

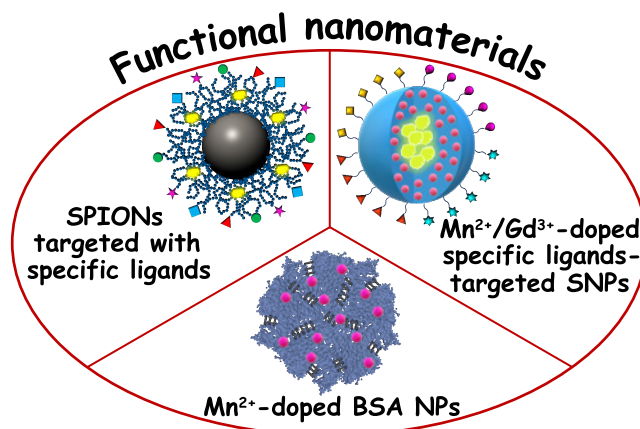
Active targeting of manganese nanoparticles for MRI contrast enhancement: prospects and challenges

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The growing interest in Mn^{2+} ions for T_1 -weighted contrast agents (CAs) stems from their biogenic nature, driving the development of Mn-based complexes and nanoparticles. To enhance tumor contrast and minimize side effects from retention in healthy tissues, active targeting of Mn-based CAs is crucial. Key targeting strategies for Mn^{2+} -based CAs are reviewed alongside those for Gd^{3+} and iron oxide agents, as Mn^{2+} CAs were developed later. In this review, the main focus is on Mn-containing nanoparticles, since from the point of view of the contrast effect and limited delivery of Mn^{2+} ions, they are a more promising basis for CA than molecular Mn^{2+} complexes. Hydrophilic nanoplateforms such as triblock copolymer micelles, silica nanoparticles and protein nanoparticles are the focus of this review due to their widespread use in the design of CAs and their ability to be easily conjugated with functional groups required for active targeting. The literature examples show that the T_1 -weighted contrast of such nanoplateforms conjugated with targeting molecules may differ from that of unconjugated ones, since the high lability of the surface exposed Mn^{2+} ions promotes their redistribution due to coordination through chelating groups on the conjugated nanoplateform. However, this aspect of the development of manganese-based nanoscale contrast agents has not been sufficiently discussed in previous reviews devoted to such nanomaterials. The bibliography includes 120 references.

Keywords: conjugation method, magnetic resonance imaging, active targeting, manganese compounds, magnetic relaxation, nanoparticles.



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1. Introduction

Although magnetic resonance imaging (MRI) is a powerful non-invasive tool in medicine, its sensitivity in contrasting cancerous tissues sometimes needs to be increased by the introduction of

contrast agents (CAs). Currently known CAs are represented by both complexes of paramagnetic metal ions (Mn^{2+} , Fe^{3+} and Gd^{3+}) and their nanosized forms, represented mainly by manganese, gadolinium and iron oxides as well as metal-organic frameworks (MOFs) based on these metal ions.^{1,2} Both types of

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contrast agents carry certain risks to living organisms, but the use of nanoparticles as CAs is a more promising direction for effective and safe contrasting of cancer tumors.²

The distribution of nanoparticles after their intravenous administration is organ-specific, depending on the size and nature of the nanoparticle surface.^{3,4} In particular, nanoparticles larger than 100 nm are efficiently taken up by spleen macrophages and liver Kupffer cells,⁵ while clearance of ultra-small (<10 nm) nanoparticles can be accomplished by alternative mechanisms including tubular filtration^{6,7} and removal by hepatocytes.⁶ Both mechanisms of clearance are possible for nanoparticles between 10 and 100 nm in size, with the preferred mechanism depending on the nature of their surface.^{3,4} Abnormal tumor vasculature, active angiogenesis and high vascular density and some other factors lead to passive entrance of nanoparticles through gaps between endothelial cells, which is followed by their retention in tumor tissues due to impaired lymphatic clearance, the well-known ‘enhanced permeability and retention’ effect (EPR).⁸ Significant difference of diseased tissue cells from normal ones is important factor in EPR.⁸ However, delivery of nanoparticles to solid tumors differs significantly from delivery to cancer cells. Thus, quantitative assessment of nanoparticle distribution in mice indicates that this effect ensures localization in tumor tissues of no more than 0.7% of the administered dose of nanoparticles.⁹ In this regard, active transport and retention (ATR) has been proposed as an alternative mechanism for nanoparticle penetration into solid tumors.¹⁰ Within this mechanism, active endothelial transport and interaction with tumor components of nanoparticles are the main reasons for their entry and retention in the tumor. Therefore, the ATR mechanism is more specific to the size and morphological features of nanoparticles than the EPR mechanism.¹⁰ It is noteworthy that there are a large number of literature results demonstrating the tumor specificity of non-targeted nanoparticles, which in turn depends on their size, shape and surface characteristics, including the formation of the so-called protein corona.^{11–16} However, the limitations imposed by these mechanisms prompt the development of the so-called active targeting approach, which is based on the introduction of certain functional groups onto the surface of nanoparticles that ensure their binding to biomolecules exposed on tumor tissues.^{8,17–20}

