

Hyaluronic acid

A key molecule in skin aging

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Abbreviations: UV, ultraviolet; ROS, reactive oxygen species; MMP, matrix metalloproteinase; HA, hyaluronic acid; GAG, glycosaminoglycan; ECM, extracellular matrix; HAS, hyaluronic acid synthases; HYAL, hyaluronidases; CD44, cluster of differentiation 44; RHAMM, receptor for HA-mediated motility; TGF, transforming growth factor

Skin aging is a multifactorial process consisting of two distinct and independent mechanisms: intrinsic and extrinsic aging. Youthful skin retains its turgor, resilience and pliability, among others, due to its high content of water. Daily external injury, in addition to the normal process of aging, causes loss of moisture. The key molecule involved in skin moisture is hyaluronic acid (HA) that has unique capacity in retaining water. There are multiple sites for the control of HA synthesis, deposition, cell and protein association and degradation, reflecting the complexity of HA metabolism. The enzymes that synthesize or catabolize HA and HA receptors responsible for many of the functions of HA are all multigene families with distinct patterns of tissue expression. Understanding the metabolism of HA in the different layers of the skin and the interactions of HA with other skin components will facilitate the ability to modulate skin moisture in a rational manner.

Skin Aging

Human skin aging is a complex biological process, not yet fully understood. It is the result of two biologically independent processes. The first is intrinsic or innate aging, an unpreventable process, which affects the skin in the same pattern as it affects all internal organs. The second is extrinsic aging, which is the result of exposure to external factors, mainly ultraviolet (UV) irradiation, that is also referred to as photoaging.¹ Intrinsic skin aging is influenced by hormonal changes that occur with age,² such as the gradual decreased production of sex hormones from the mid-twenties and the diminution of estrogens and progesterone associated with menopause. It is well established that the deficiency in estrogens and androgens results in collagen degradation, dryness, loss of elasticity, epidermal atrophy and wrinkling of the skin.³

Even though intrinsic and extrinsic skin aging are distinctive processes, they share similarities in molecular mechanisms. For example, reactive oxygen species (ROS), arising from oxidative

cell metabolism, play a major role in both processes.⁴ ROS in extrinsic or intrinsic skin aging induce the transcription factor c-Jun via mitogen-activated protein kinases (MAPK), leading to overexpression of matrix metalloproteinase (MMP)-1, MMP-3 and MMP-9 and prevention of the expression of procollagen-1.⁵ Therefore, elevated levels of degraded collagen and reduced collagen synthesis are pathologies occurring in intrinsically aged as well as photoaged skin.

Skin aging is also associated with loss of skin moisture. The key molecule involved in skin moisture is hyaluronan or hyaluronic acid (HA), a glycosaminoglycan (GAG) with a unique capacity to bind and retain water molecules.⁶ HA belongs to the extracellular matrix (ECM) molecules. During the past decades the constituents of the skin have been well characterized. In the beginning, most of the studies focused on the cells that comprise the skin layers, such as the epidermis, the dermis and the underlying subcutis. Recently, it is appreciated that ECM molecules that lie between cells, in addition to providing a constructive framework, they exert major effects on cellular function. These ECM molecules, although they appear amorphous by light microscopy, they form a highly organized structure, comprising mainly of GAG, proteoglycans, growth factors and structural proteins such as collagens. Yet, the predominant component of the skin ECM is HA.

Recent reviews have described the involvement of HA with respect to its role in angiogenesis,⁷ reactive oxygen species,⁸ chondrocytes,⁹ cancer,^{10,11} lung injury,^{12,13} immune regulation^{14,15} and skin.¹⁶ This review presents in brief recent knowledge in HA biology and function and focuses on its involvement in skin aging.

Hyaluronic Acid

Chemistry and physicochemical properties. HA is a non-sulfated GAG and is composed of repeating polymeric disaccharides of D-glucuronic acid and N-acetyl-D-glucosamine linked by a glucuronic β (1 \rightarrow 3) bond.^{17,18} In aqueous solutions HA forms specific stable tertiary structures.¹⁹ Despite the simplicity in its composition, without variations in its sugar composition or without branching points, HA has a variety of physicochemical properties. HA polymers occur in a vast number of configurations

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and shapes, depending on their size, salt concentration, pH, and associated cations.²⁰ Unlike other GAG, HA is not covalently attached to a protein core, but it may form aggregates with proteoglycans.²¹ HA encompasses a large volume of water giving solutions high viscosity, even at low concentrations.¹³

