 ORIGINAL ARTICLE

Extracellular Matrix Modulation: Optimizing Skin Care and Rejuvenation Procedures

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ABSTRACT

Normal aging and photoaging of the skin are chronic processes that progress gradually. The extracellular matrix (ECM), constituting over 70% of the skin, is the central hub for repair and regeneration of the skin. As such, the ECM is the area where changes related to photodamage are most evident. Degradation of the ECM with fragmentation of proteins significantly affects cross talk and signaling between cells, the matrix, and its constituents. The accumulation of collagen fragments, amorphous elastin agglutinations, and abnormal cross-linkages between the collagen fragments impedes the ECM from its normal repair and regenerative capacity, which manifests as wrinkled, non-elastic skin. Similar to how the chronic wound healing process requires wound bed preparation before therapeutic intervention, treatment of chronic aging of the skin would likely benefit from a "skin bed preparation" to optimize the outcome of rejuvenation procedures and skin maintenance programs. This involves introducing agents that can combat stress-induced oxidation, proteasome dysfunction, and non-enzymatic cross linkages involved in glycation end products, to collectively modulate this damaged ECM, and upregulate neocollagenesis and elastin production. Agents of particular interest are matrikines, peptides originating from the fragmentation of matrix proteins that exhibit a wide range of biological activities. Peptides of this type (tripeptide and hexapeptide) are incorporated in ALASTIN™ Skin Nectar with TriHex™ technology (ALASTIN Skincare, Inc., Carlsbad, CA), which is designed to target ECM modulation with a goal of optimizing results following invasive and non-invasive dermal rejuvenating procedures.

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INTRODUCTION

The extracellular matrix (ECM) is the largest component of the dermal skin layer and its synthesis and function is essential to wound healing and dermal regeneration. "The major structural components of the dermal ECM are collagen I and III, accounting for over 70% and 15%, respectively, of skin dry weight, providing the dermis with tensile strength and stability."[1] In addition, elastin fibers provide the elasticity and tonality to the skin that allows adaptation to intrinsic physiologic and extrinsic environmental stresses. The ECM creates an environment that encourages cross talk and signaling between cells and proteins that modulate function and cell biology.[2] These extra- or intracellular proteins are subject to degradation and modification. Metalloproteinases (MMPs) are the most significant enzymes in the ECM remodeling process but other significant matrix clearing mechanisms exist.

Extrinsic and Intrinsic Aging

"In areas exposed to ultraviolet light, acute or 'extrinsic' aging processes are superimposed on underlying chronic or 'intrinsic' aging mechanisms" with direct cosmetic and structural consequences for the aging skin.[3] Fragmentation of the elastic and collagenous protein components of the ECM transform the smoother, fine-lined appearance of intrinsically aged skin to the roughened, deeply wrinkled appearance of moderately photoaged skin, characterized histologically by the loss of elastin fibrillin microfibrils and fibulin from the papillary dermis together with collagen fragmentation and ECM disruption.[3] "In severely photoaged skin, abundant deposits of highly disorganized elastic fiber material are distributed throughout the dermis."[3]

One of the main mechanisms responsible for intrinsic and extrinsic aging of the cells is the accumulation of damaged

proteins in the cells and ECM. These proteins are modified by various post-translational mechanisms common with age such as oxidation, glycation, and conjugation with products from lipid peroxidation. In young healthy skin, the proteolytic systems can effectively prevent the accumulation of damaged proteins both intracellularly and within the ECM.

Cross linkages between collagen and elastin provide essential stabilization to these important proteins when organized enzymatically, while non-enzymatic spontaneous cross linkages can prove extremely detrimental to function and form of these proteins. The collagen matrix is very susceptible to modifications that occur with aging due to the nature of the normal slow process of collagen turnover and low levels of MMPs, which slow collagen turnover and remodelling. These cross-linkages prevent the complete removal of collagen fragments, disrupting repair or incorporation into newly made collagen fibrils. The result is the formation of voids in the three dimensional collagen matrix and continuation of the ECM disruption.[4]

Oxidative Stress

Oxygen free radicals, the chemically reactive forms of molecular oxygen (reactive oxygen species-ROS), have long been considered the primary cause of skin aging. The theory is that ROS, generated during aerobic energy metabolism within mitochondria, oxidize cellular constituents and impair cellular function.[4] Previous reports have established the link between ECM collagen fragmentation and oxidative stress.[5] In support of this concept, it has been demonstrated that when fibroblasts are removed from this fragmented collagen ECM milieu, they significantly improve their capacity to produce new collagen.[4] This provides a foundation for therapeutic intervention. One of the consequences of fragmented collagen is a decrease of focal adhesion points between the fibroblast and the collagen fiber. This results in less stretch on the fibroblast and change in form and function of the fibroblast from a spindle shaped active fibroblast to a rounded shaped senescent fibroblast that produces less collagen and elastin.[5] The "loss of cell shape and mechanical tension is closely associated with increased transcription factor AP-1," which stimulates MMP production and decreases type 1 collagen expression.[6]

