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Up-conversion Nanoparticles with Drugs Target the Tumor Microenvironment

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Abstract. The internal environment in which cancer cells develop and persist is referred to as the tumor microenvironment (TME). Cancer cells interact with the microenvironment, leading to further cell proliferation and migration. Traditional Chinese medicines (TCM) have been shown in trials that can target and improve the tumor microenvironment. Up-conversion nanoparticles (UCNPs) can exploit the properties of the tumor microenvironment for precise targeting while preventing the premature release of their loaded medications. In this overview, we review any existing research results on the targeting of tumor microenvironment by Traditional Chinese medicines and Up-conversion nanoparticles in recent years. We discuss the possibilities and advantages of combining Traditional Chinese medicines with Up-conversion nanoparticles and summarize their current unresolved issues.

Keywords: Tumor microenvironment, Traditional Chinese medicine, upconversion nanoparticles, precision targeting

1. Introduction

IARC figures show that in 2020, 19.3 million individuals received a cancer diagnosis, while 10 million people died from the disease [1]. Cancer is not only a major cause of increased mortality in the national population, but also an important obstacle to increasing the average human life expectancy. The existing cancer treatment strategies have not yet achieved the desired results. Hence, it is essential to enhance treatment strategies and develop safer and more effective anti-cancer drugs.

TME is required for tumor persistence in the body and is an important contributor to the ongoing development of cancer. TME-targeted treatment may emerge as a fresh approach to combat cancer. A vast variety of scientists have used the biological features of TME, such as hypoxia, low pH, and high H2O2 concentration, to produce innovative targeted therapies, with promising preliminary findings.

Considerable research has confirmed that active Ingredients in TCM can target TME for cancer therapy, although it's targeting still has to be improved.

UCNPs can utilize TME‘s properties for accurate aiming [2] and are capable of encapsulating insoluble drugs and minimizing drug side effects [3]. UCNPs are luminescent nanomaterials, consisting of a matrix material, an activator (activating ion), and a sensitizer (sensitizing ion) . Activated ions provide the luminescent center; sensitized ions absorb near-infrared; matrix materials provide the crystal body lattice structure, which can activate the ions and sensitize them to the target sites [4]. NIR causes the sensitized ion to become excited, and the excited sensitized ion transmits energy to the surrounding activated ion, causing it to become excited. The activated ion persists to

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sufficient energy to reach its excited state. During this procedure, Low-energy photons are converted to high-energy photons by UCNPs, thus achieving short-wavelength up-conversion emission [5]. This means that UCNPs may absorb NIR while emitting UV or visible light. In comparison to visible and ultraviolet light, NIR radiation may penetrate deeper into the body[6]. It can be used to precisely target tumor cells in deep tissues when applied to PDT.

It is not yet known whether the loading of the active ingredients of Traditional Chinese medicines onto UCNPs can significantly enhance their targeting properties. Therefore, we judge the research progress in this field and analyze the current problems by exploring the relevant studies on Traditional Chinese medicines and UCNPs in targeting TME in recent years. To lay the foundation and clarify the direction for research in UCNPs loaded with Traditional Chinese medicines targeting TME. In order to develop safer and more efficient Nano anti-cancer drugs, which will be an innovation in cancer treatment.

2. TCM active ingredients target TME

TCM active ingredients are capable of targeting TME through different mechanisms. This section focuses on the mechanisms associated with different types of Traditional Chinese medicines targeting TME.

2.1. Heat-clearing medicines

Taraxacum officinale extracts inhibited cancer cell development via inhibits the cascade of STAT3, PD-L1, and IL-10 immune-suppressive signaling. In addition, the extract reversed M2 TAMs to M1 type [7].

Ursolic acid, extracted from Hedyotis diffusa, corrects the tumor-mediated immunosuppressive microenvironment and lowers the proportion of MDSCs and Tregs in tumor tissues [8].

2.2. Exterior-releasing medicines

Puerarin, derived from Pueraria, markedly decreased the ECM's collagen content and the proportion of CAFs that were α-SMA-positive [9].