Tissue and cell distribution of HA. HA is widely distributed, from prokaryotic,^{22,23} to eukaryotic cells.²⁴ In humans, HA is most abundant in the skin,²⁵⁻²⁹ accounting for 50% of the total body HA,³⁰ the vitreous of the eye,³¹ the umbilical cord,¹⁷ and synovial fluid,^{32,33} but it is also present in all tissues and fluids of the body, such as skeletal tissues,²⁷ heart valves,³⁴ the lung,³⁵⁻³⁹ the aorta,⁴⁰ the prostate,⁴¹ tunica albuginea, corpora cavernosa and corpus spongiosum of the penis.⁴² HA is produced primarily by mesenchymal cells but also by other cell types.^{34-38,43}

Biological function of HA. Over the past two decades there was considerable evidence presented that unraveled the functional role of HA in molecular mechanisms and indicated the potential role of HA for the development of novel therapeutic strategies for many diseases.

Functions of HA include the following: hydration, lubrication of joints, a space filling capacity, and the framework through which cells migrate.³⁴ The synthesis of HA increases during tissue injury and wound healing^{25,44,45} and HA regulates several aspects of tissue repair, including activation of inflammatory cells to enhance immune response⁴⁶⁻⁴⁸ and the response to injury of fibroblasts^{49,50} and epithelial cells.⁵¹⁻⁵⁵ HA also provides the framework for blood vessel formation^{7,45} and fibroblast migration,^{56,57} that may be involved in tumor progression.⁵⁸ The correlation of HA levels on the cell surface of cancer cells with the aggressiveness of tumors has also been reported.⁵⁹

The size of HA appears to be of critical importance for its various functions described above. HA of high molecular size, usually in excess of 1,000 kDa, is present in intact tissues and is antiangiogenic and immunosuppressive, whereas smaller polymers of HA are distress signals and potent inducers of inflammation and angiogenesis.^{38,46,60-63}

Biosynthesis of HA

HA is synthesized by specific enzymes called HA synthases (HAS). These are membrane bound enzymes that synthesize HA on the inner surface of the plasma membrane⁶⁴ and then HA is extruded through pore-like structures into the extracellular space.^{24,65} There are three mammalian enzymes HAS -1, -2 and -3, which exhibit distinct enzymatic properties and synthesize HA chains of various length.⁶⁶⁻⁶⁸

Degradation of HA

HA has a dynamic turnover rate. HA has a half-life of 3 to 5 min in the blood, less than a day in the skin and 1 to 3 weeks in the cartilage.⁶⁹⁻⁷¹ HA is degraded into fragments of varying size by hyaluronidases (HYAL) by hydrolyzing the hexosaminidic β (1-4) linkages between N-acetyl-D-glucosamine and D-glucuronic acid residues in HA. In humans, six HYAL have been identified so far: HYAL-1, -2, -3, -4, PH-20 and HYALP1.⁷² The family of HYAL

enzymes received little attention until recently^{73,74} because they are found at extremely low concentrations and they are difficult to purify, characterize and measure their activity, which is high but unstable.¹⁶ New procedures have now enabled the isolation and characterization of HYAL.^{75,76} HYAL-1 is the major HYAL in serum.⁷⁷ Mutations in the HYAL-1 gene are associated with HYAL deficiency and mucopolysaccharidosis type IX.⁷⁸ HYAL-2 has very low activity in comparison to plasma HYAL-1 and it hydrolyzes specifically HA of high molecular weight, yielding HA fragments of approximately 20 kDa, which are further degraded to small oligosaccharides by PH-20.⁷⁹ HYAL-3 is mainly expressed in bone marrow and testis,⁷⁴ but also in other organs, such as the human lung.^{37,38} The role of HYAL-3 in the catabolism of HA is not clear and it is suggested that it may contribute to HA degradation by enhancing the activity of HYAL-1.⁸⁰

HA can also be degraded non-enzymatically by a free-radical mechanism⁸¹ in the presence of reducing agents such as ascorbic acid, thiols, ferrous, or cuprous ions, a process that requires the presence of molecular oxygen. Thus, agents that could delay the free-radical-catalyzed degradation of HA may be useful in maintaining the integrity of dermal HA and its moisturizing properties.¹⁶

Hyaluronic Acid Receptors

There is a variety of proteins that bind HA, called hyaladherins, which are widely distributed in the ECM, the cell surface, the cytoplasm and the nucleus.¹⁵ Those that attach HA to the cell surface constitute HA receptors. The most prominent among these receptors is the transmembrane glycoprotein "cluster of differentiation 44" (CD44) that occurs in many isoforms, which are the products of a single gene with variable exon expression.⁸²⁻⁸⁴ CD44 is found on virtually all cells, except red blood cells, and regulates cell adhesion, migration, lymphocyte activation and homing, and cancer metastasis.

