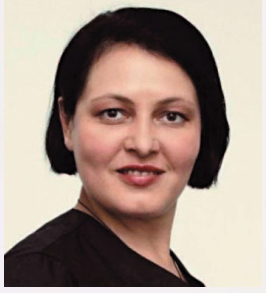
IMPROVING SKIN QUALITY WITH HYALURONIC AND SUCCINIC ACID

Alexander Turkevych, Natalia Derkach, Anna Kupriyanova, Leila Zubair, Marta Turkevych, and **Danylo Turkevych** discuss the findings from their novel new study combining succinic acid to improve HA filler results

ABSTRACT

Natural ageing is the result of years gone by and is called chronological ageing. At the same time, there is a thickening of the horn layer and thinning of other layers of skin. The amount of hyaluronic acid produced begins to reduce. The walls of the blood capillaries become thinner. There is a descent of the soft tissues of the face under the action of gravity. As a result of these changes, the skin loses elasticity and deep wrinkles are formed. A pervasive feature of ageing is a progressive and chronic state of systemic low-grade inflammation referred to as 'inflammaging'. The role of various inflammatory molecules—mainly tumour necrosis factor-α (TNF-α), interleukin- (IL-) 1b, IL-6, and transforming growth factor-β (TGF-β) in the promotion or exacerbation of a wide range of ARDs is increasingly emerging. When a patient is injected with hyaluronic acid we re-create volume and by creating more tension more hydration is achieved. Unfortunately, the effects are temporary, short lasting and somehow HA does not re-create what is continuously disappearing. The ageing phenomenon of the face is not limited to collagen and fibroblasts but also to bone loss on which HA does not have any effect. It is well-known that collagen fibres are the main frame element of the dermis and the changes that occur with them required more detailed study. Recent studies (2016-2018) of the regulation of the morphofunctional state of macrophages indicate the involvement of the succinate/SUCNR1 system in the formation of the reparative (anti-inflammatory M2) macrophage phenotype. There are data that confirm the relationship of succinate/SUCNR1 signalling with the mechanisms of angiogenesis and demonstrate the universality of the angiogenic effects of the succinate/SUCNR1 system, manifested in different tissues. We show in the study that addition of hyaluronic and succinic acid in specific concentrations with the needle, cannula or roller delivery injection methods should deliver a new useful treatment against the early inflammation stage. Also direct effect of the introduction of HA+Na succinate 1.6% on the level of synthesis of endogenous growth factors that directly affect the rate of tissue regeneration and renovation was found.





OVER THE LAST 10 YEARS, AESTHETIC dermatology has been a rapidly developing field of medicine. One of the key tasks for us practitioners is to fight the visual and structural changes to the skin brought on by the ageing process.

Changes that occur in the skin with age result from an irreversible genetically programmed process. This natural ageing is the result of years gone by and is called chronological ageing. At the same time, there is a thickening of the horn layer and thinning of other layers of skin. The amount of produced hyaluronic acid starts to reduce. The walls of the blood capillaries become thinner. There is a descent of the soft tissues of the face under the action of gravity. As a result of these changes, the skin loses elasticity and deep wrinkles are formed.

Facial ageing

The ageing process on the face is multifactorial. The ageing process causes damage to the dermis and epidermis with decreased collagen, elastin, skin, fatty layers, number of cells and the extracellular matrix. This, in turn, leads to changes in skin texture, firmness, radiance, volume, flexibility and the appearance of wrinkles.

However, the ageing process is more than this—it is a complex interaction between varieties of facial elements, and it happens in four main facial layers: skin, fat, muscles, and bones.

Facial fat volume decreases with age, causing a 'deflated' look. Also, the hydrating and elastic functions of the skin no longer work as efficiently. The fibroblasts producing elastin, collagen and hyaluronic acid work better when they are under a degree of stretch. When the fat depletes, this stretch is diminished and the skin sags.

On the muscle front, it will be noted as part of the ageing process that some muscles get looser while others get tighter.

The bony facial skeleton changes—principally the facial apertures. The nose and the eye sockets increase by 20% in size with age and the infraorbital region physically moves backwards, so the holes are not only bigger but are also pushed back.

Above the muscles, the amount of fat that decreases with age causes a deflated effect, which not only means volume loss but also that the hydrating and elastic functions of the skin don't work as efficiently. The fibroblasts producing elastin, collagen and hyaluronic acid work better when they are under a degree of stretch. When the fat depletes, this stretch is reduced and the skin sags.

