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Review Article

Role of proteoglycans on skin ageing: a review

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Abstract

This work analyses the role of proteoglycans on skin ageing, influenced by the presence of glycosylated proteins, which exercise diverse functions on the skin. They are essential components that restore the cells, providing hydration, maintaining hydration of the extracellular matrix, preventing the formation of wrinkles thanks to their ability to combine to other molecules such as collagen or hyaluronic acid and favouring the smoothness of the skin texture. The use of these proteins is a very recent and promising topic, since their application may revolutionize skin ageing therapies. Of the existing proteoglycans, decorin, versican and perlecan are of special note, playing a fundamental role on skin.

Résumé

Nous avons analysé dans cette étude le rôle des protéoglycanes dans le vieillissement de la peau, conditionné par la présence des protéines glycosylées qui exercent plusieurs fonctions sur la peau. Ce sont des composants essentiels qui restaurent les cellules, fournissent de l'hydratation en maintenant l'hydratation de la matrice extracellulaire en évitant la formation de rides cutanées grâce à sa capacité de se combiner à d'autres molécules tels que le collagène ou l'acide hyaluronique qui favorisent la douceur de la peau. L'utilisation de ces protéines est un des sujets les plus récents et prometteurs, étant donné que son application peut représenter une révolution quant aux thérapies qui luttent contre le vieillissement cutané. Parmi les protéoglycanes ressortent la décorine, le versicane et le perlécane qui jouent un rôle fondamental sur le derme.

Introduction

Currently, skin ageing is a topic of much interest, given that this ongoing process is universal and irreversible, characterized by the appearance of morphological and physiological modifications that appear over time in humans, and resulting in the decreased activity of diverse organs and tissues.

This process presents a large biological variability between individuals, so one of humanity's greatest ambitions has been to prevent and combat the ageing of the skin, a challenge that continues to be faced today [1, 2].

Skin is affected by changes caused by intrinsic and extrinsic factors [3–5]. Intrinsic ageing is biological ageing. It is a genetically determined process that occurs with ageing and is thereby inevitable. This process may be accelerated by environmental factors such as smoking or sun exposure [6–9], which are factors that are responsible for the so-called extrinsic ageing. Based on these factors [10], we can state that skin ageing is affected by inflammatory factors, hormonal levels, genetic regulation, the production of free radicals [11], exposure to UV radiation, environmental contaminants, etc. (Fig. 1).

Of these factors, genetic regulation clearly plays a key role, since it has been verified that, on a genetic level, humans are 99% identical. And it is this 0.1% difference in DNA that makes us unique from one another. This 0.1% includes genetic variations, which determine physical characteristics such as, for example, skin tone. Most genetic variation occurs at a polymorphic level of one unique nucleotide, named SNP (single nucleotide polymorphism). Each SNP represents an almost imperceptible difference in one of the units making up the DNA, the so-called nucleotides. The SNPs normally occur across an individual's entire DNA. This leads us to believe that not all skin types are the same, and therefore, different products may be necessary for their care. Determining the SNPs that exist in the genes involved in the process, at a cutaneous level, may allow us to know what type of skin the individual has, and therefore, we may determine the genetic profile of the individual and thus the ideal product for their specific skin type, so as to treat skin imperfections such as wrinkles and sagging [12, 13].

The role of telomeres is one of the factors to be taken into account. It has been shown that the shortening of telomeres is one of the most common causes of ageing in all organisms. Telomeres are repetitive nucleotide sequences found at the ends of the chromosomes. They are regions of the DNA that do not replicate fully. In each cell division, chromosomes lose *n* repetitions of nitrogenous bases. Telomerase is an enzyme having polymerase activity that, in young individuals, replicates the DNA at the ends of the chromosomes, producing an enlargement of these telomeres. However, in older individuals, this process does not take place fully.

