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A REVIEW ON NANOPARTICLES – PROMISING APPROACH FOR CANCER THERAPY

A.ANUHYA*

*M. Pharmacy, Dept. Of Pharmacy, Jntu, Vijaya Nagaram, Andhra Pradesh, India

ABSTRACT

The aim of the present review is to highlight the applications of nanoparticles as current promising drug delivery systems in the treatment of cancer. Over the last two decades, a large number of nanoparticle delivery systems have been developed for cancer therapy, including organic and inorganic materials. Conventional anticancer drugs display significant shortcomings which limit their use in cancer therapy. For this reason, important progress has been achieved in the field of nanotechnology to solve these problems and offer a promising and effective alternative for cancer treatment. Various nanoparticles based advanced formulations such as liposomes, polymeric nanoparticles are discussed in the study.

INTRODUCTION

Nanotechnology can be defined as the design, characteristics, production and application of structures, devices and systems by controlling shape and size at a nanometer scale. Nanoparticles are at the cutting edge of the rapidly developing area of nanotechnology. Nanoparticles according to the American Society for Testing Material (ASTM) standard definition are particles with lengths that range from 1 to 100 nm in two or three dimensions. In the recent days nanomaterials are widely preferred in the treatment of cancer [1].

Cancer is a class of diseases characterized by out-of-control cell growth. There are over 100 different types of cancer, and each is classified by the type of cell that is initially affected. It is an ever-increasing menace that needs to be curbed soon. Though chemotherapy is successful to some extent, the main drawbacks of chemotherapy is the limited accessibility of drugs to the tumor tissues requiring high doses, their intolerable toxicity, development of multiple drug resistance and their non-specific targeting. Nanoparticles (NPs), an evolution of nanotechnology, have the potential to successfully address these problems related to drug delivery and retention and are considered potential candidates to carry drugs to the desired site of therapeutic action[2].

Advantages in nanoparticle drug delivery, particularly at the systemic level, include longer circulation half-lives, improved pharmacokinetics and reduced side effects. In cancer treatments, nanoparticles can further rely on the enhanced permeability and retention effect caused by leaky tumor vasculatures for better drug accumulation at the tumor sites. These

benefits have made therapeutic nanoparticles a promising candidate to replace traditional chemotherapy, where intravenous injection of toxic agents poses a serious threat to healthy tissues and results in dose-limiting side effects. Nanoparticles are just as small, or even smaller, than many blood proteins. They can therefore pass through the walls of healthy and sick cells, which make them interesting carriers of drugs against cancer and other diseases[3].

Nanoparticle drug delivery systems exploit the abnormal characteristics of tumour tissues to selectively target their payloads to cancer cells, either by passive, active or triggered targeting. Additionally, nanoparticles can be easily tuned to improve their properties, thereby increasing the therapeutic index of the drug. Liposomes, polymeric nanoparticles, polymeric micelles and polymer- or lipid-drug conjugate nanoparticles incorporating cytotoxic therapeutics have been developed; some of them are already on the market and others are under clinical and preclinical research. Notable examples of chemotherapeutic nanoparticles include Doxil (a ~100-nm liposomal formulation of doxorubicin) and Abraxane (a ~130-nm paclitaxel-bound protein particle), both of which are routinely administered as first-line treatments in various cancer types.

TYPES OF NANOPARTICLES [4]

There are various types of nanoparticles of which some are discussed below.

1. Liposomes:

First described in 1965, the liposome is the most established drug-delivery vehicle, with many clinical products to date. Liposomes consist of amphiphilic lipid molecules that assemble into bilayered spherical vesicles. This assembly process usually requires external energy from homogenization, shaking or heating.

Currently, liposomal products used for cancer treatment include Doxil, DaunoXome, DepoCyt and ONCO-TCS[5] which are liposomal formulations of doxorubicin, daunorubicin, cytarabine and vincristine, respectively.

2. Polymeric nanoparticles:

Advances in biomaterials research have led to the emergence of biocompatible and biodegradable polymeric nanoparticles for drug-delivery applications. Several synthetic polymers approved by the US FDA such as poly lacticco-glycolic acid (PLGA) and polycaprolactone (PCL) and several natural polymers such as chitosan and polysaccharides

have been investigated extensively for nano particle synthesis. Compared with liposomes, polymeric nanoparticles generally have higher stability, sharper size distribution, more tunable physicochemical properties, sustained and more controllable drug-release profiles, and higher loading capacity for poorly water soluble drugs. The polymer platform also offers higher synthetic freedom that allows particles to be tailored for specific needs. Owing to these unique characteristics, polymeric nanoparticles have attracted tremendous interests from academia, industry and clinic, although they are still in a relatively early stage of development.

3. Dendrimers:

Dendrimers are a novel class of nanoparticles that are emerging as a drug-delivery vehicle for cancer therapeutics. They are highly branched globular macromolecules that are synthesized in a stepwise and iterative fashion. The structure of dendrimers can be defined by an initiator core, layers of branched repeating units and functional end groups on the outermost layer. The unique properties of dendrimers make them a desirable platform for concurrent delivery of water soluble and insoluble drugs. For instance, the hydrophobic core contains a cavity that can encapsulate hydrophobic drugs. The multivalent surface, on the other hand, can be conjugated with hydrophilic drugs. Even though dendrimers have not attracted as much attention as liposomes and polymeric nanoparticles, several attempts have been made to deliver multiple therapeutic drugs simultaneously using a dendritic platform.

