CLINICAL INSIGHTS
SPONSORED BY SKINMEDICA 2016, No. 3

The 21st Century Approach To Epidermal Health and Hydration: Endogenous Hyaluronic Acid

By Virginia L. Vega, PhD
and Mitchel P. Goldman, MD

Virginia L. Vega, is an employee of SkinMedica®, an Allergan Company.

Mitchel P. Goldman, MD is a consultant to SkinMedica®, an Allergan Company.

HYALURONIC ACID: HOW SUCH A SIMPLE MOLECULE GOT SO COMPLICATED

Hyaluronic acid (HA), probably the most recognized ingredient in the skincare industry, has undergone a remarkable scientific evolution since it was first isolated in 1934.[1] Despite its widespread use as a topical skincare ingredient and injectable dermal filler, relatively little is known about the cellular pathways that control HA in normal and diseased skin. This non-sulfated glycosaminoglycan (GAG) is formed by repeating units (up to 30,000) of D-glucuronic acid and N-acetyl-d-glucosamine, producing molecules ranging from $1x10^5$-10^7 Da in size (2-25μm length) (Figure 1A). The main roles assigned to HA to date have been as a space filler and water-binder although its high turnover rate (half-life two to three hours in epidermis and less than one day in dermis) suggest additional roles in skin biology. Moreover, the effects of retinoic acid, which triggers epidermal HA accumulation, and hydrocortisone, which decreases epidermal HA, support the hypothesis of a regulatory effect of HA on epidermal homeostasis. Epidermal proliferation (hyperplasia/atrophy) and terminal differentiation (stratum corneum thinning /thickening) are strongly correlated with HA-levels.[2,3,4] Recent scientific discoveries have challenged the outdated view of HA as a simple space filler, elevating it to a role as a key active regulator of dynamic processes such as keratinocytes proliferation and differentiation, barrier formation, inflammation, oxidative stress, skin hydration, cell survival and wound healing.

Physiological levels of HA in the dermis and epidermis (0.5 and 0.1 mg/kg, respectively) are controlled by four key processes:

- Synthesis,
- Deposition,
- Binding to hyaladherins (see below), and
- Degradation (Figure 1 B).[5]

Synthesis of HA occurs on the cell surface by a family of membrane-bound enzymes called hyaluronic acid synthases

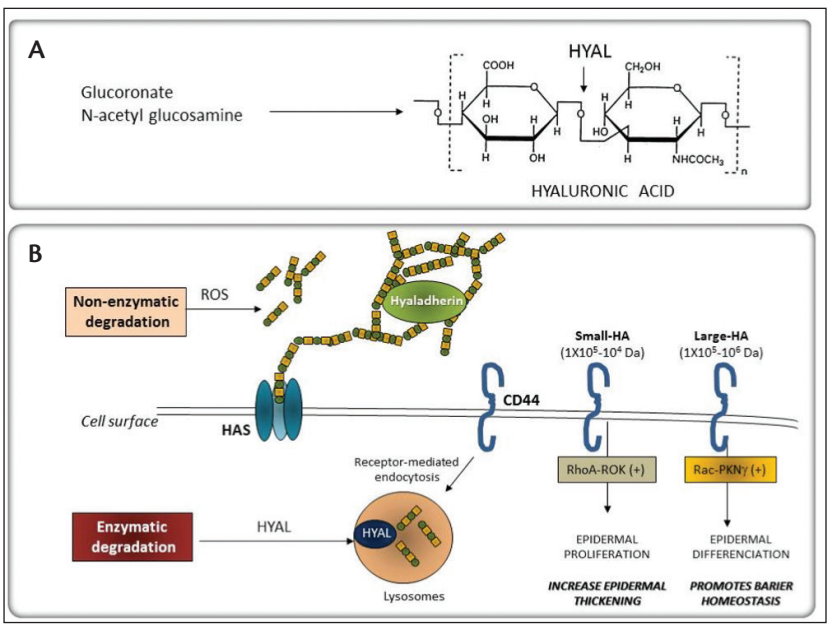

Figure 1: (A) HA structure. Site of action of HYAL is indicated by the arrow. (B) HA synthesis, degradation and signaling. Binding of HA to CD44, may trigger its lysosomal degradation or activation of different signals.