Indeed, both passive and active targeting should be combined to enhance tumor specificity of nanoparticles applied as drug delivery systems.¹⁵ However, these trends can also be considered as a tool for both improving the contrast effect of nanoparticles used as CA and reducing the specific risks of these nanoparticles for living organisms due to their limited distribution in normal tissues. These trends have already been discussed for nanoparticle-based contrast agents loaded with Gd³⁺ and Fe³⁽²⁾⁺ oxides. However, the specificity of active MRI targeting using Mn²⁺-based nanoparticles is poorly understood, although the known features of the coordination bonds of Mn²⁺ ions distinguish them from Gd³⁺ and Fe³⁽²⁾⁺ ions. Therefore, this featured article will review the known synthetic conjugation approaches presented in the literature that can allow achieving specificity of penetration of Mn²⁺-based nanoparticles into cancer cells. Possible coordination transformations of Mn²⁺ ions loaded into different nanoparticles after their conjugation with target molecules will be discussed, as well as their influence on the r_1 (T₁-relaxivity) of these nanoparticles, which is the longitudinal magnetic relaxation rate related to one paramagnetic ion. In this work, special attention is paid to the use of commercially available and widely used chemicals in the development of such nanoparticles. Although the influence of

size and shape of manganese-based nanomaterials on their relaxivity has been discussed in detail in previous reviews the challenges of developing targeted nanoscale manganese-based contrast agents have not been adequately addressed.^{1,14}

2. Targeted MRI strategies developed for iron oxide nanoparticles

Since the targeting of nanosized CAs is aimed at ensuring their binding to specific receptors on cancer cells, the surface design of these CAs, leading to the incorporation of certain functional groups on their surface, has a significant impact on targeting. Literature data represent successful examples of the surface design favoring the targeting of iron-oxide nanoparticles.^{8,21–24} To ensure strong binding to biomolecules exposed on the cell membranes of cancer cells, the surface of the nanoparticles is modified with proteins, hormones, biotin, folic and hyaluronic (HA) acids.^{8,25} Particular attention should be paid to the hydrophilic coating of iron oxides, that ensures their long-term circulation in the bloodstream and easy conjugation with target biomolecules. The so-called ‘PEGylation’ (covering with polyethylene glycol) of nanoparticles is a well-known and well-established approach to increase the lifetime in the bloodstream due to limiting their rapid uptake by the reticuloendothelial system.²⁵ Efficient hydrophilic coating of iron oxide nanoparticles can also be achieved using triblock copolymers (PEO)_n(PPO)_m(PEO)_n, built from polyethylene oxide (PEO) and polypropylene oxide (PPO) moieties, which tend to aggregate on the surface of the nanoparticles.^{26–33} Aggregates of water-soluble polymers, especially triblock copolymers (among which F68, F127 and P123 are most widely applied) and polyelectrolytes (polyethyleimines, polyaminoacids), whose molecules can be glycosylated or covalently modified with folic acid, biotin and oligopeptides, play a special role in the development of drug delivery systems.^{18,33–38} Targeting of such drug delivery systems is typically based on the conjugation of triblock copolymer molecules *via* their hydrophilic PEO block with specific functional groups to ensure their surface localization for binding to cellular receptors.³⁹ Variation in length of PEO and PPO blocks of triblock copolymers provides an opportunity to obtain the aggregates with diverse nano-architectures, including vesicular aggregates constructed from Pluronic L121 (PEO)₅(PPO)₆₈(PEO)₅, which can be both efficiently conjugated with the target peptide and loaded with iron oxides.⁴⁰ Notably, the use of a triblock copolymer with different lengths of PEO fragments and their decoration with different terminal groups provides polymer vesicles with a high anticancer effect both due to loading with superparamagnetic iron oxide nanoparticles (SPIONs) and doxorubicin and due to conjugation with FA.³³ The efficiency of targeting can be visualized using *in vitro* fluorescence microscopy measurements. This can be achieved with bimodal nanoparticles that contain both iron oxide cores and organic dyes as a fluorescent component.^{27,40,41}

