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Hyaluronic Acid and Its Use for Skin Rejuvenation

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Abstract

The skin envelopes the total surface of the body and it is made up of the epidermis, an epithelial tissue of ectodermal origin; by dermis, a conjunctive tissue of mesodermal origin, which serves as sustainment and is responsible for its nutrition; and by the hypodermis or adipose tissue. This last one is a special type of conjunction in which there is a predominance of adipose cells (adipocytes), specialized in storing lipids in the form of triacylglycerol (TAG); non-polar, hydrophobic and water-insoluble substances. It embodies the organism's main energy reservoir. And its regulation ensues by nutrients and afferent signals of the neural and hormonal systems.

Keywords: biostimulator; hyaluronic acid; rejuvenation; neocollagenesis; regenerative medicine

Introduction

The skin envelopes the total surface of the body and it is made up of the epidermis, an epithelial tissue of ectodermal origin; by dermis, a conjunctive tissue of mesodermal origin, which serves as sustainment and is responsible for its nutrition; and by the hypodermis or adipose tissue. This last one is a special type of conjunction in which there is a predominance of adipose cells (adipocytes), specialized in storing lipids in the form of triacylglycerol (TAG); non-polar, hydrophobic and water-insoluble substances. It embodies the organism's main energy reservoir. And its regulation ensues by nutrients and afferent signals of the neural and hormonal systems. On the contrary of the other tissues essentially made of cells, the conjunctive tissue owns as its main component the Extracellular Matrix (ECM): a network of molecules that consists of different fibrose proteins combinations, further the hydrophilic and adhesive macromolecules, that composes the elemental substance. This huge variety of the conjunctive tissue, establishes a reserve for growth factors that control cellular proliferation and differentiation, acting as lubricant and barrier to the penetration of invader microorganisms.

Regarding the cells of the conjunctive tissue, these are formed specially by fibroblasts that originate locally from mesenchymal undifferentiated cells and remain throughout their lives in this tissue. Mast cells, macrophages, plasma cells and leukocytes, that are also present, originate themselves from hematopoietic stem cells of the bone marrow, circulate in the blood and move to the connective tissue in which they perform their functions. The fibroblasts are vital constituents of the conjunctive tissue, as they provide mechanical strength through the synthesis of their fibers (composed of proteins, collagen and elastin) and maintain the tissue homeostasis, promoting the remodeling of the extracellular matrix (ECM). This remodeling is made by the formation of glycosaminoglycans and multi-adhesive glycoproteins that will be part of the ECM [1]. The fibroblast is also involved in the production of growth factors, such as the growth factor similar to insulin (IGF), the transforming growth factor of fibroblasts β type (TGF-β), the growth factor of fibroblasts 7 and 10 (FGF-7 e FGF-10) and diverse ligands to the receptor of the epidermal growth factor (EGFR), essential for the proliferation and cellular differentiation in the basal layer. Thus, for these reasons it is considered the main cell involved in the healing process [1,2].

On the other hand, the fundamental substance portrays a structural function, promotes tensile strength and plays an important biological role, determining cellular functions through molecular signs, besides attracting large amounts of cations as the NA+, offering hydration to the EMC. This viscous complex of anionic macromolecules (glycosaminoglycans and proteoglycan) can be found in a free-form (hyaluronic acid) or as multiadhesive glycoproteins (laminin and fibronectin) that bind to

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receptor proteins (integrins) on the cells surface and to other components of the matrix [2].

Hyaluronic Acid as Intrinsic Component in The Tissues

The Hyaluronic Acid (HA) is a key-biomolecule of the EMC consisting of repeated disaccharides of glucuronic acid and N-acetylglucosamine. Its weight represents around 0.02% of an individual's body weight due to it being abundantly present in a variety of tissues such as the skin [3]. In a work done by Missinato et al, it was demonstrated that biological processes, such as cellular proliferation, migration and differentiation, as well as inflammatory processes, besides the fibrose extension, are influenced by the HA. The difference between achieving the regeneration or healing itself, depends on the availability of the HA in sufficient quantities throughout the inflammatory process of the wound, being considered the hypothesis that the HA can be involved in the settlement and subsequently in the fibrillogenesis of the fibronectin and plays specific parts in the tissue according to the inflammatory stage of the EMC [4].

Skin Aging

The chronological aging causes thinning of the dermal thickness through biochemical and structural changes of collagen elastic fibers and fundamental substance. There is a reduction in collagen synthesis and an increase in its degradation due to increased levels of collagenase, a decrease in elastogenesis, disorganization in fiber distribution, and a decrease in glycosaminoglycans. Collagen content reduces by 1% per year throughout adulthood and the remaining collagen fibers appear disorganized, more compact and granular. Elastic fibers decrease in number and diameter [5]. In women, the reduction of the dermic content of collagen is also related to the reduction of seric levels of estrogen, further increasing the cutaneous extensibility and reducing elasticity [6]. There is atrophy of the skin, loss of elasticity, dryness and ineffective healing; however, hormone replacement therapy can mitigate these effects. These changes are more related to climacteric than only chronological aging, which explains the worsening of flaccidity in this period.

