DOCTORAL THESIS

Novel Nanomaterials Mediate Distinct Cell Differentiations of Human Neural Progenitor Cells

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ABSTRACT

Neural progenitor cells (NPCs) are self-renewing, multipotent cells that are more likely than other types of stem cells to differentiate into the desired neurons in a direct, safe, and efficient manner. Therefore, NPC therapy is a promising strategy for neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD). However, improving the survival rate and promoting neuronal differentiation after NPC transplantation under conditions of oxidative stress, the main pathological feature in the brains of AD and PD patients, remain major challenges for NPC therapy. Recently, biomaterials have played essential roles in bioscience, tissue engineering, regenerative medicine, and other related fields, and they have undergone rapid development globally. By contacting and interacting with living organisms, biomaterials can exert effects on cells, tissues, and organs. It has been reported that these interactions are influenced by the surface properties of the materials, such as the surface chemistry, surface roughness, size, shape, and chirality. Thus, novel biomaterials have been studied to provide new technologies and methods for neural stem cell and NPC culture and the treatment of neurodegenerative diseases. In this research, we explored the use of the biocompatible nanomaterials Fe_2O_3 chiral nanoparticles (Fe_2O_3 CNPs) and cerium oxide nanoparticles (CeO_2 NPs) for extracellular and intracellular stimulation, respectively, and determined the potential effects of these nanomaterials on NPC fate.

First, left-handed (LH) and right-handed (RH) Fe_2O_3 CNP matrices were assessed for their abilities to modulate NPC phenotype and function. According to our results, both LH- and RH-Fe_2O_3 CNPs showed good biocompatibility and promoted cell spread and growth. In addition, Fe_2O_3 CNPs maintained the proliferative ability of NPCs while inhibiting their differentiation. LH-Fe_2O_3 CNPs showed superior performance to RH-Fe_2O_3 CNPs.

Second, the role of facet-dependent CeO_2-mediated redox homeostasis in regulating NPC self-renewal and differentiation was investigated for the first time. The

cube-, rod- and octahedron-shaped CeO_2-nanozymes with different facets were prepared. Among the mentioned nanozymes, the cube enclosed by (100) facet exhibited the highest catalase (CAT)-like activity, indicating that it provided superior protection to NPCs from oxidative stress induced by H_2O_2. Meanwhile, the octahedron enclosed by (111) facet lowest CAT-like activity induced the greatest amount of reactive oxygen species (ROS) production in ReNcell CX cells, which promoted neuronal differentiation by activating the AKT/GSK-3β/β-catenin pathways. Further mechanistic studies indicated that the electron density of the surface Ce atoms changed continuously with different crystal facets, which led to their different CAT-like activity and the modulation of redox homeostasis in NPCs.

In summary, our findings demonstrate that 1) both inorganic metal oxide Fe_2O_3 CNPs and CeO_2 NPs have good biocompatibility; 2) LH-Fe_2O_3 CNPs show better performance at promoting cell growth and maintaining stemness; 3) the cube-shaped CeO_2 provide NPCs with superior protection from oxidative stress induced by H_2O_2; and 4) the octahedron induces the greatest amount of ROS production in ReNcell CX cells, which promotes neuronal differentiation by activating the AKT/GSK-3β/β-catenin pathway. Altogether, the different surface chemistry and atomic architecture of the active sites on CeO_2 modulate redox homeostasis and the fate of NPCs.