Pluronic F127 plays a particular role in the design of drug delivery systems due to the ability of its aggregates to load a cargo and release it in an intracellular space.^{41,42} It is important to note that according to literature data, the introduction of FA or peptides into triblock copolymer F127 molecules promotes the targeted delivery of iron-oxide nanoparticles into tumor tissues.^{26,28,31,41,43,44} Moreover, a hydrophilic coating of SPIONs with a triblock copolymer allows combining MRI targeting with drug delivery, which is considered a relevant area in nanomedicine.^{30,33,45–47} Together with the easy targeting of triblock copolymers, this demonstrates the importance of their use in developing of diagnostic and therapeutic iron oxide-based

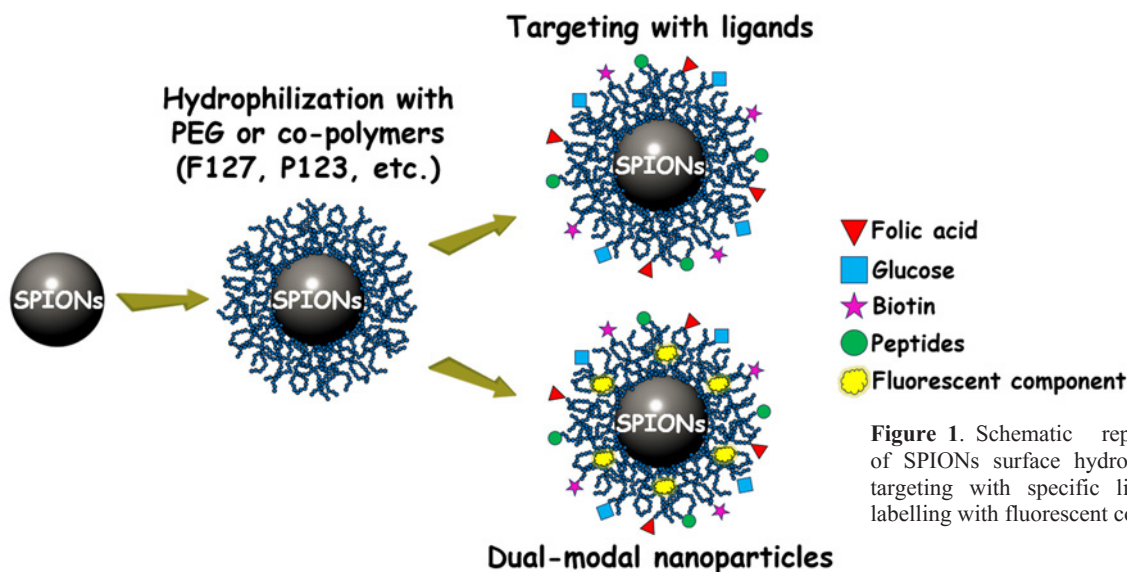


Figure 1. Schematic representation of SPIONs surface hydrophilization, targeting with specific ligands and labelling with fluorescent components.

integration nanoplatforms. The above trends are schematically shown in the cartoon image in Figure 1.

