Cells biomodulation: the future of Dermatology

Biomodulação celular: o futuro da Dermatologia

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ABSTRACT

The evolution of medicine has allowed an increasingly in-depth knowledge of diseases and medications, involving cellular structures and associated molecules. In dermatology, we begin to unveil cell modulation associated to the use of substances such as botulinum toxin, hyaluronic acid, among others. This new era allows us to comprehend information that goes beyond a macroscopic view and explore cell interaction, leading to a broader knowledge to optimize dermatologic treatment.

Keywords: Biology; Cells; Dermatology

RESUMO

A evolução da Medicina tem permitido um conhecimento cada vez mais profundo de patologias e medicações envolvendo estruturas celulares e moléculas associadas. Em Dermatologia, começamos a desvendar a modulação celular associada ao uso de substâncias como a toxina botulínica, o ácido hialurônico, entre outros. Esta nova era nos permite compreender informações que vão além de uma visão macroscópica e explorar a interação celular, adquirindo-se conhecimento mais amplo para otimizar a terapêutica dermatológica.

Palavras-Chave: *Biologia; Células; Dermatologia*

INTRODUCTION

The evolution of Medicine over the years has allowed the knowledge of the mechanism of action of diseases and medications in the intra and extracellular levels. The initial knowledge that was restricted to anatomy and a macroscopic view of physiology in many areas of Medicine, is advancing towards cellular microscopy, with better understanding of the intracellular and extracellular structures and many molecules secreted by different parts of a cell. The knowledge on cellular microenvironments allows us to observe the way cells interact and react to the external environment. However, there is still a lot of information to come.

In dermatology, we are also entering a new era once we started to unveil cell modulation associated to the use of nanoparticles and biodegradable substances. Initially, when using substances such as botulinum toxin and hyaluronic acid, we had their macroscopic action as the basic concept, meaning that hyaluronic acid acts occupying space and stimulating collagen, and the toxin acts paralyzing the muscles through acetylcholine blockage at the muscular junction.

Review Articles

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Nowadays, we understand the action of these substances is much broader: it involves cell modulation, i.e., botulinum toxin also acts controlling inflammation, pain, pruritus, among others, whereas hyaluronic acid acts beyond filling since it interacts with adipocytes, fiber networks of the extracellular matrix and mesenchymal stem cells.[1,2]

We know that cells are rarely balanced, and understanding how cellular changes occur are fundamental issues in Cell Biology. There is much to understand about how cells accumulate information on their environment over time and how external stimuli are molecularly translated into cellular decisions. Controlling the environment as much as possible can help answer these questions. The future work should focus in the development of new ways of tracking and observing the cell dynamics over long periods of time. Besides, one must note that the changes do not only take place inside the cells; cells also change their surroundings.

With this study, we aim to comprehend the cellular activity of substances frequently used in Aesthetic Dermatology. With this literature review, we bring information that will allow us to understand their mechanism of action way beyond their macroscopic view, in order to optimize and broaden their use in Dermatology and explore more benefits for our patients.

Botulinum toxin

We know that botulinum toxin blocks the release of acetylcholine and many other pre-synaptic neurotransmitters, deactivating SNARE proteins and providing therapeutic applications in neurologic conditions with safety and efficacy. The skin also interacts with the nervous system and there are increasing evidences that the neurologic system plays a part in cutaneous inflammation and wound healing.[3,4] This way, botulinum toxin has been used in many dermatologic conditions that include prevention of scarring, facial flushing, post-herpetic neuralgia and pruritus, with great results. The mechanism involved in these new indications includes suppression of mast cell activity, inhibition of substance P, peptide related to calcitonin gene and release of glutamate.[5]

There are growing evidences that botulinum toxin (BoNT) shows biologic effects in many types of human cells, with a series of clinical implications associated to its non-neuronal and non-muscular effects. BoNT receptors and intracellular targets are not exclusive for neurotransmission. They have been found in neuronal and non-neuronal cells. Non-neuronal cells that express one or more botulinum toxin binding proteins and/or proteins associated to the synapse cleavage target include: epidermal keratinocytes; subcutaneous fat tissue mesenchymal stem cells; cells of the nasal mucosa; urothelial cells; epithelial intestinal, prostate and alveolar cells; breast cell lineages; neutrophils; and macrophages. BoNT/A serotype can also cause specific biological effects in dermal fibroblasts, sebocytes and vascular endothelial cells.[6]

