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Human umbilical cord mesenchymal stem cells inhibit C6 glioma growth via secretion of dickkopf-1 (DKK1)

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Abstract Mesenchymal stem cells (MSCs) represent a potential therapeutic target for glioma. We determined the molecular mechanism of inhibitory effect of human umbilical cord-derived MSCs (hUC-MSCs) on the growth of C6 glioma cells. We demonstrated that hUC-MSCs inhibited C6 cell growth and modulated the cell cycle to G0/G1 phase. The expression of β-catenin and c-Myc was downregulated in C6 cells by conditioned media from hUC-MSCs, and the levels of secreted DKK1 were positively correlated with concentrations of hUCMSCs-CM. The inhibitory effect of hUC-MSCs on C6 cell proliferation was enhanced as the concentration of DKK1 in hUCMSCs-CM increased. When DKK1 was neutralized by anti-DKK1 antibody, the inhibitory effect of hUC-MSCs on C6 cells was attenuated. Furthermore, we found that conditioned media from hUC-MSCs transfection with siRNA targeting DKK1 mRNA or pEGFPN1-DKK1 plasmid lost or enhanced the abilities to regulate the Wnt signaling in C6 cells. Therefore, hUC-MSCs inhibited C6 glioma cell growth via secreting DKK1, an inhibitor of Wnt pathway, may represent a novel therapeutic strategy for malignant glioma.

Keywords Mesenchymal stem cells · Human umbilical cord · Glioma · Inhibition · DKK1

Introduction

Gliomas are the most common malignant brain tumor. Despite advances in surgical techniques and adjuvant radio- and chemo-therapies, the prognosis for patients with glioma remains poor [1, 2]. New trials using the combination of chemotherapeutic agents in an orthotopic model or new target agents have been attempted clinically. However, the results of these trials have not been satisfactory [3–5]. Therefore, it is necessary to develop innovative and effective treatments for glioma. Stem cells may be employed in designing novel treatments for malignant glioma [6].

Mesenchymal stem cells (MSCs) are a promising cell resource for tissue engineering and cell-based therapeutics because of their ability to self-renew and differentiate into specific functional cell types [7, 8]. Human MSCs have been isolated from Wharton's jelly of umbilical cord and studied intensively for their potential use in cancer therapy. For example, a tumor inhibitory effect of human bone marrow-derived MSCs on Kaposi's sarcoma has been reported [9]. Furthermore, two studies demonstrated that human MSCs derived from bone marrow and adipose tissue inhibited the growth of human cancer cells (MCF-7 and K562) by suppressing Wnt signaling through secretion of DKK1 [10, 11]. Nakamizo found that hMSCs were able to integrate into

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