Stimulation of Noggin Signaling in Keratinocytes by an Extract of Mulberry (Morus alba L)

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Abstract

Traditional Chinese medicine has utilized various parts of Morus alba L (white mulberry) to ameliorate chronic sicknesses caused by organ or tissue disorders. We investigated the effects of the ethanol extract of mulberry fruits on the expression of the hair cycle-associated genes of cultured human keratinocytes to explore its potential as a hair-nourishment ingredient. Two types of cultured human cells were utilized: human epidermal keratinocytes (HEKs) and HaCaT cells (a cell line of keratinocyte). Cells were treated with mulberry extracts and its effects were evaluated in terms of growth capacity and the expression of 12 known hair cycle-associated genes. Mulberry extracts significantly stimulated the growth of HEKs and HaCaT cells. Among the 12 tested genes of HaCaT cells, the expression of noggin gene (NOG) was increased most prominently by the extract. The up-regulated expression of NOG induced by the extract was also observed in HEKs. In contrast, the expression of bone morphogenetic protein 4 gene (BMP4) and p27kip1 gene, both genes associated with noggin signaling, was down-regulated in HaCaT cells by the extract, strongly suggesting that the extract may have stimulated keratinocyte growth through the suppressive effects of noggin on BMP-p27kip1 signaling. Furthermore, HaCaT cells were exposed to oxidative stress using t-butylhydroperoxide or UV and then treated with the extract in order to determine whether the extract mitigates oxidative stress-induced alterations. HaCaT cells significantly decreased the NOG expression when exposed to oxidative stress. The extract was able to recover the oxidative stress-induced suppression of NOG. These results suggest that mulberry extracts mitigate oxidative stress-induced damage in cells. Therefore the results in this study suggest the potential of the mulberry extracts as an ingredient in hair-nourishment products.

Key words: Morus alba L, hair growth, keratinocytes, noggin, oxidative stress.

1. Introduction

Morus alba L is a species of Morus in the family of Moraceae, and is commonly known as white mulberry (mulberry in this study). Its fruits have been utilized as crude drugs for nourishment, robustness, relief from anemia, and hair growth1. These fruits contain large amounts of polyphenols including apigenin, luteolin, and quercetin2, which exhibit stronger anti-oxidative activities than those of other Moraceae species such as M. nigra and M. laevigata3. Although the mulberry fruit extract has been conventionally utilized as a material that has the ability to stimulate hair growth, few studies have examined the mechanistic aspects underlying their effects on hair growth-related compromises.

Terminal hairs retain their growth capacity throughout life in a unique manner; they undergo cycles of growth and regression involving the reproduction of new (secondary) hairs and their active growth (anagen), the apoptotic involution of hair follicles (catagen), and relative resting of dermal papilla in the quiescence and shedding of hairs (telogen-exogen). The transitions from telogen to anagen and from anagen to catagen are physiologically, pathologically, and also clinically important because the duration of anagen has been directly related to the thickness and length of hair growth4.

Hair follicles (HFs) are exposed to numerous growth stimulatory and inhibitory factors, and a tightly controlled balance between these two factors causes HFs to transit between the distinct hair cycle stages5. Although the components of this network have not yet been completely revealed, bone morphogenetic protein (BMP)6 and Wnt/β-catenin7 signals have been suggested as major players in this network; BMP signals may function as a growth inhibitory factor (catagen promoter) in contrast to Wnt/β-catenin signals, which act as growth stimulatory factors (anagen promoters). BMP expression is absent in early anagen and gradually intensifies to reach its peak level in anagen. BMP expression remains high in catagen, but becomes absent in telogen7. Noggin is an antagonist of BMP signaling6, a major inhibitory regulator of HF cycling8. Noggin expression remains high in anagen and declines in catagen7. Delivery of extraneous noggin by intracutaneous implantation of noggin-soaked beads was able to decrease BMP signaling activity and initiate anagen10. BMP and