The receptor for HA-mediated motility (RHAMM) is another major receptor for HA, and it is expressed in various isoforms.⁸⁵⁻⁸⁷ RHAMM is a functional receptor in many cell types, including endothelial cells⁸⁸ and in smooth muscle cells from human pulmonary arteries³⁷ and airways.³⁸ The interactions of HA with RHAMM control cell growth and migration by a complex network of signal transduction events and interactions with the cytoskeleton.⁸⁹ Transforming growth factor (TGF)- β 1, which is a potent stimulator of cell motility, elicits the synthesis and expression of RHAMM and HA, and thus initiates locomotion.⁹⁰

Hyaluronic Acid in Skin

The use of biotinylated HA-binding peptide⁹¹ revealed that not only cells of mesenchymal origin were capable of synthesizing HA and permitted the histolocalization of HA in the dermal compartment of skin and the epidermis.^{26,92-94} This technique enabled the visualization of HA in the epidermis, mainly in the ECM of the upper spinous and granular layers, whereas in the basal layer HA is predominantly intracellular.²⁶

The function of the skin as a barrier is partly attributed to the lamellar bodies, thought to be modified lysosomes containing hydrolytic enzymes. They fuse with the plasma membranes of mature keratinocytes and they have the ability to acidify via proton pumps and partially convert their polar lipids into neutral lipids. Diffusion of aqueous material through the epidermis is blocked by these lipids synthesized by keratinocytes in the stratum granulosum. This boundary effect corresponds to the level of HA staining. The HA-rich area inferior to this layer may obtain water from the moisture-rich dermis, and the water contained therein cannot penetrate beyond the lipid-rich stratum granulosum. The hydration of the skin critically depends on the HA-bound water in the dermis and in the vital area of the epidermis, while maintenance of hydration essentially depends on the stratum granulosum. Extensive loss of the stratum granulosum in patients with burns may cause serious clinical problems due to dehydration.¹⁶

As mentioned above, skin HA accounts for most of 50% of total body HA.³⁰ The HA content of the dermis is significantly higher than that of the epidermis, while papillary dermis has much greater levels of HA than reticular dermis.⁹² The HA of the dermis is in continuity with the lymphatic and vascular systems. HA in the dermis regulates water balance, osmotic pressure and ion flow and functions as a sieve, excluding certain molecules, enhancing the extracellular domain of cell surfaces and stabilizes skin structures by electrostatic interactions.¹⁶ Elevated levels of HA are synthesized during scar-free fetal tissue repair and the prolonged presence of HA assures such scar-free tissue repair.⁹⁵⁻⁹⁷ Dermal fibroblasts provide the synthetic machinery for dermal HA and should be the target for pharmacologic attempts to enhance skin hydration. Unfortunately, exogenous HA is cleared from the dermis and is rapidly degraded.⁷⁰

Hyaluronic acid synthases in the skin. In the skin, gene expression of HAS-1 and HAS-2 in the dermis and epidermis is differentially upregulated by TGF- β 1, indicating that HAS isoforms are independently regulated and that the function of HA is different in the dermis and the epidermis.^{16,98} The mRNA expression of HAS-2 and HAS-3 can be stimulated by keratinocyte growth factor, which activates keratinocyte migration and stimulates wound healing, leading to the accumulation of intermediate-sized HA in the culture medium and within keratinocytes. The migratory response of keratinocytes in wound healing is stimulated by increased synthesis of HA.⁹⁹ HAS-2 mRNA is also induced by IL-1 β and TNF α in fibroblasts¹⁰⁰ and by epidermal growth factor in rat epidermal keratinocytes.¹⁰¹

Dysregulated expression of HA synthases has been reported during tissue injury.¹⁰²⁻¹⁰⁴ HAS-2 and HAS-3 mRNA are significantly increased after skin injury in mice, leading to increased epidermal HA.¹⁰⁴ In juvenile hyaline fibromatosis, which is a rare autosomal recessive disease characterized by deposition of hyaline material and multiple skin lesions, there is a significant decreased expression of HAS-1 and HAS-3, accounting for the reduced synthesis of HA in skin lesions.¹⁰⁵ In dermal fibroblasts, where the HAS-2 is the predominant isoform, glucocorticoids inhibit HAS mRNA almost completely, suggesting a molecular basis of the decreased HA in atrophic skin as a result of local treatment with glucocorticoids.¹⁶

Hyaluronidases in the skin. In the skin, it has not been established which of the various HYAL controls the turnover of HA in the dermis and the epidermis. The elucidation of the biology of HYAL in the skin may offer novel pharmacological targets to confront age related turnover of HA in skin.

