radiate tumor tissues, converting the light energy of external light sources into heat energy through nano-photothermal materials, thus increasing the local temperature of tumor tissues and killing tumor cells to achieve the purpose of tumor treatment. The most advantageous features of this treatment method are good specificity in inactivating tumor tissues, causing little systemic damage to the patient's body and few complications. In addition, a large number of studies have shown that this method can not only kill tumor cells, but also inhibit tumor metastasis[1,2].

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Based on the characteristics of tumor photothermal therapy, the selection and requirements of photothermal nanomaterials are particularly important, especially the photothermal conversion efficiency, surface modification activity, biohistocompatibility, biodegradability, and low toxicity of photothermal nanomaterials are the key factors to be considered in clinical applications. To date, researchers have developed many photothermal nanomaterials for photothermal therapy of tumors, mainly including inorganic photothermal nanomaterials (e.g., noble metal nanomaterials[3,4], carbon-based nanomaterials[5,6], sulfide nanomaterials[7,8], etc.) and organic photothermal nanomaterials (e.g., indocyanine green[9,10], Prussian blue[11], and other organic dyes). In terms of development history, four generations of nanophotothermal materials have been developed so far, including nanomaterials such as noble metal nanoparticles, carbon-based nanomaterials, metal and non-metal compound nanomaterials, and organic dyes.

1 Research progress of photothermal nanomaterials

1.1 The first generation of photothermal nanomaterials --- noble metal nanoparticles

The main precious metal nanoparticles used for tumor photothermal therapy are gold, silver, platinum and palladium. These precious metal nanomaterials all have strong local surface plasmon resonance effect and strong surface functionalization modification activity, which can be modified by various means of surface activity to make them obtain the maximum light absorption peak, so that they can produce the strongest photothermal conversion effect when applied in vivo. However, their disadvantages are higher cost, poor photothermal stability, and poor biodegradability, especially the poor biometabolism of precious metals, and therefore there is a high risk of developing chronic hypotoxicity in vivo, and the effects of these chronic hypotoxicity on the organism need to be determined after long-term observation. Studies have shown that the optimal near-infrared window for ideal nanomaterials is 650–950 nm, i.e., a window with strong light absorption and high photothermal conversion efficiency. With the continuous progress of nanotechnology, researchers have now developed a variety of structures of gold nanoparticles, including colloidal gold nanoparticles, gold nanorods, gold nanoshells, gold nanocages and gold nanostars. The maximum absorption peak of colloidal gold nanoparticles is between 400–600 nm, while the maximum absorption peak of gold nanorods for light can reach 800 nm, and the surface functionalization modification of gold nanorods and the stability of colloids are better[12–14]. The gold nanoshells coated with polyethyleneglycol (PEG) 5000 have been approved by the US Food and Drug Administration (FDA) and are currently in clinical trials, mainly for the clinical experimental treatment of head and neck tumors and lung cancer[15]. The recently developed gold nanostars exhibit higher photothermal conversion efficiency, better surface modification function, stronger drug loading capacity and lower cytotoxicity than gold nanorods and gold nanoshells due to their dendritic surface structure.

In addition, the application of precious metal particles such as silver, platinum and palladium in tumor photothermal therapy has been studied more extensively, while the combination of these metal particles or with organic photothermal nanomaterials has been paid more attention to the efficacy of tumor photothermal therapy. For example, wrapping gold nanorods with silver, then including a layer of gold nanoparticles on the outside, and then surface functional active modification on the surface of gold nanoparticles, together with thiolated active aptamer probes and fluorescently labeled cDNA, so that the prepared nanomaterials can both enhance the compatibility of biological tissues and achieve fluorescence imaging-guided targeted tumor photothermal therapy[16]; another example, the surface of palladium nanosheets Although platinum is a commonly used drug in tumor chemotherapy, platinum itself has a high toxicity as a nanomaterial, so its application in tumor photothermal therapy is somewhat limited, but its toxicity can be controlled by controlling the particle size and shape of platinum materials.

1.2 Second-generation photothermal nanomaterials - carbon-based nanomaterials

The more studied carbon-based nano-thermal materials are mainly graphene and carbon nanotubes. Despite their large photothermal conversion area, carbon-based nanomaterials have poor near-infrared light absorption ability and dispersion in water. However, due to their good electrochemical properties, strong non-covalent bonding properties and large absorption area on the surface of the body, they can be modified with appropriate surface functional activity (e.g. surface linked PEG or wrapped polymer) to increase both their dispersion in water and photothermal conversion efficiency, as well as their drug-carrying capacity, which can well realize the synergistic effect of tumor photothermal therapy and chemotherapy. The synergistic effect of tumor photothermal

therapy and chemotherapy can be well realized. For example, modification of chiral carbon nanotubes with C18-PMH-mPEG can both increase the biohistocompatibility of carbon nanotubes and exhibit enhanced photothermal effects and drug-carrying capacity[17]. As another example, the light absorption capacity of redoxed graphene is much greater than that of unreduced graphene, if a layer of mesoporous silica and PEG is wrapped on the surface of redoxed graphene, and then a tumor-specific targeting peptide is attached and then loaded with chemotherapeutic drugs, this not only increases the water solubility of graphene, but also increases the tumor targeting of this nanomaterial while increasing the photothermal conversion effect through promoting the release of chemotherapeutic drugs, thus achieving synergistic treatment with photothermal and chemotherapy[18].

