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Differentiation into various cell lineages of adipose derived stem cells

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Abstract

Adipose derived stem cells (ASC) can be extracted easily in large quantities with low mortality. ASC have a potential of differentiation toward mesodermal stem cell lineages such as adipogenic, chondrogenic, osteogenic and myogenic pathways and ectodermal stem cell lineage such as neuronal pathway. ASC differentiation may be achieved with specific induction cocktails in culture medium. ASC and differentiated cells could have a pivotal role in fat grafting reconstruction, bone defect healing, muscle reconstruction procedure, and recovery from central-peripheral nerve injury.

Abbreviations: ASC: Adipose Derived Stem Cells; IBMX: Isobutyl-Methyl Xanthine; C/EBP: CCAAT Enhancer Binding Protein; IL: Interleukin; TGF: Transforming Growth Factor; TNF: Tumor Necrosis Factor; BMP: Bone Morphogenetic Protein

Introduction

Adipose derived stem cells (ASC) can be easily and repeatedly extracted from liposuction and can be obtained in large quantities with minimal discomfort. In addition, ASC can also proliferate and differentiate well, have multi-lineage differentiating potential, adhere well to plastic surface, and maintain the characteristics of stem cells in all age groups compared to adult stem cells from other sources [1]. It can be differentiated into most mesenchymal cells such as adipogenic, chondrogenic, osteogenic and myogenic cells and cells of the neural ectodermal lineage. Zuk et al. obtained lipid tissue by liposuction, treated with collagenase, centrifuged and separated into the upper fat cell layer and the lower stromal vascular fraction. They induced adipogenic, chondrogenic, osteogenic, myogenic, and neurogenic differentiation pathways using lineage specific induction agents such as dexamethasone, isobutyl-methyl xanthine (IBMX), insulin, 1.25-dihydroxyvitamine D3, and ascorbate [2]. This mini review highlights the differentiation of ASC into various mesenchymal lineages and neuronal differentiation under in vitro and in vivo conditions and clinical application of ASC.

Adipogenesis

Fat transfer can be useful for reconstruction of soft-tissue defects due to trauma, surgical resection, or cosmetic procedures such as treatment of wrinkles. ASC-enriched fat grafting can enhance fat graft survival rate by reducing reabsorption of fatty tissue transplanted [3]. The standard induction cocktail for adipocytes differentiation is composed of IBMX, dexamethasone, insulin, and indomethacin [4]. Dexamethasone and IBMX induce differentiation of ASC into adipocytes by increasing expression of CCAAT enhancer binding protein (C/EBP) and intracellular cAMP, respectively [5,6]. Adipocyte differentiation can be easily confirmed by the Oil Red O staining of lipid vacuoles [7]. In contrast, high level of retinoids, interleukin (IL) -1, IL-2, transforming growth factor (TGF) β and tumor necrosis factor (TNF) α inhibit adipocyte differentiation [8]. Adipogenesis and angiogenesis are closely related, and the development of fat mass growth and microcirculation occurs together during fetal development [9]. Addition of factors involved in angiogenesis, such as vascular endothelial growth factors, fibroblast growth factor-2, platelet-derived growth factor BB, increased angiogenesis in adipose tissue and improved adipose tissue growth in vivo murine tissue [10]. Vascularized adipose tissue using ASC can play an important role in tissue replacement procedures such as cosmetic, trauma, and cancer-related reconstructive procedures.

Chondrogenesis

ASC can differentiate into cartilage. In vitro, high-density culture of ASCs induced by chondrogenic medium (supplementation with insulin, TGF β, and ascorbate-2-phosphate) resulted in increased expression of extracellular matrix proteins and formation of the cartilage compact nodule [2]. An in vivo animal experiment revealed that reconstitution ability of cultured ASCs on femoral defect was better than that of periosteum-derived stem cell or native mechanisms [11]. Treatment of ASC with bone morphogenetic protein (BMP)-7 for only 15 minutes proved to promote cartilage differentiation [12].

Osteogenesis

Lee et al. initiated ASC culture from the epididymal fat pad of Lewis rat and differentiated ASC into osteoblasts using bone induction factors [7]. Cells differentiated into osteoblasts were transplanted to Lewis rat subcutaneous tissues and in vivo bone formation was identified at 8 weeks. Differentiation into osteoblast was evidenced

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by Alizarin red staining of a calcified extracellular matrix and the immunohistochemical staining for osteocalcin [7]. Cowan et al. showed that 70-90% of critical-size mouse calvarial defects could be treated with implanted PLGA scaffolds seeded with ASC in 12 weeks [13]. Dexamethasone, β-glycerophosphate, ascorbic acid, and vitamin D can be used to promote the differentiation of stem cells into the osteogenic lineage [7,14]. As with the use of BMP-7 for chondrogenic differentiation, treatment of BMP-2 in ASC for 15 minutes can promote osteogenic differentiation [12].

Myogenesis

ASC cultures supplemented with desmin, myogenin, myogenic regulatory factor, and myosin heavy chain promote myogenesis [2]. However, the differentiation into myocytes takes more than 4 weeks, and it is the most difficult to differentiate among all the stem cell differentiation with low reproducibility [15]. Rodriguez et al. injected human ASC into the anterior tibialis of dystrophin-deficient mice as a model for Duchenne muscular dystrophy and observed that human dystrophin was expressed in the injected tibialis anterior of the mice at 6 months after administration [16]. In addition, dystrophin - positive cells were observed in the adjacent gastrocnemius muscle, suggesting human ASC migration to the surrounding muscle [16].

Neurogenesis

When ASC were cultured in no serum media with β-mercaptoethanol, new growth of cellular retraction and processes from the cell body were observed [2]. This change was associated with a concurrent increase in expression of neuronal markers such as NeuN, nestin and NSE [2]. ASC could differentiate into the neuronal and the glial pathways when valproic acid, butylated hydroxyanisole, insulin, and hydrocortisone were used as differentiation inducers [17]. Angiogenesis, enhanced immunosuppression, and an increase of the viability of endogenous neurons as well as direct cell replacement of stem cells might be involved in symptom improvement of the stroke patients [18]. Kim et al. reported that undifferentiated ASC and neuronal lineage cells derived from ASC promoted peripheral nerve regeneration (higher nerve conduction velocity) in rats undergoing nerve defect bridged by tubes made of the polycaprolactone [19].

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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