"Changes in HA distribution, organization, metabolism and molecular size have been implicated in several skin diseases such as psoriasis, atopic dermatitis and the epidermal hyper-proliferative response linked to injury. However, it is not clear whether these HA-associated changes are the result of tissue remodeling, inflammation or part of the disease pathology."

(HAS),[6,7] while HA is degraded enzymatically into fragments of varying size by hyaluronidases (HYALs). HA can also be degraded non-enzymatically by free radicals in the presence of reducing agents such as ascorbic acid, thiols, ferrous and cuprous ions. HA association with hyaladherins, which are proteins that bind HA, occurs under normal conditions to increase its stability and prevent its degradation. Hyaladherins are widely distributed in the ECM compartment, cell surface, cytoplasm and nuclei. Cell surface hyaladherins constitute HA-receptors, most prominent among these being CD44, a transmembrane glycoprotein that is ubiquitously distributed on all cells (except red blood cells). RHAMM and ICAM-1 are among other HA-receptors whose biological activity are described in more details by Day and Prestwich.[8]

HA binding to a specific receptor activates unique signaling pathways modifying cellular behavior, process that is controlled at least in part, by HA diverse range of molecular sizes present normally in skin (Figure 2), adding a new level of complexity to the already complex role of HA in skin metabolism. In general, small-molecular-weight HA (SMW-HA) modulates cell proliferation, angiogenesis, migration, maturation, sebum and inflammation. Recently, it had been shown that SMW-HA may modulate the pathogenicity of certain bacteria providing a new line of skin defense.[9] Large-molecular-weight HA (LMW-HA) has a film-forming capacity and regulates differentiation, hydration and oxidative stress.[10,11,12]

The dynamic role of HA is clearly observed during wound healing in which HA stimulates inflammation and cell infiltration during the early inflammatory phase and promotes cell proliferation and migration during the granular phase. Interestingly, prolonged elevated levels of HA during wound healing contribute to minimized scarring. This observation is supported by lack of scar formation in fetal tissues, in which the wound healing process is characterized by elevated levels of HA (due to decreased expression of HYAL and over-expression of HAS).[13] Similarly, diminished levels of HA in keloid tissues is linked to the excessive fibrosis characteristic of these lesions.[14] Finally, changes in HA distribution, organization, metabolism and molecular size have been implicated in several skin diseases, such as psoriasis, atopic dermatitis and the epidermal hyper-proliferative response linked to injury.[15,16] However, it is not clear whether these HA-associated changes are the result of tissue remodeling, inflammation or part of the disease pathology.

SKIN AGING AND DEHYDRATION

Although the process of skin aging is not well understood, one of its hallmarks is the reduction in epidermal function. HA is one of the major components of the ECM in the epidermis. Youthful-healthy skin retains its turgor, resilience and pliability due to a large water trapping capacity which is powered by

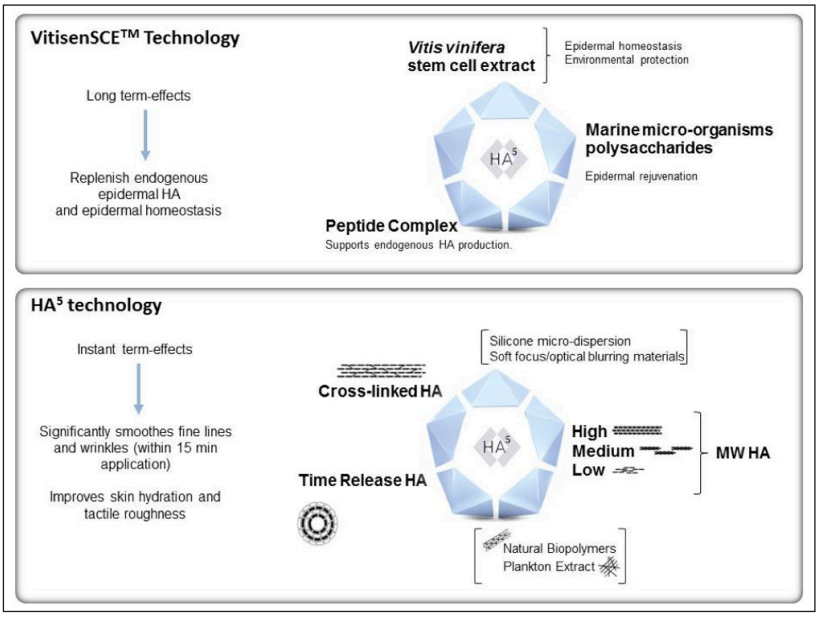

Figure 2: Two key technologies present in HA^5 Rejuvenating Hydrator from SkinMedica®. Improvements in skin hydration (measured by cutometer) were observed immediately after product application (with product present on the skin during measurement) as well as after eight weeks of usage (without product on the skin during measurement), suggesting a retraining of the skin for water trapping.