On the other hand, it has been found that an increase in the production of free radicals, such as hydroxyl (-OH), is the main cause of oxidative stress. Free radicals are reactive molecules capable of damaging the cellular structure, including lipids and proteins, accelerating the appearance of visible signs of ageing such as a decreased elasticity and the appearance of wrinkles. Under normal circumstances, humans develop processes to repair the DNA or to neutralize the free radicals with natural antioxidants of the skin. But with the passing of time, this capacity decreases, and as a consequence, the macromolecules remain damaged from the presence

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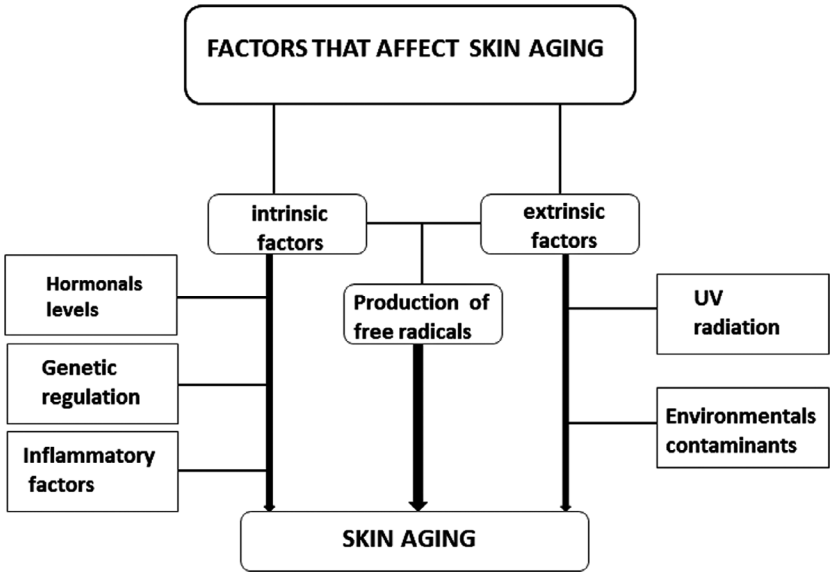

Figure 1 Diagram representing the factors that influence skin ageing.

of these free radicals, producing an excess of oxidative stress and disorders related to the failure to repair the damage caused in the cells and therefore skin ageing.

The objective of this study is to determine the importance of the use of proteoglycans on the skin, highlighting their role in combating skin ageing and determining their functions on the skin.

Substances used to treat skin ageing

Many compounds are used to treat or repair skin or as preventive measures to protect from skin ageing, for example [14]:

Vitamins, such as vitamin A (retinol): also known as the anti-ageing vitamin. Vitamin A is an antioxidant that acts on the skin, favouring proper cell metabolism. It is essential for the correct functioning of the epithelial cells. It has been demonstrated that it stimulates overall metabolic activity since it increases the synthesis of collagen and GAGs (glycosaminoglycans). Other vitamins are also used on their own or in combination with other compounds, such as vitamin E (tocopherol), vitamin C (ascorbic acid) and vitamin B5 (pantothenic acid).

Another widely used compound that has recently gained great popularity is hyaluronic acid (HA). It is a polysaccharide, of the glycosaminoglycan type, which forms in the connective tissues, specifically, in the epithelial and neural tissues. It is one of the main components of the extracellular matrix, and it plays a key role in cell proliferation. Its main function is to retain large quantities of water in the body. Due to this property, hyaluronic acid is found in large quantities in our organism – in bones, cartilage, tendons, skin, lips, etc. In the skin, hyaluronic acid is found together with collagen, and both of these substances are vital for maintaining the skin layers and structure. Young skin remains smooth and elastic because it has a high concentration of HA that keeps the skin healthy. With age, skin loses its ability to maintain this concentration of hyaluronic acid, and therefore, it becomes dryer, without the humidity that is necessary to remain hydrated, and therefore, wrinkles appear. Preclinical studies show that HC stimulates collagenic tissue regeneration by increasing not only collagen synthesis but minor components (glycosaminoglycans and hyaluronic acid) synthesis as well. Clinical studies show that HC continual ingestion helps to reduce and prevent joint pain, bone density loss and skin ageing. These results as well as its high level of tolerance and safety make HC ingestion attractive for a long-term use in bone and joint degenerative diseases and in fight against skin ageing [15, 16].

Green tea and aloe vera polyphenols are also used [17], usually in combination with other compounds.