Neutrophil elastase, secreted by stress induced neutrophils, has also been implicated in elastin degradation and photodamage.[7] Exposure of human skin to a certain threshold of UV radiation and heat leads to an influx of proteolytic enzyme packed neutrophils. In fact, some authors have hypothesized that neutrophils are major contributors to the photoaging process, which they claim is primarily represented by elastic fiber degeneration.[7] The most obvious changes seen histologically in photodamaged skin relate to elastosis and elastic fiber network rather than that related to collagen. Unlike collagen degradation, sun damage does not lead to a loss of elastic fibers but rather a loss of functional elastin primarily related to microfibrillar destruction.[3,8] In humans, neutrophil-derived proteolytic enzymes are responsible for the ECM damage observed in lung emphysema, rheumatoid arthritis, and wound infection. Similarly neutrophilderived proteolytic enzymes may be contributors to the ECM damage seen in photoaged skin.[7]

Fisher et al. have proposed that the combination of collagen fragmentation, oxidative stress, and MMP-1 up-regulation forms a self-perpetuating cycle representing human skin aging. This extends the oxidative theory of aging beyond the focus on cellular aging to include changes to the ECM.[5]

Reduced Proteasome Function

Aside from ECM degradation related to oxidative stress and neutrophil infiltration, aging, and photodamage can result in the accumulation of unfolded, misfolded, or aggregated proteins from the process of reduced proteasome function.[9] The ubiquitin protease system (UPS) plays a fundamental role in a large number of biological processes predominantly involving the removal of intracellular protein degradation products. Any reduction in the function of the UPS pathway can result in intra- and extracellular accumulation of damaged proteins.[9] Efficient removal of these protein fragments has significant impact on cellular mechanisms such as DNA repair, gene expression, neosynthesis of protein, and immune response modulation.[10]

> "One of the main mechanisms responsible for intrinsic and extrinsic aging of the cells is the accumulation of damaged proteins in the cells and extracellular matrix."

Advanced Glycation End Products

Some modified proteins, specifically advanced glycation end products (AGEs) that accumulate on collagen and elastin in the skin, are the result of reactive sugars in the blood and lymph binding to the proteins in extensive cross linkages, especially during the process of aging and after UV irradiation.[1] Glycation does not occur to a major effect in the dermis before age 35 but once it begins, along with intrinsic aging, it progresses rapidly.[11] Proteins are not the only targets, lipids such as phosphatidylethanolamine and phosphatidylserine offer the amino groups required for initial linking of a sugar.[11]

Thus, skin aging and photodamage contribute to a series of biological processes that result in ECM and cellular degradation with an accumulation of abnormal proteins, amorphous elastotic material, and a non-compliant stiffened

TABLE 1.

Key Upregulated Genes Related to ECM Remodeling -Tripeptide (Alastin)			
Linear Fold Change of Tripeptide Treated Group vs Vehicle Control Group			
Gene	Gene Name	Linear Fold Change (P<0.05)	Biological Function
MMP2	matrix metallopeptidase 2	6 X	ECM clearance
MMP3	matrix metallopeptidase 3	3 X	ECM clearance
MMP9	matrix metallopeptidase 9	2 X	ECM clearance
TIMP1	TIMP metallopeptidase inhibitor 1	9 X	ECM Integrity /MMP balance
TIMP2	TIMP metallopeptidase inhibitor 2	3 X	ECM Integrity/MMP balance
COL1A1	collagen, type I, alpha 1	2 X	ECM renewal
COL4A1	collagen, type IV, alpha 1	5 X	ECM renewal
COL4A2	collagen, type IV, alpha 2	3 X	ECM renewal
COL7A1	collagen, type VII, alpha 1	8 X	ECM renewal
DCN	decorin	7 X	ECM renewal
DPT	dermatopontin	25 X	ECM renewal
ELN	elastin	2 X	ECM renewal
FBN1	fibrillin 1	2 X	ECM renewal
LOX	lysyl oxidase	2 X	ECM (enzymatic cross links)

matrix (Figure 1). During this process, the fragmentation of collagen and elastin, which would normally stimulate neocollagenesis and renewed matrix (through the action of these matrikines), lose their stimulatory capacity in the environment of "gummed up" matrix and senescent fibroblasts resulting in less procollagen stimulation and formation. The approach to renewed matrix regeneration through rejuvenation techniques of skin resurfacing or long-term skin maintenance programs must consider these ongoing destructive processes to optimize aesthetic outcomes.

Current Practice

In current practice, almost no concerted effort has been made to sequentially and synergistically approach ECM modulation, clearance, or a "skin bed preparation" program that would prepare the skin (pre-conditioning) for optimizing wound healing and neocollagenesis and neoelastogenesis from resurfacing procedures or in general, in the maintenance of skin health.

