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Identification of Novel Markers for Skin Senescence Associated with the First Aging Peak of a Life Span

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INTRODUCTION

Aging underlies declining skin function and is the predominant risk factor for numerous skin problems [1]. Thus, a deeper understanding of aging is likely to provide insight into the mechanisms of skin diseases and facilitate the development of novel anti-aging skincare. Recent studies have revealed three significant changes in age-related molecules in the blood over a human lifetime. The results support our group's hypothesis that nonlinear age-related changes in the skin will also occur. The first peak of aging proteins is around the fourth decade of life, and the down-regulation of proteins related to structures such as the extracellular matrix is mainly observed at this time, which is expected to be a period that is closely associated with skin aging [2]. The aim of this study was to screen for skin aging markers corresponding to the first aging peak and to develop an ingredient that modulates them.

EXPERIMENTAL

Cell cultures and reagents

Keratinocyte (HaCaT) cells and human primary fibroblast cells (HDFn, normal human dermal fibroblasts juvenile foreskin, C-12300, PromoCell, Heidelberg, Germany) were cultured in Dulbecco's modified Eagle's medium high glucose (DMEM high glucose, SH30243.01, Hy-80 clone, Hyclone, Logan, UT, USA) containing 10% (v/v) of fetal bovine serum (FBS, SH30084.03, Hyclone, Logan, UT, USA) and 1% antibiotic-antimycotic agents (Anti-anti, 15240-062, Gibco, Grand Island, NY, USA). Cell cultures were maintained at subconfluence in a 95% air, 5% CO_2 humidified atmosphere at 37 °C. HDFn cells were serially passaged from passage 6 through passage 41. *Bulbine frutescens* extract (BFE), *Ganoderma lucidum* (Mushroom) Stem Extract (GLSE), and Crocin (Sigma Aldrich, St. Louis,MO, USA) were dissolved in PBS.

UVA/UVB irradiation

HDFn cells were cultured in 96-well (1×10^3 cells/well) or 6-well plates (1×10^5 cells/well). Then the cells were synchronized with DMEM high glucose without FBS for 24 h. Following a further 24 h of incubation at 37 °C with or without sample ingredients, the culture medium was replaced with PBS. Cells were then exposed to UVA/UVB light (Bio-Sun system, Vilber Lourmat, Inc., Torcy, France) at a total dose of 50 mJ/cm^2 (UVA) and 150 mJ/cm^2 (UVB). Following irradiation, the medium was replaced with a culture medium with or without sample ingredients for 3 h and 24 h.

Abstract

The mechanism of aging can be a very major target for the skincare strategy of cosmetics. Recent studies revealed that there are three major changes in age-related molecules over a lifetime. Based on this study, we tried to select genes involved in nonlinear aging of the skin. Among these age-related molecules, we found that four genes, Fstl3, Gdf15, Mmp12, and Ccdc80, showed changes in the senescent skin cells. They showed similar gene expression patterns to those in senescent cells when irradiated with UVB.

Next, we found three ingredients that can change the expression of the Fstl3, Gdf15, Mmp12, and Ccdc80 genes: Bulbine frutescens extract, Ganoderma lucidum stem extract, and crocin. To evaluate whether the four genes correlate with skin aging, we performed an siRNA knockdown of Fstl3 and Mmp12. We confirmed that the Fstl3 gene knockdown affects collagen and elastin production and the Mmp12 gene knockdown affects elastin production. In addition, it was confirmed that Bulbine frutescens extract can restore elastin production reduced by UVA by regulating Mmp12 gene expression.

On the basis of these results, it can be said that these four genes have the potential to act as skin aging markers. In this study, we discovered skin aging markers and elucidated their aging-related functions. In addition, we discovered ingredients that regulate the expression of aging markers and are valuable as cosmetic skin anti-aging ingredients.