Imaging Gliomas with Nanoparticle-Labeled Stem Cells

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Abstract

Objective: Gliomas are the most common neoplasm of the central nervous system (CNS); however, traditional imaging techniques do not show the boundaries of tumors well. Some researchers have found a new therapeutic mode to combine nanoparticles, which are nanosized particles with various properties for specific therapeutic purposes, and stem cells for tracing gliomas. This review provides an introduction of the basic understanding and clinical applications of the combination of stem cells and nanoparticles as a contrast agent for glioma imaging.

Data Sources: Studies published in English up to and including 2017 were extracted from the PubMed database with the selected key words of "stem cell," "glioma," "nanoparticles," "MRI," "nuclear imaging," and "Fluorescence imaging."

Study Selection: The selection of studies focused on both preclinical studies and basic studies of tracking glioma with nanoparticle-labeled stem cells.

Results: Studies have demonstrated successful labeling of stem cells with multiple types of nanoparticles. These labeled stem cells efficiently migrated to gliomas of varies models and produced signals sensitively captured by different imaging modalities.

Conclusion: The use of nanoparticle-labeled stem cells is a promising imaging platform for the tracking and treatment of gliomas.

Key words: Glioma; Nanoparticle; Stem Cell

INTRODUCTION

Gliomas are the most common neoplasm of the central nervous system (CNS), and poorly differentiated gliomas present invasive growth patterns. Patients with glioblastomas, the most malignant type, have been reported to exhibit a very low 5-year survival rate, and median survival times are only 12–24 months.[1] Compared to the breakthroughs in the treatment of many other cancers, the progresses of glioma therapies remain almost stagnant. The combination of microsurgery, with the latest chemotherapy such as temozolomide and radiation therapy with optimized designs, have not further significantly postponed disease recurrence in glioblastoma patients.[2,3] Clinical evidence suggests that 80–90% of glioma recurrences occur within the original resection field.[4] Instead of removing the entire anatomical unit of the malignant organ, modern oncological neurosurgery focuses on maximizing the resection of the tumor by its subjectively judged margins, while protecting as many neural functions as possible. To obtain maximal resection and maximal protection, there is an urgent need for advances to be made to push the imaging accuracy of the lesions to a higher level for better treatment outcomes.

Most recent examples of such advances have originated from the adoption of advanced imaging techniques to replace or reinforce the traditional ones, such as the integration of intraoperative magnetic resonance imaging (MRI), nuclear imaging, and fluorescence imaging modalities into surgeries. On the other hand, as the core of various types of imaging modalities, breakthroughs in the field of study of imaging agents to provide more accurate signals of the malignancies could extensively increase the efficacy of the treatment.

Nanoparticles of 1–100 nm in diameter[5] can be tailored and utilized as contrast agents for gliomas. The growth of glioma cells actively affects the integrity of the blood-brain barrier (BBB)[6] and invades the neurovasculature to cause these blood vessels to have a leaky nature during glioma development. Nanoparticles with tunable properties regarding their size, shape, and surface functionalization can greatly

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improve the factors affecting the contrast efficacy. With their controllable size, nanoparticles can gain a higher passage through a compromised BBB[7] and, together with shape and functionalization tailoring, can lead to a drastically increased circulation for an enhanced permeability and retention effect. Certain nanoparticles such as iron-based nanoparticles have an additional biological effect because iron metabolism itself is a normal physiological process; thus, contrast elimination follows normal physiology as well. Moreover, compared with traditional contrast agents such as gadolinium, they have shown advantages in terms of a slower elimination, more effective magnetic resonance relaxation, a better safety profile due to metabolization through the normal iron metabolism pathway, and better delineation of tumor margins possibly resulting from cellular uptake and aggregation of iron.[8-10]