CURRENT ADVANCES IN DRUG DELIVER SYSTEMS

1. Stimuli-Responsive Drug Delivery:

Stimuli responsive drug delivery systems are investigated for remotely controlled drug release by specific external or internal stimuli, including light , magnetic field ultrasound, pH and specific enzymes' activity. These systems allow the drug concentration to be maintained within its therapeutic window to target sites and to release the drug by changing the structures of their components.

2. Light-responsive Drug Delivery Systems:

Light as an external stimulus causes structure and temperature changes in systems, which can be used for the spatiotemporal control of drug release. Drug delivery systems with light-activated materials have been designed using various strategies, e.g., drugs conjugated with

nanoparticles via photo-cleavable ligands. After light-irradiation, the drug can be trigger-released by cleaving or activating its linkage. Scientists[6] developed nanoimpeller-based delivery systems, light-activated meso-structured silica particles containing molecular impellers, could regulate the drug release inside of living cell by remotely controlling both light intensity and the irradiation time.

3. Magnetically-Triggered Drug Delivery Systems [7]:

Magnetic nanoparticles produce heat through various energy losses under an external alternating magnetic field because of the transformation of their magnetic energy into heat by the dynamic response of a dipole with their magnetic moments. Hyperthermia by magnetic field causes cancer destruction by activating cell-death signaling. Magnetic nanoparticles are not only magnetically hyperthermic, but are also drug delivery or actuators capable of controlled drug release. Recently, the team, led by Dr. James F. Hainfeld, claims that an injection containing the nanoparticles followed by 3 minutes in a magnetic field "completely cured" test animals of cancer.

4. Ultrasound-Mediated Drug Delivery Systems:

It has been reported that the interaction of ultrasound with nanoparticles could enhance drug delivery in tumors cells, because this affects the properties of tumor vasculature and cell membrane and induces non-thermal effects by nanoparticle oscillation and acoustic streaming. This interaction allows enhancement of drug delivery. Ultrasound-absorbed nanoparticles could control the drug-releasing behavior of nanoparticles and their distribution. In addition, ultrasound has practical advantages in therapeutic usage, because of clinical accessibility, low cost and safety.

5. PH-Responsive Drug Delivery Systems:

Cancer cells produce more lactic acid than normal cells by increased glycolysis and proton-pump activity. The acid is released to extra cellular regions, leading to a lower extra cellular pH (pH 6.5 to 7.2) than blood and normal tissues (pH 7.4). On the basis of this feature, pH-responsive drug carriers have been actively developed to facilitate specific responses to cancer cells without activation under normal physiological conditions. Recently organic/inorganic nanoparticles containing aromatic molecules were investigated, of which the $\pi - \pi$ interaction was affected by ionization due to pH changes that resulted in drug release [8]. Moreover, novel pH-sensitive nanosphere designed for colon-specific delivery were prepared using polymeric mixtures of poly(lactic-co-glycolic) acid (PLGA) and a pH-sensitive methacrylate copolymer, and this nanosphere showed strongly pH-dependent drug

release properties in acidic condition and particulate targeting ability against specific colon cells in inflammatory bowel disease.

6. Enzyme-Responsive Drug Delivery Systems:

Recently, drugs conjugated with nanoparticles via peptide linkers enable triggered release by specific enzymatic activation, in, which a specific peptide sequence is hydrolyzed or cleaved in the presence of specific enzymes (cathepsin B, caspase) or protein antigens, e.g., matrix metalloproteinases.

HYPERTHERMIC TECHNIQUES

For cancer therapy, current hyperthermic techniques – applying heat to the whole body – heat up cancer cells and healthy tissue, alike. Thus, healthy tissue tends to get damaged. This study shows that by using gold nanoparticles, which amplify the low energy heat source efficiently, cancer cells can be targeted better and heat damage to healthy tissues can be mitigated. Cornell scientists have merged tiny gold and iron oxide particles to work as a team, then added antibody guides to steer the team through the bloodstream toward colorectal cancer cells and in a nanosecond, the alloyed allies then kill the cancer cells with absorbed infrared heat.

CONCLUSION

Nanotechnology is definitely a medical boon for diagnosis, treatment and prevention of cancer disease. It will radically change the way we diagnose, treat and prevent cancer to help meet the goal of eliminating suffering and death from cancer. Although most of the technologies described are promising and fit well with the current methods of treatment, there are still safety concerns associated with the introduction of nanoparticles in the human body. The most promising methods of drug delivery in cancer will be those that combine diagnostics with treatment. There are still many advances needed to improve nanoparticles for treatment of cancers. Future efforts will focus on identifying the mechanism and location of action for the vector and determining the general applicability of the vector to treat all stages of tumors in preclinical models. Further studies are focused on expanding the selection of drugs to deliver novel nanoparticle vectors. Hopefully, this will allow the development of innovative new strategies for cancer cures.

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