The influence of the size and shape of SPIONs on their ability to contrast malignant tumors is quite significant and can be comparable to the contrast created by nanoparticles that selectively bind to specific receptors on cancer cells, or so-called targeted contrast.¹¹ It is also noteworthy that FA can be chelated with the surface exposed Fe^{3+} ions of the iron oxide nanoparticles, which also results in their targeting.⁴⁸ Nevertheless, iron oxides are usually so-called negative CAs, which manifest as tissue darkening due to the T_2 -contrasting effect resulted from increased transverse magnetic relaxation rates. However, the tissue brightening due to the so-called T_1 -contrasting effect has got wider use in medicine diagnostics. T_2 -contrasting effect is typical for the iron oxide nanoparticles with the size above 10 nm, whereas the small sized (about 5 nm) iron oxide nanoparticles can give higher T_1 -contrast compared to T_2 -weighted one.⁴⁹ Thus, the work²² is noteworthy, demonstrating a nanoarchitecture where the aggregation of small sized iron oxide nanoparticles leads to T_2 -weighted contrast, whereas the disaggregation of these iron oxides caused by glutathione (GSH) provides selective positive T_1 -weighted contrast of cancer tissues due to the higher concentration of GSH in cancer cells compared to normal cells. It is noteworthy that opsonization of the SPION-based nanoarchitectures derived from the surface adsorption of serum proteins can significantly limit their targeting effectiveness.²⁵ Moreover, the use of SPIONs as CAs in MRI is limited due to the fact that inhomogeneous magnetic field of SPIONs can

cause artifacts that reduce diagnostic accuracy, whereas T_1 -weighted CAs are free from this limitation. This is the reason for the considerable attention paid to nanoparticles loaded with Mn^{2+} and Gd^{3+} ions as the basis of CAs in MRI.

3. Different nanoarchitectures in the context of Mn^{2+} specificity

The particular interest in Mn^{2+} -containing contrast agents (MnCAs) is due to nephrogenic drawbacks of the Gd^{3+} -based contrast agents.^{50–52} The advantage of target-mediated contrast in MRI using Gd^{3+} -based CAs in molecular and nanoparticle forms has already been.^{23,53} It is worth noting the successful techniques used for their targeting. In particular, Gd^{3+} ions can be doped into SPIONs, which can be coated by triblock copolymer molecules decorated with FA.⁵⁴ The work²³ demonstrates dual targeting with peptides of the dendrimer bound with Gd^{3+} ions as a route to get better accumulation in tumors compared to monotargeted analogs. However, the low r_1 values estimated for Gd^{3+} ions bound with the dendrimer indicate insufficient constraint on their internal motion.²³ The work⁵⁵ demonstrates the successful creation of dual targeting CAs by covalent introduction of gadolinium chelate complex, fluorophore and targeting group into poly-lysine molecules, but the r_1 value of this molecules is also on the level of molecular CAs, such as Omniscan, Gadovist and others (below $10 \text{ mM}^{-1} \text{ s}^{-1}$). The work⁵⁶ (Fig. 2) demonstrates specific nanoarchitecture constructed from the mixed assembly of the

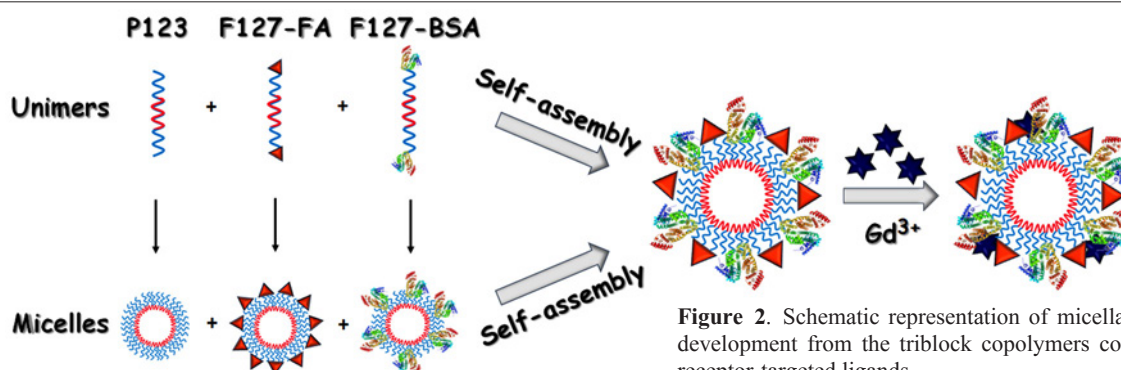


Figure 2. Schematic representation of micellar contrast agents' development from the triblock copolymers conjugated with FA receptor-targeted ligands.

triblock copolymers F127 and P123 terminated with either folates (FA) or bovine serum albumin (BSA). The triblock copolymers terminated with BSA provide the tight binding of Gd^{3+} ions, while FA-terminated triblock copolymer molecules ensure the target-mediated cancer specificity.

