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Nanomaterial-involved neural stem cell research: Disease treatment, cell labeling, and growth regulation

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ABSTRACT

Neural stem cells (NSCs) have been widely investigated for their potential in the treatment of various diseases and transplantation therapy. However, NSC growth regulation, labeling, and its application to disease diagnosis and treatment are outstanding challenges. Recently, nanomaterials have shown promise for various applications including genetic modification, imaging, and controlled drug release. Here we summarize the recent progress in the use of nanomaterials in combination with NSCs for disease treatment and diagnosis, cell labeling, and NSC growth regulation. The toxicity of nanomaterials to NSCs is also discussed.

1. Introduction

Neural stem cells (NSCs) can generate differentiated cells such as neurons [1,2] and develop various identities by expressing specific genes and activating diverse signal pathways [3]. NSCs can also self-renew [4]. Both of these properties are important for NSC-based therapy. For instance, NSCs have been used for the treatment of spinal cord injury (SCI) [5–10] and were shown to mitigate the symptoms of ischemia and promote neovascularization [11–14]. NSCs have also been engineered to produce tumor-inhibitory proteins or carry anticancer agents, and thus show promise for anti-tumor therapy [15–21]. However, acquiring NSCs is problematic due to their limited quantities and localized distribution in the hippocampal dentate gyrus and the subventricular zone (SVZ) of lateral ventricles [22,23]. Cellular reprogramming has been used to induce NSCs from fibroblasts [24,25], which has facilitated NSC research [26]. Nevertheless, there are several outstanding challenges that must be overcome before these cells can be used in clinical applications, including NSC growth regulation and labeling.

Various nanomaterials have been developed for disease diagnosis and treatment [27–38] that can also be applied to NSC research. Nanoparticles (NPs) [39–46] can be used for anti-tumor therapy or tumor imaging through passive or active targeted delivery of anti-tumor drugs or contrast agents, respectively [28,47–53]. NPs can increase the efficacy of tumor imaging in anti-tumor chemotherapy and reduce side effects [54–57]. Moreover, nanomaterials can be modified with specific molecules that enhance their affinity for cells, which can be used for cell tracking following transplantation [58–62]. Iron oxide NPs have been used for *in vivo* imaging to detect NSC biodistribution and migration, and are considered as the most sensitive types of particle for magnetic resonance imaging (MRI) [60,63]. However, nanomaterials can affect the metabolism of NSCs and cause toxicity and other adverse effects. As such, there has been increasing focus on creating nanomaterials that are less toxic [64–70].

The integration of NSCs and nanomaterials has led to major improvements in disease treatment in preclinical tests, which shows promising in future clinical translation. For instance, NSCs can serve as carriers in nanomedicine to inhibit tumor growth. Various studies have also investigated nanomaterial-based NSC differentiation and proliferation. In this review, we summarize and discuss nanomaterial-related NSC research, with a focus on their integration for disease treatment and other practical applications. Metabolism of nanomaterials by NSCs and their relative toxicity are also discussed.

2. Integration of nanomaterials and NSCs for disease treatment

2.1. NSCs as vehicles for delivery of therapeutics in cancer treatment

Tumor-targeted drug delivery has advantages over systemic administration since it can reduce adverse effects and increase drug efficacy [71,72]. NSCs are tumor tropic, and can therefore be used for targeted therapy [17,73]. The mechanisms of NSC migration to tumor

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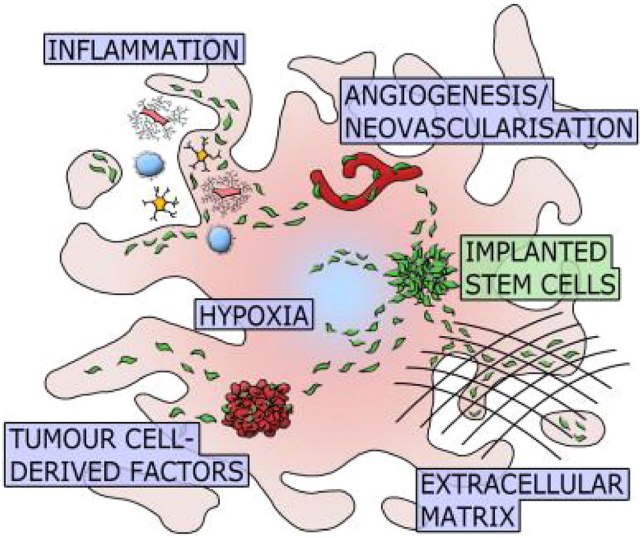

Fig. 1. Mechanisms underlying the tumor tropism of NSCs [74] (Reproduced with permissions).

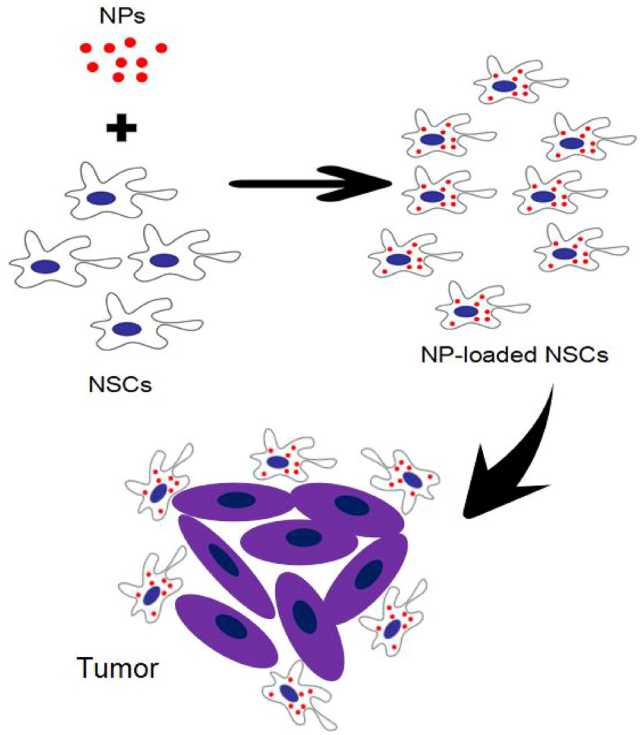

Fig. 2. Combination of nanomaterials and NSCs to tumor treatment.