A pervasive feature of ageing is a progressive and chronic state of systemic low-grade inflammation referred to as inflammaging. The role of various inflammatory molecules—mainly tumour necrosis factor- (TNF-) α, interleukin- (IL-) 1b, IL-6, and transforming growth factor- (TGF-) β—in the promotion or exacerbation of a wide range of ARDs is increasingly emerging. A number of mechanisms, pathways, and cell types have been shown to possibly contribute to inflammaging. Initial hypothesis affirmed that inflammaging was mainly due to the long-lasting exposure to acute and chronic infections and the consequent life-long antigenic burden. However, a long list of sterile potential sources of inflammatory molecules during both the cellular and the organismal ageing process has been proposed.

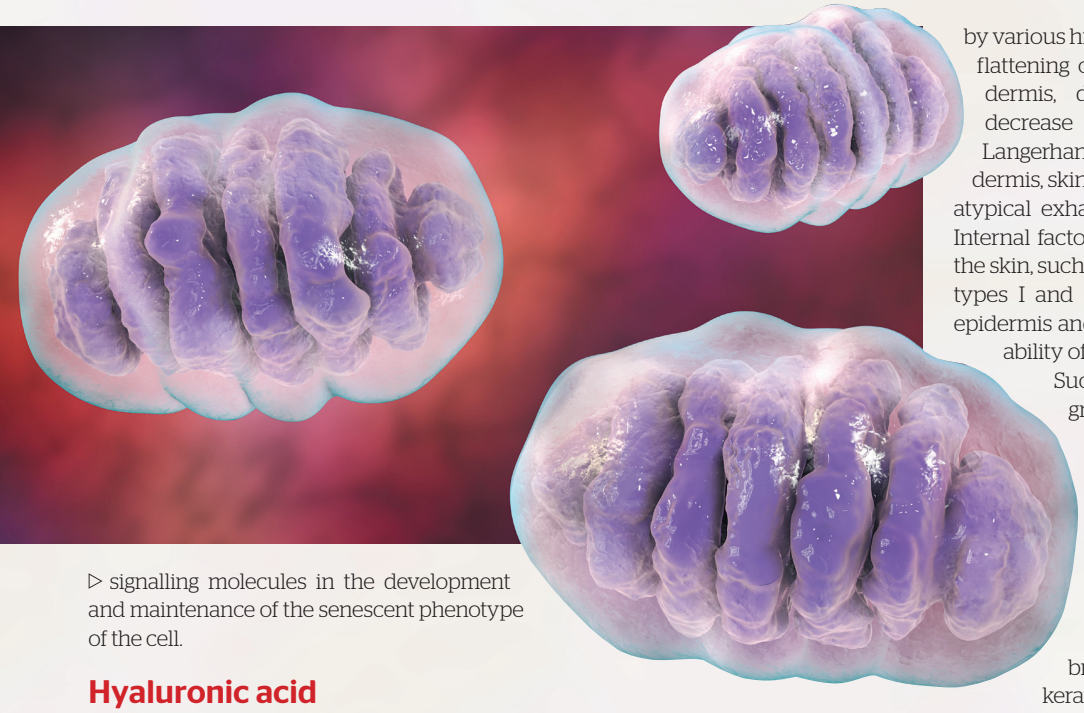
The 'old' free radical theory of ageing (FRTA) states that organisms age because cells accumulate free radical-induced damage over time. One interesting view that coupled FRTA with inflammaging is the oxi-inflammaging theory. Accordingly, excessive or uncontrolled free radical production can induce an inflammatory response, and free radicals are themselves, inflammation effectors. Oxidative metabolism at the mitochondrial level is probably the major source of intracellular ROS production, which in turn represents life-long-lasting stress. Ageing-related ROS accumulation can contribute to telomere attrition, oxidative genomic damage, but can even act as ▷

ALEXANDER TURKEVYCH MD, PhD, Assoc. Prof; **NATALIA DERKACH**, MD, PhD, MBA; **ANNA KUPRIYANOVA,** MD; **KIROVA YU,** Biologist, PhD, DSci. Prof; **LEILA ZUBAIR**, MD; **MARTA TURKEVYCH**, MD; **DANYLO TURKEVYCH**, MD

email aturkevych@gmail.com

KEYWORDS
Hyaluronan, succinate, SUCNR1, HA plus Na succinate 1.6%, VEGF, FGF2, TGFb1, inflammaging, fibroblasts, elastin, collagen

> "A pervasive feature of ageing is a progressive and chronic state of systemic low-grade inflammation referred to as inflammaging."