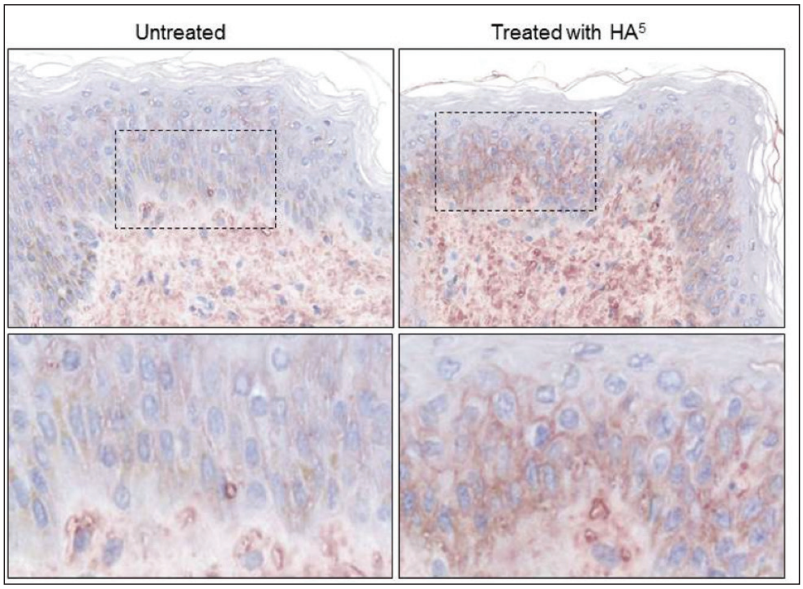

Figure 3: Induction of HA in human skin explant by HA5 Rejuvenating Hydrator treatment. Endogenous HA was detected histologically using HA-binding protein assay. Treatment with HA5 (five days) resulted in an induction of endogenous HA (pink color) in a pattern that is similar to the one observed in youthful epidermis.

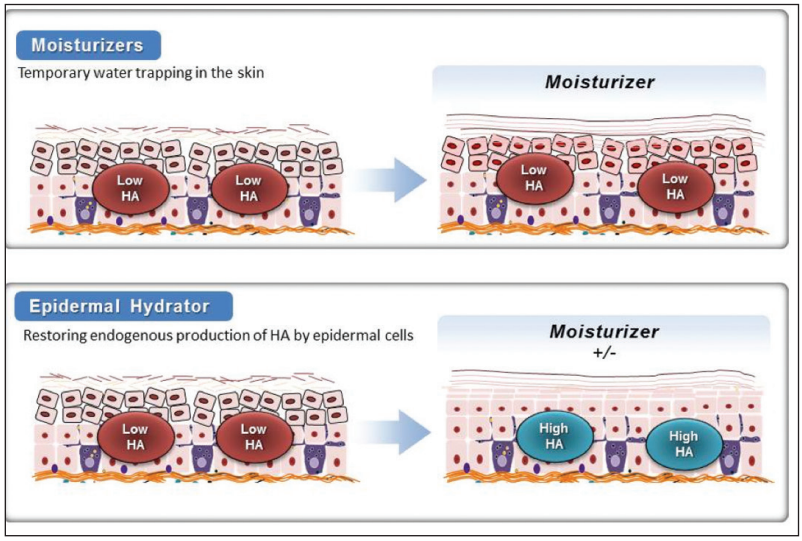

Figure 4: Moisturizers vs. a novel approach: epidermal hydrator. Environmental conditions aggravate skin dehydration (changes in humidity and temperature). Optimal air humidity (40-60 percent) facilitates the maintenance of a 10-30 percent of water contain in the stratum corneum.

endogenous HA. HA's water trapping capacity is linked to its unique coil structure in aqueous solution that allows binding of about 1,000-fold of its own weight in water.[17]

