Functionalized magnetic nanoparticles for drug delivery in tumor therapy

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REVIEW

Functionalized magnetic nanoparticles for drug delivery in tumor therapy*

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The side effects of chemotherapy are mainly the poor control of drug release. Magnetic nanoparticles (MNPs) have super-paramagnetic behaviors which are preferred for biomedical applications such as in targeted drug delivery, besides, in magnetic recording, catalysis, and others. MNPs, due to high magnetization response, can be manipulated by the external magnetic fields to penetrate directly into the tumor, thus they can act as ideal drug carriers. MNPs also play a crucial role in drug delivery system because of their high surface-to-volume ratio and porosity. The drug delivery in tumor therapy is related to the sizes, shapes, and surface coatings of MNPs as carriers. Therefore, in this review, we first summarize the effects of the sizes, shapes, and surface coatings of MNPs on drug delivery, then discuss three types of drug release systems, *i.e.*, pH-controlled, temperature-controlled, and magnetic-controlled drug release systems, and finally compare the principle of passive drug release with that of active drug release in tumor therapy.

Keywords: magnetic nanoparticles, tumor, drug carriers, targeted therapy

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1. Introduction

Traditional chemotherapeutic drugs injected into the body through the circulatory system present a number of challenges that need addressing, due to their accessibility to healthy tissues and their poor control of drug release.[1,2] Conventional treatments for tumors include surgery, chemotherapy, radiation and combined strategies,[3] which generally produce harmful side effects on healthy tissues.[4] Magnetic nanoparticles with super-paramagnetic behaviors were proposed to deal with these problems, which can increase the concentration of drugs in the infected tissue, and thus reducing the required quantity of dose of drugs.[5] In nature, magnetite (Fe_3O_4) nanoparticles are the most common magnetic materials. In the past few decades, due to their biocompatibility and relative ease of functionalization, Fe_3O_4 magnetic nanoparticles have been commonly used in various fields,[6] such as magnetic recording, catalysis, cellular therapy, selective protein separation, hyperthermia in tumor treatments, magnetic resonance imaging (MRI) contrast agent, and targeted drug delivery.[7–10] The Fe_3O_4 MNPs with high magnetization value and ultrafine particle sizes can be manipulated by external magnetic fields through which they can directionally penetrate tumor or the unhealthy tissues, and are considered as the ideal drug carrier materials for tumor therapy.[11]

Easy aggregation is a major problem for magnetic nanoparticles due to their thermodynamic instability and magnetic attraction between particles. Therefore, some organic or inorganic materials were used as the surface coatings of MNPs in order to maintain the stability and reduce the aggregation of MNPs, causing particles to accumulate in deep and inaccessible tissues, and the biological interaction at the molecular level and cellular level.[12] As a result, the MNPs coated with specific tumor-suppressor antibodies can significantly promote the drugs to move to tumor sites, and thus improving their efficacy. In addition, chemotherapy drugs can be passively or actively delivered to the tumor sites by using magnetic nanoparticles as drug carriers. However, for an ideal nanocarrier of chemotherapy drugs, biocompatibility, water solubility and appropriate sizes are essential for effective cellular uptake and safe excretion from the biological system.[13] Suitable coating materials on magnetic nanocarriers were reported to play an important role in realizing effective tumor therapy. For instance, mesoporous silica materials with high surface-to-volume ratio and high porosity can be used as an efficient absorber in the field of nanocarriers.[14] In a word, magnetic nanoparticles as drug carriers should be used to maximize drug release in tumor areas and minimize drug release in healthy areas.

Magnetic nanoparticles as carriers for drug delivery have

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been studied by more and more people due to the huge potential advantages in biomedical fields.[3–5,12] However, most of people focused on the principle of magnetic nanoparticles as drug delivery carriers. Therefore, in this review we cite many examples to compare the effects of different modified coating materials on drug delivery and make a comprehensive analysis of the respective principle of pH-controlled drug release system, temperature-controlled drug release system, and magnetic-controlled drug release system.

2. Effects of the morphologies of MNPs on drug delivery

Targeted drug delivery (TDD) systems were reported to enhance the therapeutic efficacy and improve the bioavailability of poorly water-soluble drugs. The TDD systems make an opportunity for carriers to conjugate with different biologically active molecule target-selective delivery nanomedicines.[15] The sizes and shapes of MNPs are the important characteristics determining the distribution, toxicity, and targeting capabilities of these delivery systems *in vivo*, as well as affecting drug loading, drug release, and the stability.

