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MAGNETIC NANOPARTICLE-BASED DRUG AND GENE DELIVERY: A REVIEW OF RECENT ADVANCES AND CLINICAL APPLICATIONS

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Abstract

Initial basic and clinical studies have indicated magnetic nanoparticles (NPs) as the next generation of targeted drug delivery. MNP-based targeted drug delivery and therapy provides a localized and highly selective theranostics for various diseases. MNPs possess unique features making them suitable for various medical applications including targeted drug delivery and targeted drug therapy. Non toxicity, injectability, biocompatibility, tissue specific aggregation, easy surface functionalization, and inherent ability to be remotely localized and redistributed using external electromagnetic fields are some of these features. This paper reviews the basic principles and recent advances of MNP-based drug and gene delivery techniques. In addition, the main physiochemical features of MNPs for drug delivery systems and the main research avenues on this filed are discussed.

Key word: Magnetic Nanoparticles, Drug Delivery, Gene Delivery, Targeted, Cancer Treatment.

1. Introduction

During the last three decades basic theoretical and experimental studies have revealed that micro- and nanoscale materials possess unique traits that make them very potent for different medical diagnostic and therapeutic (theranostic) applications (1, 2).

Nanotechnology can allow scientists to work at the cellular levels to provide considerable advances in the life sciences. The utilization of nanoparticles (NPs) produces numerous advantages because of their unique size and physicochemical attributes. Although the studies on the applications of NPs in life sciences are in initial steps, their outstanding features promise a brilliant future to develop novel and efficient theranostic techniques (3-7). Among the wide spectrum of NPs that have been recently investigated for biomedical applications, magnetic NPs (MNPs) have

received considerable attention because of their small size, non toxicity, injectability, biocompatibility, easy surface functionalization, and inherent ability to be remotely localized and redistributed using external electromagnetic fields. These features made MNPs a great choice for radiology and magnetic resonance imaging(MR) (8). Some applications of MNPs are: MRI contrast enhancement agents (8-10), drug and gene delivery(11, 12), magnetic cell sorting schemes (13), nano biosensors (14), and magnetic fluid hyperthermia(15).

Among various types of MNPs, superparamagnetic iron oxide NPs (SPIONs) are the most appropriate candidates for biomedical application (16).

SPION have a superparamagnetic iron core and it coated by polymer material. In addition, the iron and polymer parts of SPIONs are biocompatible and biodegradable (16). The size of SPIONs is the main factor determining the amount of their uptake by target cell and elimination from the body. For example, MNPs with the diameter size larger than 200 nm are absorbed by spleen and liver, while particles of below 10 nm are rapidly removed via renal clearance(17). Furthermore, the surfaces of SPIONs must have several biomedical applications such as: drug carrier properties, magnetic resonance imaging (MRI) contrast agents, and local heat induction (hyperthermia).

The colloidal stability of magnetic fluid will depend on the two factors including: 1- the size of particles which must be small enough to prevent precipitation 2- the charge and surface chemistry, which lead to both, steric and coulombic repulsions (18).

Using MNPs represent considerable new phenomena including high field irreversibility, high saturation field, and superparamagnetism. These events caused from both finite size and surface effects (19). It was reported that ferromagnetic particles with the sizes smaller than a critical level (below 15 nm), had a single magnetic domain (20).

Recent advances on binding chemistry of biological agents into the surface of MNPs and their surface functionalization have opened the avenues for developing efficient techniques of targeted drug delivery at cellular and molecular levels. However, in vivo applications of NPs have some challenges that are associated on the response of a living organism to alien objects such as NPs-drug assemblies. The present study reviews the basic principles of MNP-based drug delivery and recent advances in cellular and molecular drug delivery. In addition, the main characteristics of MNPs for drug delivery and clinical advances in using these targeted drug delivery techniques.

2. MNP-based Drug delivery

One of the most important and disadvantages of chemotherapy is that they are relatively non-specific. After injecting the therapeutic drugs, the systemic distribution occurs and it leads to attack drug to the normal, healthy cells in

addition to the target tumor cells. For instance, the adverse side effects of anti-inflammatory drugs on patients with chronic arthritis usually cause the discontinuation of the treatment process. However, localization of treatments provides the possibility to continue utilization of these effective agents. In this connection, numerous studies explained the use of magnetic carriers to target specific location within the body (21-23).The purposes of these studies are twofold including: (i) reduction of systemic cytotoxic drug distribution which lead to decrease the adverse effects; and (ii) reduction of the dosage which are needed for localized targeting of the drug.

In MNP-based drug delivery, the MNPs act as drug carrier where the surface of MNPs could carry the drug that could be transported to the desired tissue and delivered there. MNPs which are used in drug delivery must have some attributes such as; size, charge and surface chemistry. These properties could dramatically affect both the particles bioavailability in the body and the duration of blood circulation (23).