Heterogeneity is a very important hallmark of high-grade gliomas as well as the trickiest problem in glioma management. Similar to glioma cell heterogeneity, the vasculature and BBB impairment throughout the entire tumor are inhomogeneous.[11,12] This leaves a fatal flaw for conventional methods of nanoparticle contrast agent administration, as there always will be portions of gliomas without BBB impairment for nanoparticles to reach the tumor efficiently.[13] Studies that focus on facilitating the passage of nanoparticles through the BBB via receptor-mediated transcytosis[14] and adsorptive-mediated transcytosis[15] targeting specific glioma cell ligand molecules still lack the ability to cope efficiently with glioma cell heterogeneity, mutations, and evolution. One possible solution to the current limitations of nanoparticle-based glioma imaging contrast agents is the incorporation of cellular carriers to generate a dual-system platform. The rationale of this system originates from the discovery that stem cells, including neural stem cells (NSCs) and mesenchymal stem cells (MSCs), have an intrinsic ability to migrate to different pathologies such as inflammation, infarction, and tumors.[16-19] Furthermore, there is also evidence that NSCs efficiently track glioma stem cells;[20] thus, the inability of nanoparticle contrast agents to reach escaped glioma stem cells could potentially be solved by the application of stem cells such as NSCs for active tracking. This review aims to describe the mechanism of this combination and to summarize its preclinical applications with the major imaging modalities for a more precise imaging of gliomas, which might potentially augment the current surgical protocol for the management of this disease [Figure 1].

BASIC RATIONALE FOR NANOPARTICLE STEM CELL CARRIERS: THE TROPISM OF STEM CELLS TOWARD GLIOMA

NSCs and MSCs are currently the focus in the study of nanoparticle stem cell carriers in tracking gliomas. NSCs are the progenitor cells giving rise to the three major lineages of cells in the CNS,[21] and their migration capability
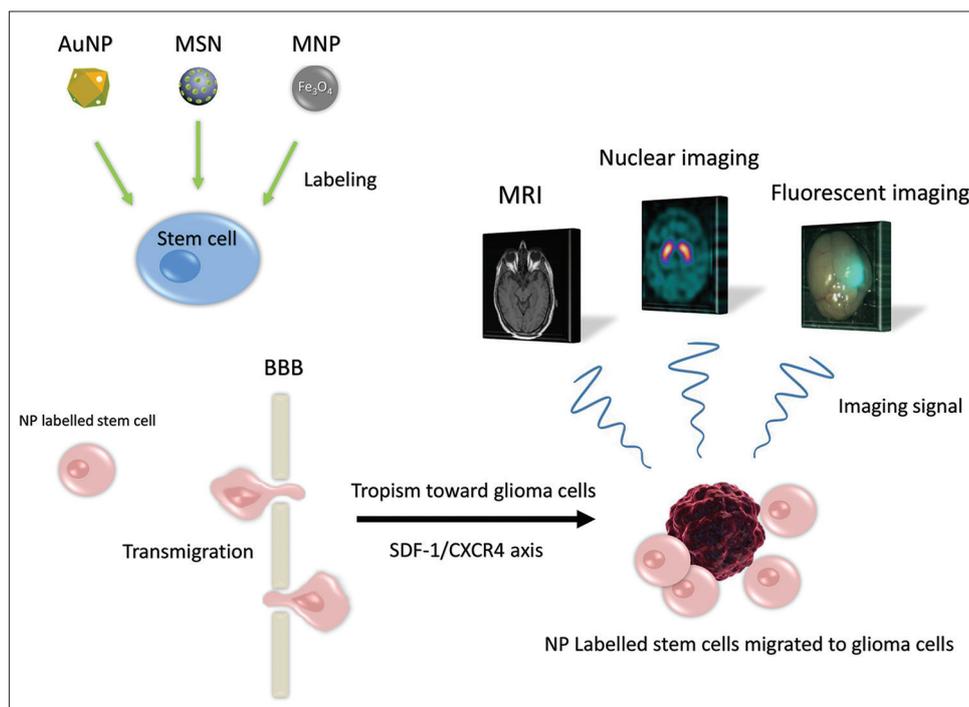

Figure 1: Nanoparticle-labeled stem cells migrate across BBB toward glioma cells for imaging. Stem cells such as NSC or MSC could be labeled with nanoparticles loaded with imaging agents. Administered via venous or intracerebral injection, the transplanted labeled stem cells could transmigrate through BBB and home toward glioma cells and glioma stem cells, while emitting or producing imaging signals which could be captured by different imaging techniques including MRI, SPECT, NIR, and confocal microscopy. AuNP: Gold nanoparticle; MSN: Mesoporous silica nanoparticle; MNP: Magnetic nanoparticle; BBB: Blood-brain barrier; NSC: Neural stem cells; MSC: Mesenchymal stem cells; NP: Nanoparticle; MRI: Magnetic resonance imaging; SPECT: Single-photon emission computed tomography; NIR: Near infrared; SDF-1/CXCR4: Stromal derived factor-1/C-X-C chemokine receptor type 4.