2.1. Effects of sizes on drug delivery

The sizes of MNPs as drug delivery carriers transporting from the microvessels to the target tissues are very important, determining the concentration distribution of nanoparticles in tissues.[16] The sizes of MNPs in manipulation sometimes must be big enough to avoid their entering into blood capillaries but sometimes they must be small enough to escape from macrophages of the reticuloendothelial system to prevent nanoparticles from being removed from the system[17] (Table 1). In short, the sizes of magnetic nanoparticles as drug carriers should be chosen and used based on the sizes of diseased cells, which are the smallest components of diseased tissues.[5]

Table 1. Effects of MNP size on drug delivery.

Sizes of nanoparticles (nm)	Effects	References
< 10	rapidly excreted by kidneys	[20]
10–100	longest circulation	[20]
100–150	more accumulation in tumors	[19]
150–200	higher cellular uptake	[18]
> 200	eliminated by reticuloendothelial system	[20]

It should be noted that the sizes of nanoparticles coated with a polymer should not exceed 100 nm because the movement of large particles in narrow capillaries may cause the particles to become lumpy and block small blood vessels and to be identified and cleared by the reticuloendothelial system.[12] Some researchers have concluded that MNPs with the sizes in a range of 150 nm–200 nm have higher cellular uptake, but smaller nanoparticles with the sizes in the 100 nm–150 nm promote more accumulation in tumors.[18,19] As a result, nanoparticles with an approximate size of 150 nm are most likely to agglomerate in tumor cells. Particles with sizes more than 200 nm tend to be eliminated by reticuloendothelial system (RES).[20] However, nanoparticles with sizes up to 200 nm can cross the tight endothelial cells of the blood–brain barrier.[21] Some studies have shown that nanoparticles less than 200 nm can escape from recognition by the reticuloendothelial system (RES) and significantly influence the biodistribution of nanocarriers after intravenous administration. Particles with sizes smaller than 10 nm are rapidly excreted by the kidneys. Therefore, magnetic particles in a range of 10 nm–100 nm have the longest circulation time.[20] In the present investigation, the sizes of MNPs are related to the distribution of these nanocarriers in the tumor tissues, illustrating that the MNPs with smaller sizes are easier to penetrate the tumor tissues. On the other hand, when the sizes of the MNPs are increased, it is harder for the nanocarriers to pass through the microvessels due to the pore size limitations.[16] Therefore, the optimal sizes of MNPs as the drug delivery carriers are in a range of 10 nm–200 nm, with smaller sizes corresponding to better transportation effects.

2.2. Effects of shape on drug delivery

Iron oxide nanocrystals have a variety of shapes like spherical shapes, nanocubes, nanowires, nanorods, nanoflowers, and nanodisks, among others (Fig. 1). In general, the shaped-controlled synthesis of iron oxide depends on the control of the precursor's formation and growth, effect of the precursor crystalline phase, crystal orientation, and crystal facets. Different shapes of magnetic nanoparticles have specific actions in various applications (Table 2), for instance, Fe_3O_4 nanodisks and nanorods seem to induce tumor cells to damage, while nanocubes, nanoflowers, and nanorings have been shown to be ideal heat mediators for hyperthermia, and elongated nanostructures and flower-like nanoparticles show the great performance for T2-contrast agents. In addition, magnetic nanoparticles can actively or passively deliver drugs to targeted organs/tissues or cells.[22]

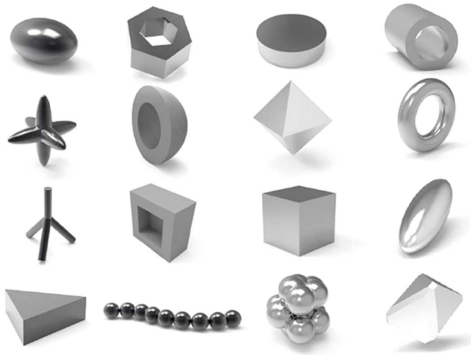

Fig. 1. Multi-morphologic iron oxide nanoparticles. Reprinted with permission from Ref. [22].

Table 2. Effects of shapes on drug delivery.

Shapes	Effects	Reference
Nanodisks and nanorods	induce damage of tumor cells	[22]
Nanocubes, nanoflowers and nanorings	ideal heat mediators	[22]
Elongated nanostructures and flower-like nanoparticles	great T2-contrast agents	[22]

According to the above theoretical analysis, Wang *et al.*[23] successfully synthesized magnetic Fe_3O_4@PVP nanotubes, showing that the temperature of nanotubes dispersions increases rapidly with the increase of the magnetic field amplitude, suggesting the great potential applications of the MRI-guided magnetic hyperthermia in the tumor theranostic fields.