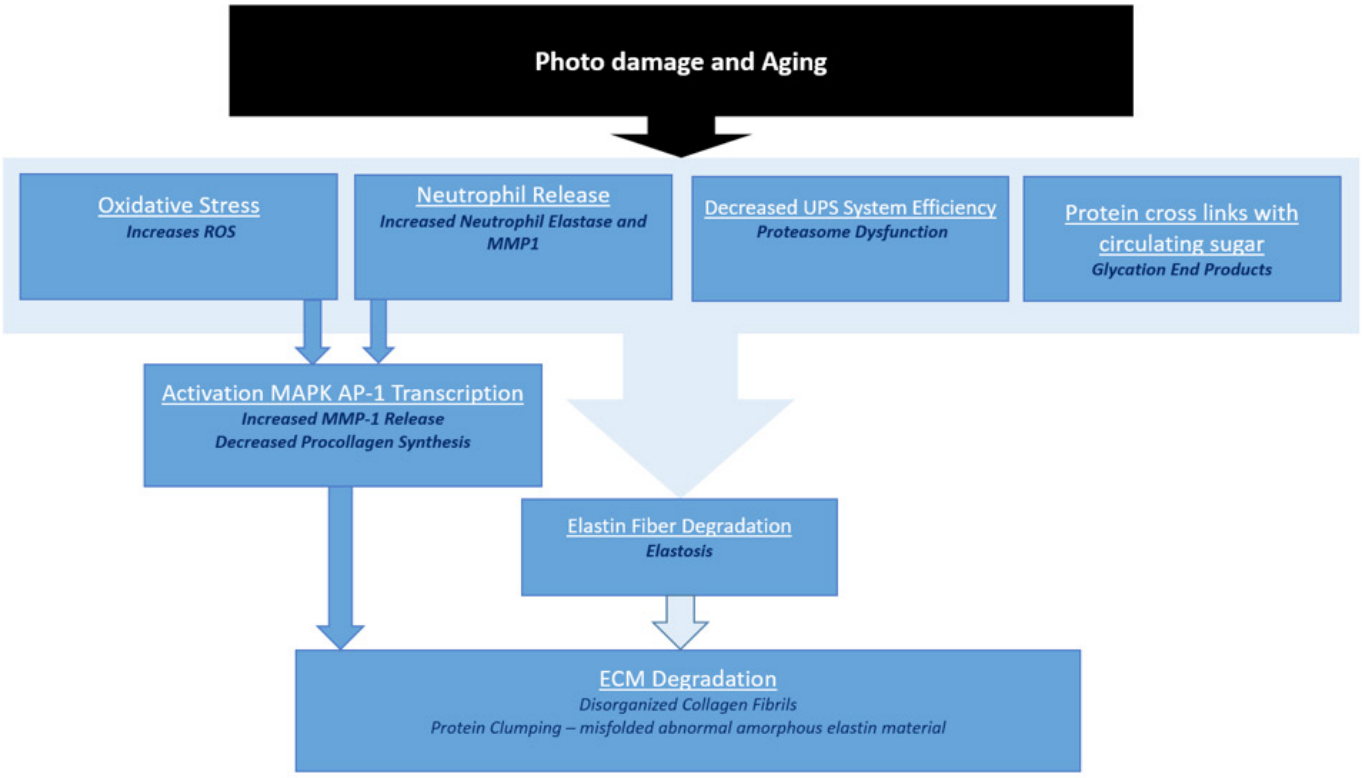
Alastin Regenerating Skin Nectar™ With TriHex Technology™

Alastin Regenerating Skin Nectar™ with TriHex Technology™ utilizes an innovative peptide combination to support matrix remodeling. The formulation was specifically designed to enhance procedure outcomes by optimizing the skin both pre- and post-procedure. The stimulation of key healing and regenerative processes by ECM modulation and remodeling serves as the mechanism for "skin bed preparation" and improves skin responsiveness to treatment. Immediately post-treatment, Alastin Regenerating Skin Nectar™ strengthens the compromised tissue and minimizes post-treatment side effects. Gene expression studies on Alastin formulations have confirmed the relevant MMP, TIMP, decorin, dermatopontin, elastin, and collagen upregulation. Elastin and collagen upregulation have been confirmed histologically in the ECM following pre-conditioning with 3 weeks of topical application of the Alastin product (no procedure performed; Figure 3b). In vitro studies (cited later) have demonstrated that a period of 14-21 days is ideal for pre-conditioning and modulating the ECM. In addition, multiple clinical cases have demonstrated less downtime and excellent symptomatic relief when used in conjunction with resurfacing procedures.