1.3 Third generation photothermal nanomaterials - metallic and non-metallic compounds

Currently, more researched are metal-sulfur compounds photothermal nanomaterials, including copper sulfide (CuS), zinc sulfide (ZnS), molybdenum disulfide (MoS_2), molybdenum diselenide ($MoSe_2$), tungsten diselenide (WSe_2) and tungsten disulfide (WS_2), etc. These materials have the advantages of low cost, strong near-infrared light absorption, high photothermal conversion efficiency, low cytotoxicity and controllable particle size morphology, and present a large potential for application in tumor photothermal therapy. For example, the flower-like structure of CuS can greatly increase the ability of near-infrared light to kill tumor cells with a lower energy density[7]; molybdenum disulfide (MoS_2), molybdenum diselenide ($MoSe_2$), tungsten diselenide (WSe_2) and tungsten disulfide (WS_2) are two-dimensional transition metal sulfides with strong covalent bonds between the layers of properties such as stronger covalent bonds and weaker van der Waals forces between the lamellar structures of 2D transition metal sulfides such as tungsten diselenide (WSe_2) and tungsten disulfide (WS_2) make them exhibit better biocompatibility[8]. The research on metallic and nonmetallic sulfides in tumor photothermal therapy is in its infancy and is a hot spot for the research on photothermal nanomaterials.

1.4 Fourth-generation photothermal nanomaterials - organic dye substances

Both noble metal nanoparticles, carbon-based nanomaterials and metal and non-metal compounds are inorganic photothermal nanomaterials. Although their biocompatibility and photothermal conversion efficiency can be enhanced by various surface modifications, they all have the problems of being difficult to biodegrade in vivo, not being easily metabolized and eliminated from the body, and having potential However, all of them have the problems of difficult biodegradation in vivo, poor metabolism and potential long-term chronic toxicity, which greatly limit their clinical applications. For example, PEG-modified gold nanoshells still accumulate in the liver and spleen within 15 days after injection[19]; carbon nanotube-based complexes tend to accumulate in the liver and kidneys, and even the carcinogenicity of some carbon nanotube complexes with aggregates is similar to that of asbestos[20]. Therefore, in recent years, attention has been directed to organic photothermal nanomaterials. Currently, the more studied organic photothermal nanomaterials mainly include nanomicelles wrapped near-infrared dyes[21], porphyrin liposome nanoparticles[22], and some polymers, etc. In addition to their good light absorption efficiency and light conversion efficiency, these organic photothermal nanomaterials also have better biodegradation and metabolic efficiency, and they show biosafety They have obvious advantages in terms of biosafety. For example, photothermal nanomaterials based on proteins (e.g., red blood cell membranes, etc.)[23], liposomes[22], and polydopamine[24] can be completely degraded in vivo, while nanomicelles wrapped with near-infrared dyes can be metabolized and excreted with urine, and photothermal nanomaterials based on polyaniline, polypyrrole, etc. nanomaterials are not easily degradable, but they do not release toxic elements either. At present, there are various problems concerning the photothermal nanomaterials

of organic dyes in tumor photothermal therapy, but they offer the prospect of wide application in tumor photothermal therapy because of their biological safety advantages.

2 Bioresponsive degradation mechanism of photothermal nanomaterials

According to the requirements of the US FDA, photothermal nanomaterials that can be clinically applied must meet the requirement of being able to be fully degraded by the organism and cleared from the body within a certain period of time[25]. Therefore, the biodegradability and biocompatibility of photothermal nanomaterials are the most essential requirements for examining whether photothermal nanomaterials can be used in clinical applications. Although all four generations of photothermal nanomaterials mentioned above have demonstrated good photothermal therapeutic effects on tumors, they can still lead to chronic toxicity[26], certain side effects[27], or inflammatory reactions[28] in the organism due to their long-term colonization in certain major organs. Therefore, it is important to understand the biodegradability and effective metabolic clearance of the photothermal nanomaterials, while ensuring their good photothermal conversion efficiency, biohistocompatibility and biotargeting.

