

Review

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# Role of the extracellular matrix in skin aging and dedicated treatment - State of the art

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## Abstract

The extracellular matrix (ECM) occupies the space between cell and cell, and serves as a sort of intranet which connects the whole organism. Current research is focused on the ECM and, it is now possible to develop increasingly effective strategies for the prevention and treatment of degenerative diseases and even, cutaneous ageing. In fact, the most advanced anti-aging treatments are those that regenerate the ECM, which is now regarded as the main player in the physical support of, and exchange with and between cells of nutrients, cellular mediators and growth factors.

**Keywords:** Collagen, elastin, hyaluronic acid, extracellular matrix, matrisome

## INTRODUCTION

Skin aging is a complex and unavoidable biological phenomenon that starts in the third decade of life<sup>[1]</sup>. The aging processes is determined by a combination of intrinsic (chronological, hormonal and genetic) and extrinsic factors. The latter can be further divided into behavioural factors like sun exposure (responsible for photo-aging), cigarette smoking, dietary habits, alcohol intake, drug abuse and environmental factors such as pollution, weather, and humidity. Between individuals, genetics, as well as lifestyle habits, are all different. Therefore, aging at large, and skin aging in particular, are extremely variable<sup>[2]</sup>. Skin aging is a dynamic process that results in structural alterations of soft and bony tissues<sup>[3]</sup>. The silhouette of the face and body change as a result of atrophy of its various constituent layers: from skin to subcutaneous adipose tissue including loss of muscle mass and, to a lesser extent, resorption of bone, wrinkles, hypotonicity, lipotrophy, sarcopenia and volume displacement may result. Furthermore, to counteract atrophy, a



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permanent muscle tone is established to neutralize incorrect relaxation of the skin through compensating mechanisms<sup>[4]</sup>.

## EXTRACELLULAR MATRIX AGING MECHANISMS

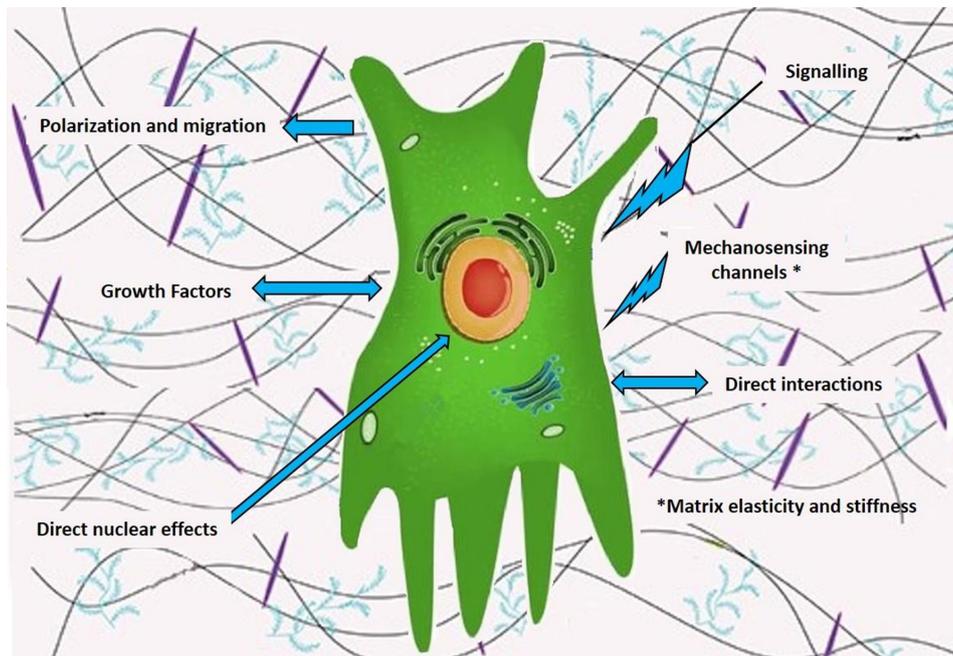
Over time, various body structures lose function in an unpredictable sequence. The aging process is thus not gradual nor uniform, and aging of the facies becomes even more complex due to the presence of mimetic muscles connected to the skin. Prevention and treatment strategies must therefore account for the above. The extracellular matrix (ECM) provides a commonality amongst these intricate processes and has emerged as an area of research focus for the development of more effective strategies against the cutaneous signs of aging<sup>[5]</sup>.

