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Mini Review

Anti-Aging Influence of Conditioned Mesenchymal Stem Cell Media Based on Tissue Origin and Culture Environment

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Abbreviations: VWF: Von Willebrand Factor; SVF: Stromal Vascular Fraction; hAD-MSCs: human adipose-derived Mesenchymal Stem Cells; hUC-MSCs: Human Umbilical Code-derived Mesenchymal Stem Cells; EGF: Epidermal Growth Factor; FGF: Fibroblast Growth Factor; GDNF, Glial cell-derived Neurotrophic Factor; HGF: Hepatocyte Growth Factor; VEGF: Vascular Endothelial Growth Factor; TGF-β1: Transforming Growth Factor; HGF: Hepatocyte Growth Factor; PGE2: Prostaglandin-E2; IL-6: Interleukin-6; IL-10, Interleukin; hA-MSCs, Human Amniotic Mesenchymal Stem Cells; RCCS: Rotating cell culture systems.

Introduction

Mesenchymal stem cells are present in multiple tissues in the body; they can self-proliferate in the undifferentiated state and differentiate into cells of other tissues. They were first isolated from the bone marrow. Bone marrow stem cells have been identified as mesenchymal stem cells through extensive research and acquisition of many stem cells [1]. Adult stem cells can be collected from umbilical cord blood after the placenta is separated and from peripheral blood, skin, nerves. The adult stem cells exist nowhere else in our bodies. Samples are difficult to obtain in a timely manner and are subject to many problems, such as long-term storage for use as self-tissue [2,3]. Stem cells in adipose tissue are microvascular endothelial cells, which can be stained for von Willebrand factor (vWF), α-smooth muscle cell actin, and cytokeratin, were isolated from the stromal vascular fraction (SVF) layer separated from human adipose tissue in 1992 [4].

Adipose tissue originates from the mesenchymal lobe of the embryo, and stem cells of mesenchymal tissue can produce bones, cartilage, muscles, and adipose tissue. Adipose tissue stem cells include adipocytes, substrate cells, processed lipoaspirate cells, multipotent adipose-derived cells, and adipose-derived adult stem cells. In 2004, they were named human adipose-derived mesenchymal stem cells (hAD-MSCs) by the International Fat Applied Technology Society. Studies have shown that the aspirated adipose tissue obtained during liposuction contains 1×107 to 6×108 adipose stem cells per 300 mL and their survival rate is more than 90%.

They are easily cultured and have been reported to divide faster than bone marrow stem cells. Adipose tissue can be obtained by liposuction, which has been performed safely using simple techniques for the past 30 years as cosmetic plastic surgery in

obese patients. In the past, these tissues were discarded; however, they are being used clinically for autologous adipose tissue transplantation and in research as a source of stem cells in recent times. Methods for isolating stem cells from liposuction aspirate or resected adipose tissue have been introduced in several studies, whereby the collected tissue is washed with buffer and enzyme-treated to separate the substrate and cells [5]. After the suspended tissue is centrifuged, it separates into an extracellular substrate in the upper layer, oil layer, and cell layer deposited at the bottom. The SVF layer deposited at the bottom contains adipose stem cells. The precipitated cells easily attach to the culture plate, and proliferation occurs within a few days. The initial sedimentary cell layer includes vascular endothelial cells, muscle cells, gap cells, fibroblasts, and blood cells; however, stem cells remain after several subcultures. Nevertheless, it is still controversial whether some fibroblasts attach and proliferate, leaving only stem cells.

In addition to stem cells, differentiated adipose cells also contain lipids, fibroblasts, vascular endothelial cells, vascular muscle cells, and immune cells [6]. To be defined as mesenchymal stem cells, three conditions must be met: first, they must be attaching to a culture container and proliferate; second, they must be able to differentiate into osteoblasts, adipocytes, and chondrocytes in the test tube; and third, specific cell surface antigens must be expressed [7]. According to the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy, the above two conditions must be met and specific antigens, such as CD105, CD73, and CD90, and hematopoietic cell antigens CD45, CD34, CD34, CD11b, or CD11b, CD11b, CD11b, CD19, and HLA-DR should be expressed [8].

The umbilical vein is surrounded by the Wharton's jelly layer, which consists of perivascular zones, intervascular zones, and sub-amnions; perivascular zones consist of differentiated myofibroblasts. Stem cells with proliferative capabilities exist in zones and sub-amnios. Human umbilical code-derived mesenchymal stem cells (hUC-MSCs) express CD73, CD90, CD105, CD10, CD13, CD29, CD44, and HLA-ABC genes, similar to mesenchymal stem cells derived from bone marrow and other tissues. Hematopoietic stem cell markers CD34 and CD45, and tissue compatibility antigens CD14, CD31, CD33, and HLA-DR are not expressed. hUC-MSCs can be differentiated into bone, cartilage, and adipose cells. They have a better dividing ability than bone marrow or adipose-derived stem cells under in vitro conditions; additionally, they are relatively differentiated cells compared to those derived from adipose tissue or bone marrow. These features facilitate the use of umbilical cord-derived stem cells in cell therapy [9,10].