Turning to manganese-based contrast agents, it is worth noting that the high kinetic lability and insufficient thermodynamic stability of Mn^{2+} complexes represent a challenge when using coordination of paramagnetic ions by polydentate ligand molecules as an approach to creating CAs.⁵¹ Moreover, the specificity of the electronic structure of Mn^{2+} ions, which have only five unpaired electrons, as opposed to seven for Gd^{3+} , is the reason for lower T_1 -relaxivity for Mn^{2+} complexes compared to Gd^{3+} complexes.^{50–52} These drawbacks can be minimized within the nanotechnological approach to the creation of Mn^{2+} -containing CAs by tuning parameters such as the retention time of inner-sphere water molecules and the rotational and translational motion rates of paramagnetic ions, as clearly demonstrated in the relevant reviews.^{1,51,57–60} To appreciate the advantage of using nanoparticles instead of molecular complexes as CAs, it should be noted that the r_1 values of commercial Mn-based molecular CAs are in the range of $2.8\text{--}8.0\text{ mM}^{-1}\text{ s}^{-1}$ at 20 MHz,^{51,61,62} while these values for Mn-containing nanoparticles are typically far above $10\text{ mM}^{-1}\text{ s}^{-1}$, with the top values above $50\text{ mM}^{-1}\text{ s}^{-1}$.^{1,49,59,63,64} In this regard, the work⁶⁵ exemplifies both the use of MnFe_2O_4 nanocrystals instead of the iron oxides and HA-mediated targeting of breast cancer cells *via* binding with CD44 antigen, which is a cell-surface glycoprotein. In this case, the incorporation of aminated Polyoxyethylene (80) sorbitan monooleate conjugated with HA into the hydrophilic coating of MnFe_2O_4 provides both long-term circulation in the bloodstream and the targeting function. The literature data represent successful use of F127 for hydrophilic coating of Mn-loaded nanoparticles based on manganese oxides or MOF-nanocrystals based on Mn^{2+} complexes.^{63,66,67} Notably, F127 molecules are readily conjugated with functional groups required for targeting, although this strategy is underrepresented in the literature for Mn-based nanoparticles.

Surface-exposed silanol groups both play a major role in the cytotoxicity of silica nanoparticles (SNs) and open up wide opportunities for their covalent modification with amino or carboxyl groups, thus, providing a good basis for a targeting of SNs.⁶⁸ Thus, the doping of SNs with a wide range of d-f-metal ions, complexes or organic compounds along with their targeting is actively used in the creation of targeted theranostic systems (Fig. 3).^{68–75} Mesoporous SNs play a special role in the creation of drug delivery systems and this type of SNs is represented by various sizes of both the nanoparticles and their pores.^{76–78} In this regard, it is worth noting the reports that emphasize that the porosity of rather small SNs with sizes of $30\text{--}50\text{ nm}$ is sufficient for efficient hydration of manganese ions incorporated into the silica matrix when these Mn-doped SNs are synthesized by the water-in-oil microemulsion method using Triton X-100 or Igepal CO-520.^{79,80} Such porosity is provided by molecules or aggregates of these non-ionic surfactants, which are adsorbed on the silica surface during synthesis, leaving pores when they are further washed out of the silica nanoparticles. Moreover, the incorporation of manganese chelates into SNs using a water-in-oil microemulsion method with Igepal CO-520, in addition to achieving much higher r_1 values than for molecular complexes, demonstrates target-mediated selectivity in tumor tissue MRI contrast due to folate (FA) targeting.⁸⁰

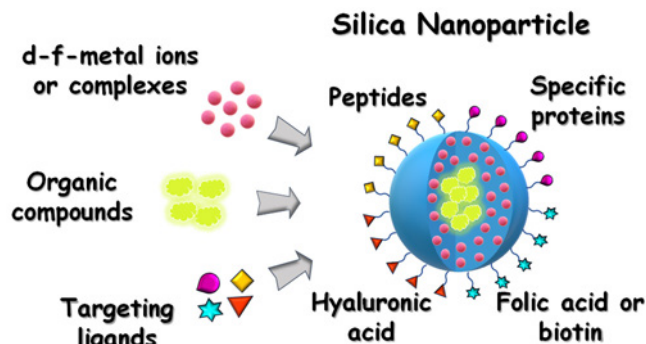


Figure 3. Loading of silica nanoparticles with various metal ions or complexes, fluorescent components mainly represented by organic dyes and targeting with specific ligands.