during embryo development[22] is preserved throughout adulthood at certain CNS locations, thus retaining their neuroplasticity.[23,24] The initial evidence of NSC glioma tropism was the striking discovery in the D74 and CNS-1 model of intracerebrally or intravenously administered migrating NSCs.[25] The phenomenon was later confirmed by numerous studies and quantified, with an estimated 70–90% coverage of the glioma tumor mass and the invasive tumor foci.[26-29] Moreover, one recent study conducted an investigation into the quantification of NSC coverage in glioma tissue via different administration routes; they reported a homing rate of 50–60% of transplanted stem cells with intracerebral administration and 1.5% with intravenous administration. The coverage in the glioma sections could reach as high as 100% with intracerebral administration and 70% with intravenous administration.[30] Other studies on this topic have further developed the research on NSC-based drug administration,[31,32] gene therapy,[33,34] and application of the bystander effect.[35-37] Conversely, the incorporation of nanomedicine to NSCs has led to extensive research in this realm, including the effect of nanomaterials on NSC biology,[38-41] enhanced material loading,[42-45] stem cell tracking,[46-51] and tumor treatment.[32,52]

A huge challenge with the broad application of NSCs is the scarcity of its source, mainly fetal cells or autologous CNS cells from the patient. Immortalized cell lines with oncogenes[53] again raise safety concerns in transplantation.[54] As an alternative, MSCs with a broader source, including bone marrow-cultured cells[55] and other tissues,[56-61] and an easier expansion protocol[61,62] have been quantified to show a similar glioma-specific migration capability with slightly more nonspecific migration in multiple glioma cell lines and specimens.[17,63] One drawback of MSCs exists, which is their inability to track glioma stem cells at a resting state.[64]

The mechanism of glioma tropism is partly shared by NSCs and MSCs. Stromal cell-derived factor 1, together with its receptor C-X-C chemokine receptor type 4 (CXCR4), has been confirmed as one of the most critical factors mediating the tropism.[65] Other mechanisms dictating the tropism include glioma extracellular matrix remodeling and hypoxia for NSCs[66] as well as glioma interleukin-8, platelet-derived growth factor-BB, and transforming growth factor-beta production for MSCs.[67,68] Regarding the alternative sources of MSCs, one recent study has compared the migratory capacity toward glioma-conditioned medium between bone marrow-derived, adipose-derived, and synovial fluid-derived MSCs, among which synovial fluid-derived MSCs presented the strongest migration capacity. Activated lymphocyte cell adhesion molecule and N-cadherin were confirmed as participants of the responsible mechanisms, and they could be upregulated by microRNA-192 and -218 downregulation.[60]

Stem cells and cancer cells have diverse interactions based on the histological origin of the latter. While the cancer-promoting effect of stem cells has been observed in malignancies such as breast cancer[69] as well as head and neck cancers,[70] the existing evidence has generally supported the use of transplanted NSCs and MSCs as safe therapeutic platforms to treat gliomas. Several recent studies have suggested their inhibitory effects against gliomas, such as the reported study of NSCs directly inhibiting the invasion and proliferation of gliomas[71] and their association with a survival benefit.[72] Transplanted MSCs also have been reported to improve the survival of rats with U87MG xenografts, showing a reduction in tumor growth, cell proliferation, and microvascular density[73] as well as a cytotoxic effect toward C6 glioma cells through gap junctions.[74] Contrary to this evidence, the tumor-promoting effect of MSCs from certain sources cannot be completely ignored. One study published in 2016 investigated the effect of the secretome from adipose-derived stem cells on glioblastoma cells, which increased the migration capacity of the malignant cells.[75] Hence, caution is still needed in order to apply the homing capacity of stem cells for glioma treatment.