▷ signalling molecules in the development and maintenance of the senescent phenotype of the cell.

Hyaluronic acid

The presence of hyaluronic acid (HA) in the skin declines over the years, resulting in a loss of moisture, elasticity, firmness and volume. Our bodies are in a continual state of rebuilding—new skin cells, for example, replace old ones about every 20 to 30 days. Usually, hyaluronic acid in skin tissue is broken down by hyaluronidase, and the rate of degradation can be increased by an excess intake of riboflavin (B2), ultraviolet radiation exposure or viruses. Signs of natural skin ageing become apparent with wrinkles, loss of volume in the cheeks and thinning lips.

Hyaluronic acid is a polysaccharide composed of alternating molecules of N-acetyl glucosamine and D-glucuronic acid, and are present in almost every cell in the human body. It can be found within collagen throughout the body but 50% of hyaluronic acid is concentrated in the skin. In the extracellular matrix, hyaluronic acid performs a range of biological functions but it mainly regulates moisture, increases fibroblast activity, and stimulates collagen synthesis.

When a patient is injected with hyaluronic acid, we re-create volume and by creating more tension, more hydration is achieved. Unfortunately, the effects are temporary, short-lasting, and somehow HA does not re-create what is continuously disappearing. The ageing phenomenon of the face is not limited to collagen and fibroblasts but also to bone loss on which HA does not have any effect.

However, the use of HA alone may not reduce many of the effects of ageing. Sodium succinate can provide an antioxidant effect by actively blocking free radicals and stimulating sluggish metabolic processes in the skin, therefore aiming to reduce the signs of ageing.

Ageing and collagen

Ageing of the skin due to internal factors is accompanied by various histological changes in all its layers, including flattening of the border between the epidermis and dermis, disappearance of the dermis papillae, decrease in the number of melanocytes and Langerhans cells in the epidermis, atrophy of the dermis, skin clades, disappearance of elastic fibres, and atypical exhaustion and fragmentation in the dermis. Internal factors of ageing lead to functional changes to the skin, such as a decrease in the production of collagen types I and III, decrease in speed of regeneration of epidermis and activity of cells of the skin, as well as the ability of the skin to repair.

> “Oxidative metabolism at the mitochondrial level is probably the major source of intracellular ROS production, which in turn represents life-long-lasting stress.”

Such changes due to ageing are primarily the gradual destruction of collagen and elastin, which leads to a decrease in the amount of intercellular matrix, depletion of cellular composition, the commencement of microcirculatory dysfunction, and a reduction in the strength and elasticity of the dermis. These changes are especially noticeable in skin exposed to the sun, where we can see the appearance of bruises and haemorrhages, senile purpura, keratomas and angiomas. The subcutaneous fat layer becomes thinner, increases the risk of skin damage and decreases the ability to maintain body temperature.

It is well-known that collagen fibres are the mainframe element of the dermis and the changes that occur within them required a more detailed study. The prospect of deep analysis and understanding of the processes of stimulation of collagen genesis and biodegradation can have a significant impact on the development of new methods of visible and functional skin correction, as well as allow us to review existing strategies for their rationality and effectiveness.

Collagen is not homogeneous in structure and origin. Currently, 20 types of collagen are described, differing in amino acid sequence and degree of modification. Fibrillar collagen—it includes collagen I, III, and V. It is the bulk of collagen in the skin, which is woven from bundles of fibres.

95% of all collagen in the human dermis is type I and III collagen, which form very strong fibres: approximately 80-90% is type I collagen (type V collagen morphologically represents heterotypic type I collagen fibres) and 8-12% of collagen is type III. Moreover, type I collagen is the main ‘adult’ and ‘strong’ collagen, and type III collagen is the embryo-dermis collagen, i.e. very young collagen. Collagen type V is combined into fibrils with collagen of the first and third types and is involved in the regulation of the diameter of the fibrils. Thus, it is collagen types 1 and 3 that is crucial in ensuring the turgor of the skin and retaining its essential properties.