3. Effects of surface coating of MNPs on drug delivery

The Fe_3O_4MNPs as drug carriers are facing many challenges to be solved, such as fast clearance by the reticuloendothelial system, thermodynamically unstable, and quickly agglomerate as well as poor drug carrying capacity of magnetic nanoparticles, specifically, hydrophobic drugs, surface spin disorder, uncontrolled oxidation, and the like. These setbacks can be reduced or minimized by coating MNPs with various multi-functional organic or inorganic entities such as proteins, peptides, antibodies, polymers, dendrimers, silica, gold, *etc*. (Table 3).[5,13,24–27]

Table 3. Effects of multi-functional organic or inorganic coatings on drug delivery.

	Examples	Effects	References
Organic coatings	HSA	a strong affinity for most drugs	[28]
	PEG	enhance drugs solubility and bioavailability	[24]
	sugar alcohol	good colloidal stability and magnetic responsively	[26]
Inorganic coatings	silica	offer sufficient capacity to carry drugs	[14]
	gold	provide photothermal therapy	[3]
Multifunctional materials	PLA–PEG–PLA	improve long-term blood circulation and control the release of drugs	[18]
	caf-MCaP	enhance the delivery of siHER2 to human breast cancer cells	[27]

3.1. Magnetic nanoparticles coated with proteins

The most widespread protein in serum is human serum albumin (HSA). The HSA has a strong affinity for most drugs, therefore it is important to study its interaction and binding capacity with MNPs.[28]

Electrostatic interactions between positively charged drugs amine groups and negatively charged groups on MNPs surface lead to the fact that iron oxide nanoparticles (IONPs) coated by serum albumin and polyethylene glycol (PEG) can efficiently bind doxorubicin (DOX) molecules. Currently, Ostroverkhov *et al.*[29] successfully synthesized MNPs functionalized with HSA. The HSA protein coated on MNPs forms a shell where polar side chains are exposed to water and unpolar ones are hidden inside of protein global.

3.2. Magnetic nanoparticles coated with polymers

Ayubi *et al.*[24] combined a functionalized MNP core with PEGylated curcumin to form antitumor drugs. Polyethylene glycol (PEG) is a biocompatible polymer with "stealthy" properties and very suitable to being used as the surface modification material for various drug delivery systems. Thus, MNPs functionalized with PEG can enhance drug solubility and bioavailability.

3.3. Magnetic nanoparticles coated with polysaccharides

Polysaccharides such as dextran, starch, and sugar alcohol are known to passivate the surface of iron oxide nanoparticles and render them colloidally stable.

A promising approach was developed by Gawali *et al.*[26] who generated a novel magnetic carrier system with the surface coated with sugar alcohol. The sugar alcohol can be used as a water-soluble solid dispersing carrier material to improve the solubility of drugs. The surface modification of MNPs enables the electrostatic binding of positively charged anticancer drugs. Therefore, the sugar alcohol-modified MNPs have good colloidal stability and magnetic responsiveness, which can be applied to drug delivery and magnetic hyperthermia.

Wang *et al.*[30] used dextran to perform the surface coating of Fe_3O_4 nanoparticles, which can improve the dispersion, solubility and biosafety. Figure 2(a) shows the tumor growth curves of three groups (respectively corresponding to PBS, Fe_3O_4, and dextran/Fe_3O_4 different tumor drug carriers) *in vivo* for mice after being irradiated by an 808-nm laser (3 $W{\cdot}cm^{-2}$) through photothermal therapy, indicating that the maximum inhibition of tumor growth occurs when dextran/Fe_3O_4 is used as the drug carrier. Figure 2(b) shows the morphologic evolution of tumors in mice injected with chemotherapeutic drugs for the above three drug carriers, with the black spot corresponding to the aggregation of magnetic Fe_3O_4 nanoparticles in the tumor area, and demonstrates that the tumor disappeared after 28 days when dextran/Fe_3O_4 was used as the drug carrier.

