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Osteoarthritis of the Ankle Fluid Enhances the Activity of Adipose Stem Cells

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Abstract

Osteoarthritis of the Ankle, or Ankle OA, is an irreversible condition that causes bone deformity, degeneration of articular cartilage, joint pain and limited joint movement. Clinical signs of Ankle OA are reduced when cultured adipose stem cells (ADSCs) are injected into the Ankle joint space. However, the impact of SF filling the joint space of injected ADSCs is still unknown. By adding SFs from Ankle OA patients to treatment-prepared cultured ADSCs, joint space was simulated in this study. Addition of SF improved the survival rate of ADSCs. DNA microarray-based gene expression profiles of SF-treated ADSCs revealed that a number of survival-related genes were altered. We focused on FOSL1, which is involved in both ADSC therapeutic efficacy and cancer stem cell survival and proliferation. Upregulation of FOSL1 mRNA and protein expression was confirmed by RT-PCR and Western blot, respectively. Then, we knocked out FOSL1 in ADSCs with siRNA. A decrease in cell viability was observed, suggesting that ADSCs cannot survive without FOSL1. Based on these findings, SF appears to increase cell viability by increasing her FOSL1 expression in her ADSCs. ADSC therapeutic efficacy using cultured ADSCs can be enhanced if a more conducive environment for upregulation of FOSL1 expression in ADSCs can be created.

Keywords: Human Ankle Osteoarthritis; Fosl1; Human Adipose-Derived Stem Cell

Introduction

ADSCs have properties similar to mesenchymal stem cells (MSCs), are abundant in adipose tissue, and can be easily harvested in large quantities using relatively minimally invasive methods. ADSCs have excellent proliferative ability, and it is possible to culture and prepare the number of cells required for treatment in a relatively short period of time [**1**]. The therapeutic effects of ADSCs on various diseases include not only their ability to differentiate into other cells, but also the secretion of various cytokines and exosomes that have immunosuppressive, angiogenic, and anti-apoptotic effects. ADSC is currently used clinically to treat ankle OA, rheumatoid arthritis, urinary incontinence, scleroderma, skin injuries, and other conditions [**2-5**]. Favorable short-term outcomes were reported in all patients, suggesting that it could be further developed as a safe and effective therapeutic option for disease management.

Treatment for Osteoarthritis of the Ankle

Ankle OA is an irreversible degenerative disease that causes chronic pain and movement disorders due to bone deformation and degeneration of the articular cartilage that makes up the ankle. In recent years, there has been an interest in cell therapy and regenerative medicine for patients who are unable to control pain with conservative treatments such as drug therapy, physical therapy, and intra-articular hyaluronic acid injections, and who are unsuitable or unwilling to undergo surgery [**6**]. increase. surgery. Cell therapy and regenerative medicine for ankle osteoarthritis involves intra-articular administration of cultured ADSCs. A clinical trial using cultured ADSCs is currently underway, and it has been reported that ADSCs increase cartilage mass, improve clinical symptoms such as pain suppression, and delay the progression of ankle OA based on the results of MRI. increase.

In general, frozen ADSCs are used to treat ankle osteoarthritis because the cells are readily available at the facility in a ready-to-use state without the need for cell processing facilities. ADSCs are isolated from adipose tissue primarily by enzymatic treatment, expanded in standard medium at 37°C/5% CO2, and cryopreserved. Frozen ADSCs are thawed and washed prior to intra-articular injection and then injected into the joint cavity, typically by suspension in saline.

Animal studies have reported that less than 1% of systemically administered ADSCs survive to her 1 week. In addition, ADSCs administered into the ankle cavity of osteoarthritis model rats disappeared in about 2 weeks. Therefore, many studies have been initiated to develop spherical ADSCs to prolong the survival time of ADSCs in the joint space [**7**]. Improved media for ADSCs. Optimization of the environment prior to dosing. For cell therapy with ADSCs, high viability and high differentiation potential of ADSCs in joints are important to achieve therapeutic efficacy. On the other hand, apoptotic ADSCs may exert therapeutic effects in OA due to their immunomodulatory effects. Therefore, multiple mechanisms underlie the therapeutic efficacy of his ADSCs. Manferdiny et al. We also reported that inflammatory factors and hypoxic environment in SFs are involved in the proliferation and migration potential of ADSCs. However, there are few reports on the relationship between the SF filling the ADSC-administered joint space and the SF produced in a realistic clinical manner.

Properties of SF [8]

SF is a viscous fluid that accumulates in joint cavities. It has electrolytes similar to those of blood, but has a lower concentration of globulins and almost no fibrinogen. SFs are involved in lubrication of sliding surfaces of joints, absorption of shock, and nutrition of cartilage. Patients with ankle OA have decreased levels of hyaluronic acid in the SF and increased levels of the SF and the inflammatory cytokine

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interleukin (IL)-6. It has also been reported that IL-6 activates ADSCs in SFs [**9**]. Thus, ADSCs administered into the joint space are in direct contact with the SF, the culture environment or fluids not present during the administration process.

Materials and Method

Evaluation of SF

SF is approved by the Kanazawa Medical University Medical Ethics Review Committee (approval number: I583). SFs were collected from her OA patient with untreated ankles because administration of drugs such as NSAIDs (nonsteroidal anti-inflammatory drugs) has been reported to alter the immunomodulators of SFs. After disinfecting the ankle area with povidone-iodine, using an ultrasound-guided superior-lateral approach he collected SFs by co-aspiration using an 18-gauge needle. The collected SF was centrifuged to remove cell debris and the supernatant was frozen at -80°C [**10**], were used according to the manufacturer's protocol. To confirm the presence of blood in the SF, hemoglobin concentration was measured using an automated miniature 6-fraction blood analyzer XN-450.