Many methods of possible collagen stimulation were described, as well as many biochemical formulations were designed. But many of them are not as effective as we need, some are fiction, and the majority have a lack of evidence. Most popular are biorevitalization and mesotherapy. Biorevitalization is a series of injections ▷

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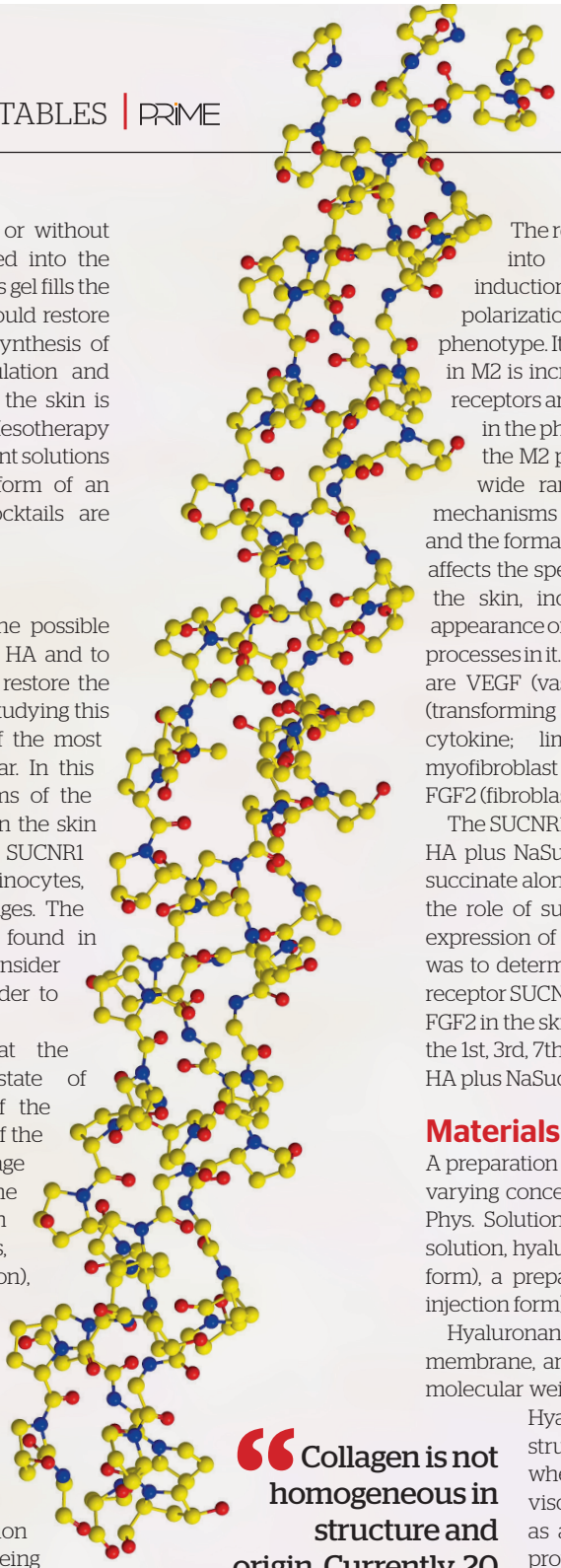

▷ of non-cross-linked hyaluronic acid with or without other active ingredients, which are injected into the subcutaneous dermis in the form of a gel. This gel fills the volume deficit with hyaluronic acid and should restore the water-lipid balance and enhance the synthesis of collagen, elastin, and improve microcirculation and nutrition of the subcutaneous layers. Next, the skin is tightened and wrinkles are smoothed out. Mesotherapy is the procedure in which injections of different solutions are administered subcutaneously in the form of an aqueous solution into which various cocktails are sometimes added.

Study

In this article, we would like to analyze the possible behaviour of succinic acid salt mixed with HA and to present evidence of how this solution can restore the aesthetic quality of the skin. We have been studying this topic for years and, in our opinion, one of the most indisputable studies was prepared this year. In this study, the succinate-dependent mechanisms of the succinate SUCNR1 receptor were detected in the skin and the presence of the succinate receptor SUCNR1 was highlighted in fibroblasts, keratinocytes, endotheliocytes, mast cells, and macrophages. The highest level of SUCNR1 expression was found in macrophages, which made it possible to consider them as the main target of exposure in order to stimulate the regeneration of the skin.