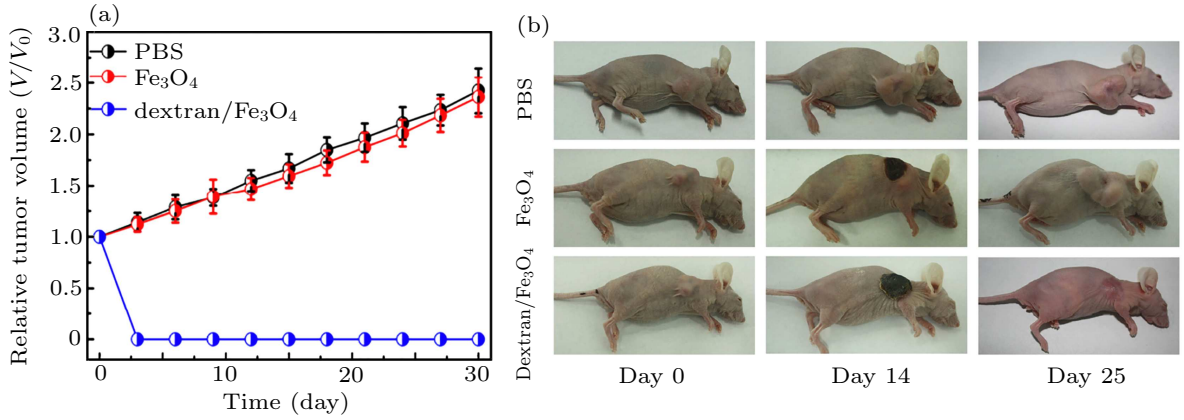

Fig. 2. (a) Tumor growth curve of each group, after being irradiated by 808-nm laser (3 W·cm^{-2}), and (b) representative photos of each group before and after treatment. Reprinted with permission from Ref. [30].

3.4. Magnetic nanoparticles coated with silica

Due to its large functionalizable surface and large pore volumes, mesoporous silica has a strong affinity with various biomolecules, which is highly conducive to drug delivery applications.

Teng *et al.*[14] introduced a drug delivery system based on mesoporous silica as the functional coating, which provides a simple way to produce hollow-structural nanocomposites. Magnetic iron oxide nanoparticle coated with mesoporous silica spheres can form a hollow-structural nanocomposite to carry drug molecules, where the mesopores silica is used for transporting drugs and the pH-triggered drug is released from the interior cavity.

3.5. Magnetic nanoparticles coated with gold

Elbialy *et al.*[3] synthesized the functionalized MNPs coated with gold for drug delivery. The inner core magnetic nanoparticles of multi-functional magnetic/gold nanoparticles (MGNPs) act as a magnetic guide for targeted drug delivery under an external magnetic field and the gold shell allows photothermal therapy by increasing the temperature of the target tissues upon exposure to a near-infrared laser. In addition, the MGNPs can be used as a contrast agent for magnetic resonance imaging (MRI) due to the super-paramagnetic properties of the iron oxide core.

3.6. Magnetic nanoparticles coated with multifunctional materials

Single ligand-modified MNPs are insufficient to cope with the complex physiological microenvironment *in vivo*.[31] Thus, multifunctional materials modified MNPs are proposed to solve the above problems. The multi-functional materials can better control particles' distribution and adjust particles' sizes suitable to the *in-vivo* conditions for specific targeting to tumors and their stimuli-responsive properties enable the releasing of the drug from the carriers.[4,18]

3.6.1. Tree block PLA–PEG–PLA copolymer

Shojaee *et al.*[16] synthesized tri-block poly(lactide)-poly(ethyleneglycol)-poly (lactide) (PLA–PEG2000–PLA) copolymer by using ring-opening polymerization. The EPPT peptide and oleic acid-Fe_3O_4 nanoparticles (OA-Fe_3O_4) were prepared by the double emulsion solvent evaporation technique. The polyethylene glycol (PEG) coated on PLA-MNPs can improve long-term blood circulation of nanoparticles. The human epithelial mucin encoded by the gene MUC1 is over-expressed on breast cancer but silent on normal tissues, thus making MUC1 a promising tumor-antigen with therapeutic as well as diagnostic potential. The EPPT peptide has a significant relation with the MUC1-derived peptides (Fig. 3).

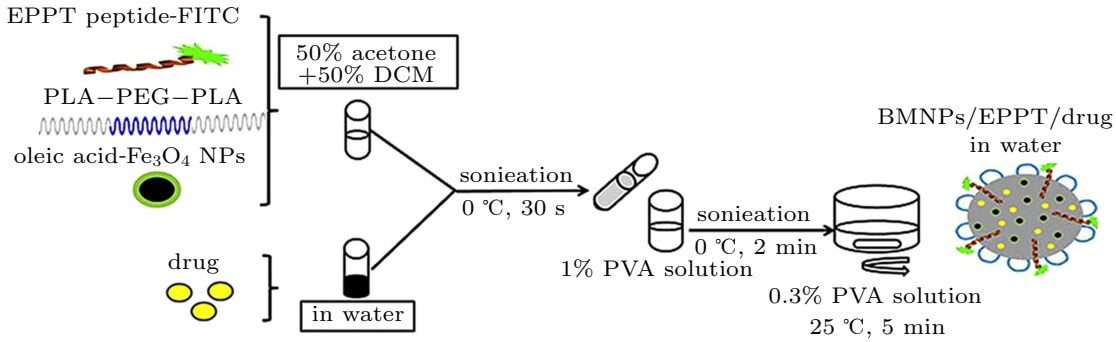

Fig. 3. Schematic diagram showing encapsulation of drug, EPPT peptide, and Fe_3O_4 nanoparticles into tri-block PLA–PEG–PLA copolymer by using double emulsion solvent evaporation technique. Reprinted with permission from Ref. [18].