Viability

Human-derived ADSCs were cultured in serum-free KBM ADSC-4 medium (Kohjin Bio Co., Ltd.,at 37°C/5% CO2. After his purchased ADSCs were thawed and seeded in dishes, the cultures were expanded within his 6 passages and used for experiments. Cultured ADSCs were then separated from the cells with 0.25% trypsin-EDTA (Fujifilm Wako Pure Chemical Industries, Ltd., Osaka, Japan), suspended in CELLBANKER® (Takara Bio, Shiga, Japan), and incubated at -80 °C. Frozen. Cells were then incubated with KBM ADSC-4 medium and frozen at -80°C. Immediately prior to use, the frozen tubes were placed in a 37°C water bath and he incubated for 5 minutes to fully thaw before use. Thawed ADSCs were suspended in serum-free medium, centrifuged, washed with 0.9% saline, and resuspended in saline. ADSCs were then stained with trypan blue to determine cell number and cell viability. We have confirmed a cell viability of 90% or more. 100 µl of saline containing 0%, 20%, 40% or 80% SF was then seeded into each well of a 96-well plate containing ADSCs (1×10 5 cells/ml). After 30 min, 1 h, 2 h, and 4 h incubation, CellTiter-Glo 3D cell viability assay (Promega Corp., Madison, WI, USA) was performed according to the manufacturer's protocol. Relative light units (RLU) for each well were measured using a GloMax 96 Microplate Luminometer (Promega Corp.). The percentage of RLU in the samples at each time point was calculated by subtracting the RLU of each solution without ADSC as a blank and dividing by the RLU at time 0.

Results

First, we evaluated the characteristics of SFs collected from untreated ankle OA patients in our study. Age, gender, weight, height, K-L classification, hemoglobin contamination, body mass index (BMI), hyaluronic acid concentration, and IL-6 concentration of each sample. All SFs were of medium to high viscosity, clear yellow and were collected from 3 males and her 3 females. The KL classification was grade 2 in 4 specimens and grade 3 in 2 specimens. The mean hyaluronan concentration was 88.8 ± 10.7 µg/ml, and all six samples showed a decrease in hyaluronan concentration compared to normal human SF. No hemoglobin contamination was detected in the samples, ruling out the effects of blood contamination. These results were consistent with other studies involving SFs from ankle OA. SF has been reported to increase levels of the inflammatory cytokine IL-6 in ankle OA patients with high BMI, increasing the risk of OA progression. Moreover, IL-6 is a key mediator of cartilage destruction in her OA. Therefore, we evaluated the correlation between IL-6 concentration in SF and her BMI. We also found that all SF samples contained IL-6. As shown, her BMI in 3 of the 6 patients was greater than or equal to her 25 kg/m2. However, the concentration of her IL-6 in SF was not significantly different between patients with BMI ≥25 kg/m2 and those with her BMI <1. 25 kg/m2, and no correlation was found between BMI and IL-6 concentration in SF.

Discussion

In this experiment, saline, which has been reported to be used in many cultured ADSC treatments for ankle OA, was used for analysis. Since the saline solution did not contain any other additives, we thought that we could clearly assess the effect of SF on ADSCs. ADSCs suspended in saline alone showed significantly lower viability at 2 and 4 hours. A previous study reported that the survival rate of ADSCs suspended in saline was approximately 60% at 2 hours, consistent with the results of this study. As shown, the average cell viability of frozen ADSCs suspended in saline was 24.6% at 4 hours.

ADSC survival was significantly increased in the SF-treated group compared with the untreated group at 20%, 40% and 80% SF. We found that the admixture of ADSCs and SFs improved cell viability even in a hostile saline environment. This suggests that SF promotes cell survival compared to saline and that the presence of basic nutrients such as glucose and albumin in SF, components of human plasma, are responsible for increased ADSC survival. It was confirmed that the cell survival effect of SF was sufficient for up to 4 hours, so shorter time periods were evaluated.

Although existing reports indicate that SF is cytotoxic. These reports are based on media comparisons. ADSCs suspended in serum-free medium as a positive control in this study showed the highest cell viability over time. Therefore, we can assume that SF is not cytotoxic, but SF is not superior to properly conditioned media for cell culture. In saline-suspended ADSCs, the clinically relevant protocol used in this study, SF was effective in increasing cell viability. When injecting ADSCs into the joint space, one protocol is to wash the joint space to remove SFs and then administer ADSCs suspended in saline.

In a previous study on ADSC treatment of ankle OA, ADSCs were administered in 3–5 mL of saline, whereas the normal ankle SF volume was 6.7 ± 2.3 mL, which is similar to that in patients with osteoarthritis. It was 18.47 ± 4.67 ml. SF in patients with ankle osteoarthritis is increased compared to healthy subjects. Therefore, it is believed that the actual ankle cavity environment in which ADSCs are administered to osteoarthritis patients has an SF concentration of approximately 80%. that the However, further studies are needed to determine the optimal SF concentration required for long-term cell survival of ADSCs in the joint space and its impact on overall efficacy.

Conclusions

In this study, we found that ADSC therapy in ankle OA increased FOSL1 expression through exposure to SFs in the joint space, contributing to improved cell viability. Based on these findings, targeting FOSL1 in treating ankle osteoarthritis with cultured frozen ADSCs is expected to aid in the development of cell preparations to improve long-term cell viability in the joint space. Furthermore, for the treatment of ankle OA by cultured ADSCs, it is necessary to develop a therapeutic method that further enhances the therapeutic efficacy of ADSCs by optimizing the ADSC culture conditions and increasing the expression of FOSL1.

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