Integrated Approach and Solutions

Similar to how the chronic wound healing process benefits from wound bed preparation before therapeutic intervention, treatment of chronic aging of the skin may be improved with a "skin bed preparation" to optimize rejuvenation procedures and skin maintenance programs. This involves introducing agents that can combat stress-induced oxidation, proteasome dysfunction, and non-enzymatic cross linkages involved in glycation end products, to collectively modulate this damaged ECM, and upregulate neocollagenesis and elastin production. Agents of particular interest are matrikines, peptides originating from the fragmentation of matrix proteins, which exhibit a wide range of biological activities relating to matrix modulation.[12] Peptides of this type (tripeptide and hexapeptide) are incorporated in ALASTIN™ Skin Nectar with TriHex™ technology (ALASTIN Skincare, Inc., Carlsbad, CA), which is designed to target ECM modulation with a goal of optimizing results following invasive and non-invasive dermal rejuvenating procedures. Additionally,

FIGURE 1. ECM changes consequent to photodamage and aging.



oleuropein (a lypo-oxygenase activity inhibitor) and phosphatidylserine (PS) (a signal enzyme activator) are included in the ALASTIN™ Skin Nectar with TriHex™ technology formulation to decrease inflammation.

'Skin Bed Preparation' (Prior to Skin Rejuvenation Procedures)

The basic pre-requisite for regenerative wound healing, particularly in the case of chronic non-healing wounds, is that of adequate wound bed preparation. The logical approach to changing the degradative ECM wound environment in wound bed preparation is wound debridement and absorption of corrosive wound fluid to stimulate vascularization and decrease bacterial burden.[13,14] Removal of the senescent cells and their products may contribute greatly to this change.[15] Only then can exogenously applied growth factors and biologics be expected to stimulate the surrounding healthy tissue and promote wound healing.[13]

In much the same way, it is logical to adopt this paradigm in dealing with the changes seen in photo-damaged and aged skin. This sequence too, is a chronic one, with disturbances in ECM matrix constitution, senescent cells, and an imbalance of proteolytic mechanisms. Invasive resurfacing procedures are designed to denature collagen and proteins, producing more protein fragments that normally stimulate collagen regeneration. However, in a background of excessive existing photoinduced protein fragmentation, clearance of these fragments may facilitate the regenerative phase and hasten healing. Thus, in order to stimulate matrix regeneration, improve skin health maintenance, and to optimize rejuvenative procedures, a sequence of 'skin bed preparation' and matrix modulation would seem appropriate. This would take the form of ECM modulation by aiding in the removal of protein degradation products, balancing inflammatory mediators and proteases, and stimulating basal keratinocytic stem cells and fibroblasts setting the stage for regeneration of procollagen, collagen, elastin, and ECM ground substance. In effect, this constitutes a 'recycling of the ECM' for optimizing regenerative functions.

From the aspect of matrix degradation described above, a sequence of targeted approaches to repair and regenerate would appear logical as follows:

- "Mopping-up" of excess collagen and elastin fragments in the ECM with balanced MMP production
- Combatting oxidative stress, ROS end products generated in ECM
- Stimulation of procollagen and collagen to regenerate the ECM, increasing lysyl oxidase beneficial cross linkages and improved fiber alignment (decorin, dermatopontin)

- Stimulation of elastin (particularly fibrillin) to regenerate the ECM
- Increased efficiency of the proteasome system in eliminating dysfunctional proteins
- Reduction of MMP-1 destruction of normal collagen fragments
- Management and decrease of glycation end product alterations in the ECM
- Possibly volumizing dermal ECM to improve fibroblast function

Matrikines

With respect to skin, the term "matrikines," proposed by Maquart, is used to describe peptides liberated by partial proteolysis of ECM macromolecules.[12] Some of the fragments generated, possess stimulating and signaling activity in a feedback loop, initiating the repair process of the tissue matrix, hence their name. These peptide fragments normally participate in the wound healing as natural, non-toxic, locally acting, and highly potent messengers. Matrikines are able to regulate cell activities, modulate cellular proliferation and migration, protein expression and synthesis, protease production, or apoptosis. A number of different matrikines have by now been identified, some with very specialized functions including stimulation of collagen and fibronectin synthesis.

Tripeptide GHK (TP1), a matrikine, simultaneously activates the production of metalloproteinases and anti-proteases that remove damaged proteins from the ECM macromolecules while activating the synthesis of new proteins for rebuilding the ECM.[16-19] TP1 increased MMP-2 (and to a lesser extent MMP-9) levels in conditioned media of cultured fibroblasts demonstrating increased MMP-2 proteolytic activity. MMP-2, a gelatinase, is important in digesting the gelatin fragments that remain after cleavage of normal collagen by MMP-1 related to sun damage (Figure 2).[20] It is thus evident that pre-conditioning is optimal for a 14- 21 day period during which time the MMP-2 levels are still rising and effective in ECM clearance of gelatin fragments.