3.6.2. Caffeic acid–magnetic calcium phosphate

Calcium phosphate (CaP) is an inorganic compound which can enhance endocytosis, avoiding endosomal degradation and being gradually released into the cytoplasm of target cells. Caffeic acid coating is used to increase particle stability and reduce the preparation time by weakening the tendency of iron oxide to being aggregated. The PEG-polymer coating can improve the ability of nanoparticles to extend the blood circulation time and evade immune system cells *in vivo*.

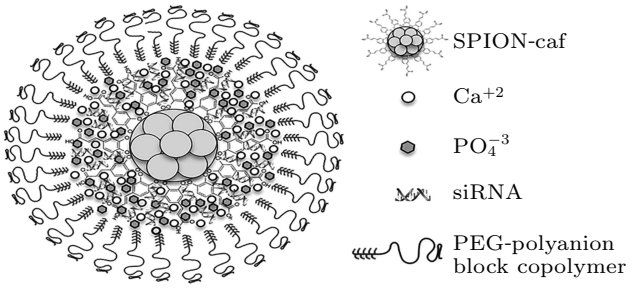

Fig. 4. Schematic illustration of caffeic acid–magnetic calcium phosphate (Caf-MCaP) particle. Reprinted with permission from Ref. [27].

A block copolymer can be used to prevent the large CaP aggregates from forming, to achieve the synthesis of size-controlled nanoparticles in biomedical applications. Cristofolini *et al.*[27] designed a multifunctional magnetic nanostructure of SPIONs coated with caffeic acid and stabilized by layers of CaP and PEG–polyanion for the incorporating of siRNA (Fig. 4).

4. Drug release mechanism

Effective control of drug release not only enhance the efficacy of medications, but also improve the patience compliance with medication.[32] According to the special microenvironment of the tumor, such as slightly higher temperature, slightly lower pH, and more reductive enzymes, the drug release systems are divided into pH, temperature, restoration response, magnetic field controlled, and ultrasonically controlled drug release systems. The pH-controlled drug delivery system, magnetically-controlled drug release system, and temperature-controlled drug release system are described in Table 4.

Table 4. Three types of drug release systems.

Drug release mechanism	Examples	Effects	References
PH-controlled drug delivery system	DOX-MMNPs	The release of DOX from DOX-MMNPs at pH 5 more than pH 7.4 due to the electrostatic interaction between DOX and MMNPs	[26]
Magnetic-controlled drug delivery system	PCL-Fe_3O_4NPs	The Fe_3O_4NPs can generate heat in response to an AC magnetic field and raise the local temperature of the polymer particles to break the polymer chains to release more drugs.	[34]
Temperature-controlled drug delivery system	Fe3O4-UA-g-P(UA-co-NIPAAm)	PNIPAAm has a lower critical ssolution temperature at about 32 °C.	[35]

4.1. pH-controlled drug release system

In the pH-controlled release system, the body's own pH information feedback is used to control the release of drugs, which is not affected by external changes. The mechanism of drugs release is that the bond between drug molecules and transport carrier is sensitive to acid media.

Gawali *et al.*[26] investigated the release of DOX from the mannitol functioalized MNPs (MMNPs). The release of DOX from DOX-MMNPs increases at pH 5 compared with the case at pH 7.4. The drug loading can be attributed to the electrostatic interactions between positively charged DOX and negatively charged groups on MMNPs. However, the electrostatic interactions between DOX and hydroxyl groups on MMNPs become weaker at lower pH. This is desirable for tumor therapy because the relatively low pH in tumors will stimulate the DOX release at the target sites.

4.2. Magnetic-controlled drug release system

In the magnetic-controlled release system, the magnetic guidance of MNPs or the unique magneto caloric effect is utilized to create the dislocation of the structure of the drug control release system or the phase change of the temperature-sensitive materials, so that the drugs can be released from the drug carriers.

The release of acetaminophen from zein/NPs composite films was investigated by Marín *et al.*[33] Without applying a magnetic field, the zein/NPs/drug composite films exhibit the slowest drug release. This result indicates that the barrier effect of nanoparticles stops the drugs removing from films. Under external magnetic field conditions, the release rate of zein/NPs/drug increases with the intensity of the applied magnetic field increasing. The behaviors of magnetic nanoparticles are responsible for promoting the magnetically responsive drug release performance of the zein/MNPs/drug system.