GLIOMA IMAGING MODALITIES AND LABELING NANOPARTICLES FOR STEM CELLS

Magnetic resonance imaging and magnetic nanoparticles

Magnetic nanoparticles

Upon its first development, iron-based nanoparticles, usually termed magnetic nanoparticles (MNPs), have shown potential for a wide range of applications as imaging contrast agents and therapeutic carriers. The so-called MNPs usually consist of nanoparticles with a magnetic core composed of magnetite (Fe_3O_4) or maghemite (Fe_2O_3), containing of a type of product termed superparamagnetic iron oxide nanoparticles (SPIONs). Miniaturizing the iron oxide particles to certain sizes in which each particle consists of a single magnetic domain with thermal energy high enough to overcome the energy barrier of magnetic flipping could generate local interactions with water protons that can induce proton dephasing and shorten transverse T2 relaxation.[76,77] Thus, the aggravation of these iron oxide particles causes a reduced signal that is easily detected on the MRI T2 sequence, achieving a contrast effect. Multiple methods to synthesize iron oxide nanoparticles exist, including coprecipitation,[78] thermal decomposition,[79] and microemulsion,[80] which generally yield hydrophobic particles; therefore, different coatings to enhance biocompatibility are often needed. In the specific scenario of labeling stem cells with MNPs to track gliomas, the choice of the labeling agent depends on several factors. This often involves the selection of iron cores of different sizes and coatings to balance between imaging sensitivity and potential toxicity as well as the addition of different types of transfection methods to ensure proper carriage of the MNPs without leaking to scavengers such as macrophages, thus causing false positivity.

Labeling with standard superparamagnetic iron oxide nanoparticles

SPIONs can be categorized into three classes: standard SPIONs (50–180 nm), ultra-small superparamagnetic iron oxide-based nanoparticles (USPIONs, 10–50 nm), and

very small SPIONs (<10 nm). The earliest application of labeling stem cells to track gliomas with SPIONs can be dated back to 2005. In this study, a standard SPION was applied to label endothelial precursor cells to track local glioma angiogenesis. After systemic administration, the labeled stem cells were distributed as a hypointensive dark ring circumscribing the glioma rim on both *in vitro* and *in vivo* MRI at about day 10.[81] A similar study imaged glioma angiogenesis using SPION-labeled human cord blood endothelial progenitor cell AC133 cells to track C6 gliomas in rats, and linear hypointense regions in the tumor could be observed at the periphery and the center of the tumor mass when reaching 1 cm, or 7 days after transplantation.[82] The standard SPION used in these two studies was Ferumoxide, which was initially approved by the U.S. Federal Drug Administration as an MRI contrast agent. Ferumoxide is a type of SPION coated by dextran with a hydrodynamic diameter of approximately 100 nm. The particles are biodegradable after entering into the body by joining the iron metabolism pathway and are eventually incorporated into hemoglobin in red cells within 30–40 days.[83,84]

Besides tracking glioma angiogenesis, Ferumoxide also has been proven to label gliomas directly with NSCs and MSCs. With NSCs, it has been reported that more than 95% of the iron cores could be retained in NSCs after tissue culturing for 96 h, and the threshold reached nine labeled cells per voxel or as few as 600 NSCs in 300 μm thick slices to generate a detectable signal reduction on 7T T2-weighted multispin multiecho MRI.[85] This enables detecting U251 gliomas as small as 200–500 μm (resembling residual gliomas) by 7T MRI, with a signal reduction equivalent to that of 1×10^4–2.5×10^5-labeled NSCs, which is not possible by conventional 7T MRI.[85] Similar to NSCs, Ferumoxide could label MSCs with an average uptake of 9 pg of intracellular iron in each cell, which could migrate to the U87 glioma surrounding the tumor periphery and was distributed throughout the main tumor mass, resulting in a significant signal change on MRI.[86]

Enhancing the sensitivity of glioma imaging by standard SPION-labeled stem cells has also been studied. These enhancements include modifying SPION coating with carboxy dextran to enhance cellular uptake,[87] using the transfection agent poly-L-lysine[81] or protamine,[85] increasing the incubation concentration,[86] and doping the core of SPIONs.[88] These methods have increased the sensitivity of imaging and even the stem cell glioma tropism.

