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Trigger-responsive nanoparticles: control switches for cancer therapy

"The translation of the next generation of triggered nanotechnologies in the clinic that are responsive to multiple triggers, both external and internal, may provide cost-effective and efficient ways of improving the efficiency of chemotherapeutic agents."

KEYWORDS: hyperthermia ■ pH sensitive ■ photothermal effects ■ sonoporation ■ trigger responsive

Conventional chemotherapy in cancers suffers from drawbacks of toxicity and nonspecificity. Nanotechnology has the potential to develop diagnostic and therapeutic platforms for the efficient diagnosis and treatment of cancers. One of the crucial aspects of the success of nanoparticle-based technologies is its ability to specifically attack the cancer cells due to several strategies like passive targeting by the enhanced permeation and retention effect, active biological targeting as well as triggered responses at the desired sites.

Need for trigger-responsive nanoparticles

Trigger-responsive nanoparticles have generated a lot of attention in recent years as they have the potential to act as 'remote switches' that can turn on or off the therapeutic effects of the nanoparticles, based on the presence or absence of the stimulus or trigger to which the nanoparticle is sensitive. The development of smart, stimuli-responsive nanoparticles offers the possibility of controlling the response of the therapeutic agent precisely and specifically. Triggered nanoparticles can achieve specificity without the high costs associated with biological targeting moieties, which are often inefficient as they are associated only with a small fraction of cancer types.

Different types of trigger-responsive nanoparticles

Trigger-responsive nanoparticles are designed such that they respond to some unique physicochemical properties of cancers that may act as internal triggers to make the nanoparticles leaky. Some of the commonly used triggers are low pH and high levels of certain enzymes such as proteases and phospholipases, which

are 'internal triggers' that are associated with cancers. Another type of trigger-responsive nanoparticles are switched on by the specific application of the trigger from outside or 'external triggers', for example, temperature-triggered nanoparticles that can be switched on due to the presence of hyperthermia or laser-induced photothermal therapy. Ultrasound-responsive nanoparticles and microbubbles are another interesting platform that control release from the nanoparticles at specific sites in the presence of high-intensity focused ultrasound. Ultrasound triggered nanoparticles allow the simultaneous imaging of the nanoparticles while controlling the delivery. External triggers such as temperature and ultrasound are easier to control than internal triggers, and are not associated with the problems of variability that may be associated with internal triggers.

Low extracellular pH has been correlated with the aggressiveness of tumors and their drug resistance. For example melanoma cells on incubation at pH 6.8 for 48 h doubled their tendency for pulmonary metastasis when injected intravenously in nude mice when compared with those grown at pH 7.4 [1]. Therapeutic strategies that can exploit this pH trigger are of interest to researchers.

There is evidence for the specificity of triggered nanoparticles that respond to the presence of any of these triggers individually, however, there are only a few studies utilizing multiple triggers simultaneously or sequentially. Such approaches can lead to multifunctional smart nanocarriers that will reduce the errors due to unwanted leakage of drugs and increase the burst phase due to the presence of the triggers while minimizing the baseline leakage under normal physiological conditions.

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Current status, advantages & disadvantages

■ Nanoheaters

Temperature-sensitive nanoparticles are used for simultaneous hyperthermia- and temperature-triggered drug delivery. Magnetic nanoparticles encapsulated within thermosensitive polymeric nanoparticles and thermosensitive lipid nanovesicles can cause hyperthermia followed by a temperature-dependant release of encapsulated drugs, when exposed to an alternating magnetic field. Most of the literature using combined thermochemotherapy revolves around thermosensitive liposomes or polymeric nanoparticles using dipalmitoyl/distearoylphosphatidylcholine or poly(*N*-isopropylacrylamide), respectively, along with magnetic nanoparticles predominantly formed of iron oxides. A number of other magnetic materials also have the potential to be useful in magnetic hyperthermia and combined thermochemotherapy. One challenge for these nanoparticles is to prevent overheating of the tissues. In a recent study Lee *et al.* developed magnetic core-shell nanoparticles using combinations of cobalt, manganese and iron-based core and shell components to optimize the efficiency of conversion of magnetic energy to heat [2]. The challenge is to exploit the unique magnetic properties of such materials while suitably modifying their surface to mitigate any associated toxicity.

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Another limitation of magnetic nanoparticles and temperature-triggered nanoparticles is the extent of penetration of the trigger for deep tumors, which still remain largely inaccessible. The approach is, however, very attractive for surface and near-surface tumors such as skin cancers and breast cancer, where they may be used as alternatives to high cost, biologically targeted nanoparticles. The effectiveness of magnetic nanoparticles when given intravenously for deep-seated tumors will depend on the biological targeting strategies of the magnetic nanoparticles. An interesting study by Dames *et al.* showed the possibility of exploiting alternate routes while using magnetic targeting, for example nanomagnetosols (aerosol droplets comprising superparamagnetic iron oxide nanoparticles) can be focused with

a target directed magnetic gradient field to different areas in the respiratory system and are of potential use for the treatment of tumor nodules in the lungs [3].

■ Acid-based changes

pH-sensitive nanoparticles are made of synthetic polymers and of nonlamellar phospholipids that release their cargo due to a phase transition of the carrier in the presence of acidic environments. Recently, some other nanomaterials have also been proposed for pH sensitivity; for example, mesoporous pH-sensitive silica nanoparticles that respond to the acidic pH of endosomes after endocytosis showed enhanced effects of chemotherapeutic agents in drug-resistant cancers [4].