Manganese ions are inferior to gadolinium ions in terms of coordination efficiency, which, together with the high lability of their complexes, facilitates the leaching of manganese ions from the corresponding nanoparticles in solutions of increased acidity or due to their coordination with phosphate ions. Literature results including the design of stimuli-responsive Mn-loaded nanoparticles and nanoarchitectures obtained using the so-called Kirkendall effect illustrate the above trends (Fig. 4).^{81–85} The easy leaching of Mn^{2+} ions from various Mn-containing nanoparticles makes it necessary to take into account the coordinating ability of functional groups conjugated to the nanoparticle surface, since some of them, such as folates (FA) or peptides, can initiate the leaching of Mn^{2+} ions. In this case, part of the loaded Mn^{2+} ions can be relocated from the surface of nanoparticles to these functional groups. This should be followed by changes in the hydration numbers of these Mn^{2+} ions, which can lead to changes in both r_1 and r_2/r_1 values, since the latter are specifically dependent on the hydration number of the Mn^{2+} ions.^{86,87} Notably, some reports on Mn-containing nanoparticles show an increase in r_1 values after their conjugation with FA or after adsorption of serum albumins onto their surface.^{80,88} However, the coordination aspects of the change in relaxivity values after both covalent and non-covalent decoration of the surface of Mn-containing nanoparticles still await detailed discussion.

4. Nanoarchitectures of Mn-based CAs with high biocompatibility and biodegradability

While highlighting the diversity of stimuli-responsive nanoarchitectures based on SNs suitable for biomedical use, their slow clearance and long-term localization in the liver should also be noted.^{75,89} Since the *in vivo* toxicity of SNs is significant only when administered in high doses,⁹⁰ the toxic effect can be limited by administering lower doses, which in

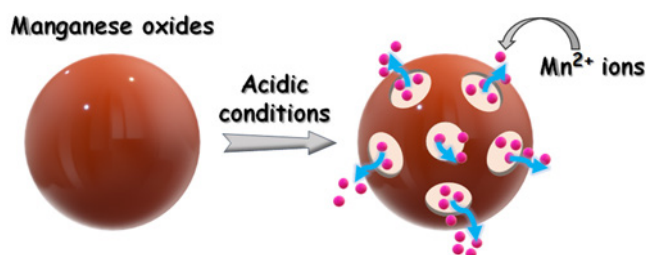


Figure 4. Schematic illustration of the Kirkendall effect.

turn can be achieved by creating Mn-doped SNs with high T_1 -contrast effect. Moreover, the creation of biodegradable silica-based nanoarchitectures⁷⁸ represents an alternative way to address the toxicity problem. In this regard, the use of protein molecules as building blocks of nanoarchitectures provide a good basis for the creation of biodegradable nanoparticulate CAs.

Serum albumins are the most common and cheapest base for creating a hydrophilic shell for nanoparticles, which has been successfully demonstrated on titanium and iron oxides, and the possibility of combining with the transport function of serum albumin towards drug molecules and/or organic dyes has also been shown.^{91–101} Of course, bovine serum albumin (BSA) is the cheapest and most abundant, so it is more widely used than other serum albumins. Importantly, amino groups exposed on the surface of BSA can be conjugated with such targeting molecules as biotin^{97,98} and FA.^{99–101} Typically, the synthesis of BSA-based nanoparticles occurs by denaturing BSA molecules followed by their cross-linking. Moreover, denatured BSA molecules can be used in creating hydrophilic biodegradable shells on a surface of inorganic nanoparticles due to the high affinity of denatured BSA to nanoparticle surfaces. This makes BSA a good alternative to artificial polymers in the development of therapeutic agents^{102–104} or biosensors.^{105,106} Acidification-induced swelling of BSA molecules mediates drug release from BSA-based nanostructures, making them a promising platform for lysosome-mediated drug delivery.¹⁰⁷ In turn, the BSA-based coating of manganese-doped copper selenide nanoparticles¹⁰⁸ or manganese-doped iron oxide nanoparticles¹⁰⁹ favors their use as CAs in MRI along with the therapeutic function.