MSCs have immune suppression and inflammatory functions, and several trophic factors are known to confer a homing effect that contributes to tissue recovery after damage [11]. MSCs secrete various cytokines such as epidermal growth factor (EGF), fibroblast growth factor (FGF), glial cell-derived neurotrophic factor (GDNF), hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF). Active cytokines secreted from stem cells are beneficial in tissue regeneration because secreted cytokines and growth factors can improve the host tissue microenvironment [12]. Several molecules produced by MSCs, such as transforming growth factor (TGF)-β1, hepatocyte growth factor (HGF), prostaglandin-E2 (PGE2), interleukin-6 (IL-6), interleukin (IL-10), and nitric oxide (nitrogen) can affect the immune response. The detailed mechanisms by which these molecules inhibit or modulate immune cells are not yet fully understood and are beyond the scope of this review. Another important mechanism by which MSCs inhibit and/or regulate the immune response is through the production or expansion of immune regulatory cells [13].

Cosmeceuticals containing human tissue-derived mesenchymal stem cell-conditioned media are products for which the main ingredients are obtained from a human stem cell culture, and they have been shown to influence skin health recovery, skin regeneration, and skin cell aging delay. Stem cells are present in various tissues in the human body, but the stem cells used are extracted from the umbilical cord, bone marrow, and adipose tissue [14]. Adipose-derived and umbilical cord-derived stem cell-conditioned medium contains various growth factors, cytokines, and bioactive protein components; therefore, they have been proposed as potential ingredients for functional cosmetic products [12,15,16]. It has been reported that conditional media from various tissue-derived mesenchymal stem cell cultures can improve the signs of aging skin [12,17,18,19].

As mentioned above, there is evidence that conditioned media contain multiple cytokines, and these can be boosted using the right culture system environment. Recent studies have confirmed that the characteristics of cells and cell cultures differ depending on the tissue origin of MSCs, as well as the environment in which they are

cultured, between two-dimensional (2D) and three-dimensional (3D) culture systems [12,14]. Specifically, 2D culture systems, such as plastic culture plates, cause changes to the cell shape, internal cell skeletons, and nuclear shape, which can affect gene expression and change cell fate, as well as differentiation potential. In 2D culture systems, MSCs tend to undergo non-specific differentiation, which can be fractionally differentiated or differentiated owing to the loss of functionality [21]. However, 3D cultures systems vary widely, and include complex systems that use dynamic bioreactors that incorporate biomaterials into simple cell aggregates. Human amniotic mesenchymal stem cells (hA-MSCs) were elevated in spiroids stored in 3D culture systems compared to those maintained in 2D culture for viability, multifunctionality, and secretion capacity for angiogenesis and immunosuppressive factors [19,20]. In addition, the improved paracrine effect was recorded in vitro in the form of increased capillary maturity and inhibition of peripheral blood mononuclear cell proliferation in the 2D and 3D conditioned media [23]. In another study, experiments were conducted to compare the conditioned media of hUC-MSCs and hAD-MSCs for anti-aging formulations using 2D and 3D culture methods. These experiments confirmed that the conditioned medium of hUC-MSCs cultured in a 3D environment showed higher levels of cytokines, which play an important role in skin regeneration, whitening, and wrinkle improvement, compared to those in a 2D environment [12,22]. From these results, the culture environment and type of human tissue are expected to have a considerable influence on the type and quantity of conditioned medium-containing factors.

Rotating cell culture systems (RCCSs) combined with 3D culture provided an effective means for the proliferation of MSCs in vitro; a microarray analysis of bone marrow derived MSCs cultured showed that proliferation and clustering were improved and maintained [23]. In MSCs culture, a dynamic bioreactor culture system with 3D culture, in which culture variables such as pH, temperature, oxygen, and carbon dioxide concentration are properly controlled and monitored, is essential for in vitro culture and maturation of tissue engineering grafts [24]. These closed systems maintain a uniform physicochemical environment required for cell culture and reduce the number of handling steps, thereby reducing the likelihood of contamination according to quality standards [1,12]. 2D culture systems are limited by requests for batch medium changes; however, 3D culture systems are highly controllable, enabling better homogeneous media and cell space distribution despite increased scaffolding [1,15].

Further studies on the impact of the mesenchymal stem cell culture environment should be conducted to support experiments for the anti-aging effect. This review is expected to significantly contribute to the development and activation of cosmeceuticals containing MSC-conditioned media derived from various human tissues in the cosmetics industry.

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