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Nonsenescent Hsp27-Upregulated MSCs Implantation Promotes Neuroplasticity in Stroke Model

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Cellular senescence induces changes in cellular physiology, morphology, proliferative capacity, and gene expression. Stem cell senescence might be one of the major issues of limited efficacy of stem cell transplantation. In this study, we demonstrated that implantation of human umbilical cord mesenchymal stem cells (hUCMSCs) cultured in human umbilical cord serum (hUCS) significantly enhanced neuroplasticity and angiogenesis in stroke and ischemic limb models. Immunophenotypic analysis indicated that hUCMSCs cultured in hUCS had more small and rapidly self-renewing cells than those expanded in FCS. The main cause of greater senescence in FCS-cultured cells was increased generation of reactive oxygen species (ROS). Proteome profiling showed significantly more senescence-associated vimentin in FCS-cultured hUCMSCs than in hUCS-cultured hUCMSCs. In contrast, there was significant upregulation of heat shock protein 27 (Hsp27) in the hUCS-cultured hUCMSCs. By gene targeting, we found that overexpression of Hsp27 may downregulate vimentin expression through inhibition of the nuclear translocation of p65 (NF-κB signaling). Thus, an interaction between Hsp27 and vimentin may modulate the degree of senescence in hUCS- and FCS-cultured hUCMSCs. In summary, hUCMSCs exhibiting senescence are detrimental to cell engraftment and differentiation in animal models via activation of NF-κB pathway. Human stem cells incubated in hUCS might reduce the senescent process through upregulation of Hsp27 to increase implantation efficiency.

Key words: Human umbilical cord mesenchymal stem cells (UCMSCs); Human umbilical cord serum (hUCS); Fetal calf serum (FCS); Senescence; Vimentin; Heat shock protein 27 (Hsp27); Reactive oxygen species (ROS); NF-κB; Stroke; Ischemic limbs

INTRODUCTION

Cellular senescence is the limited ability of primary human cells to divide when cultured in vitro. The molecular mechanism of senescence is not known, although possible causes include oxidative damage, genomic instability, genetic reprogramming, and cell death (19). Senescence-associated alteration of the function and expression of cytoskeletal proteins such as vimentin is still not completely understood. It has, however, been demonstrated that aged cells and cells undergoing replicative senescence have diminished heat shock response and a higher incidence of death when subjected to severe stress (26). Because heat shock protein 27 (Hsp27) is thought to protect cells from oxidative stress, alterations in the production of Hsp27 can further promote aging by increasing the accumulation of damaged proteins.

Mesenchymal stem cells (MSCs) obtained from bone marrow stroma and human umbilical cord matrix are attractive candidates for clinical use in stem cell therapy because they can enhance neurogenesis and angiogenesis in stroke and ischemic limb models (7,21). However, fetal calf serum (FCS) induces anaphylactic reactions (39) and poor cellular engraftment (16). If MSCs are to be used in cell transplantation in humans, it is important to minimize these risks, which result from the use of nonhuman sera in the culture system (4,15,24).

In this study, we applied human umbilical cord serum

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