2.3. Wind-dampnessdispelling medicines

Triptolide, derived from Tripterygium wilfordii, inhibits the infiltration of TAMs into TME by downregulating CXCL12 and suppresses the movement of cancerous cells by decreasing VEGF expression[10].

2.4. Blood-activating and stasis-resolving medicines

Curcumin, derived from Turmeric, significantly inhibited the synergistic interaction between CSCs and TME, thereby suppressing the survival of cancer stem cells [11].

2.5. Tonifying medicines

Astragalus membranaceus activates M1-type TAMs via NFκB, TLR4 as well as MyD88 signaling cascade and increases T cells' capability in TME to destroy tumors, thereby reducing the immunosuppressive state [12].

2.6. Detoxication and promoting granulation medicines

YTE-17 derived from Yunnan Garcinia blocked TAM polarization of M2-type in tumorigenesis by downregulating JNK, STAT3, and ERK signaling cascades. Furthermore, it dramatically reduced TAM expression by suppressing M2 main markers like CD206, Arg-1, IL-10, and TGF-β and upregulating M1 major markers like IL-12, iNOS, and TNF-α [13].

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3. UCNPs target TME

Recently, there has been boosting evidence that TME exhibits distinctive characteristics of normal tissue in terms of angiogenesis, perfusion, oxygenation, and metabolic status. Taking use of the distinctions between normal and sick situations to trigger drug release does not require external mediators and therefore is not invasive. Therefore, UCNPs with TME self-responsive therapy is gaining popularity in terms of minimizing side effects and enhancing therapeutic results. In this section, PH-responsive UCNPs, redox-responsive UCNPs, hypoxia-responsive UCNPs, and multi-responsive UCNPs are highlighted.

3.1. PH-responsive UCNPs

TME has a pH of roughly 6.5-6.8 below that of normal tissue, which has a pH of 7.4. Despite the fact that the pH difference between TME and normal tissue is smaller than one pH unit, many compounds are still able to respond to such minute pH variations. They can respond to such fine pH changes that they have been widely used to fabricate a variety of different acidic TME-responsive cancer nanotherapies. Thus, the pH difference existing between TME and normal tissue can serve as a trigger signal for drug release.

Li et al. Developed a low pH-triggered nanopreparation (PPNs) relying on tumors, consisting of photosensitizers (PSs), pH-responsive polymeric ligands, and UCNPs for targeted PDT in deeper malignancies [14]. The PSs aggregated in PPNs were self-quenched at a pH of 7.4. However, when entering the TME with a lower pH (pH=6.5), the PPNs decomposed into individual UCNPs. Aggregated PSs (self-quenched state) are encouraged to decompose through the breakdown process into extended free molecules (unquenched state). Under NIR radiation, upconversion luminescence from PPNs could enable stray PSs to become protective in an acidic TME, which can damage malignant cells.

Xie et al. Created a nanocarrier laden with O2 that can release medicine in the low pH environment of malignancies [15]. It consists of lanthanide-ion-doped UCNPs, photosensitizer RB, photosensitizer carrier mSiO2, and oxygen reservoir ZIF-90. For superior synergistic therapy and to overcome malignant hypoxia, the ZIF-90 shell decomposes in acidic environments, enabling the speedy release of O2 as well as DOX loaded on this nanocarrier at low pH TME.

3.2. Redox-responsive UCNPs

TME exhibits high H2O2 and GSH concentrations, which are significantly different from healthy tissues. Therefore, the difference in H2O2 and GSH concentrations between TME and normal tissues could serve as a trigger signal for drug release.

Bi et al. Designed a GSH-mediated nanocomposite composed of UCNPs, Pt(IV), and ZnFe2O4[16]. UCNPs were used as UV-Vis light sources to excite the ZnFe2O4 Fenton reaction as well as PDT impact. By using GSH, the Pt(IV) prodrug may be turned into the very poisonous Pt(II), which kills malignancy cells. When the Pt(IV) prodrug that linked UCNPs and ZnFe2O4 was removed, the composite dissolved into UCNPs, ZnFe2O4, and the more dangerous Pt(II). These smaller nanoparticles can penetrate deeper into the malignancy and are more cytotoxic.