As we age, a decrease in HA synthesis and increase in degradation significantly diminish the net deposit of cutaneous HA. The "perfect storm" created by the combination of lower synthesis, higher degradation and the intrinsic short half-life of HA may start as early as in the 20s triggering the loss of half of endogenous HA by the ages of 40-50s. This decrease in cutaneous HA levels affects both dermis and epidermis. Injections of chemically (cross-linked) modified HA has been used successfully to restore dermal HA-levels, however, restoration of epidermal-HA is a critical unmet need, as topically applied HA does not penetrate into the epidermis and if a small fraction does penetrate, it is rapidly degraded.

SkinMedica's approach to the epidermal HA dilemma led to the creation of two key technologies that target instant and long-term hydration as well as restoration of epidermal health (Figure 2). Both, VitisenSCE™ and HA5 technologies were designed to improve skin hydration. VitisenSCE™ technology is powered by the *Vitis vinifera* flower stem cell extract in combination with marine micro-organism polysaccharides and peptides complex that restore epidermal homeostasis and endogenous levels of epidermal HA (Figure 3).[18] HA5 technology is responsible for delivering instant hydration through the combination of five different forms of HA (Figure 2), natural biopolymers and plankton extract. The rationale behind this mix is to provide an instant hydration that can be sustained throughout the day (up to eight hours).

MOISTURIZATION VS. HYDRATION

A perceived benefit associated with youthful skin is the feeling of being well-hydrated. Dry and flaky skin does not automatically mean dehydrated skin as other symptoms must be present for this condition to be established, such as oiliness, severe sensitivity/redness and itchiness. Environmental factors such as decreased humidity levels below 30 percent (cold weather, dessert conditions, plane travel) tend to aggravate skin dehydration. Dehydrated skin is more prone to inflammation, aggravating other skin conditions. One commonly used approach in the cosmetic industry is to improve water-retention or to decelerate water-loss using moisturizers (Figure 4). The "anti-thirst" effect of moisturizers happens by preventing evaporation (occlusion using ingredients such as cocoa butter, lanolin, shea butter and mineral oil), leading to temporarily trapping

"The 'perfect storm' created by the combination of lower synthesis, higher degradation and the intrinsic short half-life of HA may start as early as in the 20s triggering the loss of half of endogenous HA by the ages of 40-50s...Injections of chemically (cross-linked) modified HA has been used successfully to restore dermal HA-levels, however, restoration of epidermal-HA is a critical unmet need as topically applied HA does not penetrate into the epidermis and if a small fraction does penetrate, it is rapidly degraded."

of water on the skin. These ingredients only provide a transient solution to the problem.

Another commonly used approach to try to normalize superficial cutaneous water is the use of products containing high molecular weight HA, which acts differently than occlusive and other low molecular weight humectants (glycols and glycerin) that have better penetration. Topically applied LMW-HA provides a sealing effect over dehydrated/compromised skin resulting in large water trapping capacity that provides better short-term barrier replacement than the one observed by occlusive or humectant moisturizing ingredients alone.

Topical HA also provides other benefits, such as binding of key active molecules on the skin surface promoting their stability and functionality. Unfortunately, despite the benefits associated with topically applied HA, years of product commercialization has proven that it is not the "holy grail" of skin hydration, as many of its theoretical benefits disappear quickly with the rapid degradation on the skin surface. A new approach to resolve the long-term saga of skin hydration would be the development of "epidermal hydrators," which are products that increase HA deposition in the epidermis by stimulating endogenous HA synthesis and preventing its degradation, thereby improving the skin's natural ability to rejuvenate itself. Normalization of epidermal HA would not only represent a natural solution to skin dehydration but also would normalize many other functions that are controlled by this unique GAG, providing a more comprehensive approach for epidermal rejuvenation. ■

Virginia L. Vega, PhD is the Director of SkinMedica® Skin Biology Laboratory. A biochemist by training, Dr. Vega obtained a doctorate in Cellular and Molecular Biology and immediately pursued her post-doctoral training in the fields of inflammation, stress response, and aging at Johns Hopkins School of Medicine. Before joining SkinMedica®, Dr. Vega held an Assistant Professor's position at the School of Medicine at the University of California, San Diego.