Labeling with ultra-small superparamagnetic iron oxide-based nanoparticles

In a study of stem cell labeling to track gliomas, Ferymoxytol was used because Ferumoxide was removed from the market in 2009.[89] Ferymoxytol is a colloidal suspension of carbohydrate-coated second-generation USPIONs and was approved to treat iron deficiency in anemic patients with chronic kidney disease. Compared to standard SPIONs, USPIONs have a longer half-life and are more often applied as an imaging contrast agent; even with

gliomas, USPIONs exert a much higher penetration through an impaired BBB to enhance gliomas directly.[90] In a study using NSCs, Ferymoxytol with heparin and protamine sulfate achieved a satisfactory NSC-labeling efficiency and early migration to a U251 glioma xenograft across the midline on days 1–4 after intracerebral administration or 4 days after intravenous administration.[91] Another study also has reported successful transfection of NSCs with USPIONs synthesized in the laboratory with different coatings; in addition, efficient labeling and retention of NSC viability also have been reported.[92]

In labeling MSCs, USPIONs show advantages of more homogenous cell labeling compared with SPIONs as the latter are more prone to aggregation in the culture medium, resulting in localized uptake and nonhomogeneous labeling among the cell population.[93] A recent report has confirmed such labeling with MRI, and MSCs labeled with Ferymoxytol have been shown to migrate successfully in the brain.[94] Furthermore, a quantification study has determined the optimal lower limit of 21 h of incubation and 10 μg of USPIONs/10^5 MSCs for positive detection with 1.5 Tesla MRI.[95]

NON-MAGNETIC RESONANCE IMAGING-BASED IMAGING
Nuclear imaging

As a major nuclear imaging technique, single-photon emission computed tomography (SPECT) adopts γ-rays to image biochemical activities with a three-dimensional output of the imaging information. Conventional radionuclides for SPECT imaging include 111In (half-life, 67 h) and 99 metastable (mTc, half-life, 6 h), and their applications compensate for each other in terms of sensitivity and duration of cell tracking. Compared with conventional contrast MRI, SPECT has a higher sensitivity because the technique can directly record cellular metabolism or other bioactivities as long as the radionuclide tracers are marked correspondingly, instead of relying totally on vasculature abnormalities in the tumors. Some recent studies cover many advances of SPECT for the evaluation of gliomas, such as the assessment of glioma cell response to chemotherapy,[96] monoclonal antibodies,[97] and peptides targeting specific glioma cell markers.[97] The published literature regarding SPECT tracking stem cells mainly uses the direct application of 111In. In labeling MSCs and NSCs, their homing behaviors have thus been scrutinized in terms of neuroblastoma[98] and myocardial infarction.[99] Viability assessment has been reported as unaffected cell viability but a significantly reduced metabolic activity and migration.[100,101] 111In still shows an advantage over 99mTc as clear evidence exists that the labeling significantly affects stem cell viability.[102]

Mesoporous silica nanoparticles (MSNs) are a type of homogeneously sized porous silica nanoparticles with a pore size ranging from 2 nm to 50 nm. MSNs have large surface areas and pore sizes to load a variety of agents for both therapy and imaging; the pore sizes are adjustable to

control the loading and release processes, and the surface can be modified to reduce toxicity. MSNs also have shown good biocompatibility and thermal/hydrothermal stabilities.[103] These features make MSNs another important tool for glioma therapy and diagnosis. Currently, several types of radioisotopes have been studied for loading MSNs, including zirconium-89,[104] copper-64,[105] Ho-165,[106] fluorine-18,[107] and 111In.[108] For 111In as a SPECT isotope, one recent study has described the application of 70 nm MSNs in NSC labeling and glioma homing. MSNs were radiolabeled with 111In with a labeling efficiency of 95% and an average activity of 21.2 MBq/mg. NSCs were then uploaded with MSNs with an efficiency of 58% and a viability slightly affected by the 111In component of the MSN complex. Three-dimensional views of SPECT images revealed very early signs of NSC migration to the U87MG glioma xenograft at 4 h after cerebral injection of the labeled NSCs, and the signals were sustained at the tumor site for 2 days. Furthermore, systemic administration of MSN-labeled NSCs successfully migrated to the tumor site in 48 h with a peritumoral and partial intratumor distribution; compared with intracerebral administration, this finding is consistent with NSC dynamics crossing the BBB.[108] These results clearly indicate a significant sensitivity of SPECT in dynamic monitoring of NSC glioma tropism compared to MNP-based MRI monitoring, which has not been reported for very early stem cell migration.