Feng and colleagues [17] Created a mesoporous material (Fe@Sn-UCNPs). The nanoparticles could be activated via endogenous H2O2 and effectively decompose endogenous H2O2 in TME through an enzyme-like catalytic reaction to decompose O2 in situ to reduce hypoxia and boost O2-dependent Photodynamic antitumor therapeutic effectiveness.

3.3. Hypoxia-responsive UCNPs

Normal tissue oxygen concentration is 2%-9% (40 mmHg pO2), whereas in TME it is 0. 02%-2% (<2.5 mmHg pO2) [18]. Therefore, the oxygen concentration difference that exists between TME and normal tissue can serve as a trigger signal for drug release.

Shao et al. Developed a UCNP@MOF core-shell nanostructure (UCS) consisting of a core of UCNPs and a porphyrinic MOF shell [19]. To create the final TPZ/UCS, The prodrug TPZ may be

activated under hypoxic circumstances by encapsulating it in the nanopore of MOF. TPZ may be induced by hypoxia TME to produce hazardous oxidative radical species, which are more damaging to hypoxic cancer cells than in healthy cells, through a single-electron reduction process.

3.4. Multiple-responsive UCNPs

TME is a complex biological system containing various features such as low pH, high GSH and H2O2 levels, and hypoxia, and the stimulus-response procedure is not only dependent on one TME feature. In UCNPs systems, the application of near-infrared light, the generated UV-visible light, and the generated heat are crucial elements in accelerating the response process to various stimuli.

Wang et al. Synthesized a NIR and pH dual-responsive drug-release nanocapsule [20]. The lanthanide-ion-doped UCNPs cores and convertible poly-o-nitrobenzyl shells. DOX, an anti-cancer medication, was included in the nanocomposite. The capacity of the nanocapsules to release pharmaceuticals in the NIR response is due to the capacity of the poly-o-nitrobenzyl shell to experience hydrophobic-hydrophilic transformation at 980 nm radiation. This cleavage results in side groups of the poly (o-nitrobenzyl) ester being split apart. The DOX and the nanocapsules form hydrogen bonds and interact electrically, which allows the nanocapsules to release medications in a PH-responsive way.

Wang et al. Prepared upconversion nanocomposites consisting of UCNPs cores and convertible polyspiropyran shells [21]. On its medication delivery layer, around 10 weight percent of the anti-cancer medicine DOX is loaded. Multihelical prawn shells can undergo a reversible hydrophobic-hydrophilic transition of switching between UV and visible light or by changes in pH. Thus, the cancer cells' weak acidic environment, or NIR, encourages medication release from the nanocomposite.

4. UCNPs loaded with Chinese medicines target TME

Plumbagin, which is derived from Plumbinis, significantly inhibits the development of cancer. Qiao and colleagues developed a pH-responsive bone-targeted medication delivery device that loads albendanin onto UCNPs, targets TME, and enables the release under pH control to achieve targeted therapy [22].

Curcumin, derived from Curcuma, is effective in inhibiting the growth of tumor cells. Chen et al. Loaded curcumin on Mn2-modified UCNPs, and curcumin can be utilized as a photosensitizer as well as a chemotherapy drug to boost antitumor activity[23].

5. Conclusion

Combining Chinese medicine with UCNPs has undoubtedly provided more options and possibilities for the prevention and treatment of tumors. However, there are also some urgent problems: first, there are still few studies conducted in this direction, and there is a lack of experimental data to support the theory; second, the research is still at the stage of animal experiments, and has not yet reached the conditions for clinical application; third, the toxicity of UCNPs in human body still needs further research. Therefore, more in-depth studies on the issues related to UCNPs targeting TME are needed in order to develop safer and more efficient nanoscale anticancer drugs and provide another possibility for cancer treatment.

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