HA receptors in the skin. In the dermis and epidermis HA is co-localized with CD44. However, the exact CD44 variants in the different skin compartments have not yet been elucidated. CD44-HA interactions have been reported to mediate the binding of Langerhans cells to HA in the matrix surrounding keratinocytes by their CD44-rich surfaces, as they migrate through the epidermis.^{106,107} RHAMM is also expressed in the human skin.^{28,29} The TGF- β 1 induced stimulation of fibroblast locomotion is mediated via RHAMM,⁹⁰ while overexpression of RHAMM can lead to the transformation of fibroblasts.¹⁰⁸

Hyaluronic Acid and Skin Aging

The most dramatic histochemical change observed in senescent skin is the marked disappearance of epidermal HA, while HA is still present in the dermis.⁹² The reasons for this change in HA homeostasis with aging is unknown. As mentioned above, the synthesis of epidermal HA is influenced by the underlying dermis and is under separate controls from the synthesis of dermal HA.^{16,98} Progressive reduction of the size of the HA polymers in skin as a result of aging has also been reported.¹⁰⁹ Thus, the epidermis loses the principle molecule responsible for binding and retaining water molecules, resulting in loss of skin moisture. In the dermis, the major age-related change is the increasing avidity of HA with tissue structures with the concomitant loss of HA extractability. This parallels the progressive cross-linking of collagen and the steady loss of collagen extractability with age.¹⁶ All of the above age related phenomena contribute to the apparent dehydration, atrophy and loss of elasticity that characterizes aged skin.

Premature aging of skin is the result of repeated and extended exposure to UV radiation.^{110,111} Approximately 80% of facial skin aging is attributed to UV-exposure.¹¹² UV radiation damage causes initially a mild form of wound healing and is associated at first with an increase of dermal HA. As little as 5 min of UV exposure in nude mice caused enhanced deposition of HA, indicating that UV radiation induced skin damage is an extremely rapid event.¹⁶ The initial redness of the skin following exposure to UV radiation may be due to a mild edematous reaction induced by the enhanced HA deposition and histamine release. Repeated and extensive exposures to UV ultimately simulate a typical wound healing response with deposition of scarlike type I collagen, rather than the usual types I and III collagen mixture that gives skin resilience and pliability.¹⁶

In the skin, photoaging results in abnormal GAG content and distribution compared with that found in scars, or in the wound healing response, with diminished HA and increased levels of chondroitin sulfate proteoglycans.¹¹¹ In dermal fibroblasts this reduction in HA synthesis was attributed to collagen fragments, which activate $\alpha\beta_3$ -integrins and in turn inhibit Rho kinase signaling and nuclear translocation of phosphoERK, resulting in

reduced HAS-2 expression.¹¹³ We have recently unraveled some of the biochemical changes that may distinguish photoaging and natural aging. Using photoexposed and photoprotected human skin tissue specimens, obtained from the same patient, we have shown a significant increase in the expression of HA of lower molecular mass in photoexposed skin, as compared with photoprotected skin. This increase of degraded HA was associated with a significant decrease in the expression of HAS-1 and an increased expression of HYAL-1, -2 and -3. Furthermore, the expression of HA receptors CD44 and RHAMM was significantly downregulated in photoexposed, as compared with photoprotected skin. These findings indicate that photoexposed skin, and therefore extrinsic skin aging, is characterized by distinct homeostasis of HA.²⁹ We have also assessed photoprotected skin tissue specimens from adults and juvenile patients and observed that intrinsic skin aging was associated with a significant reduction in the content of HA and downregulation of HAS-1,

HAS -2, CD44 and RHAMM.²⁸ Similar results for photoprotected skin have also been reported for both genders for HA, HAS-2 and CD44.¹¹⁴

Conclusion

The available data suggest that HA homeostasis exhibits a distinct profile in intrinsic skin aging, which is totally different of that in extrinsic skin aging. Additional insight needs to be gained in understanding the metabolism of HA in skin layers and the interactions of HA with other skin components. Such information will facilitate the ability to modulate skin moisture in a rational manner and may contribute to the refinement of current drugs and the development of novel treatments for skin aging.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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