In MNP-based drug delivery, a cytotoxic drug is conjugated to the surface of MNPs. These complexes which are in the form of colloidal suspension are administered intravenously into the patient. With the entrance of these complexes into the bloodstream, exposing magnetic fields are lead to direct these complexes at a desired site. With concentrating these complexes at the target, the drug diffused either via enzymatic activity or manipulations in the physiological conditions such as pH and afterward absorbed by the tumors (24). The efficiency of this method depends on different factors such as the strength of field, volumetric and magnetic properties of the particles. In addition, some parameters such as hydrodynamic parameters including rate of blood flow, ferrofluid concentration, the route of injection and time of circulation also can affect the drug delivery (25). Generally, as the size of particles is increased, their effectiveness at tolerating flow dynamics is enhanced in the body especially in the larger veins.

Some researchers surveyed the effect of magnetic microspheres in drug delivery. The results were indicated that magnetic microspheres were gained greater response in tumor size and animal survival. In this regard, Widder et al (1983) surveyed the utilization of magnetic albumin microspheres (MM-ADR) in animal tumor. They gained greater responses both in tumor size and animal survival with MM-ADR as compared with adriamycin (26). Also Gupta et al (1993) surveyed the effect of magnetic microspheres in the drug delivery. They concluded that magnetic effects of magnetic microspheres lead to enhance the effect of them (27, 28). Afterward Gallo et al (1998) showed the ultra structural disposition of adriamycin correlated magnetic albumin microspheres (29). One of the most important challenges for carriers in drug delivery is the rapid reticuloendothelial system (RES) clearance. One of great solution for this problem is using magnetic microspheres. Magnetic microspheres are usually injected into the arterial of the

target organ. As the size of these particles is smaller than 1 mm, they can traverse via target capillaries before systemic clearance. Once the magnetic particles pass the capillaries of target organ, applying magnetic field can entrap the particles within small arterioles. As a result, the entrapped particles may be absorbed extravascularly, which causes intracellular drug uptake (30).

For the first time, Zimmermann et al (1980) suggested that applying magnetic field can direct the erythrocytes or lymphocytes containing ferromagnetic particles to a desired site (31). Also they reported that iron particles traversed through capillaries if appropriate condition was provided (32). In this regard, Meyers et al(1966) explained that applying external magnetic field caused to provide the possibility to control iron particles in the vascular system (33). In addition, the efficacy of magnetic microspheres in drug delivery for brain was investigated. It was showed that under properly conditions, using magnetic microspheres lead to increase the concentration of brain (34).

Several research groups have investigated the synthesis of nanoscale particles containing a certain amount of magnetite (35-37). One of the most current methods for diffusing the drugs is using albumin with entrapped magnetite (38, 39). Nevertheless, albumin has the disadvantage of provoking a possible immune response. Thus, scientists change their focus on the magnetite particles which coated by polylactide/glycolide (40). In conclusion, the side effects associated with the presence of inorganic particles within the tissue of body are the main issue for further development of these compounds. Ex vivo trial were conducted on the toxicity of magnetite or magnetite with polymer coating. The results of these trial showed that magnetite with polymer coating have lower toxicity (41), and also these particles have fewer side effects (42).

3.1. Parameters influencing drug delivery efficiency

Typically the targeted drug and a magnetically active component are combined into a pharmacologically stable system with controlled releasing in the blood vessels. Adjusting the magnetic field can control the amount of drug which must be released. Drug delivery can be effective to lower toxic effects and also to increase the therapeutic efficacy because it has great accuracy of magnetic drive, targeting, and high drug-capacity (43, 44). Application of MNPs for drug delivery depends on different factors associated to the size and magnetism of the MNPs. However, other parameters such as physicochemical properties of the drug-loaded MNPs, depth of the target tissue, rate of blood flow, magnetic field strength can affect the successfulness of the drug delivery (8). It was reported that enhancing the magnetization can help to facilitate changing in the drug delivery methods (45). The size of MNPs must be small enough to become superparamagnetic because this event leads to preventing accumulation after the

magnetic field is stopped and maintains MNPs in the circulation without eliminating them via the body's natural filters such as the liver (46). Also in majority of studies, Superparamagnetic NPs are preferred because of their ability to become magnetized when they are exposed to magnetic field and they lose their magnetization when the field is turned off. Thermal effect in material can induce Superparamagnetism. In these particles, thermal oscillations are strong so that spontaneously demagnetize a previously saturated.