sites have been well studied (Fig. 1) [74]; it is known to occur in response to inflammatory factors [75], hepatocyte growth factor [76], and various angiogenic signaling molecules [77]. NSCs can be genetically modified to carry therapeutic genes or express anticancer proteins for tumor treatment [15,21,78], and a clinical trial in patients with recurrent high-grade glioma has demonstrated the safety and feasibility of NSCs for cancer therapy [79]. However, genetic modification of NSCs is complex; combining NSCs with nanomaterials broadens the range of possible therapeutic strategies (Fig. 2).

Gold (G) NPs are an emerging technology for cancer treatment given their stability, lack of cytotoxicity, and ease of modification [80,81]. In addition, they efficiently produce heat when activated by near-infrared light; for instance, 11-mercaptoundecyl trimethylammonnium bromide-coated GNP-loaded NSCs have been employed for photothermal ablation of tumors [82]. Exposure of NP-loaded NSCs to an 810-nm Ti-sapphire two-photon laser beam at 2 W/cm^2 resulted in cell death via a photothermal effect (Fig. 3a). NPs have a uniform appearance upon examination by transmission electron microscopy (Fig. 3b) and their biosafety has been confirmed by cell viability assays (Fig. 3c). NSCs can also improve the distribution of loaded NPs in tumor tissue, as was demonstrated in triple-negative breast cancer (MDA-MB-231) xenografts [83]. Tiled, flattened, dark-field micrographs of tumor cross sections showed that NSCs enabled greater accumulation of nanorods in tumor tissues (Fig. 3d1, e1), which was substantiated by mapped cross sections (Fig. 3d2, e2). In addition, a three-dimensional (3D) reconstruction revealed the widespread distribution of nanorods carried by NSCs in tumor tissues (Fig. 3d3, e3), which could reduce tumor recurrence following near-infrared light exposure and thereby improve overall survival (Fig. 3f).

Self-destructive NSCs have been used to control drug release. NSCs carrying pH-sensitive doxorubicin-loaded mesoporous silica (Si) NPs underwent programmed self-destruction after migrating into tumor tissues, releasing the MSNs that inhibited the growth of glioblastoma cells [84]. A magnetic field has been used in some experiments to control payload release by triggering NSC destruction for the treatment of malignant glioma. For instance, NSCs that had internalized 2-μm magnetic discs were induced to deliver the payload through NSC destruction by a rotating magnetic field. Following internalization of these magnetic discs by glioma cells, another magnetic field was applied to induce apoptotic cell death [85]. Thus, nanodrugs loaded in NSCs can be released in tumor tissues by different methods by taking advantage of NSC tumor tropism, thereby suppressing tumor growth.

NPs conjugated to the surface of NSCs can also be selectively delivered and distributed in target cells [86]. NSCs can promote intracranial NP retention when surface-conjugated to NPs, suggesting that they can improve intracranial drug delivery [87]. NSCs with NPs conjugated to the surface via a hydrazone bond efficiently distributed the particles before drug release [88]. Interestingly, NP-loaded NSCs more effectively targeted ovarian tumors by intraperitoneal as compared to intravenous administration [86].

NP-loaded NSCs can also be used to track glioblastoma via single-photon emission computed tomography. Additionally, ^{111}In-conjugated MSNs (Fig. 3g) provide a new technology of non-invasive tumor tracking [89]. These new therapies are based on the tumor tropism of NSCs and unique features of nanomaterials (Table 1).

2.2. Reparative effects of NSCs in other diseases

Nerve injury (SCI and brain injury), neurodegenerative disease, and ischemia are three common neurological disorders. There is considerable interest in nanomedicine to exploit the reparative effects of NSCs to restore neurological function.

SCI patients usually have a poor prognosis due to limited delivery of therapeutics to the spinal cord [7,90–92]. NSCs have been labeled with and tracked via poly-L-lysine-coated superparamagnetic iron-oxide NPs, which has allowed observation of NSC distribution and penetration in injured tissue [93]. In addition, nanomaterials can serve as gene delivery vehicles to facilitate nerve recovery. Chitosan-methylprednisolone NPs loaded with plasmid DNA combined gene therapy with anti-apoptotic and -inflammatory effects while having minimal cytotoxicity in NSCs [94]. 3β-[N-(*N*′,*N*′-Dimethylaminoethane) carbamoyl] cholesterol-modified nanospheres loaded with the vascular endothelial growth factor gene accelerated the recovery of locomotor function and promoted tissue regeneration [95]. Axonal alignment by NSCs induced with graphene oxide (GO) and SiNPs could potentially promote functional recovery of injured spinal cord (Fig. 4a) [96].

Brain injury is associated with the loss of various functions and can also trigger neuronal death via multiple mechanisms [97]. Treatment options for brain injury are limited [98]. However, drug-loaded nanomaterials are a novel strategy for nerve repair. The stromal cell-derived