Fluorescent imaging
Near-infrared imaging
Imaging modalities on a subcellular level are not usually a capability of conventional clinical imaging techniques such as MRI and positron-emission tomography (PET)/SPECT; therefore, they sometimes fail to provide a high-contrast image of pathologies at an early stage. Fluorescence imaging captures the light signal emitted by living cells with bioluminescent sources at a certain wavelength in response to excitation of light of a different wavelength. Among this type of imaging technique, near infrared (NIR) imaging achieves a higher penetration depth of up to several centimeters and provides more specific signals by capturing light of a NIR wavelength.[109,110] Thus, this technique holds broad application potential in the *in vivo* imaging of physiological, metabolic, and molecular functions. NIR imaging requires NIR probes to emit a light signal under excitation. Currently, several categories of probes have been studied, which generally include organic NIR dyes such as cyanine dyes, rhodamine dyes, BODIPY-based NIR probes, squaraine-based NIR probes, phthalocyanines and porphyrin derivatives, and nanoprobes such as NIR dye-containing nonmetallic nanoparticles, gold nanostructures, and quantum dots.[111]

Several aspects of stem cell NIR imaging with nanoprobes have been described. NIR imaging of cardiac progenitor cells has been reported to track ischemic hearts,[112] adipose-derived stem cells in Alzheimer's disease,[113] and MSCs in a Parkinson's disease model.[114] For glioma imaging, a recent report by Kim *et al.*[115] offers the detailed tracking progress under NIR. MSCs labeled with fluorescent magnetic NEO-LIVE™-Magnoxide 675 nanoparticles were administered to a U-87MG glioma model with intravenous delivery. According to the study, the injected MSCs predominantly resided in the lung at the early stage, and then later migrated to the spleen and liver. Four days after MSC administration, the bioluminescence signal could be observed in the location of the tumor and was maintained until 7 days after injection, indicating MSC migration.[115] This successful example shows the value of NIR nanoparticle-labeled stem cells for glioma imaging.

Two-photon microscopy
Two-photon microscopy is another imaging modality based on fluorescence that uses infrared light. The advantage of two-photon microscopy compared with other fluorescence imaging modalities is that it uses the combination of the energy of two photons using a pulsed laser of high peak power to compact photons, therefore leading to higher chances of two photons simultaneously hitting the fluorophore. This achieves reduced background noise, photo-damage/toxicity, and photo-bleaching, which is more commonly encountered in NIR, and offers a high three-dimensional resolution of the observed tissue to observe cellular interactions as well as cells and structures at much higher depths within the tissue.[116] Zhang *et al.*[117] have reported the utility of MSCs with two-photon microscopy. They used gold nanocages to label MSCs. Gold nanoparticles or nanostructures have become another interest in the realm of nanomedicine in recent years because of their attractive optical properties known as localized surface plasmon resonance (LSPR), which is the scattering and absorption of light at resonant wavelengths due to the excitation of plasmon oscillations. Of the different types of gold nanostructures, gold nanocages can be readily tuned to have a LSPR peak in the NIR region that covers the transparent window of soft tissues to maximize the tissue penetration depth, increasing its clinical applicability.[118] In a recent report, gold nanocage-labeled MSCs did not significantly affect the cell viability or differentiation capacity, while they were distributed in the cytoplasm encompassed by endosome-like structures. A significant result of this study was the confirmation of the long-term stable retention of AuCN in the MSCs as the particles did not participate in cellular metabolism as with iron oxide MNPs. An increased two-photon intensity could be observed after the MSCs were injected into the tail vein and migrated to the subcutaneously implanted U87MG cells.[117]

PERSPECTIVES

In this review, we briefly summarized the basic biology and mechanisms of stem cell glioma tropism. Numerous studies focusing on different imaging techniques and nanoparticle-labeled stem cells have been successfully performed [Table 1]. MNP labeling and imaging by MRI was a main focus. In addition, SPECT nuclear imaging, NIR

Table 1: Summary of preclinical studies of nanoparticle-labeled stem cell glioma tracking

Nanoparticle (type)	Stem cell	Imaging modality	Glioma model (animal)
Ferumoxides (SPION)[86]	MSC	MRI	U87MG (NM)
Ferumoxides (SPION)[119]	MSC	MRI	F98 (Fischer 344)
Ferumoxide-protamine sulfate (SPION)[85]	NSC	MRI	U251 (NM)
Ferumoxide-protamine sulfate (SPION)[82]	EPC	MRI	C6 (BALB/c)
Ferumoxides-poly-Lysine (SPION)[81]	EPC	MRI	RT2 (SCID)
Resovist (SPION)[87]	MSC	MRI	U87MG (NM)
Zn0.4Fe2.6O4-HA-CA (Zinc-doped SPION)[88]	MSC	MRI	U87MG (NM)
FeraTrack Direct (SPION)[120]	MSC/NSC	MRI	C6 (NM)
Ferumoxytol (USPION)[91]	NSC	MRI	U251T (NM)
111In-MSN[108]	NSC	SPECT	U87MG (NM)
AuNC[117]	MSC	Two-photon microscopy	U87MG (NM)
NEO-LIVE™-Magnoxide 675[115]	MSC	NIR	U87MG (NM)