MMP2 can mobilize vascular endothelial growth factor and release proteases resulting in ECM modulation and fragmentation absorption (mop-up). Both MMP-2 and -9 degrade denatured collagen (gelatin) and elastin.[21,22] TP1 is a potent activator of ECM synthesis and remodeling generated during proteolytic degradation of proteins in the ECM after tissue injury and tissue turnover.[23] To counteract the MMPs, skin expresses natural inhibitors – tissue inhibitors of matrix metalloproteinases (TIMPs) that slow the process of collagen breakdown. The tripeptide -1 (TP1) also increased levels of MMP inhibitors TIMP-1 and TIMP-2 in cultures. TIMP-1 preferentially inhibits MMP-9, whereas TIMP-2 is more active on MMP-2.[20] Taken together, these results suggest that, by modulating MMPs-2,9 and TIMPs expression and release by fibroblasts, the tripeptide can modulate a large array of physiological processes, particularly those which require a rapid ECM clearance and turn over, such as cell migration, angiogenesis and tissue remodeling.[20]

In addition, tripeptide has been shown to upregulate genes associated with the proteasome UPS system, activating the system and thus aiding in removing misfolded proteins.[24] The biochemical uniqueness of tripeptide-1 resides both in its very small size, which would permit it to approach membrane receptors more easily than larger proteins, and its unique copper-binding characteristics that allow copper transfer into and from cells, both of which facilitate its entry into the cell.[19]

Once in the cell, tripeptide has a unique capacity to control inflammation, a major factor in promoting satisfactory wound healing and scar outcome. It does this by suppressing cellular synthesis or activity of key acute phase cytokines such as tumor necrosis factor-alpha (TNF-α) in wounds and interleukin-1, both of which induce further tissue damage after injuries.[19] While stimulating new collagen formation, TP1 also increases levels of lysyl oxidase the beneficial enzymatic cross linker.

In addition, during this regenerative process the alignment of collagen fibers into uniform structures of appropriate length is important. Proteoglycans of the dermis – decorin and dermatopontin,[25] both stimulated by tripeptide – are vital to this process. Elastin production is also stimulated by this tripeptide, particularly fibrillin-1, the component that is most severely

FIGURE 2. Dotted line GHK application to wound chamber vs control (solid line). GHK activates MMP2 (gelatinase, Y-axis) to a far greater degree than the control from day 3 and peaking at days 18-22.
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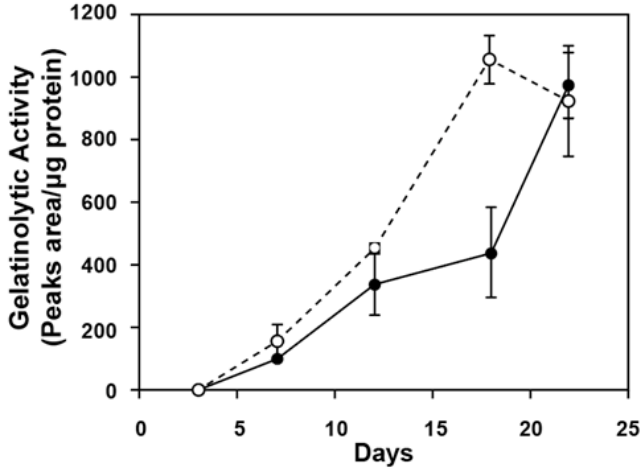


affected by solar elastosis. The presence of iron complexes in damaged tissues proves detrimental to wound healing since they increase local inflammation and microbial infection by supplying iron. TP1 stops the release of oxidizing iron from ferritin and also has sun-protective properties blocking lethal ultraviolet radiation damage to cultured skin keratinocytes and reducing UV-induced erythema.[16,19,26] Alastin has studied the effect of their products' tripeptide on human fibroblasts and shown elevations in gene expression for all of these important ECM modulating proteins at 48 hours (Table 1).

Finally, studies analyzing stem cell function in the keratinocytic basal layer of the epidermis revealed that treatment with TP1 increased the proliferative potential of basal keratinocytes possibly by modulating the expression of integrins and p63.[27] p63 is a putative stem cell marker of the skin, suggesting that TP1 promotes the survival of basal stem cells in the skin.[27,28] Having achieved the capacity to activate, synthesize and remodel collagen and elastin using TP1, a focus on elastin generation would supplement the picture for ideal skin remodeling.

Hexapeptide (Hex-12) has the repeating amino acid sequence found in tropoelastin and the key sequence found at the binding site for the elastin protein to its cell surface receptor. Matrikines that predominantly activate elastin formation, elastokines, are amongst the most important matrikines yet described. This is because these elastin-derived peptides are chemotactic for fibroblasts and monocytes and have the capacity to stimulate the generation of elastin (Figure 3).[29,30] Hexapeptide functions as a signal transduction cytokine, binding to Elastin Binding Protein (EBP) on the fibroblast and keratinocyte surface and stimulating the generation of elastin. This is key as most rejuvenating procedures are designed to stimulate collagen production but regeneration of elastin is limited.