There are several molecular mechanisms underlying the aging process. Although still not completely undisclosed, such knowledge is very important clinically and is the focus of many current studies. The main extrinsic factor responsible is still photodamage, which causes the release of collagenases and neutrophil elastases that result in fragmentation of structural and tonic proteins. Additionally, the cellular responses of autophagy and Ubiquitin Proteasome systems are slowed. Current strategies of ECM remodeling are thus based on eliminating cellular debris and the stimulation of neocollagenesis, elastogenesis and glycosaminoglycans production through the use of various peptides and other active agents<sup>[6-8]</sup>. As far as we know, the main mechanism involved in preventing ECM changes is to keep free radical (i.e., ROS, reactive oxygen species) production under control. ROS are characterized by the presence of an unpaired electron, which is responsible for their instability and reactivity towards chemical structures to which they bind to capture another electron. In turn, this process generates unstable molecules and promotes chain reactions that ultimately, lead to functional and structural damage both within cells and extracellularly. ROS are produced in cellular structures such as membranes, lysosomes, and mitochondria. Their formation can be exacerbated by external agents including ultraviolet (UV) light, tobacco, infections and chemicals. The human body protects itself from ROS by utilizing antioxidant enzymes (SOD), such as catalases and glutathione peroxidases, which neutralize radicals and produce less harmful substances. However, as one's body declines with age, levels of these antioxidant enzymes also decrease correspondingly<sup>[9]</sup>.

Alteration of matrix metalloproteinase (MMP) levels can lead to dysregulation of skin homeostasis<sup>[10]</sup>. In the elderly, the levels of zinc-dependent proteases increase, causing degradation of ECM protein components. Physiologically, MMPs ensure protein turnover by stimulating the renewal of elastic and collagen fibers. MMP levels are regulated by tissue inhibitors, the expression of which can be disturbed by UV light, smoke and ROS. Protein-degrading MMPs in contrast, render connective tissue less elastic. Another critical point to be considered is protein glycation, namely the reaction of glucose and other sugars such as fructose. This post translational protein modification is associated with increased levels of glucose, affects protein structure and function through increased cross-linking, and results in the formation of "Amadori" and advanced glycation end products. Glycated proteins increase the formation of free radicals and release toxic products and pro-inflammatory components that cause protein damage, which ultimately is the fundamental cause of aging<sup>[11,12]</sup>. In women, menopause is associated with reduced ovarian endocrine activity leading to an increase in follicular stimulating hormone and decrease in estrogen and progesterone, with downstream metabolic disturbances. Alterations start from sexual organs and involve all tissues targeted by estrogen, in a multisystem framework that affects all connective tissues. Collagen atrophy is the main factor associated with menopause-related skin aging, which contributes to reduced skin elasticity<sup>[13]</sup>. In menopause, skin thickness and collagen content are initially reduced by 1.13% and 2.1% per year respectively; type I and III collagen decrease by 30%. The skin is not only a target for sex-hormones but also produces and releases estrogen from the enzymatic conversion of estrogen precursors. Estrogen exerts a number of functions on connective tissue such as counteracting the degradation of collagen by MMPs induced by UV light and ROS through the activation of the TGF- $\beta$ 1 pathway. Skin and bone thickness

**Table 1. Extracellular matrix components can be divided into 3 main groups**

Structural proteins	Adhesion proteins	Glycosaminoglycans	Proteoglycans
Collagen	Fibronectin	laluronan	Biglican
Elastin	Fibrillin	Heparan-sulphate	Agregacan
	Laminin	Chondroitn-sulphate	Versican
	Tenascine		Neurocan
	Vitronectine		
	Osteonectine		



**Figure 1.** Interactions extracellular matrix cell

are also positively correlated with estrogen levels. Post-menopausal women with less estrogen, show a decreased expression of TGF-β1 in skin fibroblasts, which may hamper the ability of fibroblasts to produce collagen, elastin and proteoglycans.