The main challenge in pH-sensitive nanocarriers is to maximize the stability of the nanocarriers in normal conditions while maintaining the pH-dependant leakage. This is particularly true for cancer therapy where the range of the extracellular pH changes is very narrow (from around 6.8 to 7.4). Also, the role of pH-induced intracellular delivery needs to be clearly differentiated from extracellular pH-dependant drug delivery in cancerous cells. The former requires active endocytosis of the nanocarriers and is associated with endosomal pH changes, which also occur in normal cells.

■ Enzymatic cleavage

Enzyme-sensitive nanoparticles are another attractive option where the presence of enzymes that are overexpressed at the diseased sites is responsible for the increased leakage of drugs at the target site. Proteases are overexpressed in tumors and are often present at the sites of angiogenesis and at the invasive front of cancers, making them more accessible to nanoparticles by enhanced permeation and retention strategies. Proteases can act as triggers that can be exploited to expose an otherwise hidden surface of the nanoparticles such that the nanoparticles are inactive in the absence of the enzyme and become biologically active on exposure of the underlying surface in the presence of the enzyme [5]. Enzyme triggers also allow prodrugs to be converted to more active forms on release from nanoparticles and cleavage of labile linkages of polyethylene glycol which were useful in creating a stealth nanoparticle while in systemic circulation. Wong *et al.* have recently developed a multistage nanoparticle delivery system for deep penetration into tumors that shrinks a 100 nm sized gelatin

nanoparticle to 10 nm due to degradation by matrix metalloproteinase 2 expressed in the tumor microenvironment [6].

■ Sound strategy

Ultrasound was traditionally used only for diagnostic purposes. However, in recent times the possibility of using ultrasound for triggered delivery of drugs has gained impetus. Sonoporation is a feasible strategy as it can be applied from outside the body but can be focused to reach into deep tissues. The carriers for ultrasound-mediated drug delivery range from microbubbles to liposomes, perfluorocarbon droplets, and hollow nanocapsules and nanobubbles. Such nanocarriers can also extravasate extravascularly to the vicinity of the tumors and may be actively internalized by the cancerous cells [7]. Ultrasound-responsive nanocarriers have the advantage of simultaneous detection, easy control and deep reach within tissues.

■ Light-induced cell death

Photothermal therapy has been widely exploited using the optical properties of gold nanostructures to generate heat and kill cancer cells. The effects of photothermal therapy are particularly relevant if tuned to the near infrared region in order to maximize the tissue penetration. Gold nanocapsules, nanorods and nanocages are particularly suitable for photothermal therapy. These structures are coupled to thermosensitive lipid or polymeric nanostructures to allow a temperature-dependant drug release. Gold carbon nanotubes are another interesting structure that can be used for photoacoustic and photothermal imaging [8], as well as triggered therapy. Recently smart gold nanostructures of 10 nm were developed that are internalized by the cells and show a pH dependant self-assembly to form aggregates that shift the absorption to the near infrared region, as desired for efficient photothermal therapy [9].

■ Multipronged approach

Simultaneous deployment of two or more triggers can greatly improve the efficiency of triggered drug delivery. For example, Yang *et al.* have developed pH-induced thermosensitive polymers as core-shell nanoparticles that are particularly useful for intracellular drug delivery in tumors [10]. Similarly, Lim *et al.* have combined pH and magnetic sensitivity to develop pH-triggered drug-releasing magnetic nanoparticles that can be tracked using MRI [11]. However, the

nanoparticles were not used for combined hyperthermia and pH-induced chemotherapy. A recent study showed the efficacy of temperature-sensitive liposomes coencapsulating doxorubicin and gadolinium using high-intensity focused ultrasound under magnetic resonance image guidance [12]. Such multiple strategies improve the precision and control of the triggered nanostructures.

Translational challenges

The success of triggered drug delivery depends on our ability to control them as remote access switches to start and stop drug delivery in the cancerous sites. We need to find answers to questions regarding the power or trigger level required to be effective without causing undue losses or damage to surrounding tissues, how long the switch needs to be on, the frequency of the on and off states (particularly in the case of external triggers) and the safety margins required for the surrounding normal tissues in case of accidental prolonged 'on' state of the switch. The other aspect that poses a challenge to the translation of this technology is toxicity, and the long-term effects of different types of nanoparticles, their degradation profiles, biodistribution patterns and cellular responses need to be carefully studied.

Future perspective

If suitably fine-tuned, triggered nanoparticles can act as efficient switches for the precise control of drug delivery at cancerous sites. Complex layered nanostructures with sequential responses of the different layers or compartments to specific triggers are particularly promising (nano-onion-like peeling of different layers in response to different triggers) and open up interesting possibilities of smart multifunctional therapeutics that can also be actively imaged or tracked. Further, external triggers can be used to activate a single dose of nanocarriers repeatedly in predecided frequencies. Such complex triggered nanostructures have the potential to deal with the multiple challenges of drug resistance, nonspecificity and toxicity seen with conventional chemotherapy. Triggered nanostructures can be engineered for sequential release of actives in response to triggers, for example thermosensitive magnetoliposomes where hyperthermia is set due to magnetic nanoparticles, which in turn triggers a phase transition and leakiness of the liposomes, causing temperature triggered drug release. The translation of the next generation of triggered nanotechnologies in the clinic that are responsive to multiple triggers, both external and internal, may provide cost-effective

and efficient ways of improving the efficiency of chemotherapeutic agents.

Financial & competing interests disclosure

The author has patents pending for work related to that discussed in the article. The author has no other relevant

affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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