Recent studies (2016–2018) looking at the regulation of the morphofunctional state of macrophages indicate the involvement of the succinate/SUCNR1 system in the formation of the reparative (anti-inflammatory M2) macrophage phenotype[1-5]. Dermal macrophages are the main population of skin immune cells that, in addition to immune function (phagocytosis, cytokine secretion and antigen presentation), mediate the mechanisms of tissue development, tissue homeostasis, inflammation and repair[6,7]. According to the literature[3], macrophages of type 1 (pro-inflammatory phenotype, M1) play one of the key roles in inflammation, as well as in 'inflammaging'[8-11].

One of the well-known theories of ageing is the theory of inflaming (chronic inflammation in the skin, during which the main signs of ageing are formed—a dull complexion, the formation of dermal depressions, pigmentation and other signs by which we are used to determining the condition of the skin). Currently, great importance is attached to resident macrophages in the development of inflaming. At the outset of inflammation, macrophages are activated, and more than 400 genes are needed to eliminate bacteria and regulate other cells through the secretion of cytokines and chemokines. Type 1 macrophages are the most active tissue producers of succinic acid, which is associated with the activation of glycolytic ATPh production and a partial blockade of the Kreb's cycle[4].

> "Collagen is not homogeneous in structure and origin. Currently, 20 types of collagen are described, differing in amino acid sequence and degree of modification. Fibrillar collagen—it includes collagen I, III, and V. It is the bulk of collagen in the skin, which is woven from bundles of fibres."

The release of succinic acid by M1 macrophages into the extracellular space leads to the induction of SUCNR1 and their subsequent polarization into a reparative/anti-inflammatory M2 phenotype. It was shown that the expression of SUCNR1 in M2 is increased compared to M1[4,12-16]. Thus, SUCNR1 receptors are involved in the regulation of the changes in the phases of inflammation and the formation of the M2 phenotype macrophages, which express a wide range of growth factors that realize the mechanisms of angiogenesis, fibroblast proliferation, and the formation of the dermal matrix, which generally affects the speed and quality of reparative processes in the skin, including the processes of restoring the appearance of the skin and the activation of rejuvenation processes in it. Markers of the M2 macrophage phenotype are VEGF (vascular endothelial growth factor), TGFb1 (transforming growth factor; immunosuppressive cytokine; limits neutrophil chemotaxis, initiates myofibroblast differentiation and collagen synthesis), FGF2 (fibroblast growth factor)[15,17,18].

The SUCNR1-dependent mechanisms of activity of the HA plus NaSuc 1.6% were compared with just HA and succinate alone. The aim of the study was to understand the role of succinate/SUCNR1 in the regulation of the expression of growth factors in the skin. The main task was to determine the expression level of the succinate receptor SUCNR1/GPR91 and growth factors VEGF, TGFb1, FGF2 in the skin of the anterior abdominal wall of rats on the 1st, 3rd, 7th day after a single intradermal injection of HA plus NaSuc 1.6% solution[19,20].

Materials and methods

A preparation containing Succinate 1.6% was mixed with varying concentrations of hyaluronic acid 1.1%, 1.8%, 2%, Phys. Solution (injection form), 1.6% sodium succinate solution, hyaluronic acid solution (commercial injection form), a preparation containing peptides (commercial injection form).

Hyaluronan is a normal constituent of the basement membrane, and in its native form, HA exists as a high molecular weight polymer, typically in excess of 106 Da. Hyaluronan plays a role in maintaining the structural integrity of tissues such as the joint where it is responsible for maintaining the viscosity of joint fluid. In addition to existing as a soluble polymer, HA is bound to large proteoglycans such as aggrecan and versican. Hyaluronan side-chains of aggrecan are important in cartilage organization and recent data have suggested that HA is essential for maintaining cartilage integrity. At sites of inflammation, such as during inflammatory arthritis or in wound healing, HA becomes depolymerized into lower molecular weight forms[21-23].

There appear to be two mechanisms for depolymerizing HA, enzymatic and non-enzymatic. The enzymes that degrade HA are hyaluronidases, chondroitinases and ▷

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▷ hexosaminidases. Most hyaluronidases are lysosomal enzymes and require an acid pH for maximal activity. However, the hyaluronidase PH-20, found in sperm, is active at pH7. Recently, a soluble form of PH-20 has been identified.

In addition, a novel hyaluronidase (Hyal-2) that generates HA fragments of 10–20×103Da has been described. Hyal-2 is expressed in fibrotic lung injury.