It should be noted that, of the compounds that are currently used, Argireline® [18, 19] is a peptide consisting of three amino acids: glutamic acid, methionine and arginine. It has been demonstrated to be effective in preventing the appearance of wrinkles in skin and is specifically defined to combat expression lines. Argireline® decreases the depth of these wrinkles, especially in the forehead and in the eye area.

CoQ10 (ubiquinone): is one of the most popular anti-ageing compounds [20, 21]. Coenzyme Q10 is present in all of the cells in our body, in a higher concentration in the mitochondrial membrane. Over time, the levels of Coenzyme Q10 decrease, and therefore, the antioxidant capacity of the skin also decreases. Another of its benefits is that it acts at the collagen and elastin levels; so, it is commonly used in anti-ageing formulations.

Melatonin: it has been found that a decrease in the secretion of melatonin accelerates the ageing processes. One of the most noteworthy benefits of melatonin is that it acts as an antioxidant and cell protector, given its capacity to neutralize the free radicals that cause tissue damage [22].

Dehydroepiandrosterone (DHEA): This endogenous prohormone is secreted by the adrenal glands and acts as a precursor for sexual hormone production. It is present in the production of estrogens and testosterone and is called 'the youth hormone', although, over recent years, this concept has been subject of considerable international debate. Our organism begins producing small quantities of this hormone around the age of 7 until approximately 25, when

reaching its maximum level, only to decrease its production by some 20% every ten years [23, 24].

Proteoglycans: these highly glycosylated proteins are found in the extracellular matrix of connective tissues such as the dermis and epidermis. Given their structural diversity, proteoglycans are functionally diverse both in the extracellular matrix and in the cell. Proteoglycans are the fundamental component of the extracellular animal matrix; therefore, they are the main substance that fills up the spaces existing between the organism's cells. Here, they form large complexes, both with other proteoglycans and with hyaluronic acid and proteins such as collagen, maintaining the skin's firmness and preventing the formation of wrinkles. Below we offer a more detailed examination of the role of proteoglycans and their use and role in skin ageing [25].

Figure 3 Graphic representation of the crystalline structure of monomeric decorin that represents its curve aspect and leucine-rich repeats. (A) LRR 4-6(leucine-rich repeats of the decorin).

Proteoglycans

In the connective tissue, most glycosaminoglycans (GAGs) are united to central proteins to form proteoglycans, which may range in size from 10 to 400 kDa [26]. Glycosaminoglycan chains are attached to these proteins whose composition leads to the classification of proteoglycans (PG). The GAG chains are united to the peptide chains via O-glycosidic bonds [27]. These GAGs are unbranched polysaccharide chains that form from repeated units of disaccharides. One of these disaccharide units is always an amino sugar, and the other is a uronic acid. The quantity of GAGs attached to the central protein varies from one to over 200 (Figs 2). A central protein may have identical GAGs attached to it, like the versican, or different molecules, such as the aggrecan.

These proteoglycans may be located both in the extracellular matrix and in the plasmatic membrane or intracellular vesicles. Glycosaminoglycan chains located in the intercellular space are capable of retaining large quantities of water and resisting external pressure. Thus, they are responsible for mechanically supporting the tissue structure and permitting cell migration. So, proteoglycans are some of the most important structural components of the extracellular matrix of connective tissues of the skin, given the diverse functions that they have in the dermis and they are essential for maintaining the skin's structural integrity.

Connective tissue, also known as conjunctive tissue, includes the following tissues: loose connective tissue, dense connective tissue, elastic tissue, adipose tissue, cartilaginous tissue and bone tissue. This tissue is made up of cells, fibres and ground substances, with the latter two making up the extracellular matrix.