Hyun[34] prepared core–shell Fe_3O_4 MNPs (core) coated with poly(ε-caprolactone) (PCL) (shell) to load drugs. The Fe_3O_4 MNPs entrapped in PCL shell can generate heat in response to an AC magnetic field in a time-controllable manner. When the field is switched off, the shell made of hydrophobic PCL and impermeable Fe_3O_4 NPs acts as a water diffusion barrier, thus retarding the release of DOX from the hollow particles. When the magnetic field is switched on, a rapid release

of the drug molecules is observed because the Fe_3O_4 MNPs generate heat and raise the local temperature of the polymer particles to break the polymer chains when exposed to an AC magnetic field.

4.3. Temperature-controlled drug release system

In the temperature-controlled release system, the MNPs are used as drug carriers, the chemical molecules with temperature-sensitive effect on the MNPs are increased, and the chemotherapeutic drugs are loaded into the temperature-sensitive molecules. Taking advantage of the fact that the temperature of tumor cells is higher than that of normal cells, with the temperature-sensitive molecular structure changing, the chemotherapy drugs are released from the drug carriers.

Kim *et al.*[35] used temperature-responsive amphiphilic polymers poly (undecylenic acid-co-isopropylacrylamide) functionalized Fe_3O_4-(undecylenic acid) to obtain Fe_3O_4-UA-g-P(UA-co-NIPAAm) nanoparticles. Poly (N-isopropylacrylamide) (PNIPAAm) is a typical temperature-responsive polymer, which demonstrates a lower critical solution temperature (about 32 °C). When the PNIPAAm based Fe_3O_4-UA is used as drug carriers, the curative effect can be significantly improved by changing the external temperature. In addition, the nanosized Fe_3O_4-UA-g-P(UA-co-NIPAAm) magneto micelles exhibit magnetic character and temperature-sensitivity.

5. Tumor targeted therapy

In recent years, the in-depth study of tumor pathogenesis and pathophysiology, has indicated that the tumor microenvironment has some significant features, such as weak lysosomes and endosomes in tumor cells, acidic environment, over-expressed enzymes in tumor cells (like matrix metalloproteinases, esterases, α-amylases, cathepsin B, *etc.*), high concentration of reducing substances in tumor cells, tumor cytoplasm rich in adenosine triphosphate (ATP), enhanced permeability and retention (EPR) effect and so on. Nanocarriers (20 nm–200 nm in diameters) can transport drugs and other therapeutic molecules, and are now considered as a new standard for targeted tumor treatment, because they can be targeted to the tumor microenvironment and further achieve molecular-targeted therapy.

The specific enrichment of nanomaterials in tumor tissues is the prerequisite for non-destructive diagnosis and targeted therapy of tumor in vivo. It is achieved mainly through two types of mechanisms (Fig. 5). One is passive targeting known as accumulation of NPs at the tumor sites with a high concentration due to the pathophysiological difference between normal tissues and tumor tissues. The other type is active targeting where the targeting moiety is connected to NPs through molecular recognition, and therefore a method of delivering the target into specific cells, tissues or organs is obtained.[36]

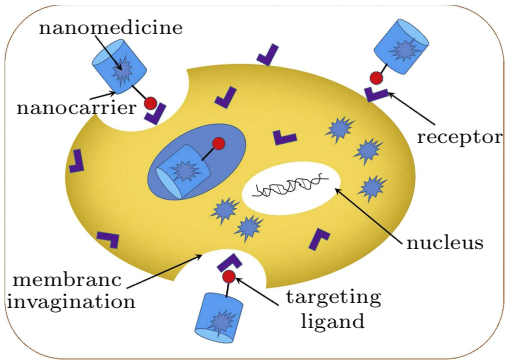

Fig. 5. Active and passive transport of nanomedicine. Reprinted with permission from Ref. [17].

5.1. Passive targeting

Passive targeting refers to the use of specific structural characteristics of tissues and organs to allow drugs to produce natural distribution difference in the body, thereby achieving a corresponding targeting effect. The passive targeting mainly depends on the size effect of drugs. For example, particles larger than 7 μm in size are usually trapped in the lung by small capillaries through mechanical filtration, and are absorbed into lung tissue or lung air bubbles by monocytes, while particles larger than 200 nm in size are easily swallowed by the reticuloendothelial system of the spleen and liver. The most well-known passive targeting is the EPR effect, which is based on the difference in microvascular structure between solid tumors and normal tissues. The normal microvascular endothelial space is dense and the structure is complete, thus macromolecular and large-sized particles are difficult to penetrate the blood vessel wall. In solid tumors, there are many new blood vessels, wide vascular wall space, poor structural integrity, as well as lack of lymphatic reflux. These characteristics will make it easier for macromolecular drugs or nanoparticles with a diameter of about 100 nm to accumulate inside the tumor tissues. In addition, the special pH and reductase environment of the tumor site can also achieve the release of drugs at a specific location for the purpose of targeted administration.

