Next Generation Cosmeceuticals

The Latest in Peptides, Growth Factors, Cytokines, and Stem Cells

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KEYWORDS

• Cosmeceuticals • Stem cells • Growth factors • Peptides • Photoaging • Rhytides • Cytokines

KEY POINTS

- Collagen, elastin, and other components of the skin diminish with age and may be replaced through the use of cosmeceuticals.
- Peptides induce neocollagenesis replacing lost extracellular matrix and reducing the appearance of wrinkles.
- Cosmeceuticals containing growth factors and cytokines involved in wound repair aid in the repair of chronic damage to the skin.
- Allogenic stem cells derived from human adipocytes produce growth factors which promote fibroblasts within the skin along with promoting wound healing.
- Xenogenic stem cells derived from plants have anti-senescent properties.

INTRODUCTION

As the population grows, there is a particular increase in the middle-aged and elderly population, the so-called "baby boomers." Among this population is a continued increase in the desire for younger looking skin. Areas of particular concern include loss of elasticity, rhytides, irregular texture, pigmentation, and dryness.[1,2] This desire has led to the development of cosmeceuticals, which are in between cosmetics and physiologically altering pharmaceuticals.

Aging occurs by two mechanisms: intrinsic and extrinsic aging. Intrinsic aging is inevitable and results in atrophy, fibroblast reduction, and thinning blood vessels.[3] Collagen is particularly affected, as the synthesis steadily declines with age.[4] Likewise, elastin also declines with age.[4,5] Extrinsic aging primarily results from the effects of UV damage. Other causes include environmental factors, such as smoking, pollution, and poor nutrition.[3,6] This type of damage leads to increased degradation of collagen and elastin. Aged skin shows a decrease in extracellular matrix (ECM) proteins, increased collagen degradation, and decreased fibroblasts.[7] Furthermore, there is a reduction in the immune response, wound repair, and fiber synthesis.[8] Extrinsic aging leads to the production of free radicals, which in turn activate matrix metalloproteinases (MMPs). This activation of MMPs also leads to ECM degradation.[9] Additionally, free radicals inhibit the tissue inhibitors of metalloproteinase (TIMPs). The goal of

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cosmeceuticals is to mitigate some of these effects of aging.

Effective cosmeceuticals must be able to penetrate through the stratum corneum while maintaining their effectiveness. They also must have visible benefits without impacting the skin's barrier function.[10] There has been a recent surge of new cosmeceuticals, and this article discusses the functions, limits, and benefits of peptides, growth factors, cytokines, and stem cells used in these products.

PEPTIDES

Peptides are short amino acid chains with a functional ability to alter skin physiology.[11] The basic cosmetic mechanism behind peptides is to increase collagen production, replacing lost ECM and reducing the size and appearance of wrinkles. Peptides are able to regulate fibroblast production of ECM components,[12,13] mainly through the use of signal peptides. It is hypothesized that the introduction of subfragments of these components, such as elastin and collagen, will act as feedback stimulators inducing their own synthesis.[11]

Use of peptides for topical application is limited by the ionic nature of the amino acid chains.[14] However, this may be circumvented through the incorporation of a lipophilic derivative, such as palmitoyl. Peptides generally have a short half-life when delivered orally because of significant first-pass effect. By delivering them transdermally, fully functional peptides may be delivered to the desired site. The length and membrane permeability are important when assessing them for use in cosmeceuticals.[15] Addition of peptides to products can get very costly; however, minimal compositions of peptides have shown significant results. Peptides are thus very potent and require only minor amounts, minimizing cost.

Signal Peptides

This discussion focuses on signal peptides, which stimulate ECM production, specifically increasing collagen synthesis. A list of functional peptides found in cosmeceuticals can be found in **Table 1**. One of the longest used peptides, oligopeptide-20, consists of 12 amino acids. This peptide increases collagen and hyaluronic acid in cultured keratinocytes and fibroblasts.[16] Another peptide shown to increase collagen production is palmitoyl pentapeptide-4 (Pal KTTKS). Pal KTTKS is a fragment of procollagen I. It increases production of collagen I and III through the stimulation of fibroblasts, and also stimulates production of fibronectin and elastin.[10,17,18] The palmitoyl derivative was added to the pentapeptide, increasing its lipophilic properties and enhancing absorption. Pal KTTKS also inhibited the production of glycoasaminoglycans in the skin, an increase of which is associated with increased age and photodamaged skin.[19]

Palmitoyl-lysine-threonine (pal-KT) is one of the shortest peptides. When tested with human skin equivalents, it was found to enhance differentiation of the epidermis, basement membrane zone, and dermal fibroblasts.[20] Within dermal fibroblasts, pal-KT increased collagen I, collagen IV, and fibronectin.

The hexapeptide, consisting of amino acids val-gly-val-ala-pro-gly, is an elastin fragment with chemotactic properties. It attracts cells to wound sites[10] and significantly stimulates fibroblast proliferation within human skin.[11] It also decreases the expression of elastin.[21] Conversely, this peptide has been found in another study[3] to induce proteolytic and inflammatory damage by upregulation of MMP-1 and MMP-3, requiring further study.

Tripeptide-10 citrulline (T10-C) is a decorin-like molecule. Decorin is a leucine-rich proteoglycan directly involved in matrix organization. By binding to the surface of collagen molecules, decorin regulates their interaction with other collagen molecules, stabilizing and orienting them, thus establishing a uniform tissue shape. This mechanism increases the tensile strength of collagen and reduces collagen disruption. With age, however, comes a lack of functional decorin within the skin.[22] Instead, it is replaced with a truncated, nonfunctional fragment known as decorunt.

T10-C contains the collagen-binding site sequences of decorin and, like decorin, is able to regulate collagen fibers. Unlike other peptides, which increase the quantity of collagen, it increases the quality of the collagen, enhancing uniformity and increasing cohesion. T10-C showed a decrease in collagen fiber diameter, similar to decorin, which led to increased skin suppleness and firmness.[23] Another peptide, arg-gly-asp-ser, enhances ECM structure. This tetrapeptide is a fragment of fibronectin and enhances cell and collagen cohesiveness.[10]

Peptamide-6 is derived from the yeast *Saccharomyces*. It is a firming peptide that works by upregulation of growth factors and increasing collagen synthesis. This peptide has been shown to improve skin elasticity and deformation response.[23]

Acetyl tetrapepide-9 and -11 (AcTP1 and AcTP2, respectively) increase skin thickness and firmness. AcTP1 increases collagen I and lumican synthesis. AcTP2 stimulates keratinocyte growth and syndecan-1 synthesis.[24]

In addition to their effects on the ECM, peptides may also function as skin whitening agents. PKEK,