The use of BoNT in hypertrophic scars and keloids has been associated to the significant reduction of erythema, pruritus, elasticity and size of the scar.[7,8] The molecular mechanism involved in this process encompasses the inhibition of the proliferation of fibroblasts derived from the scar tissue, besides suppression of the expression of the transforming growth factor TGF-beta1, collagen I and II and muscle proteins actin and myosin II in keloid fibroblasts.[5,9,10,11] The symptoms of pruritus and pain are alleviated with the reduction of tension in the skin and local muscles, releasing nerve fibers trapped in the scar.[5]

The prevention of surgical scars and the improvement in their appearance can also be achieved with botulinum toxin. A study performed in patients with thyroidectomy scars, treated 10 days after surgery showed significant improvement in comparison with the group treated with saline 0.9% (control).[12,13] The anti-inflammatory action of botulinum toxin in the cutaneous vascularization reduces the inflammatory phase of the cicatricial process; besides, its action in fibroblasts and in the expression of TGF-beta1 acts improving the appearance of the scar.[5]

Regarding evidences of the action of botulinum toxin for the treatment of rosacea and facial flushing, it is known that BoNT acts inhibiting the release of inflammatory mediators such as the gene related to calcitonin peptide and substance P. Therefore, reduction of the local cutaneous inflammation causes improvement of the erythema. Flushing also improves due to the blockage of the release of acetylcholine from the peripheral nerves of the cutaneous vascular system.[14,15,16]

Post-herpetic neuralgia is a very common complaint due to the neuropathic pain resulting from herpes zoster infection. Botulinum toxin is an effective therapeutic alternative in relation to the main treatments used (anti-inflammatory, gabapentin, opioid and tricyclic antidepressants). The exact mechanism of action of BoNT in post-herpetic neuralgia is still unclear, however, there is the action of peripheral and central mechanisms involved. The peripheral effects are associated to the inhibition of release of neuropeptides from nociceptive peripheral nerves, whilst the central nervous system acts through the transport of peripheral axons (area of application) towards the central.[5, 17,18]

Pruritus, present in many dermatologic conditions, when peripherally induced (pruriceptive pruritus) shows significant improvement with the application of intradermal botulinum toxin.[19] The molecular mechanisms involved in the improvement of pruritus with botulinum toxin are mast cell stabilization and inhibition of its degradation caused by BonT.[20] Furthermore, BonT interacts with substance P, which is associated to the release of histamine by the activation of mast cells and vasodilation. Peripheral pruritus is usually accompanied by cutaneous inflammation in the majority of cases, such as atopic dermatitis and psoriasis. Therefore, the anti-inflammatory capacity of BoNT improves inflammation with subsequent improvement in the pruritus.[5]

The use of botulinum toxin for the treatment of dyshidrosis can be explained by its action in the muscles surrounding the sweat glands and by the inhibition of the release of acetylcholine, which reduces sweating, associated to the inhibition of substance P, which causes reduction in pruritus.[21,22] For hidradenitis, BoNT also acts reducing sweating; as a consequence, it reduces bacterial flora and subsequent inflammation.[23] In Hai-

ley-Hailey disease, there is reduction of sweating, pruritus and inflammation, also associated to the inhibition of acetylcholine and substance P.[5]

Recently, BoNT has been used in the control of skin oiliness.[24,25] Sebum contributes to the delivery of soluble antioxidants in fat on the skin surface and has antimicrobial activity, working as a cutaneous barrier. However, excessive sebum blocks the pores and offers nutrients to bacteria, which can result in inflammation of the skin.[5] The exact mechanism of botulinum toxin in the reduction of sebum is not completely clear, but it is likely that erector pilli muscles and local muscarinic receptors in sebaceous glands are the targets of the neuromodulatory effects of BoNT. It is known that the acetylcholine nicotinic receptor á7 (nAchRá7) is expressed in human sebaceous glands in vivo, and acetylcholine signal enhances the synthesis of lipids in vitro in a dose-dependent fashion.[26]

