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Research Report

Effects of human marrow stromal cells on activation of microglial cells and production of inflammatory factors induced by lipopolysaccharide

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ABSTRACT

There has been an increasing appreciation of the role that microglial cells play in neural damage. Marrow stromal cells (MSCs) can dramatically lessen neural damage in animal models, but the mechanisms involved have not been defined. This study aimed to investigate the effects of human MSCs (hMSCs) on the activation of primary microglia and the attendant production of pro-inflammatory factors stimulated by bacterial endotoxin lipopolysaccharide (LPS). Our study showed that hMSCs in co-cultures and in transwell cultures inhibited the activation of microglial cells, reduced the production of tumor necrosis factor-α (TNF-α) and nitric oxide (NO), downregulated the expression of inducible nitric oxide synthase (iNOS) and phosphorylated p38 mitogen-activated protein kinase (p38 MAPK), whereas hMSCs conditioned medium did not have any effect on microglial inflammation. To further investigate the mechanisms by which hMSCs exert anti-inflammatory effects, we examined the production of neurotrophic factors by hMSCs with enzyme linked immunosorbent assay (ELISA). Our results showed that the production of insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), and hepatocyte growth factor (HGF) was significantly increased by hMSCs when cultured in the conditioned medium from activated microglia. We conclude that hMSCs can inhibit microglial activation and the production of attendant inflammatory factors. In addition, hMSCs can interact with microglial cells through diffusible soluble factors, whereas cell contact is not a prerequisite for anti-inflammatory effects. Finally, hMSCs within inflammatory environment can significantly increase the production of neurotrophic factors, which may involve with the anti-inflammatory mechanisms.

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Abbreviations: BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; CM, conditioned medium; CNS, central nervous system; ELISA, enzyme linked immunosorbent assay; HGF, hepatocyte growth factor; hMSCs, human MSCs; IGF-1, insulin-like growth factor-1; IFNγ, interferon γ; iNOS, inducible nitric oxide synthase; IL-1, interleukin-1β; LPS, lipopolysaccharide; MNCs, mononuclear cells; MSCs, marrow stromal cells; MTT, 3-(4,5)-dimethylthiahiazo (-z-y1)-3,5-di-phenytetrazoliumromide; NO, nitric oxide; p38 MAPK, p38 mitogen-activated protein kinase; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor

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1. Introduction

Microglial cells are the resident immune cells of the central nervous system (CNS). As the source of inflammation, activated microglia produce a variety of inflammatory factors, including nitric oxide (NO), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and reactive oxygen species. Inflammation in the CNS has been closely associated with the pathogenesis of neural damage resulting from cerebral ischemia and neurodegenerative diseases (Skaper, 2007; Wang, Tang and Yenari, 2007). Therefore, the effective control of microglial activation in these neurological diseases is regarded as an important therapeutic target.

Stem cell transplantation is a promising therapeutic strategy for neural damage. Human marrow stromal cells (hMSCs) are isolated from adult bone marrow, and easy access suggests the feasibility in clinical therapies. These

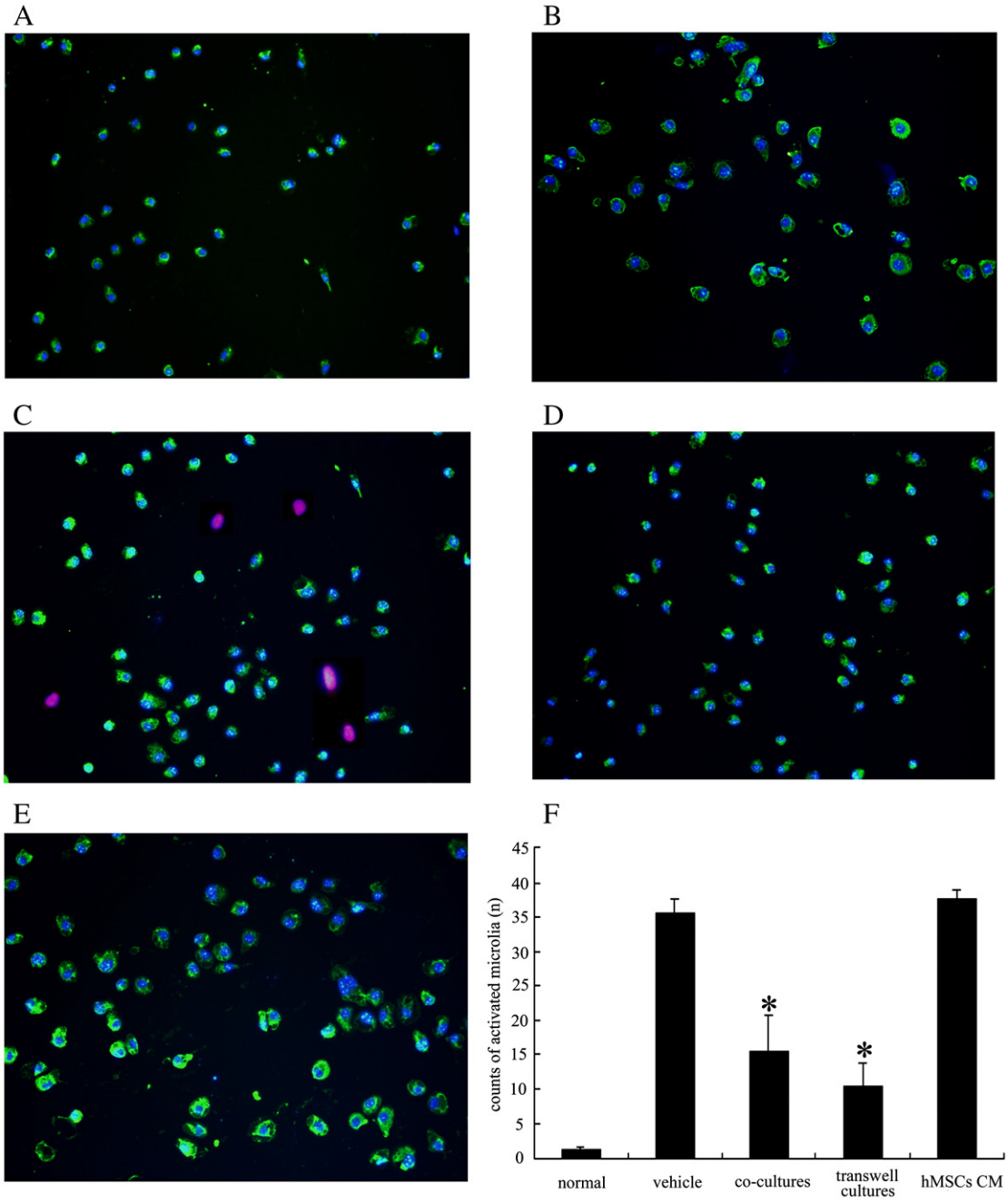

Fig. 1 – Effects of hMSCs on LPS-induced activation of primary microglia. (A–E) Microglial cells were treated with vehicle (B), hMSCs co-cultures (C), hMSCs transwell cultures (D), and conditioned medium (CM) from hMSCs (E). Cells were stimulated with 1 μg/ml LPS for 6 h. Unstimulated microglia were as normal controls (A). Microglial cells were immunostained with an antibody against the F4/80 antigen, and hMSCs were stained with anti-HuNu antibody. (F) Quantitative cell counts of activated microglia per field (*$p < 0.01$ versus LPS alone).