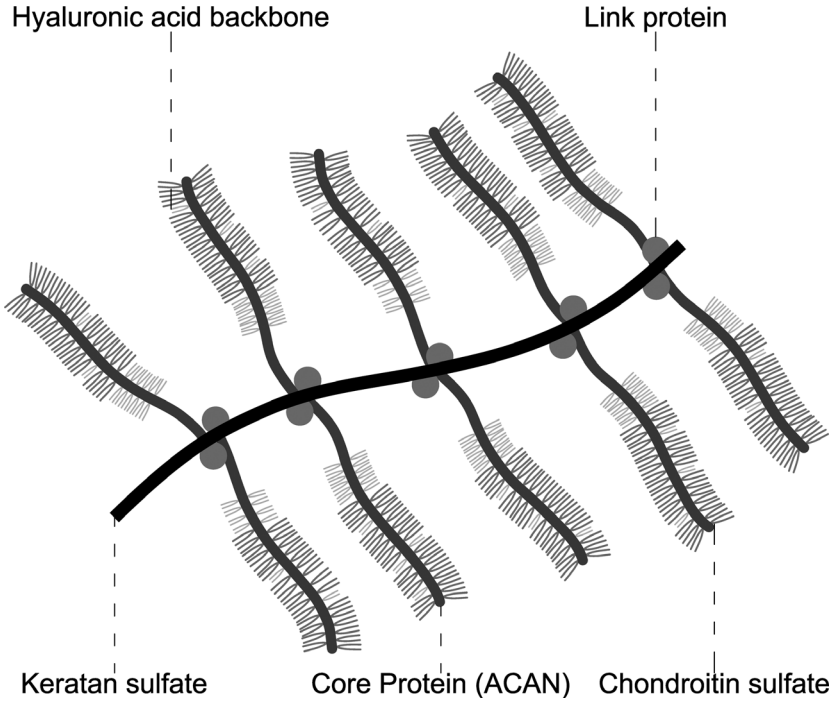

Figure 2 Structure of the proteoglycans.

The connective tissue performs the following functions:

- Serving as support and sustaining the organs since the bone and cartilaginous tissues are those that are mainly responsible for sustaining the human body.
- Nourishing the other tissues, mainly the epithelial tissue.
- Protection and defence through plasmatic and macrophage cells, making up the immune system which defends against foreign agents such as viruses and bacteria.
- Filling function, joining together neighbouring structures.

The extracellular matrix of the connective tissue is the material forming the majority of the dermis, apart from water and the cells. A large part of this extracellular matrix is synthesized by the fibroblasts, which are the most abundant cells in the connective tissue and which are responsible for synthesizing proteins such as elastin, collagen and glycosaminoglycans.

This matrix is primarily made up of complex proteins and sugars that are laid out forming an ordered network of fibres and fundamental substances. Its main components are collagen and the proteins making up the elastic fibres, as well as the proteoglycans and glycosaminoglycans, which carry out diverse functions regarding the skin.

Proteoglycan synthesis takes place in distinct cellular compartments. Ribosomes are responsible for carrying out the synthesis of the protein component of the proteoglycans, which is translocated into the lumen of the rough endoplasmic reticulum. Glycosylation of the proteoglycan occurs in the Golgi apparatus, and the entire proteoglycan is exported in secretory vesicles to the extracellular matrix of the cell.

Because polysaccharide chains (glycosaminoglycans) have many carboxyl and sulphate groups with negative charges that attract large numbers of cations, they play an important role in retaining large quantities of water in the extracellular matrix. For example, hyaluronic acid may contain water molecules of up to 1000 times its molecular weight [28].

Classification

As for the type of glycosaminoglycan that can attach to the protein and depending on the combination of units of disaccharide in the proteoglycans, they may be classified as: chondroitin sulphate (CS), dermatan sulphate (DS), keratan sulphate (KS), heparan sulphate (HS), heparin (HP) and hyaluronic acid (HA)-type proteoglycans.

There are diverse types of proteoglycans such as decorin, biglycan, perlecan, versican, aggrecan and syndecan.

- Aggrecan: found in cartilage and chondrocytes. It contains 100–150 molecules of keratin sulphate and chondroitin sulphate. Its function is to maintain the hydration of the extracellular matrix of the cartilage.
- Decorin and Biglycan: found in the connective tissue, fibroblasts, cartilage and bones, and they are proteoglycans that are rich in leucine with only one chondroitin sulphate or dermatan sulphate chain. Biglycan, especially, is expressed in mesenchymal tissues. They act on collagen fibrogenesis since they attach to neighbouring collagen molecules and contribute to directing the fibres. They regulate the thickness of the fibril and interact with the transforming growth factor beta (TGF- β).
- Versican: it is located in fibroblasts, skin, smooth muscle, the brain and mesangial cells of the kidney. It is associated with a protein and contains oligosaccharides and 12–15 chains of chondroitin sulphate attached to the central protein.
- Syndecan: found in the embryonic epithelium, cells of the lymphatic tissues, mesenchymal cells, lymphocytes and plasmocytes. It belongs to the family of transmembrane proteoglycans that contain variable quantities of heparin sulphate and chondroitin sulphate molecules. Its extracellular domain attaches collagens, heparin, and fibronectin; the intracellular domain attaches to the actin cytoskeleton.
- Perlecan: it is found in the basal membrane and belongs to the family of proteoglycans that have a chain of heparin sulphate-type glycosaminoglycan. It is expressed in a wide range of tissues where diverse cellular processes are regulated such as the formation of bone and cartilage, inflammatory processes and the curing of wounds, angiogenesis processes.