Hyaluronan can also be degraded into smaller fragments by exposure to ROI. This is an important mechanism for generating HA fragments at sites of inflammation. Interestingly, hyaluronidases are endoglucosaminidases, whereas ROIs fragment HA randomly at internal glycoside linkages[21-23].

Hyaluronan degradation products appear to have biological functions distinct from the native high molecular weight polymers. Oligosaccharides of less than 20 disaccharides have been shown to be angiogenic. Low and intermediate molecular weight HA (2×104–4.5×105Da) stimulate gene expression in macrophages, endothelial cells, eosinophils and certain epithelial cells. Hyaluronan degradation products are purported to contribute to scar formation. To put it into context, fetal wounds heal without scar formation and wound fluid HA is of a higher molecular weight. When hyaluronidase is added to generate HA fragments, there is increased scar formation. Collectively, data supports the concept that high molecular weight HA promotes cell quiescence and supports tissue integrity, whereas the generation of HA breakdown products is a signal that injury has occurred and initiates an inflammatory response. Interestingly, whether it be wound healing, liver injury or lung injury, there is a potent mechanism for clearing HA following tissue injury. This suggests that while the generation of HA breakdown products may be important in initiating the inflammatory response, the removal of these fragments may be critical for the resolution of the repair process.

The mechanisms by which HA accumulates in tissue injury have been studied. Elegant work from Swedish investigators has demonstrated that growth factors such as PDGF and TGF-β that accumulate following bleomycin lung injury stimulate lung fibroblasts to produce HA. However, whether increases in HA are due to increased production or decreased degradation were difficult to ascertain at that time because the genes encoding HA synthases were unknown.

However, as stated above, three isoforms of HA synthase have recently been cloned. The three isoforms exhibit different patterns of expression in developing embryos. HAS1 is expressed early from day 1-5, HAS2 is expressed throughout development, and HAS3 is expressed in late development. The three isoforms map to three distinct chromosomes, suggesting that they arose from ancient gene duplication.

Targeted deletion of HAS2 has recently been reported. HAS2 deletion results in an embryonic lethal condition, whereas HAS1 and HAS3 mice develop normally. The HAS2 deletion appears to present a similar phenotype to that described for a naturally occurring versican knockout. Interestingly, *in vitro* data suggests that HAS1 and HAS2 produce high molecular weight HA, whereas HAS3 produces lower molecular weight HA.

The intradermal administration of the succinate-containing preparations and comparison preparations was performed once. Skin samples were taken 1, 3, and 7 days after drug administration.

Key points

- Changes that occur in the skin with age results from an irreversible genetically programmed process.
- A pervasive feature of ageing is a progressive and chronic state of systemic low-grade inflammation referred to as inflammaging. The role of various inflammatory molecules in the promotion or exacerbation of a wide range of ARDs is increasingly emerging
- However, the use of HA alone may not reduce many of the effects of ageing. Sodium succinate can provide an antioxidant effect by actively blocking free radicals and stimulating sluggish metabolic processes in the skin, therefore aiming to reduce the signs of ageing
- The addition of hyaluronic and succinic acid in the needle, cannula or roller delivery injection methods should deliver a new useful treatment against the early inflammation stage. Patients in clinical practice are usually treated with a range of products and treatments to provide synergistic effects. This combination will improve patients' satisfaction, minimise the possible adverse reactions and improve aesthetic outcomes

Data objective methods

Immunoblotting (Western blot analysis)

This method allows combining protein electrophoresis and the use of antibodies to conduct highly specific identification of proteins in the lysates of biological tissues.

For the extraction of SUCNR1, VEGF, TGFb1, and FGF2, two buffers were used: hypotonic and cytoplasmic.

Next, Western blots were incubated in a solution of the first polyclonal antibodies (Abcam, USA; anti-GPR91 antibody (ab41505), anti-VEGF antibody (ab53465), anti-TGFβ1 antibody (ab92486), anti-FGF2 antibody (ab8880)) in a dilution of 1:500. Proteins were detected by reaction with ECL reagents (Pierce Biotechnology, Inc., USA) on a Kodak film followed by densitometry using Adobe Photoshop. The content of the desired proteins was judged by the density of the staining band of the antibody-protein binding band. The result was expressed in relative densitometric units (ODE).

Statistical analysis of the data was performed using the Statistica 10 programme, using the nonparametric rank U-test (Wilcoxon-Mann-Whitney). Statistical significance between the compared groups was considered at $p < 0.05$.