**THE MATRISOME: SIGNIFICANCE AND FUNCTION**

In recent years, both antiaging and medical research have focused on ECM biochemistry and pathophysiology as well as matrix dysregulation which can lead to disease progression<sup>[14,15]</sup>. The ECM fills the intercellular space and is present in all connective tissues [Table 1]. Dermis and adipose, muscle, bone, cartilage, and the surrounding parenchyma of organs, are all connective tissue, which highlights the relevance of the ECM in maintaining tissue homeostasis. Within the intercellular space, phenomena like cellular polarization and migration, regulation of growth factors, activation of signaling molecules, and processes translating mechanical stimulation into a chemical signal through the involvement of mechanosensitive channels are all essential for the maintenance of ECM elasticity and physiological tissue stiffness [Figure 1]. Mechano-transduction in particular, is an increasingly well-studied process. When the fibroblast is located in a stiff microenvironment, it will be stimulated continuously to produce new ECM. In addition, basement membranes play a fundamental role in maintaining tissue homeostasis and the transmission of mechano-transduction signals to the underlying dermis.

The molecular structure of the ECM is responsible for the above essential functions. The ECM is also comprised of a complex network of proteins defined as the “matrisome” [Table 1]. The matrisome is now

a matter of intense study, not only for the identification of all component proteins but also, for defining the molecular mechanisms regulated by the ECM<sup>[16]</sup>. To date, about 300 matrisome proteins have been identified including: 43 types of collagen subunits in fibrillar and non-fibrillar form (the most common is type 1 representing 80%-90%); 36 types of proteoglycans dispersed amongst collagen fibers to take up the interstitial space and maintain hydration; growth factors linked to glycosaminoglycans that are retained in the extracellular space to increase functionality; about 200 soluble proteins, which not only promote assembly of the ECM but are also involved in cell-ECM interactions, and act as ligands with receptors (integrins); and enzymes such as lysyl-oxidase, transglutaminase and hydroxylase<sup>[17]</sup>. To simplify, the matrisome is composed of 3 main molecular groups: structural proteins, adhesion proteins and proteoglycans. Among structural proteins, collagen is most abundant. Its peculiar amino acid sequence provides essential functions<sup>[18]</sup>. Aging reduces collagen synthesis and alters its structure (collagen fibers become fragmented and stiff). Amino acids are fundamental to the structure and thus, function of collagen - for example, the interaction of specific amino acids with potassium ions favors non-covalent binding and binding to proteoglycans. There is less elastin overall but it is still essential for maintaining the elastic properties of skin. Elastin fibers stretch under traction but with mechanical stress, can be restored to their original conformation. This process is due to the presence of hydrophobic amino acids such as valine and alanine, both of which are exposed to the hydrophilic components of ECM during mechanical stress. When the mechanical force is removed, elastin folds back on itself and its fibers become shortened. It goes without saying that the optimal functionality of elastin would also be dependent on adequate tissue hydration<sup>[19]</sup>.

Therefore, the aging process would undoubtedly influence the ECM and matrisome as a whole. All 300 matrisome proteins are affected and their turnover is related to their individual half-lives. To illustrate, the half-life of collagen is about 3 years and that of elastin is 70, which means that post-translational modifications like glycation have an essential role in skin elasticity and structure. The increase in MMPs is also part of aging and correspondingly, structural proteins such as collagen and elastin lose function and contribute towards a loss of skin tone. The imbalance of peptide content has to be taken into account as well, in terms of cellular cross-talk alterations.

## TREATMENT OF ECM ALTERATION IN SKIN AGING

Given the above discussion, the most advanced antiaging treatments would therefore be those that are able to rebuild the ECM, which is responsible for both physical support and the exchange of nutrients, cellular mediators, and growth factors<sup>[20,21]</sup>. The most effective treatment would target cell metabolism, autophagy, cell renewal and the production of new ECM. Such results can theoretically be obtained by providing the right metabolic and structural support to cells (i.e., hyaluronic acid, specific amino-acids and peptides, antioxidants) as well as mechanical stimulation which would, in turn, stimulate mechano-transduction (that is the conversion of mechanical forces into biochemical signals) through the creation of a scaffold in reduced volumes to enable stimulation of interstitial fluid circulation.