Oleuropein

Oleuropein is a polyphenol isolated from olive leaves with great interest to researchers.[31,32] It demonstrates major anti-inflammatory effects by inhibiting lypoxygenase activity and the production of leukotriene.[32] In particular, researchers have demonstrated that oleuropein enhances proteasome activities in vitro more effectively than other known chemical activators, possibly through conformational changes of the proteasome.[31] In this regard, it decreases reactive oxygen species (ROS), reduces the amount of oxidized proteins through increased proteasome-mediated degradation, and retains proteasome function during replicative senescence.[31] Inhibition of AGE formation via blocking sugar attachment to proteins, scavenging the reactive intermediates, or breakdown of established AGE-induced cross-links, constitutes an attractive therapeutic/preventative target.[33] Oleuropein has been demonstrated to inhibit AGE formation and breakdown AGE products through its proteasome enhancing function.[31, 33]

Phosphatidylserine (PS)

The initial approach to altering the destructive ECM milieu needs to halt the destructive enzymes and end products causing protein fragmentation, misfolding, abnormal cross linkages

FIGURE 3A. Linear fold change in mRNA expression following tripeptide-hexapeptide (Alastin) application vs. vehicle control.

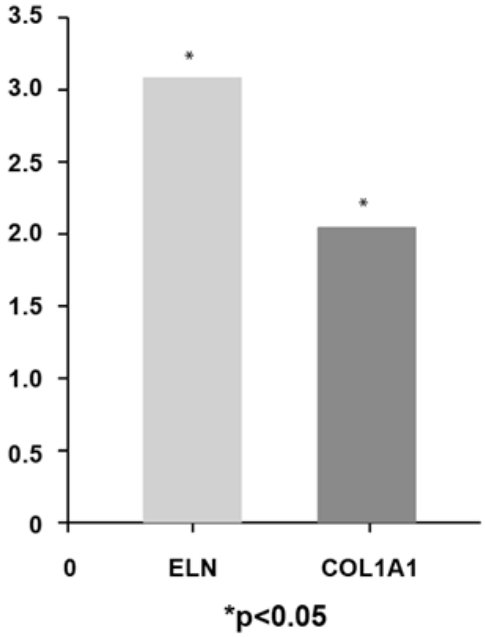


FIGURE 3B. Changes in Elastin staining 3 weeks after application.

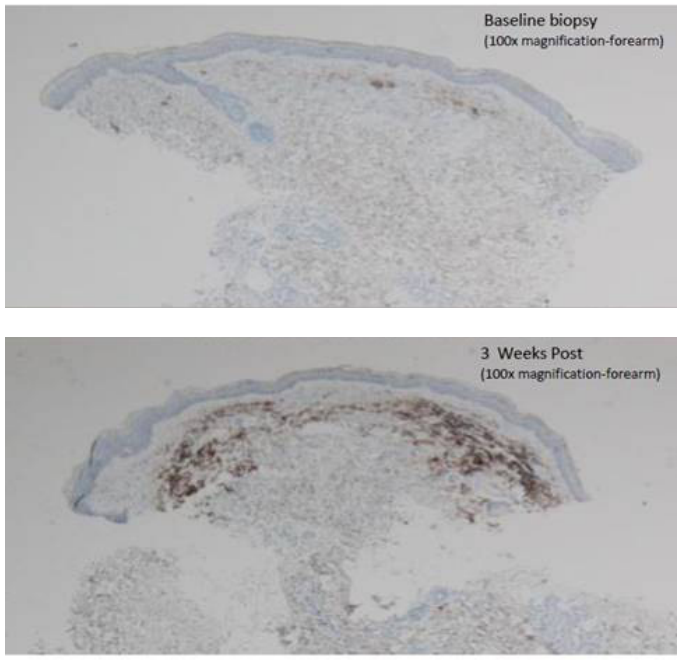
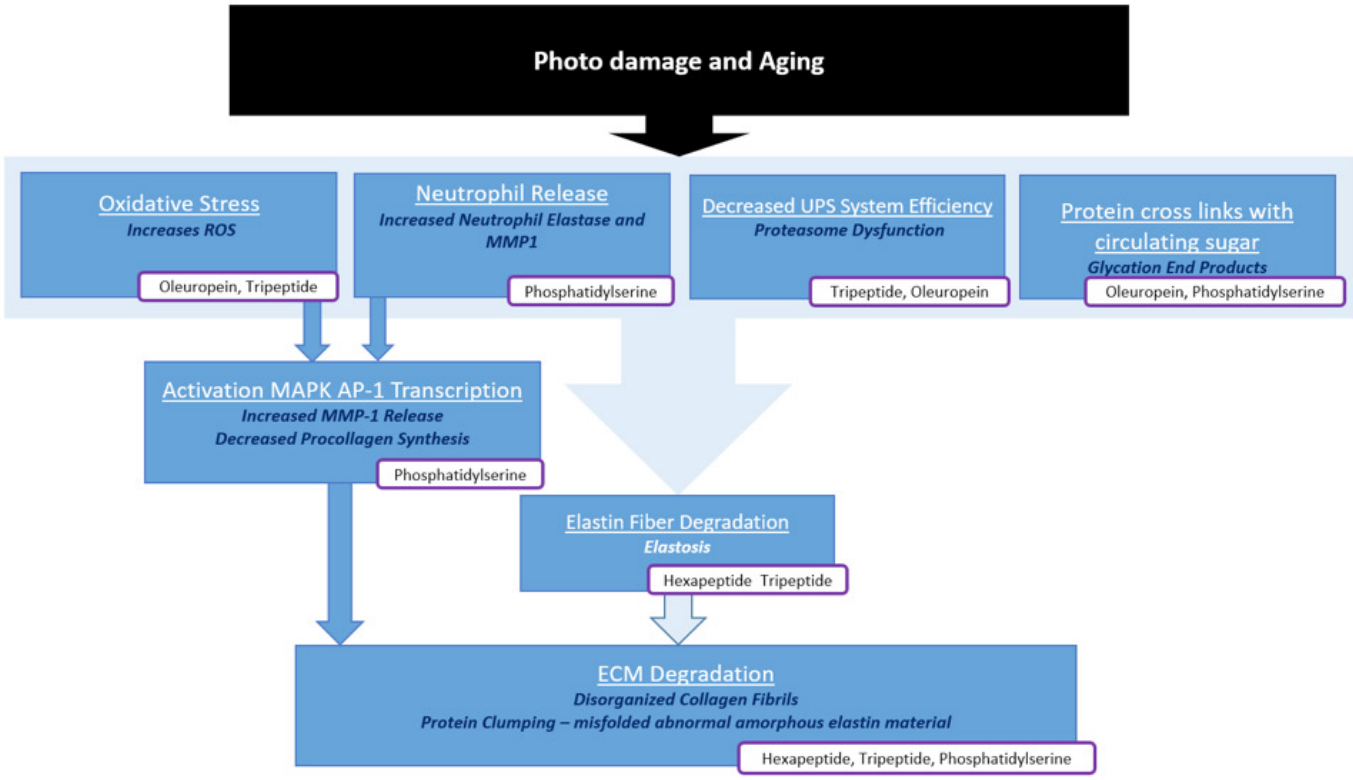