Photodamage, present in the corporal areas of sun explosion, also tends to aggravate this process, reducing the synthesis of type I procollagen and increasing collagenase levels. The major amount of the degradation products inhibits the synthesis of new collagen and this way, degradation negatively regulates neocollagenesis. In addition to UV radiation, other extrinsic factors (prevenient from the environment) are inadequate eating habits, pollution, which are called exposomes and accelerate the cell senescence. In a study conducted by the Department of Dermatology and Pathology at Michigan State University, comparing histological differences in skins of women aged 18 and 29 with women, aged 80 and over, has been demonstrated that both the advanced age of fibroblasts and mechanical stimulation defects in older tissues reduce collagen synthesis. It was also stated that although the destruction of the existing collagen plays a central part in the deleterious changes observed in the aged and photodamaged skin, the failure to replace damaged collagen is also very important in the pathophysiological process [7].

The cutaneous healing process is also affected by the chronological aging and estrogens reduction, as it depends on the regeneration capacity of the conjunctive tissue. We know that initially occurs the presence of the inflammatory infiltrate, followed by the formation of a granulation tissue. This tissue is constituted by the proliferation of the conjunctive, being vastly vascularized and rich in inflammatory cells and provisional extracellular matrix. Subsequently, re-epithelialization occurs (the cells of the epidermis migrate and close the lesion). It is also observed the remodeling of the dermis, the extracellular matrix is gradually degraded and replaced by the matrix of the normal dermis, rich in collagen type I. In patients with older age, the inflammatory capacity is reduced, with a delay in the renewal of the epidermis. In a study comparing whether in vitro production of procollagen type 1 over isolated dermal fibroblasts of skin of youthful individuals (18 up to 29 years-old) versus elderly (80+ years-old), was identified a reduced synthesis of type 1 and 3 collagens, arising out of morphological, ultra-structural and microscopic fluency studies. The outcomes caught the attention that both the aging of fibroblasts, as the defective mechanical stimulation in the age-old issue contribute to the collagen synthesis devaluation. It was also perceived as a high percentage of adhered cellular surface to collagen fibers and even extensive cell scattering in the youth skin in comparison to the aged skin [8].

Thus, the changes that occur in the mechanical properties of the skin during adulthood include the progressive loss of consistent elasticity with the

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gradual loss of the fibers net and the prolonging of the necessary time to the skin returns at its original state after clamping, that outline the skin sagging [7]. Moreover, as a consequence, changes occur in facial volume with cutaneous lipodystrophy, appearance of rhytids, furrows and expression marks [9,10]. There are several treatments depicted in the literature for skin aging aimed at expanding collagen production, equally to: chemical peels, fractional CO2 laser, micro focal ultrasound and other technologies; Intraderemotheraphy; micro needling with drug delivery, such as poly-L-lactic acid, Ca hydroxyapatite and polycaprolactone. Relevant research in the last two decades has established that the elasticity or stiffness of ECM affects fundamental cellular processes, including formation, growth, proliferation, migration, differentiation and dissemination of organoids in tissue models in vitro.

From the discovery of the importance of matrix viscoelasticity, new insights about cell-matrix interactions have been suggested, explaining how they can modulate mechano-sensitive molecular pathways into cells. These results have helped in the development of new generations of biomaterials that best correspond to the mechanics of tissues and ECM, both for obtaining tissue models in vitro and for applications in regenerative medicine [11]. In this context, the use of hyaluronic acid (HA) applied intradermally can also occupy a substantial role for the rejuvenation treatment, although its results are still incipients regarding the effectiveness in the collagen production itself.