Mitchel P. Goldman, MD is Medical Director of Cosmetic Laser Dermatology. A graduate of Boston University and the Stanford University Medical School, Dr. Goldman is a Volunteer Clinical Professor in Dermatology at the University of California, San Diego. Dr. Goldman is Board Certified by both the American Academy of Dermatology and the American Society of Cosmetic Surgery. He is Past-President, of the American Society for Dermatologic Surgery and the American College of Phlebology. Dr. Goldman is a co-founder of SkinMedica®.

1. Meyer K, Palmer JW. J Biol Chem. 1934;107:629–634.

2. Sakai S, Yasuda R, Sayo T, Ishikawa O, Inoue S. Hyaluronan exists in the normal stratum corneum. J Invest Dermatol. 2000 Jun;114(6):1184-7.

3. Tammi R, Ripellino JA, Margolis RU, Tammi M. Localization of epidermal hyaluronic acid using the hyaluronate binding region of cartilage proteoglycan as a specific probe. J Invest Dermatol. 1988 Mar;90(3):412-4.

4. Agren UM, Tammi M, Tammi R. Hydrocortisone regulation of hyaluronan metabolism in human skin organ culture. J Cell Physiol. 1995 Aug;164(2):240-8.

5. Papakonstantinou E, Roth M, Karakiulakis G. Hyaluronic acid: A key molecule in skin aging. Dermatoendocrinol. 2012 Jul 1;4(3):253-8.

6. Weigel PH, Hascall VC, Tammi M. Hyaluronan synthases. J Biol Chem. 1997 May 30;272(22):13997-4000.

7. Itano N, Sawai T, Yoshida M, Lenas P, Yamada Y, Imagawa M, Shinomura T, Hamaguchi M, Yoshida Y, Ohnuki Y, Miyauchi S, Spicer AP, McDonald JA, Kimata K. Three isoforms of mammalian hyaluronan synthases have distinct enzymatic properties. J Biol Chem. 1999 Aug 27;274(35):25085-92.

8. Day AJ, Prestwich GD. Hyaluronan-binding proteins: tying up the giant. J Biol Chem. 2002 Feb 15;277(7):4585-8.

9. chommer NN, Muto J, Nizet V, Gallo RL. Hyaluronan breakdown contributes to immune defense against group A Streptococcus. J Biol Chem. 2014 Sep 26;289(39):26914-21.10. Lesley J et al J Biol Chem. 2000 275(35):26967-75.

11. Slevin M, Kumar S, Gaffney J. Angiogenic oligosaccharides of hyaluronan induce multiple signaling pathways affecting vascular endothelial cell mitogenic and wound healing responses. J Biol Chem. 2002 Oct 25;277(43):41046-59.

12. Fieber C, Baumann P, Vallon R, Termeer C, Simon JC, Hofmann M, Angel P, Herrlich P, Sleeman JP. Hyaluronan-oligosaccharide-induced transcription of metalloproteases. J Cell Sci. 2004 Jan 15;117(Pt 2):359-67.

13. Bullard KM, Longaker MT, Lorenz HP. Fetal wound healing: current biology. World J Surg. 2003 Jan;27(1):54-61.14. Meyer LJ et al J Invest Dermatol. 2000 114(5):953-9.

15. TTammi R, Paukkonen K, Wang C, Horsmanheimo M, Tammi M. Hyaluronan and CD44 in psoriatic skin. Intense staining for hyaluronan on dermal capillary loops and reduced expression of CD44 and hyaluronan in keratinocyte-leukocyte interfaces. Arch Dermatol Res. 1994;286(1):21-9.

16. Wells AF, Lundin A, Michaëlsson G. Histochemical localization of hyaluronan in psoriasis, allergic contact dermatitis and normal skin. Acta Derm Venereol. 1991;71(3):232-8.

17. Cowman MK, Matsuoka S. Experimental approaches to hyaluronan structure. Carbohydr Res. 2005 Apr 11;340(5):791-809.

18. Narurkar VA, Fabi SG, Bucay VW, Tedaldi R, Downie JB, Zeichner JA, Butterwick K, Taub A, Kadoya K, Makino ET, Mehta RC, Vega VL. Rejuvenating Hydrator: Restoring Epidermal Hyaluronic Acid Homeostasis With Instant Benefits. J Drugs Dermatol. 2016 Jan 1;15(1):s24-37.