5.2. Active targeting

Active targeting mainly refers to the ability of drugs or their carriers to bind to the tumor targets. The principal methods include coupling probe molecules, such as antibodies, which can be specifically combined with nanocarriers containing chemotherapy drugs by chemical or physical techniques. Therefore, nanocarriers coupled probe molecules are more likely to bind to partially overexpressed or aggregated receptors. (*e.g.*, HER2, folate receptor, CD44, *etc*).[37]

Avedian *et al.*[38] synthesized polyethyleneimine combined folic acid (PEI-FA) gated mesoporous magnetic nanoparticles. The Folate receptor (FR) is particularly known

for its overexpression in many tumors. Due to the high folate-FR binding constant, low immunogenicity, and easy surface functionalization with folate molecules, tumor targeted therapy with FR is very attractive.

6. Conclusions and perspectives

The MNPs with high magnetization response and small sizes can directly act on tumors or diseased tissues through external magnetic fields. Nanoparticles can be transported from capillaries to tissues. The optimal particle sizes of the drug delivery carriers are in a range of 10 nm–200 nm, with smaller sizes corresponding to better transportation effects.

Magnetic nanoparticles with different shapes have specific actions in biomedical applications. Proteins, peptides, antibodies, polymers, dendrimers, silica, and gold are used to modify MNPs to obtain excellent performances.

According to the characteristics of tumor tissue microenvironment, such as low pH and high temperature, and the magnetic orientation and unique magnetothermal effect of MNPs, drug pulse release systems are divided into pH, temperature and magnetic field controlled drug delivery systems. Tumor targeted therapies include active targeting therapy dependent on over expressed or aggregated receptors of tumors and passive targeting therapy dependent on the EPR effect.

The MNPs enclosed by drugs in tumor therapy with high magnetization response and ultrasmall sizes can be manipulated by external magnetic fields, thereby penetrating the body tissues. The MNPs can also be functionalized with various multi-functional organic or inorganic coatings. However, the MNPs with functional coatings still have some problems to be solved due to tedious preparation procedures. The biological evaluation of most magnetic nanodrugs controlled release systems is currently still *in vitro* cell experiments and in vivo mice experiments, degradation process and antitumor efficiency with degradation process in vivo has not been thoroughly studied. These make the magnetically nanocontrolled release system still be in the theoretical stage for clinical experiments, which limits the practical applications of nanodrug controlled release systems. More simple and effective drug delivery systems in tumor therapy need further exploring. A large number of experiments are still needed before the magnetic nanocarriers are used in clinical practice.

References

[1] Agiotis L, Theodorakos I, Samothrakitis S, Papazoglou S, Zergioti I and Raptis Y S 2016 *J. Magn. Magn. Mater.* **401** 956

[2] Mahmoudi M, Sant S, Wang B, Laurent S and Sen T 2011 *Adv. Drug Deliv. Rev.* **63** 24

[3] Elbialy N S, Fathy M M, Al-Wafi R, Darwesh R, Abdel-Dayem U A, Aldhahri M, Noorwali A and Al-Ghamdi A A 2019 *Int. J. Pharm.* **554** 256

[4] Mirza Z and Karim S 2019 *Semin. Cancer Biol.* **19** 30177

[5] Dafeh S R, Iranmanesh P and Salarizadeh P 2019 *Mater. Sci. Eng. C* **98** 205

[6] Li X, Lu W, Song Y, Wang Y, Chen A, Yan B, Yoshimura S and Saito H 2016 *Sci. Rep.* **6** 22467

[7] Moya C, Freire O I, Pérez N, Batlle X, Labartaaand A and Asenjo A 2015 *Nanoscale* **7** 8110

[8] Arsalani S, Guidelli E J, Silveira M A, Salmon C E G, Araujo J F D F, Bruno A C and Baffa O 2019 *J. Magn. Magn. Mater.* **475** 458

[9] Wang Z L, Ma H, Wang F, Li M, Zhang L G and Xu X H 2016 *Chin. Phys. Lett.* **33** 107501

[10] Gou G P, Gao Y, Li Y Z, Ma Q Y, Tu J and Z D 2020 *Chin. Phys. B* **29** 034302

[11] Wang N, Guan Y P, Yang L, Jia L W, Wei X T, Liu H Z and Guo C 2013 *J. Colloid Interface Sci.* **395** 50