Proteoglycans of the skin

The most common proteoglycans of the human skin are decorin, perlecan and versican. It is of special note that decorin interacts with collagen, and versican is located in the elastic fibres of the skin. Both proteoglycans play a major role in the changes that take place over time in the skin properties of humans.

Decorin

Is a small proteoglycan that is rich in leucine with a chain of chondroitin sulphate (CS) or dermatan sulphate (DS)-type glycosaminoglycan. It regulates a wide range of cellular processes, such as collagen fibrogenesis, wound repair, angiogenesis, tumour growth and autophagy. These functions arise from a series of decorin/protein interactions, which also include interactions with its sole lateral chain of glycosaminoglycan. Two main functions should be noted: the maintenance of the cell structure and the external signalling, which culminates in anti-tumour effects (Fig. 3).

Decorin structure

This proteoglycan has a central domain that hosts 12 leucine-rich repeats (LRR) and an N-terminus attachment site for a unique chain of chondroitin or dermatan sulphate GAG. Its shape has been described as a horseshoe or banana-like, with a concave internal surface consisting of 14 curved β-sheets and a convex external surface that includes multiple α helices. Although it has been demonstrated that the GAG chain is important for some decorin/ligand interactions, most of the decorin attachments take place in its central protein. In fact, LRR 4–6 acts as an attachment site with a high affinity for collagen I. Besides, these same regions that are rich in leucine are responsible for the attachment of decorin to the receptor tyrosine kinase (RTK), such as receptor 2 of the vascular endothelial growth factor (VEGFR2) and the epidermal growth factor receptor (EGFR) [29].

Decorin/ligand interactions

Decorin interacts with a wide variety of ligands including constituents of the extracellular matrix, cellular receptors, growth factors, protease and other signalling molecules. The interactions between decorin and its ligands include its chain of glycosaminoglycans, as well as the attachments arising with its protein core. This lets decorin participate in many functions, thanks to its ability to activate or inhibit receptor signalling, kidnapping growth factors and, either directly or indirectly, altering the production of key matrix components, such as collagen.

In addition, it appears that monomeric decorin explains the majority of the interactions, since the dimerization of decorin means that its central region is not available for attachment to other substrates. In fact, studies carried out recently have demonstrated that the dimerization of decorin is reversible and also highlight decorin's capacity to alternate between the formation of homodimers or the interaction with collagen as a monomer [30].

The decorin GAG N-terminus chain also plays a large role in the availability of adjacent collagen fibrils. Specifically, the dermatan sulphate chain simultaneously attaches to a collagen molecule that interacts with the decorin protein core. Functionally, this interaction between decorin and collagen is crucial for the suitable formation of the fibrils. In addition to the interaction with type I collagen, decorin also attaches to types II, III, IV, V, VI, XII and XIV collagens, where there is a high affinity for the interaction with type VI collagen.

As is the case with collagen, decorin may interact with fibronectin (a protein responsible for adhesion, migration and cell differentiation). This interaction between decorin and fibronectin may be the result of an alteration of cell adhesion to the extracellular matrix.

Oddly, Tenascin-X (an extracellular glycoprotein that is expressed in connective tissues that modulates the maturity of the matrix and is involved in the pathogenesis of Ehlers–Danlos syndrome and glaucoma), which surround the collagen fibrils, is believed to have an association with decorin, which may help to maintain the mechanical resistance of the connective tissues. So, the presence of decorin is very important in the adequate formation of collagen and in ensuring the integrity of the matrix.