Mechanism of Action of Extrinsic Hyaluronic Acid

Exogenous hyaluronic acid is a highly molecule biocompatible as being composed in the same way as the endogenous, which is present in most species and tissues. Its application for aesthetic and therapeutic purposes, has low potential for hyper sensibility, requiring no previous skin tests and can be performed in patients with autoimmune diseases [11,12]. The formulations available in the market are obtained by bacterial fermentation, such as Streptococcus culture, and stabilized in gel form. Its viscosity depends on the size of the gel particles and the number of units per unit of volume, beside the different methods of cross-linking. The stronger the cross links, the greater the stability, viscosity and durability of the filling. Its duration in the tissues is about 6 to 9 months and the abasement is due the formation of free radicals, occurring by a mechanism that depends on the surface of the product, depth of application and the characteristics of the treated area, such as its mobility, as example. On the other hand, the HA without crosslinking are very fluid products used only for the dermis rehydration, lasting about 24 to 48 hours [13]. Reticulated fillers (with crosslinking) are classified as monophasic or biphasic. Monophasic ones are homogeneous materials and are formed by a mixture of HA of high weight and low molecular weight facilitating its application. There are two categories: monodensified (reticulated once) or polydensified (continuously reticulated). Biphasic fillers have heterogeneous particles and possess high viscosity and elasticity [14]. Hyaluronic Acid is pliable and easy to handle. Its application results in a natural aesthetic aspect, besides having the advantage of presenting reversible results through the use of hyaluronidase enzyme, which catalyzes its degradation. The different concentrations can be an adaptable form for each region to be treated (furrow, lips, fine wrinkles) [15]. In dermatological treatments, it can be used isolated or combined with other technologies such as the use of botulinum toxin and collagen biostimulators. Their different appearance determines its use for intradermal therapy, skinbooster, fillers or volumizers, according to its individual characteristics and types of crosslinking. The most commonly indicated locations for skin fillers, with the aim of mitigating signs of aging or volumizing are: perioral wrinkles, nasolabial folds, labial commissure, corner of the mouth, lips, ear lobes, infraorbital fold, eyebrows, temporal region, malar, zygomatic and mandibular for facial contour remodeling. It can be also used for cicatrice treatments [15].

Injection techniques vary alongside with the depth of wrinkles and furrows to be treated. For fine wrinkles, low cross-linking HA is applied to the papillary dermis (bevel with an angle of 10 to 30 degrees), or reticular (bevel with angles of 30-45 degrees). For treatment of furrows, we must aim the deep dermis at an angle of 45-90 degrees. Subcutaneous applications and the periosteal are used to restore lost volumes of soft parts or even in deep furrows [12]. There are not many studies in the literature on superficial dermal injection of HA with crosslinking. A previous study by Flynn et al [16] has demonstrated that different HA gels, when injected into the medium human dermis, can interact and integrate with predictable behavior patterns. Biphasic gels migrate to deep and subcutaneous dermis. Monophasic cells usually remain in the medium dermis, but retain clusters and

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characteristic cellular aggregates without fully integrating with dermal collagen. Contrariwise, monophasic polydensified gels, that shall be the object of this study, when injected into the dermis, are evenly distributed in the reticular dermis and blend themselves between the collagen bands, provoking clinical and histological alterations, as an eosinophilic infiltrate [16], which could favor the stimulation of new collagen. These discoveries are found 2 weeks after the application and remain in biopsies performed within 1 year maximum after the implementation.

Another study accomplished by the University of Genova [17], which aimed to analyze the inflammatory response and tolerability of fillers, tested the bio-integration of three different types of hyaluronic acid regarding cohesiveness, with a follow-up of 114 days. It was stated that all have preserved the integrity of the dermal cells and the extracellular matrix. The tissue integration was related to the viscoelastic properties of the product used, whereas the cohesive fillers with polydensity have demonstrated major homogeneity when blended to the reticular dermis [18]. In a study conducted in Seoul by the St. Mary's Hospital Ophthalmology Department (The Catholic University of Korea), the protective function of hyaluronic acid in bovine corneal endothelial cells (BCEC) was evaluated. It has been demonstrated that HA suppresses the release of superoxide of polymorphonuclears (PMN), protecting the BCEC from activated PMNs in a dose-dependent manner. It was also observed that the suppression of the superoxide liberated by the PMNs is not an exclusive action of HA, but would be a general property of viscoelastic substances. In such a manner, a hypothesis that the HA also acts as a physical barrier and/or eliminator of free radicals scavenger [19].

Because of its protective mechanical effect, the HA can be used in situations of cataract and glaucoma, besides in addition to its property of inhibiting the phagocytosis of macrophages and the fixation of leukocytes to the intraocular lens. In another study performed in Korea, a treatment was accomplished with a mixture of hyaluronic acid and botulinum toxin (S-HA) in 102 patients with acne scars. They were submitted to evaluations by computational topographic analysis of each roughness, point depth measurements evaluation by Global Aesthetic Improvement Scale (GAIS) 1 and 6 months after the treatment. Further, six patients have volunteered for planned facing lifting surgeries 1 month and 1 year after the injection to eto assess injection depth, longevity of materials and S-HA reactions, including neocollagenesis and neoelastinogenesis. The study of histopathological examination has proven that the extent of the injection was exactly in the dermis and showed evidence of neocollagenesis and neoelastinogenesis [20]. In addition, the HA particles remained after 1 year, stating its longevity for at least this period of study.

Conclusion

Despite numerous reports on the behavior of different types of hyaluronic acid and their interaction with the skin, there are no more specific descriptions of neocollagenesis. Hence, we are developing a work demonstrating the specific histological alterations observed by the application of HA for skin rejuvenation purposes, in addition to the different interactions observed in the skin related to the age of the treated patients [18,21].

The path to be taken is promising and includes in addition to its functions in biostimulation, applications of the use of the hyaluronic acid as remodeling of extracellular matrix and its impact for Regenerative Medicine.

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