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IGF-1 gene-modified muscle-derived stem cells are resistant to oxidative stress via enhanced activation of IGF-1R/PI3K/AKT signaling and secretion of VEGF

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Abstract Reactive oxygen species (ROS)-induced oxidative stress increases in skeletal muscle with aging and decreases the viability of implanted cells. Type 1 insulin-like growth factor (IGF-1) promotes the survival of skeletal muscle cells under oxidative stress. It is unknown whether IGF-1 protects muscle-derived stem cells (MDSCs) from oxidative stress. In this study, we genetically engineered rat MDSCs to overexpress IGF-1 and determined cell viability, apoptosis, and VEGF secretion under oxidative stress. Overexpression of IGF-1 prevented MDSCs from H_2O_2-induced caspase-dependent apoptotic cell death by upregulating the PI3K/AKT pathway, accompanied with an increase of NF-κB, p-NF-κB, Bcl-2, and VEGF, as well as a decrease of Bax. In contrast, pre-administration of picropodophyllinb, wortmannin, 1L-6-hydroxymethyl-chiro-inositol-2-((*R*)-2-*O*-methyl-3-*O*-octadecylcarbonate), or pyrrolidine-dithiocarbamate, specific inhibitors of IGF-1R, PI3K, AKT, and NF-κB, respectively, followed by treatment with H_2O_2, resulted in cell death of MDSCs. Our data indicated that IGF-1 suppresses apoptosis and enhances the paracrine function of MDSCs under oxidative stress via enhancing IGF-1R/PI3K/AKT signaling. Thus, IGF-1 gene-modified MDSCs present a potential application in the treatment of muscle wasting, such as urethra intrinsic sphincter deficiency.

Keywords IGF-1 · Muscle-derived stem cells · Oxidative stress · IGF-1R/PI3K/AKT · VEGF

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Introduction

There are more than 200 million people suffering from urinary incontinence (UI) [1]. Stress urinary incontinence (SUI) is the most common type of UI. Age is one of the important risk factors of SUI [2]. In addition, reactive oxygen species (ROS) have been shown to be increased in skeletal muscle with aging and probably promote SUI by reducing the bioenergetic efficiency of muscle fibers [3]. SUI is mainly caused by urethral hypermobility and urethra intrinsic sphincter deficiency (ISD) [4]. Most SUI patients display both disorders, especially older women [5]. Current therapies for SUI are not efficient for ISD and often involve the introduction of foreign materials [6]. With the rapid development of tissue engineering techniques targeting regeneration and repair of damaged tissues and organs, muscle-derived stem cell (MDSC) therapy has emerged to be an effective and novel treatment for the regeneration and repair of urethral sphincter function in SUI animals and patients [7, 8]. The survival of implanted MDSCs plays an important role in the curative effect, and activation of survival pathways is a key mechanism by which MDSCs carry out their protective function. However, the viability of implanted cells is decreased by ROS. Several strategies have been introduced to improve the longevity of engrafted cells in hostile environments [9], one of which is to make them more robust and resistant to apoptosis by genetic modification of donor cells [10].

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