Lately, there have been evidences of the use of botulinum toxin for the treatment of androgenetic alopecia. In order to understand the mechanism of action involved it is necessary to understand that, in areas affected with hair rarefaction, there is relative hypoxemia, slower capillary filling and high levels of dihydrotestosterone.[27] The enzymatic conversion of testosterone into dihydrotestosterone depends on oxygen. In low concentrations of oxygen, the conversion is favored, leading to increased hair loss, whereas in high concentrations of oxygen, the favored conversion is testosterone into estradiol, favoring reduction of hair loss. Therefore, the application of botulinum toxin in the scalp reduces the vascular pressure when reducing muscular tone, creating increased local vascular flow and, consequently, increased oxygen, which reduces the enzymatic conversion of testosterone into dihydrotestosterone.[28] In a study conducted by Singh *et al* (2018), 10 patients with androgenetic alopecia were treated with five-unit injections of botulinum toxin in 30 points in the scalp; 80% had an excellent improvement in 24 weeks. Only one patient failed the treatment, and another patient showed poor response to treatment, therefore demonstrating the therapeutic efficacy and safety of BoNT in androgenetic alopecia in this pilot study.[29]

Hyaluronic acid

Hyaluronic acid (HA) fillers are widely used in aesthetics due to their efficacy, safety, versatility and low allergenic potential. They are used with the goal of occupying physical space and/or volume enhancing, since it is a hydrophilic material that is also a natural component of the skin. This way, we use hyaluronic acid broadly to rejuvenate, when filling areas of skin atrophy and also in cases of bony resorption, loss of elasticity and fat caused by ageing.[30,31]

However, it is important to understand that the action of hyaluronic acid is broader than just filling spaces, since there are evidences of the interaction between hyaluronic acid and adipocytes, extracellular matrix network and mesenchymal stem cells.[32] Thus, besides filling, HA has cell interactions, participating in biomodulation.

Regardless of the application technique of hyaluronic acid fillers, most of them are knowingly applied into the subcutis.[33,34,35] In the study by Arlette and Trotter (2008), 16 patients that had the nasolabial fold area treated with hyaluronic acid filler and were subsequently submitted to Mohs micrographic surgery with resection of the skin from the nasolabial fold had the specimen histologically analyzed, and in all of them, hyaluronic acid was present in the subcutis with a thickness of 2.1+/-0.6mm (mean dermis thickness of 1.04 to 1.86mm).[33]

Filling creates microtraumas in adipocytes caused by the hyaluronic acid injected, that creates a stress response in the fat tissue. In order to prevent rupture of adipocytes, there is collagen stimulation (induction of fibrillar fibrosis by type I collagen and pericellular fibrosis by type IV and VI collagen).[36] The mechanical stress created by the filler is also one of the factors inducing mesenchymal stem cells derived from the fat tissue, that will encounter a microenvironment favorable for expansion and differentiation, what probably explains the prolonged duration of the filler (up to 12 months).[32]

Adipocytes present in the subcutis control the activity of dermal fibroblasts through the secretion of cytokines. Dermal fibroblasts express receptors for adiponectin and leptin, and both cytokines significantly increase the production of HA by fibroblasts; besides, adiponectin stimulates the production of collagen.[37] Therefore, the activation of mature adipocytes and stem cells is likely to contribute for the effects of HA injections.[32]

Furthermore, there is an interaction between hyaluronic acid and molecules and receptors involved in signal transduction. Molecules such as aggrecan, versican and neurocan and receptors like CD44, RHAMM and TSG6 are examples that illustrate the fact. Due to its wide distribution, CD44 is considered the primary HA receptor in most cells. HA induced a strong proliferative response of fibroblasts and keratinocytes in cell cultures.[38,39]

Turlier *et al* (2013) demonstrated that the injection of hyaluronic acid into the skin caused increase in pro-collagen, in the gene expression of pro-collagen I and III and of matrix metalloproteinase inhibitor-1. Moreover, the activation of fibroblasts was also observed, possibly due to the elongation of its cellular shape.[40] In the study by Wang *et al* (2007), a similar effect was observed on the damaged forearm skin that, after being treated with hyaluronic acid, showed elongation of fibroblasts and increased expression of pro-collagen I and III and of various pro-fibrotic growth factors.[41]

