ORIGINAL ARTICLE

Mesenchymal stromal cell-based therapies reduce obesity and metabolic syndromes induced by a high-fat diet

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Obesity is an alarming global health problem that results in multiaspect metabolic syndromes in both genders and most age groups. The lack of effective therapies for obesity and its associated metabolic syndrome is an urgent societal issue. To elucidate whether mesenchymal stromal cell (MSC)–based therapies can ameliorate high-fat diet–induced obesity and compare the effectiveness of several methodological approaches, we transplanted human MSCs, MSC-derived brown adipocytes (M-BA), and MSC lysateinto obese mice. All 3 MSC-based treatments improved obesity-associated metabolic syndromes including nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, glucose intolerance, and inflammation in obese mice after repeated administration for 10 weeks. MSC-based treatments altered the ratio of adiponectin to leptin and regulated the expression of *Pparα* and *Pparγ*, which are involved in maintaining energy homeostasis, in major metabolic tissues. Among treatments, M-BA showed the strongest beneficial effect. Importantly, M-BA administration not only reduced obesity-associated metabolic syndromes but also reduced body weight and hyperlipidemia, indicating that it is an effective therapy for obesity. Together, our findings revealed the therapeutic potential of MSCs for the treatment of metabolic syndrome. (Translational Research 2016;■:1–14)

Abbreviations: Acta2 = smooth muscle aortic alpha-actin; Adipoq = adiponectin; Alb = albumin; Ccl2 = chemokine (C-C Motif) ligand 2; Col1a1 = Collagen, type I, alpha 1; Col1a2 = Collagen, type I, alpha 2; Fn1 = fibronectin; G6pc = glucose-6-phosphatase catalytic-subunit; Glut2 = Slc2a2, glucose transporter 2; Glut4 = Slc2a4, glucose transporter 4; Got = glutamyl oxaloacetic transaminase; Gpt = glutamyl pyruvic transaminase; HDL = high-density lipoprotein; HFD = high-fat diet; Il10 = interleukin 10; Il1rn = interleukin 1 receptor antagonist; Il1β = interleukin 1β; Il4 = interleukin 4; Il6 = interleukin 6; LDL = low-density lipoprotein; Lep = leptin; M-BA = MSC-derived brown adipocytes; M-L = MSC lysate; MSC = mesenchymal stromal cell; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; Ppars = peroxisome proliferator-activated receptors; Tnfα = tumor necrosis factor α

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AT A GLANCE COMMENTARY

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Background

Obesity is a global health crisis, but it is lack of effective therapies. Mesenchymal stromal cell (MSC) is an ideal cell source for autologous cell-based therapies. However, therapeutic effects and mechanisms of MSC-based treatments on obesity are still unclear.

Translational Significance

We compared therapeutic effects of 3 human MSC-based treatments on high-fat diet–induced obese mice. Although, injection of MSC-derived products could reverse pathogenic changes of obesity-related syndromes, treatment of the high-fat diet mice with MSC-derived brown adipocyte also resulted in reductions in body weight and hyperlipidemia. Therefore, we suggest that autologous MSC-derived brown adipocyte is the most efficient and suitable cell source for clinical application.

INTRODUCTION

Obesity is reaching epidemic levels worldwide due to changes in diet and lifestyle, and it is associated with an increasing prevalence of metabolic complications such as type 2 diabetes, dyslipidemia, and nonalcoholic fatty liver disease (NAFLD). Lifestyle interventions have shown poor success rates for the management and prevention of obesity due to the lack of long-term adherence by most subjects.

Mesenchymal stromal cells (MSCs) hold great promise for clinical application as a personalized cell therapy because they can be conveniently isolated and expanded in culture, lack immunogenicity, tumorigenicity, and ethical issues, and have multipotent differentiation potential. Recent studies have supported that MSCs are effective due to a paracrine mechanism.[1] We have previously reported that the transplantation of MSCs improved obesity-induced glucose and insulin resistance but did not alter blood glucose level, glucose intolerance, the expression of proinflammatory cytokines in pancreas, or liver functions in a chow-diet (CD) group.[2] Transplantation of primary brown adipose tissue (BAT)[3] also has been reported to improve high-fat diet (HFD)-induced obesity. However, the therapeutic effects and mechanisms of MSC-based treatments in obesity and its related metabolic complications remain elusive.

Adipose tissues secrete a variety of adipokines, including chemokines, cytokines, and hormones, to communicate actively with liver and muscle,[4,5] and these factors play a pivotal role in energy homeostasis.[6,7] Excess adiposity results in the dysregulation of various adipokines and leads to the development of obesity-associated metabolic diseases. Peroxisome proliferator–activated receptors (Ppars), which are expressed in response to adipokines such as leptin and adiponectin, are key elements in the process of lipid metabolism in adipose and nonadipose tissues. Coordination is required between the activities of *Ppar-α* and *Ppar-γ* for the maintenance of an equilibrium between the oxidation and synthesis of fatty acids. Recent studies have proposed that Ppars expression may be altered in obesity and hepatosteatosis, thereby facilitating lipogenesis over oxidation and favoring inflammation.[8,9]

In this study, we compared the therapeutic effects of human adipose–derived MSC-based treatments, including the administration of MSCs, MSC-derived brown adipocytes (M-BA), and MSC lysate (M-L), on HFD-induced obesity.

MATERIAL AND METHODS

MSC characterization and cell preparation. Human adipose-derived MSCs at 12th passage were purchased from Steminent Biotherapeutics Inc. (Taipei, Taiwan) and cultured in MesenPRO RS medium (Gibco, Thermo Fisher Scientific, Waltham, Mass). Cell surface phenotyping was determined by flow cytometry. BD Biosciences (San Jose, Calif) supplied anti-CD34, CD45, CD31, CD73, CD90, and CD105 antibodies (Supplemental Fig S1). Cells at the 13th–17th passage were used for experiments. To prepare M-L, MSCs were lysed through sonication and then centrifuged at 4°C and 13,000 × *g* for 5 minutes. The supernatant was collected, diluted with phosphate-buffered saline, and stored at −30°C until use. To differentiate MSCs into brown adipocytes, we modified the previously reported 4-stage protocol[10] by applying partial medium replacement to improve the efficiency of differentiation. Briefly, 4500 cell/cm^2 were seeded and cultured for 2 days in MesenPRO RS medium. After the cells reached confluence, the medium was replaced by high-glucose Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% (v/v) fetal calf serum (Invitrogen, Carlsbad, Calif) for 2 days. Cells were then maintained in DMEM/F12 supplemented with 10 μg/mL of transferrin, 0.85-μM insulin, 0.2-nM triiodothyronine, 1-μM dexamethasone (DEX), and 500-μM isobutyl methylxanthine (IBMX). After 3 days, the medium was replaced with DMEM/F12 supplemented with