MRI: Magnetic resonance imaging; MSC: Mesenchymal stem cell; MSN: Mesoporous silica nanoparticle; NIR: Near infrared; NM: Nude mouse; NSC: Neural stem cell; EPC: Endothelial progenitor cell; SPECT: Single-photon emission computed tomography; SPION: Superparamagnetic iron oxide nanoparticles; USPIONs: Ultra-small superparamagnetic iron oxide-based nanoparticles; AuNC: Gold nanocage.

fluorescence imaging, and two-photon microscopy possibly show a higher sensitivity than MRI. The reported studies describing these different imaging modalities presented different considerations, advantages, and limitations related to the complexity the labeling process, the effect of labeling on stem cell viability and migration, labeling efficiency, time from stem cell administration to the appearance of a positive signal at the tumor site, and the duration of positive signals in glioma models. These factors support the potential combination of these imaging modalities in clinical applications at every step of glioma therapy, as the whole process provides a gradually deepened understanding from gross anatomy to cellular and molecular biology. The integration of the applications of these modalities involves the combination of MRI and SPECT/PET in preoperative diagnosis, choosing the operation procedure, intraoperative surgery guidance, and postoperative residual tumor evaluation, forming an intact surgical evaluation and useful system. Another integration encompasses the combination of NIR with surgical microscopy for real-time optical detection of the tumor local infiltration, a concept that has already been demonstrated in several studies.[121-123] For these integrations to be effective, the stem cell platform and the nanoparticle used for labeling should be selected carefully for specific applications based on the different labeling and imaging characteristics of nanoparticles as well as the different glioma tropism between different stem cells. Therefore, studies to compare and quantify each of these factors under a standardized study protocol are warranted. Further studies focusing on stem cell glioma tropism, especially for the ability to cope with glioma heterogeneity and the active/quiescent state of glioma stem cells, are needed to figure out flaws of the platform and then to deal with these issues. Moreover, the development of multifunctional nanoparticles is required to enable simplified labeling of stem cells to label functions suitable for different imaging modalities simultaneously.

The dual-system imaging platform of stem cells labeled with nanoparticles is a powerful imaging tool that is applicable for various imaging modalities. Instead of totally relying on neurovascular and BBB leakage, nanoparticle-labeled stem cells bypass these restrictions and directly trace glioma cells and glioma microenvironment alterations, providing the option of nanoparticles and the corresponding imaging modalities to determine early glioma development and residual tumors, even tracing and imaging single cells. To improve the diagnosis and prognosis of gliomas, this platform needs to be further studied in clinical trials or used in clinical work.

Conflicts of interest

There are no conflicts of interest.

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纳米颗粒标记干细胞对胶质瘤进行成像的最新进展

摘要

目的： 胶质瘤是中枢神经系统最常见的肿瘤，传统的显像方式对其边缘显像欠佳。有学者发现可通过利用具有纳米级别尺寸和针对特定治疗目的具有多种属性的纳米颗粒与干细胞相结合，从而对胶质瘤进行示踪。本文对利用纳米颗粒标记干细胞作为胶质瘤成像的显像剂这一策略进行了文献综述，并介绍其基本原理和临床应用。

数据源： 本文利用PubMed数据库对包括2017年以前的文献通过"干细胞"、"胶质瘤"、"核磁共振"、"核成像"以及"荧光成像"等关键词进行文献筛选。

研究选择： 本文对纳入了有关纳米颗粒标记干细胞对胶质瘤进行成像的基础研究和临床前研究。

结果： 许多研究表明，纳米颗粒可成功地对干细胞进行标记。被标记的干细胞在不同胶质瘤模型中可有效地向胶质瘤迁移、产生信号并用多种影像学技术进行成像。

结论： 利用纳米颗粒标记的干细胞是一种对胶质瘤进行显像和治疗的具有应用前景的技术平台。