Results and discussion

According to Western blot analysis, the expression level of the SUCNR1 receptor in HA plus Na succinate and just Na succinate solutions increased in skin samples. In other samples, injected once—phys. with a solution, hyaluronic acid, and a peptide containing a preparation—there were no changes in the expression level of SUCNR1. This confirms the highest tropism of SUCNR1, specifically to HA plus Na succinate and Na succinate solutions, and the lack of influence of other substances involved in the experiment on the activation of the SUCNR1 receptor.

The level of VEGF increased significantly only in skin samples injected with HA plus Na succinate or Na succinate solutions, increasing 150% in comparison with the control (1 day after administration of saline solution). Injected with hyaluronic acid, an increase in the level of VEGF was also noted, which did not exceed 20% relative to the control. VEGF expression did not change in skin samples injected with nat. a solution. In a sample treated with a preparation containing peptides, the expression of VEGF was not more than 15% of the initial level.

The data obtained confirmed the relationship of succinate/SUCNR1 signalling with the mechanisms of angiogenesis and demonstrate the universality of the angiogenic effects of the succinate/SUCNR1 system, manifested in different tissues.

Induction of FGF2 was observed in skin samples of all

experimental groups. However, a 200% increase in the level of FGF2 expression was detected only in samples treated with HA plus Na succinate or Na succinate solutions. In other comparison groups (hyaluronic acid, peptides), the level of expression of growth factors did not exceed 140% of the control (1 day after injection of saline solution). Accordingly, HA plus Na succinate is more active in stimulating fibroblast proliferation, and it is these substances that must be considered primarily to stimulate collagen synthesis in the skin.

The maximum increase in the expression level was observed for TGFb1 and amounted in samples injected with HA plus Na succinate or Na succinate solutions (2 and 3 times, respectively), while in other groups (hyaluronic acid, peptide-containing preparations) did not exceed 50%. In the samples injected with nat. solution, the level of TGFb1 did not change.

Weak induction of growth factors was observed in the comparison groups (injection of saline solution, hyaluronic acid, peptide-containing preparation) was not associated with the induction of succinate receptor SUCNR1 and could be caused by skin damage during a single intradermal injection procedure (20 injections on a skin area of 10 cm^2). This fact confirms that needle injury also causes skin repair at the site of injury and rollers with high-quality needles is an important device in skin rejuvenation.

Thus, in the study, the conjugate induction of the succinate receptor SUCNR1/GPR91 and all the studied growth factors (VEGF, FGF2, TGFb1) in the samples injected with succinate-containing preparations (HA plus Na succinate and Na succinate) was revealed. In this case, the HA plus Na succinate 1.6% formula is effective (pronounced induction of all growth factors) and safe.

The data obtained are consistent with the results of stage I of the study, during which the standard HA plus Na succinate 1.6% administration course (3-fold with two-week intervals) was accompanied by an increase in the number of fibroblasts, the density of the vascular network and the density of collagen fibres. During the first stage of the study, methods of immunohistochemical analysis of the skin and analysis of histological sections were used.

Conclusion

During the second stage of the study, a direct effect of the introduction of HA plus Na succinate 1.6% on the level of synthesis of endogenous growth factors that directly affect the rate of tissue regeneration was found. It was also proved that it is possible to directly influence the processes of chronic inflammation and the possibility of using the HA plus Na succinate 1.6% preparation to consciously begin the processes of polarization of macrophages in the skin (the pro-inflammatory phenotype M1 into the anti-inflammatory phenotype M2) was revealed. This revelation, in turn, opens up great opportunities for doctors of various specialties, including dermatologists and plastic surgeons, in the planned initiation of regeneration, repair and rejuvenation processes, as well as the blockade of the willow processes in the tissues associated with the presence of chronic inflammation because it is widely understood that the process of chronic inflammation is one of the fundamentals in the pathogenesis of ageing.

> **“The addition of hyaluronic and succinic acid with the needle, cannula or roller delivery methods should deliver a new useful treatment against the early inflammation stage.”**

The addition of hyaluronic and succinic acid with the needle, cannula or roller delivery methods should deliver a new useful treatment against the early inflammation stage. Patients in clinical practice are usually treated with a range of products and treatments to provide synergistic effects. This combination will improve patients' satisfaction, minimise the possible adverse reactions and improve aesthetic outcomes.

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