Furthermore, decorin can attach to EGFR (epidermal growth factor receptor) and may suppress the cell cycle through the induction of p21WAF1, partially explaining the ability of decorin to halt the tumour formation.

Finally, another important group of growth factors that interacts with decorin is the family of fibroblast growth factor (FGF). This factor attaches to the dermatan sulphate chain of decorin. This is a relevant interaction in the context of wound healing.

Changes taking place in decorin due to the ageing process

A study performed by Li Y. et al. in 2013 [31] analysed decorin extracted from the skin of young individuals aged 21–30, with that of others aged approximately 80 years, with results revealing that the molecular size of the decorin in the older skin was smaller than that found in the younger skin. This demonstrates that during the ageing process, the glycosaminoglycan chains of decorin in the human skin shorten. Therefore, it may be concluded that the reduction in size of the glycosaminoglycan chain may contribute to the fragility of skin in elderly individuals.

Decorin is known to regulate fibrogenesis of collagen, due to the interactions that are produced with its GAG chain. It is important to note the interaction produced between this molecule and collagen to ensure the proper formation of collagen fibrils. In addition, it was observed that with the passage of time, a decrease in molecule size takes place in the decorin of ageing skins, due to the shortening of the glycosaminoglycan chains, potentially resulting in the skin's increased fragility.

Perlecan

This is a proteoglycan that has a heparin sulphate-type glycosaminoglycan chain. Its structure consists of a protein core to which several linear heparan sulphate chains are covalently attached [32].

Given that it is expressed in the vascular tissues, it may be involved in a series of processes such as thrombosis, cell adhesion and vascular development. In addition, it is involved in angiogenesis, since it presents pro and anti-angiogenesis properties in the same molecule. Therefore, it may inhibit angiogenesis, capillary morphogenesis and the migration of endothelial cells. The role of perlecan in the functions of angiogenesis and autophagy is of great interest in terms of tissue homeostasis. This is due to its participation in the regulation and maintenance of the integrity of the epidermis, including tissue repair.

These activities are attributed to its ability to modulate the biological activities of the mitogenic and angiogenic growth factors such as vascular endothelial growth factor (VEGF) and FGF. In addition, they can protect heparin-binding growth factors from thermal denaturation and proteolytic degradation. Heparan sulphate proteoglycans (HSPGs) may increase the efficiency of heparin-binding growth factor since they stimulate the attachment to the receptor and the signalling and may influence the specificity of the adhesion of the growth factor/receptor [33].

Perlecan interactions

Perlecan interacts with components of the basal membrane, such as laminin-1, collagen IV, and the cellular adhesion molecules such as integrin β1.

It also interacts with microfibrils and fibrillin-1. It may connect fibrillin-1 to fibronectin fibres in the initial stages of microfibril biogenesis. Fibrillin-1 interacts with the heparin sulphate chains of perlecan domain I. Thus, the interaction between fibrillin-1 and perlecan may be important in the stabilization of the basal membranes [34].

Functions of perlecan

It has been shown that perlecan in keratinocytes is necessary for the correct formation of the epidermis and for cell proliferation and differentiation, increasing their levels. In the absence of perlecan, a decrease takes place in the biological levels or activities of the factors involved in cell survival and differentiation of keratinocytes. A strong correlation exists between the presence of perlecan and the normal formation of the epidermis. Studies have demonstrated that the administration of exogenous perlecan restores epidermal formation since it acts on the proliferation and differentiation of the keratinocytes [35].

Perlecan's role in the signalling of the growth factor has been demonstrated since it participates in the presentation of growth factors to their receptors. To conclude, during ageing, levels of perlecan decrease, potentially affecting tissue homeostasis.

Changes taking place in the perlecan levels due to exposure to UV radiation

Given heparin's ability to attach to diverse growth factors and promote cell proliferation, an increase in these chains caused by UV radiation may allow its participation in epidermal hyperplasia, caused by UV radiation and may lead to an accumulation of heparin sulphate in the photo-aged skin [36].

Versican

This proteoglycan has a chondroitin sulphate-type chain. It is expressed in tissues such as skin, blood vessels and the heart. It

affects a series of processes such as elastogenesis, the composition of the extracellular matrix and cellular adhesion and proliferation [37].