[12] Rayegan A, Allafchian A, Sarsari I A and Kameli P 2018 *Int. J. Biol. Macromol.* **113** 317

[13] Dey C, Baishya K, Ghosh A, Goswami M M, Ghosh A and Mandal K 2017 *J. Magn. Magn. Mater.* **427** 168

[14] Teng Y, Du Y, Shi J and Pong P W T 2020 *Curr. Appl. Phys.* **20** 320

[15] Dhavale R P, Waifalkar P P, Sharma A, Dhavale R P, Sahoo S C, Kollu P, Chougale A D, Zahn D R T, Salvan G, Patil P S and Patil P B 2018 *J. Colloid Interface Sci.* **529** 415

[16] Shojaee P, Niroomand-Oscuii H, Sefidgar M and Alinezhad L 2020 *J. Magn. Magn. Mater.* **498** 166089

[17] Raj S, Khurana S, Choudhari R, Kesari K K, Kamal M A, Garg N, Ruokolainen J, Das B C and Kumar D 2019 *Semin. Cancer Biol.* **19** 30216

[18] Amani A, Begdelo J M, Yaghoubi H and Motallebinia S 2019 *J. Drug Delivery Sci. Technol.* **49** 534

[19] Zein R, Sharrouf W and Selting K 2020 *J. Oncol.* **2020** 1

[20] Ansari M, Bigham A, Hassanzadeh-Tabrizi S A and Ahangar H A 2017 *J. Magn. Magn. Mater.* **439** 67

[21] Hoshiar A K, Le TA, Amin F U, Kim M O and Yoon J 2017 *J. Magn. Magn. Mater.* **427** 181

[22] Roca A G, Gutiérrez L, Gavilán H, Brollo M E F, Veintemillas-Verdaguer S and Morales M d P 2019 *Adv. Drug Delivery Rev.* **138** 68

[23] Wang X, Pan F, Xiang Z, Jia W W and Lu W 2020 *Mater. Lett.* **262** 127187

[24] Ayubi M, Karimi M, Abdpour S, Rostamizadeh K, Parsa M, Zamani M and Saedi A 2019 *Mater. Sci. Eng. C* **104** 109810

[25] Oroujeni M, Kaboudin B, Xia W, J?nsson P and Ossipov D A 2018 *Prog. Org. Coat.* **114** 154

[26] Gawali S L, Barick B K, Barick K C and Hassan P A 2017 *J. Alloys Compd.* **725** 800

[27] Cristofolini T, Dalmina M, Sierra J A, Silva A H, Pasa A A, Pittella F and Creczynski-Pasa T B 2020 *Mater. Sci. Eng. C* **109** 110555

[28] Ziegler-Borowska M 2019 *Int. J. Biol. Macromol.* **136** 106

[29] Ostroverkhov P V, Semkina A S, Naumenko V A, Plotnikova E A, Melnikov P A, Abakumova T O, Yakubovskaya R I, Mironov A F, Vodopyanov S S, Abakumov A M, Majouga A G, Grin M A, Chekhonin V P and Abakumov M A 2019 *J. Colloid Interface Sci.* **537** 132

[30] Wang F, Li X S, Li W T, Bai H, Gao Y, Ma J H, Liu W and Xi G C 2018 *Mater. Sci. Eng. C* **90** 46

[31] Xu C H, Ye P J, Zhou Y C, He D X, Wei H and Yu C Y 2020 *Acta Biomater.* **105** 1

[32] Wu J, Zhang Z X, Gu J, Zhou W X, Liang X Y, Zhou G Q, Han C C, Xu S S and Liu Y 2020 *J. Controlled Release* **320** 337

[33] Marín T, Montoya P, Arnache O, Pinal R and Calderón J 2018 *J. Magn. Magn. Mater.* **458** 355

[34] Hyun D C 2015 *Polymer* **74** 159

[35] Kim G C, Li Y Y, Chu Y F, Cheng S X, Zhuo R X and Zhang X Z 2008 *Eur. Polym. J.* **44** 2761

[36] Bruniaux J, Allard-Vannier E, Aubrey N, Lakhrif Z, Djemaa S B, Eljack S, Marchais H, Herve-Aubert K, Chourpa I and David S 2019 *Int. J. Pharm.* **569** 118572

[37] Rosenblum D, Joshi N, Tao W, Karp J M and Peer D 2018 *Nat. Commun.* **9** 1410

[38] Avedian N, Zaaeri F, Daryasari M P, Akbari Javar H and Khoobi M 2018 *J. Drug Delivery Sci. Technol.* **44** 323