American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Mini Review

Nanotheranostics-An Emerging Technique in Nanomedicine

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To Cite This Article: *Nida Tabassum khan. Nanotheranostics-An Emerging Technique in Nanomedicine. Am J Biomed Sci & Res. 2021 - 14(1). AJBSR.MS.ID.001945.* DOI: 10.34297/AJBSR.2021.14.001945.

Received: August 23, 2021; **Published:** August 27, 2021

Abstract

Nanotheranostics is a novel yet developing field which promises advanced methods for clinical diagnostics and treatment. Certain biological molecules present inside human body and their varying concentrations are used as detectable signals for nanoparticles or nanoconjugates to identify cancerous or tumors cells and also targeting these effected cells for the treatment of disease. At present, available treatments are expensive, time consuming with potential side effects. Therefore, application of nanotheranostics will surely help to minimize such issues and promises better therapeutics in nanomedicine

Keywords: Diagnostic; Surface Plasmon Resonance; Nanosensors; Radiotherapy; Photosensitizer

Introduction

The word theranostics means when the efforts of diagnostic imaging and therapy are combined together [1]. It can be used in clinical diagnostics, disease determination of early progression of disease, selection of therapy, prognosis and follow-ups [2,3]. It can be used in personalized particularly for the treatment of cancer [4]. The main role in which combines diagnostics and therapeutics to design personalized medicine for various devastating diseases like cancer and tumor's [5,6]. Nanotheranostics can be used to identify biomarkers for cancer diagnosis and the same molecules can be targeted for therapeutic purpose as well [7]. Use of nanosized particles in diagnostics helps in designing specific nanosensors for disease identification and treatment in nanomedicine [8]. These nanosensors are capable of detecting specific biomarkers in clinical samples for targeted drug delivery [9]. At present, available treatments are expensive, time consuming with potential side effects. Therefore, application of nanotheranostics will surely help to minimize such issues [10]. However, this technology is yet to be fully developed because diseases are diverse with different microenvironment, so it requires different nanomaterials to meet the growing need for better treatment [11]. There are some unique properties of nanoparticles that make them great for clinical purposes such as their small size and high surface area to volume ratio enables targeted drug delivery in vivo [12].In addition, intrinsic imaging properties of specific nanoparticles can be utilized for nanotheranostics applications [13].These properties are highly helpful in screening and diagnosis of different molecules associated with molecularly complex diseases like cancer, autoimmune disorders and neurodegenerative diseases [14,15].

Types of Nanomaterials Used in Nanotheranostics

a) Gold Nanoparticles: Gold nanoparticles of various structural conformation such as nanocages, nano shells or nanorods could be employed in nanotheranostics [16]. These differential structural conformation of gold nanoparticles contributes for distinct localized surface plasmon resonance (LSPR) property [17], a characteristic which plays an important role in nanotheranostics particularly in killing tumorous/cancerous cells by using laser energy set to a particular LSPR which will excite the nanoparticles resulting in instantaneous release of thermal energy that will destroy the targeted cancerous cells [18]. On the other hand, photothermal therapy can also be used at targeted

tumorous regions that cannot be operated with surgeries by employing laser beam set at infrared regions to penetrate body deep tissues [19]. Besides being used in nanotherapeutics, nanoparticles are also employed in imaging diagnostics such as gold nanoparticles fluorescent-quenching abilities make them useful for the detection of particular biomarkers [20]. In addition, Gold nanoparticles display high X-ray absorption coefficient which can be used in radiotherapy sensitizers and as imaging agents for tomography [21,22]. Therefore, taking advantage of these unique properties in combination with an effective surface binding method, gold nanoparticles act as an effective nanotheranostics in personal medicine [23].

b) Polymeric Nanoparticles: Clinically the most commonly used FDA approved nanoparticles are polymer-based and are readily available in the market [24]. Such polymeric nanoparticles include PEGylated, albumin-encapsulated, liposomal and lipid encapsulated drugs [25,26] as given in Table 1. Polymeric nanoparticles are composed of amphiphilic substances and are used as imaging agents or in chemotherapeutics and provides an external surface [27-30] for binding of ligands for targeting disease specific biomarkers [31]. For successful treatment, polymeric nanoparticles must remain in the blood stream long enough to generate an immune response [32]. An example of such nanomaterial is PEGylated conjugate which is composed of hyaluronic acid (P-HA-NPs) and is capable of carrying hydrophobic substances into the intracellular regions of tumor cells [33]. P-HA-NPs display low toxicity and accumulates inside tumor cells and then targets an antigen that is overexpressed on the effected cells [34,35]. For disease diagnosis, P-HA-NPs surfaces were coated with a specific dye for tumor visualization [36].

Table 1: US FDA-approved Polymeric nanoparticles.

Commercial Name	Composition	Drug	Indication	Company
DaunoXome	Lipid	Daunorubicin	HIV-associated Kaposi's sarcoma	Galen Ltd [27]
Abraxane	Nanoparticulate albumin	Paclitaxel	Metastatic breast cancer	Celgene Corporation [28]
Oncaspar	PEGylated	Asparaginase	Acute lymphoblastic leukemia	Enzon pharmaceuticals [29]
Doxil	PEGylated liposome	Doxorubicin hydrochloride	Ovarian cancer	Janssen biotech, inc [30]

c) Magnetic Nanoparticles: Since magnetic nanoparticles can easily be imaged by MRI so they are commonly used for diagnosis and for effective drug delivery [37]. Though MRI is an effective method for visualizing tissues deep inside the body with high resolution, but it needs external agents that can enhance the contrast to depict things clearly [38]. There are numerous metallic nanoparticles which can be used to increase the contrast by increasing the photon relaxation time [39]. Some metal ions that possess this ability are paramagnetic gadolinium, manganese and super-paramagnetic iron oxide [40]. A lot of gadolinium-based contrast agents for MRI are already FDA approved [41]. Iron oxide nanoparticles are mostly employed because of their good magnetic properties, large surface area to volume ratio and their ability to deliver drugs which makes it suitable for nanotheranostics [42]. Micelles and liposomes on the other hand were reported to be more effective imaging agents and also displayed improved drug delivery therefore were more popular in nanotheranostics applications [43].