Structure of versican

This proteoglycan has a core with a protein that consists of three structural domains: N-terminus domain, the C-terminus region and the central domain, to which the glycosaminoglycan (GAG) chains attach. This domain is made up of two sub-domains (GAG-α and GAG-β).

There are four possible isoforms of versican having distinct sizes according to the domain structure of the gene and the protein of the core of the proteoglycan extracellular matrix: V0 (which has two regions to attach to GAG-α and GAG-β); V1 (which contains the GAG-β exon); V2 (which contains the GAG-α exon); and V3 (which does not contain the GAG exon, formed from the N-terminus G1 domain and the C-terminus G3). Hence, the N- and C-terminus ends are common to all of the isoforms, since in their N-terminus side (amino-terminus end), they have a protein attachment structure and a domain that mediates the interaction of versican with hyaluronic acid (HA). In its C-terminus end (carboxyl-terminus end), they have a C-type lectin domain and a CRP module [38]. The differences between isoforms are due to the GAG-α and GAG-β domains, which are found in the central domain. Thanks to the combination of the previously mentioned structural domains, an essential characteristic of this proteoglycan would be the ability to attach to complex carbohydrates in its N-terminus end, such as hyaluronic acid and, in its C-terminus end, to less complex sugars. Differences in the central subdomain give it diverse properties to modulate the viscosity of the matrix. This is because of the negative charge of the chondroitin sulphate chains, which permit its interaction with water molecules. This property allows it to regulate many of the positively charged molecules such as cytokines, growth factors and chemokines [39, 40].

Versican interactions

The central protein of versican is capable of binding to a variety of factors that are involved in the remodelling of the extracellular matrix and the regulating of the cellular phenotype. These variants have distinct effects that may influence cell proliferation, cellular adhesion and migration, the formation of pericellular coatings and elastogenesis [41]. But it is unclear if the specific domains of versican's central protein may imitate these effects or present different biological activities [42].

It has been demonstrated that the G1 domain in the N-terminus end interacts with hyaluronic acid and promotes the aggregation of chains of the same in the extracellular matrix.

In addition, it produces the compacting of collagen and elastin. So, this specific domain may permit versican activity to affect the remodelling of the extracellular matrix and cellular phenotype.

Changes produced in versican as a result of sun exposure

A study by Knott in 2008 [43] demonstrated that versican mRNA expression levels were not modified in skin that was protected from sun exposure. However, skin that was exposed to UV radiation experienced an increase in versican production. Therefore, it is suggested that sun exposure increases versican levels, resulting in large quantities of glycosaminoglycan chains in the extracellular space, protecting fibroblasts from the apoptosis produced by oxidative stress and favouring tissue repair and water absorption.

It may be interesting to note the role of versican on the skin since it influences processes such as elastogenesis, the composition of the extracellular matrix, cellular adhesion and proliferation. All of this is possible due to the nature of the protein of the versican molecule, which permits participation in the remodelling of the extracellular matrix, attaching to the hyaluronic acid and producing the compacting of collagen and elastin.

Commercialization of proteoglycans

Currently, and due to the great popularity, they have reached, and there are numerous laboratories (Martiderm, Endocare, Farline…) that formulate proteoglycans in different cosmetic forms such as ampoules, serums or creams.

Therefore, we can suggest that, given the nature of the proteoglycans, they may be included in dermatological preparations and, given their similarity to our own molecules, they will act effectively in the repair of the support tissue, hydrating and smoothing the skin and reducing wrinkles.

Conclusions

Most of the changes occurring in the skin over time take place in the dermis layer, where alterations in collagen and proteoglycans occur. Therefore, the study of these components is of great interest, as is the role of these components in human skin.

The proteoglycan structure is responsible for diverse functions that are exercised on the skin, preventing the appearance of wrinkles, increasing skin hydration and elasticity, as well as antioxidant effects and protection from oxidative stress caused by an increase in free radicals.

During the ageing process, a decrease in the size of endogenous proteoglycans takes place in the extracellular matrix, and skin becomes more fragile and delicate; therefore, an exogenous contribution of this molecule may delay or prevent ageing, helping to hydrate and repair the cutaneous tissue.

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