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The protection of MSCs from apoptosis in nerve regeneration by TGFβ1 through reducing inflammation and promoting VEGF-dependent angiogenesis

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ABSTRACT

Our previous report demonstrated that autologous adipose-derived mesenchymal stem cells (ADSCs) combined with xenogeneic acellular nerve matrix (XANM) can support the regeneration of defective nerves. Although ADSCs had the potential to replace Schwann cells in engineered-tissue nerves, apoptosis easily obstructed the ability to treat serious nerve injury in the host, such as a >50-mm-long nerve defect. In the present study, we found that, in combination with transforming growth factor β1 (TGFβ1), an ADSCs-XANM graft was sufficient to support the regeneration of a 50-mm sciatic nerve defect, which was not achieved using an ADSCs-XANM graft alone. Based on this finding, we further investigated how TGFβ1 coordinated with ADSCs to enhance nerve regeneration. In vitro, cell culture experiments demonstrated that TGFβ1 did not have a direct effect on ADSC proliferation, apoptosis, the cell cycle, or neural differentiation. The expression of VEGF, however, was significantly increased in ADSCs cultured with TGFβ1. In vivo, fluorescence labeling experiments demonstrated that the survival of transplanted ADSCs inoculated with XANM-TGFβ1 was higher than with XANM. Further study showed that TGFβ1 was capable of impairing the host immune response that was trigged by transplanted XANM. Additionally, we discovered that XANM-ADSCs in immunodeficient mice had apoptosis rates similar to XANM-ADSCs-TGFβ1 over a short time course (7 days). Once we blocked VEGF with a neutralizing antibody, the protective effect of TGFβ1 was impaired over a long time course (28 days). These results suggested that TGFβ1 was capable of enhancing the regenerative capacity of an XANM-ADSCs graft, mainly by protecting transplanted ADSCs from apoptosis. This effect was achieved in part through decreasing inflammation and promoting VEGF-dependent angiogenesis.

1. Introduction

In recent years, numerous nerve grafts have been prepared to replace the auto-transplantation treatment of peripheral nerve defects [1]. Aimed at long-length nerve defects (>20 mm) that were difficult to regenerate, a variety of cells, including Schwann cells and mesenchymal stem cells (MSCs), were inoculated in combination to provide more regenerative properties [2,3]. Our previous study showed that an XANM graft combined with ADSCs had the potential to cure nerve defects more effectively than either treatment alone [4]. Although successful cases had been reported for the repair 20-mm-long sciatic nerve damage, the regeneration of peripheral nerve defects >50 mm was rarely reported. Our work demonstrated that by introducing an XANM-ADSC graft into a 50-mm sciatic nerve gap, the regeneration of nerve function was poor in comparison with the treatment of a short nerve gap. When we performed a histological analysis at different time points, we found that transplanted cells were incapable of maintaining long-term survival to support the regeneration of 50-mm sciatic nerve defects. This phenomenon also occurred in other 3-dimensionally constructed tissues, such as bone, muscle, and adipose tissue [5]. According to previous reports, two factors played key roles in influencing the survival of transplanted cells; one was host adverse immune response, and another was tissue angiogenesis [6,7]. To avoid an adverse immune response, growth factor had been reported to modulate host response through increased capacity for graft survival and integration [8]. In addition, many growth factors identified as regulatory in the process of angiogenesis have been used to accelerate the ingrowth of blood vessels into implanted tissue constructs [6]. In constructed nerve grafts, however, the

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