Mechanisms in Nanotheranostics

There are several mechanisms through which different nanoparticles or nanoconjugates detect and destroys the cancerous cells some of which are as follows:

a) Smart Nanotheranostics: Smart nanotheranostics is the mechanism in which the specific nanoparticles with unique structural conformation get activated in response to certain biological conditions or internal stimuli in order to identify or deliver the drug to the designated target [44].

b) PH Responsive Nanotheranostics: In response to changes in PH around the areas where the tumors are localized versus the normal tissues, nanoparticles after entering the effected cells become entrapped into lysosomes which are sensitive to PH changes [45]. The procedure relies on the attachment of PH sensitive molecules called linkers. In order to stabilize nanoparticles [46]. Examples of such linkers includes acotinyl, gold nanoparticles conjugated with polyamidoamine dendrimers which displayed good contrast in computed tomography [47]. In addition, dendrimers could be modified with folic acid for high tumor targeting [48]. Another example is of doxorubicin attached to particles with a PH sensitive molecule Cis-aconitic anhydride and the release of drugs were triggered or controlled by acidic environment but not an in vivo case has yet been reported [49]. Organic nanoparticles like bovine serum albumin were linked by cis-aconityl PH sensitive linkers to

porphyrin photosensitizer pheophorbide and the nanoparticles were made stable by graphene oxide attachment [50]. Though this has great screening and tumor targeting properties, but still encapsulation is required since prophrins are hydrophobic but possess fluorescent and therapeutic efficiency [51]. Several other nanoconjugates like MCDION-Se displays good contrast in MRI and provides limotherapy and chemodynamic at the same time [52]. This specific nanoconjugate is composed of manganese carbonate-deposited iron oxide core with a selenium surface attached to the core through polyethylenimin which imparts an overall negative charge [53]. Another reported example is of biodegradable magnetic mesoporous nanocubic nanoconjugates which when exposed to external magnetic field can generate hyperthermia and had the ability to kill cancerous cells by the production of H2O2 and ascorbate radical when incorporated with vitamin C [54].

c) ROS Responsive Nanotheranostics: In this mechanism's generation of reactive oxygen species by the cancerous cells act as a biological trigger in nanotheranostics however this mechanism is not possible in oxygen deficient zones [55]. For this approach nanoparticles are designed to allow the release of drugs in response to generation of ROS for an effective chemotherapeutic treatment and also ensures no harm to the nearby normal cells [56]. However, there are different conditions where theranostics based on ROS were implemented. For example, a nanotheranostics system based on boronated maltodextrin works by releasing 4- hydroxybenzyl alcohol in the presence of H2O2 and generate carbon dioxide bubbles for ultrasound imaging due to its echogenic properties [57].

d) Enzyme Responsive Nanotheranostics: this theranostics mechanism depends on enzyme responsiveness [58]. An example of which is ferratin based nanocages that are responsive towards pH and matrix metalloproteinase MMP-13 activity in osteoarthritis effected individuals [59]. The process is based upon the ability of ferratin to attack collagen II after being genetically modified and a peptide was added in it since the microenvironment of joint on osteoarthritis is acidic and MMP-13 is overexpressed [60]. To make these particles work for enzyme-based diagnostics, MMP-13 peptide which were cleavable plus near-infrared Nir dye cy5.5 and quencher were conjugated [61]. This modification made the process of diagnosis much easier and faster as MMP-13 causes the separation of quencher and dye resulting in the emission of detection signal [62]. Joints have protein matrix that are quite dense and for the nanoparticles to diffuse, their sizes was kept 20nm [63]. When administered through intra articular injection these particles showed good detection of high expression of MMP-13 and therapeutic abilities [64]. Another example is the overexpression of CD44 receptors in cancer cells which were targeted by a carrier HA-Ce6 DOX that contained hyaluronic acid ultrastructure [65]. For enzyme sensitive detection these particles were modified with Ce6 and DOX via hydrazine bond and tumor environment is marked with the overexpression of hyaluronidase which made the release of these chemotherapeutics and photosensitizers faster [66]. Another method that can be used to identify and target cancer cells is the detection of glutathione which is overly expressed in cancer cells and can be used for development of nanotheranostics [67]. Besides, another reported method is the generation of hydrophobic drugs conjugated with hydrophilic polymers [68]. The monomers that are produced are amphiphilic and cause nanoparticles to assemble themselves. This principal is used to create therapeutics and multimodal imaging nanotheranostics [69].

Conclusion

Thus, nanotheranostics offers promising future in revolutionizing the field of nanomedicine by designing novel nano-based conjugates for effective diagnosis and targeting of cancerous cells by employing unique responsive mechanisms such as enzyme-based, PH-based, ROS-based etc., for therapeutics and multimodal imaging nanotheranostics.

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