Quan *et al* (2013) studied the buttock skin of elderly patients that were treated with hyaluronic acid fillers. The authors demonstrated elongated fibroblasts adjacent to the deposition of the filler, besides three times the induction of transforming growth factor beta (TGF-beta) and ten times the induction of connective tissue growth factor compared to controls. Improvement in the extracellular matrix promoted fibroblast growth and vascular support.[42]

Poly-L-lactic acid

Poly-L-lactic acid (PLLA) is a synthetic biocompatible and biodegradable polymer produced through fermentation of renewable plant sources. Its clinical effect is due to the stimula-

tion of neocollagenesis. Neocollagenesis caused by poly-L-lactic acid is due to the stimulation of a desired controlled inflammatory response, that leads to the slow degradation of the material and culminates with collagen deposition in the tissue. Once injected in the skin, there is a subclinical inflammatory response with the recruitment of monocytes, macrophages and fibroblasts. A capsule is formed individually around each microsphere. As poly-L-lactic acid is metabolized, the increased collagen deposition produced by the fibroblast remains, with subsequent increase in dermal thickness. Therefore, fibroplasia is a determinant of the cosmetic results, but there is no evidence of residual fibrosis. The production of type I collagen starts around 10 days after the injection and continues for a period that ranges from eight to 24 months, while the product is degraded and the subclinical response fades.[43] Kim *et al* (2019) evaluated the molecular biologic effect of PLLA in the synthesis of collagen and the signaling pathways related through human dermal fibroblast (Hs68) culture in vitro, which were stimulated with PLLA and analyzed regarding expression of the type I collagen gene, induced by the polymer through RT-PCR, Elisa and Western-Blot. The results obtained suggest that PLLA acts directly on dermal fibroblasts. There was up regulation in the expression of the type I collagen gene and in the protein synthesis in the first 48 hours of incubation, a mechanism mediated through the activation of signaling proteins p38, Akt and JNK.[44]

Stein *et al* (2015) evaluated the biological mechanism associated to the use of poly-L-lactic acid through characterization of the cell infiltrate and the type of collagen present in the tissue treated with poly-L-lactic acid, analyzed by immunofluorescence. Macrophages CD68 and fibroblasts CD90 were found around the treated tissue. Structures positive for áSMA indicated myofibroblasts and neovascularization. Deposition of type III collagen was detected close to the PLLA particles and type I collagen was found in the periphery of PLLA encapsulation. The expression of mRNA for type I and III collagen transcription, as well as for TGF-beta1, increased significantly. Thus, the authors concluded the effect induced by PLLA is likely based in the formation of capsules, orchestrating macrophages, myofibroblasts and type I and III collagen fibers.[45]

Goldberg *et al* (2013) evaluated tissue response to PLLA in 14 patients that underwent PLLA injection and, subsequently, were biopsied in the area after 3, 6 and 12 months. In a qualitative and quantitative analysis of the collagen, there were evidences of increased type I collagen 6 months after the treatment. The inflammatory response observed to PLLA was mild or absent, and no patient showed moderate to severe inflammation in the 3, 6 and 12 months biopsies.[46]

Calcium hydroxylapatite

Calcium hydroxylapatite (CaHA)-based fillers are biodegradable and biostimulants. They are composed of two minerals found in bones and teeth (calcium and phosphate), and therefore are biocompatible and non-toxic. Their use was approved by the FDA (Food and Drug Administration) in 2006 for facial filling, being initially used for the correction of moderate and deep wrinkles and for the treatment of lipoatrophy in patients with the human immunodeficiency virus. In view of the good results with CaHa fillers, their off label use expanded to other indications, such as: regeneration of volume in the aged hand, correction of marionette lines, enhancement of volume in the malar, zygomatic and submalar areas, lip augmentation and acne scars. The initially known mechanism of action of CaHA filler involves the distribution of microspheres of calcium hydroxylapatite in soluble gel in the area of injection, which are responsible for promoting collagenesis.[47]

Zerbinat *et al* (2017) evaluated the interaction of CaHA and the extracellular matrix and connective tissue cells. With electron microscopy performed 2 months after filling of abdominal skin with CaHA, more basophilic fibroblasts, high in rough endoplasmic reticulum and electrodense filamentous material were seen, corresponding to the precursors of fibrillar components, particularly collagen, of the extracellular matrix. Besides, a well-developed Golgi apparatus was present, responsible for the synthesis of molecular components of the extracellular matrix (proteoglycans, glycosaminoglycans and multiadherent glycoproteins). These structural changes demonstrate the involvement of stimulated fibroblasts in the production of new molecular components of the extracellular matrix, with active renovation and remodeling of the connective tissue. This renovation of the molecular components of the extracellular matrix increases skin support, creating an additional action, restorative and physiologic of the filler, aesthetically and functionally.[48]