2.1 Mechanism of enzyme-induced bioresponsive degradation

Enzyme-induced bioreactive degradation mainly includes enzyme-catalyzed hydrolytic degradation and enzyme-catalyzed oxidative degradation. Phospholipase A2 (PLA2) is a known hydrolytic agent in organisms that recognizes and hydrolyzes the sn-2 acyl bond of phospholipids and releases free fatty acids and lysophosphatidic acid, which is very common in mammalian tissues and highly expressed in tumor cells[29]. Therefore, the lipid-based structural modification of photothermal nanomaterials to increase their biodegradability using the enzyme-catalyzed hydrolytic properties of PLA2 in vivo is a typical representative of the enzyme-catalyzed hydrolytic biodegradation mechanism. For example, lipid-containing bilayer liposomes are approved by FDA as drug carriers due to their biodegradability. There are studies to promote the photothermal conversion efficiency of liposomes by loading indocyanine green in the aqueous core or lipid bilayer on liposomes to increase the near-infrared light absorption peak of liposomes[30]. As another example, Liposome-gold clusters (LGCs) are another lipid structure formed by assembling gold clusters in an aqueous core on liposomes, where the high density filling of gold clusters preserves the NIR absorption properties of the metal shell and the liposomal scaffold provides the biodegradability of the clusters[31].

Horseradish peroxidase (HRP) is one of the metalloenzymes widely used for oxidative catalysis of various substrates, usually in the presence of hydrogen peroxide (H_2O_2), and this oxidation is often considered to mimic the redox process in cellular metabolism. Both graphene and single-walled carbon nanotubes (SWNTs) can be degraded by HRP in the presence of H_2O_2, and their degradation products gradually evolve from oxidized aromatic fragments to CO_2[32–33]. Due to the slow degradation rate of HRP-induced carbon-based nanomaterials in vivo, their degradation by-products such as reactive oxygen species are still not suitable for clinical applications. Another study has shown that SWNTs can also be degraded by myeloperoxidase[34].

2.2 PH-induced bioresponsive degradation mechanism

The intertumor tissue pH was 6.8, which is lower than normal tissue (pH=7.2–7.4). In addition, the pH of endosomes and lysosomes is lower (pH<6). This difference in pH can be used to degrade the primary structure of nanomaterials. In the last few years, a large number of biodegradable polymers such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(ε-caprolactone) (PCL) and poly(lactic acid- glycolic acid) (PLGA) have been approved by the FDA for in vivo applications[35]. These acid-unstable groups similar

to esters and anhydrides can be introduced into polymer matrices to modify chain degradation. In an acidic environment, these groups can be hydrolyzed by their ester bonds and the remaining part can be metabolized by the normal acid cycle. Since these biodegradable polymers usually do not absorb light in the near-infrared region, researchers have integrated these polymers into photothermal nanomaterials through extensive efforts to enhance the absorption in the near-infrared region of the spectrum.

In addition, pH-dependent oxidative biodegradation processes of low valence states have been found in some inorganic photothermal nanomaterials. For example, MoOxPEG has a unique pH-dependent degradation process, mainly because it can maintain its stability in acidic environments and can be rapidly degraded in the physiological pH range[36].

2.3 Mechanisms of bioresponsive degradation induced by other factors

In addition to the bioresponsive degradation mechanisms described above, there are many more mechanisms regarding the bioresponsive degradation of photothermal nanomaterials, both known and unknown that cannot be addressed in this paper. For example, systemically administered IOPS is first taken up by the mononuclear phagocytic system in the liver and spleen, and then degraded to Fe ions via lysosomes. The degraded Fe ions are retained in storage proteins or eliminated from the body via typical iron metabolism pathways[37].

3 Outlook

With the continuous advancement of scientific and technological means, more and more inorganic or organic photothermal nanomaterials have been developed. From the perspective of physicochemical and material properties, scientists' previous studies have focused more on the near-infrared light absorption ability and photothermal conversion efficiency of these materials as well as biohistocompatibility and tissue cell low toxicity studies, and as these materials will be used in clinical applications, the photothermal nanomaterials limitations still face great challenges. The development of safety-oriented biodegradable photothermal nanomaterials is preferred, and the ideal photothermal nanomaterials should be biologically inert, stable in the biological environment, and can be degraded and metabolically cleared from the body immediately after the completion of their functions; future research should focus more on the bioresponsive degradation and metabolic clearance mechanisms of the materials, as this is the key pathway for the safety of photothermal nanomaterials for clinical applications; bioresponsive nanomaterials are the key pathway for the safety issues. In addition, current biohistocompatibility evaluation methods focus on acute toxicity, and long-term toxicity and non-toxicity responses of tissue cells need to be further evaluated through large-scale cohort follow-up studies, as well as multimodal targeting and stimulus response of biodegradable photothermal The study of the biological effect mechanism of the combination of nanomaterials acting in vivo is an important issue that needs to be urgently addressed for future clinical applications.

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