3.2. Magnetic drug carriers

Since 1970s, different MNPs and microparticle carriers have been extended to deliver drugs to desired target sites in vivo. Attachment of drugs to MNPs can be utilized in order to decrease the dose of drugs and potential adverse effects to healthy tissues and the costs correlated with drug therapeutic. Up to now the optimization of these carriers are continues. Also the MNPs are coated by a biocompatible polymer such as dextran, although recently inorganic coatings like silica have been developed. The coating can shield the magnetic particle from the surrounding environment and can also be functionalized by attaching carboxyl groups, biotin, avidin and other molecules (47-49). Typically the carriers have either one of two structural configurations: (i) a magnetic particle core (usually magnetite, Fe_3O_4, or maghemite, γ -Fe_2O_3) which are coated with a biocompatible polymer or (ii) a porous biocompatible polymer in which MNPs are precipitated inside the pores (50).

MNPs which their surface are modified have a long blood circulation times, however, may assert very beneficial for the vascular compartment imaging , imaging of lymph nodes, perfusion imaging, target specific imaging (51). With the expansion of biocompatible polymer-coated SPIONs loaded with DOX, Yu et al successfully evaluated its tumor-reduction efficacy in lung cancer(52).

Recent studies about carriers have widely focused on new inorganic or polymeric coatings on magnetite NPs (53-57). Research also followed continues into alternative magnetic particles, such as iron, nickel or cobalt (58, 59) or yttrium aluminum iron garnet (60). Currently Cobalt/silica carriers are being examined in order to use them to repair detached retinas (61, 62).

3.3. Targeting studies

Magnetic carriers were first used to target cytotoxic drugs to sarcoma tumors implanted in tails of rat (26). The primary outcome demonstrated a total improvement of the sarcomas as compared with another group that were administered ten times the dose but without magnetic targeting which no remission were found. Afterward, several researches have been conducted by using animal models containing swine, rabbits and rat in order to investigated the

cytotoxic drug delivery and improvement of tumor using animals models including swine (63), rabbits (24) and rats (24, 64).

Kubo et al recently proposed diversity on these techniques. They located implanted permanent magnets at solid osteosarcoma sites in hamsters and delivered the cytotoxic compounds via magnetic liposomes. They demonstrated that a four-fold increase in cytotoxic drug delivery to the osteosarcoma sites increased 4 times as compared with normal intravenous non magnetic delivery (39), also a great increase in activity of anti-tumor and the weight loss deletion as an adverse effect (38). This model has also been applied to target cytotoxic drugs to brain tumors. Due to the drug must pass the barrier of blood brain, brain tumors are difficult targets. It was revealed that particles with the sizes ranged 1–2μm could be accumulated at the position of intracerebral rat glioma-2 (RG-2) tumors (65). Although the particles concentration in the tumor was low; it was considerable higher than non-magnetic particles. Then it was found that magnetic particles which had size ranged between 10-20 nm were more useful at targeting these desired tumors in rats (64).

The magnetic carriers were found in the interstitial space in tumors but they were observed only in the vasculature of normal brain tissue. So far, a few studies were performed about magnetic targeting in human. Mykhaylyk et al (2001) had less success utilizing magnetite–dextran NPs. Nevertheless, they disrupted the blood brain barriers prior to the injection of MNPs and eventually they were enabled to target glial tumors of the rat (66). In addition, MNP-based drug delivery has some restrictions (67, 68). These restriction includes (i) due to the accumulation of magnetic carriers, there is a possibility of embolization of the blood vessels in the target site (ii) there is a large distance between the target site and the magnet, so this can lead to scale up from animal (iii) when the drug is released, it is no longer adsorbed to the magnetic field, and (iv) toxic responses to the magnetic carriers (69, 70)

4. Gene delivery

Gene therapy comprises the delivery of a therapeutic gene to the target tissue to replace a defective gene and cure the pathological genotypes by expression of a therapeutic gene. These therapeutics have been integrated into MNP preparations, which can help to protect the nucleic acids against enzymatic degradation and accelerate release of endosomal (71, 72). In order to deliver DNA by MNPs, the surface of MNPs must be modified to attach desired molecules. There are various ways to attach target molecules to the surface of particle such as by applying electrostatic interactions between the pharmacological drug and the surface of MNPs. The desired molecule will be coated by an outer shell which is degradable and diffuses the molecule at target site when the shell is broken down.

Cathy Mah et al (2000) performed the first study which surveyed the effect of using magnetic particles on targeted delivery of DNA (73). In that experiment, they coated adeno-associated virus (AAV) encoding Green Fluorescent Protein (GFP) to the surface of magnetic particles by utilizing a cleavable heparin sulfate as a linker (74).