An excellent example of covalent grafting of human serum albumin (HSA) with diethylenetriaminepentaacetic acid (DTPA) ligand followed by coordination of Gd^{3+} ions, resulting in T_1 -weighted relaxivity, is worth noting.⁹⁶ However, the contrast effect of Gd^{3+} ions bound to DTPA residues grafted onto HSA is similar to that achieved by the Gd -DTPA complex in solution, indicating that the internal motion of the Gd -DTPA complex is not significantly restricted by its grafting onto the HSA nanoplatform.⁹⁶ However, it is worth noting the possibility of the tight binding of d- and f-metal to the specific binding site (binding site VI) of BSA, which provides its transport function towards transition metal ions.¹¹⁰ The tight binding of metal complexes to BSA molecules is manifested in significant changes in the spectral properties of the complexes, which are caused by the limited vibrational motion of the complex molecules localized in specific BSA binding sites.¹¹¹ Thus, it is to be expected that these types of binding can provide a significant slowing of the internal motion of paramagnetic ions necessary for high T_1 relaxivity, which follows from the high levels of T_1 and T_2 relaxivity of manganese ions in BSA solutions.^{112,113} It is noteworthy that the literature data provide the series of the well-developed approaches to convert native serum albumins into the albumin-based nanoparticles, which have been shown to serve as drug delivery systems.¹¹⁴ Relatively recently, it has been shown that the efficiency of such binding persists even after partial denaturation of BSA, further crosslinking of which allows the formation of Mn^{2+} -containing nanoparticles with high T_1 and T_2 relaxivities (Fig. 5).¹¹⁵ It has been shown that the molar ratio Mn:BSA should be kept at a level of 4:1 for high negative surface charge required for high colloidal stability of BSA-based nanoparticles loaded with Mn^{2+} ions.¹¹⁵ For the best of our knowledge, there are very few papers focused on the loading of manganese ions through their coordinative binding with protein-based nanoplatform, although

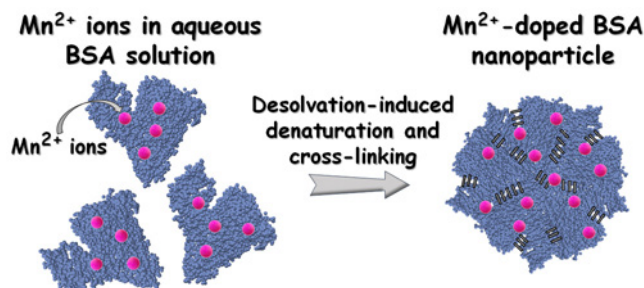


Figure 5. Schematic representation of high contrasting Mn^{2+} -containing BSA nanoparticles synthesis.

there are enough papers on the loading of copper ions into BSA-based nanoarchitectures.^{116–120} These copper-containing nanoarchitectures are in the spotlight due to their laccase-like enzymatic activity,^{116–118} whereas the Mn-loaded BSA-based nanoparticles exhibit antioxidant properties.¹¹⁵ All this makes Mn-loaded BSA-based nanoparticles convenient basis for development of targeted CAs.

5. Prospects and conclusions

In summary, targeting methods well developed for drug delivery systems have been successfully used to enhance contrast effect of iron-oxide nanoparticles under their use as contrast agents, while the examples of targeted Mn^{2+} -containing contrast agents are clearly insufficient. Numerous examples in the literature show that the use of triblock copolymers and serum albumins for hydrophilic coating of inorganic nanoparticles is a promising tool for creating targeted contrast, since they provide easy conjugation with functional groups. However, their application for creating Mn-containing nanoparticles with targeted contrast has not yet been studied. The targeted Mn-loaded nanoparticles conjugated through silanol groups have been represented as very successful example due to the additional raising in T_1 relaxivity after the conjugation with folates (FA). However, a deeper understanding of the reasons for this trend is still awaited. Notably, the active targeting of Mn-containing nanoparticles can be largely overlapped by the EPR and ATR effects when these nanoparticles are used in living organisms. Therefore, different target-induced contrast effect can be expected for nanoparticles with different sizes, shapes and surface properties. The relationship between the active targeting effects and the morphological specificity of manganese nanoparticles needs to be studied both *in vitro* using standard cancer and normal cell lines and *in vivo* using MRI studies in living mice.

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