FIGURE 4. Strategy for ECM clearance and modulation using a combination of potent peptides, lipids and botanicals (Ingredients of Alastin Regenerating Skin Nectar indicated in red – PS= phosphatidylserine).



and amorphous elastin clumps. To this end *phosphatidylserine (PS*), a highly enriched membrane phospholipid component, is known to have several physiological roles, such as activating signaling enzymes and antioxidant activity.[34] It has been found to decrease MMP-1 in a dose dependent manner, to increase procollagen formation and may act as a substrate for AGE targets thus reducing the damage from glycation effects.[11,34,35] Clearance of apoptotic cells is necessary for tissue development, homeostasis, and resolution of inflammation. PS provides an "eat me" signal on the cell surface, and phagocytes recognize the signal using specific receptors such as the receptor of advanced glycation end products (RAGE). This then binds to PS and assists in the clearance of apoptotic cells and end products of AGE.[35]

As described above, one of the main processes responsible for cellular and extracellular aging is the accumulation of damaged proteins in the cell and the ECM. The ECM proteins are subject to various abnormal post-translational modifications such as oxidation, glycation and conjugation with products from lipid peroxidation, and proteasome dysfunction, all of which may be associated with aging and hastened by UV irradiation. The accumulation of damaged proteins can affect the efficacy of the proteolytic systems, including extracellular MMPs, cytokines, anti-oxidants, and the intracellular proteasomal system, that are responsible for eliminating damaged proteins.