It was revealed that superparamagnetic iron oxide (SPION) have a great biocompability and also target-functionalized. These features made up SPION as a great choice for siRNA delivery (75). This process was performed by adjoining the genes into the SPION. As noted above these magnetic particles lead to protect the nucleic acids against enzymatic degradation and accelerate release of endosomal. In addition, to deliver hard-to-transfer cells, plasmid DNA or siRNA should be used by modern techniques such as magnetofection. In this method, the SPION are subjected to the external magnetic field exposure and hence it can facilitate caveolae-mediated endocytosis of SPION and cargo nucleic acid (76, 77).

Some studies have proposed some target specific linkers to attach target molecules to MNPs. However, this method is not evermore possible. One of the most great methods for attaching DNA to the surface of particles is applying the electrostatic interactions between the negatively charged phosphate backbone of DNA with negative charge and molecules that are linked to the surface of particle which positively charged (78).

Medarova et al (2007) proposed another method in order to cationic coatings. They were capable to bonded siRNA to CLIO NPs by using covalent graft. Also in order to facilitate transfaction they used the cell penetrating peptide. This method has very high successfulness for delivering the siRNAs to human colorectal carcinoma tumors. Also this method is the first targeted siRNA MNP which was utilized for therapeutic application (79).

Some choices for this approach are the polyamidoamine (80), or chitosan (81). However, the most current choice for this approach is the cationic polymer polyethylenimine (PEI). This was The first reported transfection agents and binds and condenses DNA due to the large number of secondary amine groups present along it's chain length (82). Applications of PEI-coated MNPs were first reported by Schere et al (2002) where provided the first example of in vitro MNP mediated non-viral gene delivery (83). They reported that PEI increases lysosomal release of the complex following internalization by buffering the intralysosomal pH causing the lysosome to rupture and releases its contents (84). Due to the particle DNA composition can enter to the cell via endocytosis through clathrin-dependent pits, these characteristics of PEI can be useful for gene delivery (85). This method has two principle advantages: 1-facilitates targeted gene delivery. 2- The rapid sedimentation of the combination of gene and particle onto the target which leads to decrease both the time and dose which required achieving efficient transfection.

It was reported that association of DNA vectors with superparamagnetic NPs can enhance the transfection performance of transfection reagents and considerably decreases the time of gene delivery (83). In this regard, it was proved that the linkage of adenoviral vectors to the particles makes the transfection of many cell lines with little or no coxsackie and adenovirus receptor.

These results emphasized on the idea that associating viral vectors with MNPs could develop the host tropism to non-permissive cells. Afterward, some studies have used magnetofection in order to transfect some cells such as blood vessel endothelial cells (86). In addition, some experiments have used these particles for delivering antisense oligonucleotides (87) and small siRNA to adjust the gene expression. Recently, it was revealed that using siRNA associated with magnetic particles lead to decrease the retroviral mediated expression of luciferase in Hela cells (85).Then, Mc Bain et al (2007) used covalent linkage to attach PEI to the surface of iron oxide, dextran silica particles in order to preparing PEI coated magnetic particles (88). Up to now, a lot of coupling DNA vectors to magnetic particles-based researches focused on the ability of this method to decrease the time which is required to transfect, or minimize the vector dose. Also Mc Bain et al (2008) surveyed the overall transfection efficiency of this technique by applying dynamic magnetic fields(72). They demonstrated that using this strategy lead to improve the transfection more than10 fold comparing with static magnetic fields.

Cai et al (2005) proposed other method to NP mediated gene delivery which were called termed nanotube spearing (89). This approach is based on using nickel embedded carbon nanotubes coated in DNA. When nanotubes are introduced to cells in the presence of a specifically oriented magnetic field, the nanotubes align with the magnetic flux lines as they are pulled toward the cells. This enables the nanotubes to spear the cells, pass through the membrane and deliver the target DNA, and has been successfully used to transfect a number of different cell types including Ball 7 B-lymphoma, ex vivo B cells and primary neurons, whilst maintaining a high rate of cell viability after transduction (78).

5. Conclusion

The present study has reviewed the basic principles and recent advances of MNP-based drug and gene delivery techniques. In addition, the main physiochemical features of MNPs for drug delivery systems and the main research avenues on this filed have been discussed. Non toxicity, injectability, biocompatibility, tissue specific aggregation, easy surface functionalization, and inherent ability to be remotely localized and redistributed using external electromagnetic fields make the MNPs suitable candidate for targeted drug delivery methods. In addition, the blood

flow rate, ferrofluid concentration, route of injection and time of circulation are the main factors important for clinical development of MNP-based drug delivery techniques. .

In conclusion, MNP-based drug delivery systems have shown promising efficacy in animal studies. However, these techniques are currently under investigation in initial human experiments. Further controlled clinical trials are needed to develop these techniques for clinical setting, especially their possible side effects including toxicity on body tissues should be carefully studied.

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