Low and/or high molecular weight, natural (not cross-linked) hyaluronic acid have been reported to be capable of hydrating the ECM, thereby stimulating cellular activity when administered as injectable formulas. Low molecular weight hyaluronic acid has the ability to stimulate cells thereby preventing aging, increasing skin brightness, hydration, tone, reducing wrinkles and restoring volume. On the other hand, high molecular weight forms exert powerful antioxidant activity by neutralizing free radicals and becoming a scaffold for the skin. Hyaluronic acid however, must be continuously produced as they have particularly short half-lives and are degraded by specific enzymes, hyaluronidases. To increase the consistency and longevity of injected hyaluronic acid in the dermis, it is necessary to render it less susceptible to hyaluronidases by chemical modification with cross-linking agents to bridge its filaments. The such chemically-modified hyaluronic acid has a greater filling effect but its biological properties are drastically reduced in favor of the filling capacity (filler) making fillers a different issue (they consist of cross-linked

hyaluronic acid, made denser and chemically modified by crosslinking agents) which actually fills the tissue with immediate results compared to natural hyaluronic acid, but with lower biological activity<sup>[22,23]</sup>.

It should be highlighted that the use of dermal fillers does not exclude treatment with hyaluronic acid and vice versa. Often, a combination of treatment strategies allows one to easily achieve the desired results<sup>[24]</sup>. Fibrous proteins of the dermis, such as collagen and elastin, are characterized by a specific amino acid composition. With age, the ability of fibroblasts to synthesize collagen is reduced. Furthermore, alteration of collagen fibers imparts increasing stiffness and decreased elasticity to skin, with a consequent loss of tone and softness. An anti-aging treatment should therefore, always have, among others, the ability to increase the quantity and quality of collagen fibers. This can be achieved through specific cosmetic treatments capable of stimulating the production of collagen (peptides, retinol, vitamin C), food supplements containing specific amino acids or compounds capable of stimulating fibroblasts activity (i.e., collagen, amino acids and specific peptides), and even bio-revitalizing injections. In fact, in the absence of adequate amounts of amino acids, cells react by blocking catabolism. As a result, proteins age and become less efficient. "Old" proteins, whether enzymes, structural or contractile, become increasingly fragile<sup>[25]</sup>.

## CONCLUSION

Various factors associated with an individual's genetic background and physical environment can affect one's skin in different ways with regards to skin aging. Previously, skin aging was thought of as physiological or chrono-aging, and environmental or photo-aging. Other external factors have now been recognized to influence the skin aging process including gravity, environmental pollution, climate, and smoking. In order to provide a personalized treatment plan, a thorough analysis of an individual's aging processes will be required. For example, the shape of the face is of utmost importance - overtime, round faces tend to sag while thin and elongated faces have a tendency to become hollow. In the former, lifting would be required while in the latter, volumizing would be necessary. Treatment choice should be based on demonstrated safety and efficacy while injection technique is very important for delivery and stems from an in-depth knowledge of the anatomy and physiology of the treatment sites<sup>[26]</sup>. To illustrate, by specifically defining injection points or by combining injections with facial lymph node drainage, results will be immediately visible and continue to improve over the ensuing weeks and months<sup>[27]</sup>. Treatment protocols (number of sessions, frequency, maintenance, mix of introduced substances, combination with cosmetics, and nutraceuticals even) have to be individualized in order to suit the patient's needs. Aesthetic dermatology is perhaps the first medical discipline dedicated towards studying the properties of ECM and its treatment but has increasingly, gained the attention of other clinical fields<sup>[28]</sup> such as orthopedics, dentistry, pulmonology and gastroenterology. We believe that in the near future, the ECM will be recognized as a master element of many organs and body systems, overcome the barriers and concepts of current specialty fields, and improve our mechanistic understanding of the many internal and external dysfunctions and disease states for better treatment.

## DECLARATIONS

### Authors' contributions

The author contributed solely to the article.

### Availability of data and materials

Not applicable.

### Financial support and sponsorship

None.

### Conflicts of interest

The author declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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