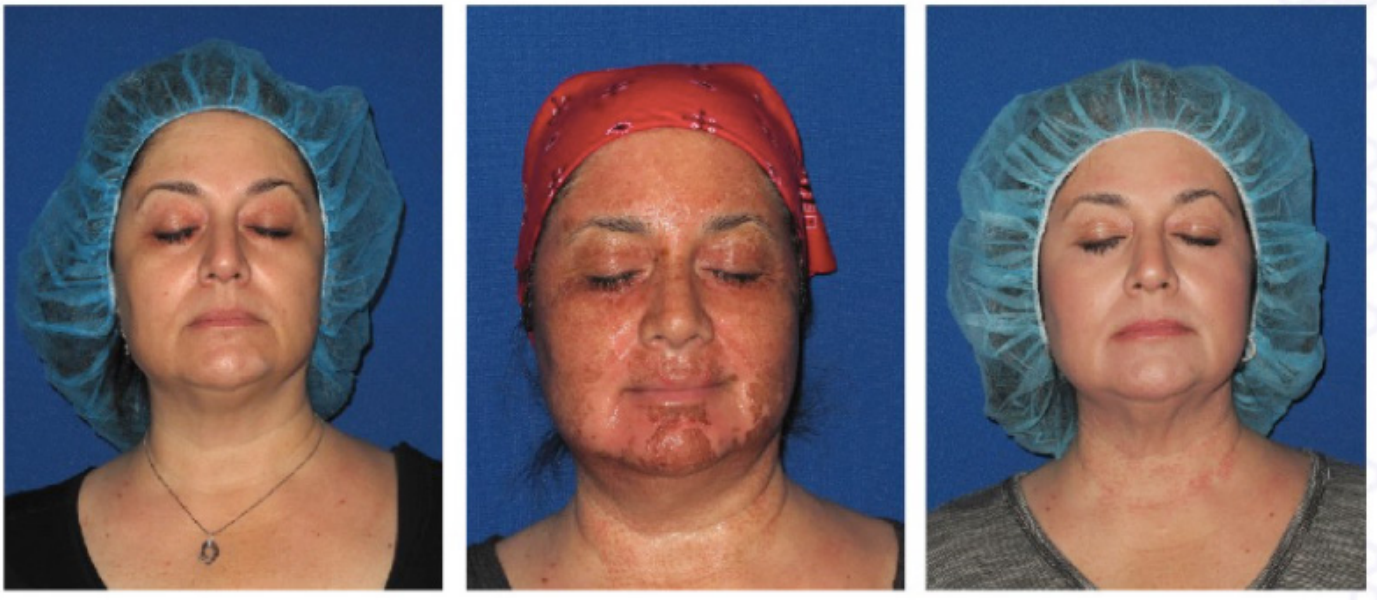
Alastin TriHex Technology™

By combining this group of potent peptides, lipids, and botanicals, a sequential ECM modulation range (Alastin SkinCare Inc, Carlsbad, CA) has been formulated to aid in clearing and regenerating the ECM (Figure 4). This formulation, designed with specific solubilizing moieties, facilitates rapid skin penetration and provides good compatibility with non-aqueous formulations.

Thus Alastin Regenerating Skin Nectar™ with TriHex Technology™ utilizes innovative peptide technology to support matrix remodeling optimizing the skin both pre- and postprocedure. This "skin bed preparation" improves skin responsiveness to treatment and after treatment, strengthens any compromised tissue, and minimizes post-treatment side effects.

As with all therapeutic dermatologic preparations, the skin penetration and absorption is critical to efficacy of any product. In that regard, the tripeptide, hexapeptide, phosphatidylserine, and oleuropein are suspended in a proprietary, non-aqueous conjugate - like delivery system within a silicone elastomer gel designed specifically to deliver rapid penetration of the

FIGURE 5. Preconditioning program used for 3 weeks prior to procedure followed by procedure program during and after deep fractionated CO2 laser showing hastened healing from day 4 post-procedure to day 8 of the procedure.



materials through the stratum corneum. Lipid based materials absorb much more efficiently than aqueous bases. Thus, the volatile silicone elastomer aids in material delivery then rapidly evaporates.

Gene expression studies on Alastin formulations have confirmed the relevant MMP, TIMP, decorin, dermatopontin, elastin, and collagen upregulation (Table 1) with histological biopsy confirmation (Figure 3b) of changes in the ECM following pre-conditioning and treatment. In the interim, multiple clinical cases have demonstrated less downtime and excellent symptomatic relief when used in conjunction with resurfacing procedures (Figure 5).

"Similar to how the chronic wound healing process benefits from wound bed preparation before therapeutic intervention, treatment of chronic aging of the skin may be improved with a "skin bed preparation" to optimize rejuvenation procedures and skin maintenance programs."

CONCLUSION

Skin photodamage and aging results in characteristic changes that have been well defined. These changes have long lasting effects predominantly on the dermis, the major constituent of skin thickness. The dermal ECM orchestrates much of the repair and regeneration that occurs within all skin layers. The ECM is severely disrupted by photodamage with collection of protein aggregates following collagen, elastin, and proteoglycan fragmentation secondary to oxidative stress reactions, glycation end products, and dysfunctional proteasomic systems. Skin rejuvenation is complicated by these factors with a background of unstructured fragmented ECM creating less focal adhesion points causing rounded senescent fibroblasts, less collagen and elastin production, amorphous collections of elastin and other protein fragments disturbing normal cell to cell cross talk, and abnormal non-enzymatic cross linkages creating glycation end products.

Using the model/paradigm of chronic wound healing, it is suggested that adequate wound/skin bed preparation is an essential pre-requisite to any therapeutic rejuvenating procedure. Pre-conditioning and post-treatment management with Alastin Regenerating Skin Nectar™ with TriHex Technology™ (Alastin Skin Care, Carlsbad, CA) is aimed at optimizing post procedure neocollagenesis and elastin production by modulating the ECM. Thus, the ECM is better able to address fragments created by the procedure as well as fragments accumulated through years of sun exposure and aging. By targeting various mechanisms of ECM fragmentation, the matrix is altered to a proregenerative milieu rather than one of scarring and inflammation. The select peptides and botanical extracts synergistically and sequentially aid in ECM modulation to optimize and "prime" the skin for resurfacing procedures. Furthermore, this approach allows for modulation to occur over time, maintaining results achieved.

DISCLOSURES

Alan Widgerow is Chief Medical Officer for Alastin Skincare. Sabrina Fabi, Alexander Rivkin, and Vivian Bucay are paid consultants for Alastin Skincare's Scientific Advisory Council. Arisa Ortiz is conducting a clinical trial on behalf of Alastin Skincare. Paul Chasan is a paid consultant for Alastin Skincare.

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