Moreover, scattered microgranular material was also detected in the space of the interstitial matrix, related to the activity of the cells surrounding the microspheres of CaHA. Observations in the interface between the microspheres of CaHA and the adjacent cells, such as the increase in number of invaginations of plasma membranes of these cells, demonstrate an important communication between the filler and surrounding cells. There is probably an active cellular mechanism of enzyme delivery through the surface of the plasma membrane.[48]

Zerbinati and Calligaro (2018) evaluated the effects of CaHA fillers in the molecular arrangement of the collagen, performing a biopsy of the area treated two months after the procedure. With polarized light microscopy, it was shown that the subdermal injection of CaHA stimulates the formation of new collagen and dermal remodeling, with type III collagen neoformation, which is gradually replaced by type I collagen for the support of the optimal structure. Probably, the microspheres of CaHa in the connective tissue provide a tridimensional environment for the adherence of fibroblasts, similarly to the structure of young skin, allowing CaHa to induce biostimulation to the target collagen in the injection site.[49]

Actives for body contouring

The female complaint that the fat in the hips and thighs is harder to mobilize was always common, however, these empirical observations were not initially validated. These observations are now scientifically confirmed, for it is understood that the distribution of fat is determined by the lipolytic thresholds

relative to fat cells in different body areas. We know that a higher number of á-2 adrenergic receptors is found in the fat cells of the hips and thighs in women, and that these á-2 adrenergic receptors inhibit lipolysis. Estrogen increases the number of á-2 receptors in these areas, and it is responsible for the distribution of the gynoid fat of women.[50,51]

Many times, fat reduction in a certain part of the body is not possible under normal conditions because the endogenous lipolytic stimulants, such as catecholamines, reduce all body lipolytic thresholds in the same degree, without creating any relative change between the deposits.[50,51]

Recent studies evaluated factors that regulate and affect the lipolytic process. There are at least three general mechanisms by which lipolysis can be enhanced: inhibition of phosphodiesterase or of the adenosine receptor; activation of the â-adrenergic receptor or inhibition of á-2 receptor. These mechanisms are the basis for lipolytic mesotherapy.[51,52]

Besides lipolytic stimulation to increase lipolysis, another mechanism can be used for lipolysis: the destruction of fat cells using a detergent (ablative mesotherapy). This technique is usually performed using substances such as phosphatidylcholine and sodium deoxycholate.[51,52]

Here, we will report the mechanism of biomodulation of substances used for body contouring improvement through lipolysis:

L-carnitine: amino acid that acts as an essential cofactor for the metabolism of fatty acids, reducing triglycerides and total cholesterol, improving lipid metabolism. It enhances the transportation of fatty acids into the mitochondria, where the process of beta-oxidation occurs (fat breakdown). Its absence prevents this transportation from taking place.[50]

Benzoic caffeine: induces lipolysis via inhibition of phosphodiesterase, what generates an increase in cyclic adenosine monophosphate (cAMP), transforming it in an inactive form, 5'cAMP. cAMP activates the enzyme proteinokinase A and, consequently, hormone-sensitive lipase enzyme (HSL), inducing lipolysis through mobilization of fatty acids and glycerol. It also increases catecholamines (epinephrine), activating the sympathetic nervous system.[50]

Organic silicon: natural component, ingested in the diet, with an important role in bones and connective tissue, however, when in high doses, benefits these tissues even further. Studies evaluated the stimulation of this active when associated to an antioxidant compound, revealing increased expression of mRNA of the enzyme type 2 hyaluronic acid synthetase (HAS2 – responsible for the production of hyaluronic acid), of collagen and elastin. Thus, silicon started to be recommended as a supplement, besides being used in mesotherapy, where it can be used alone or combined to other actives, contributing not only to localized fat, but also to facial rejuvenation.[50,53]

Chrysin: is a flavonoid extracted from the plant *Passiflora caerula*. It has anti-inflammatory properties associated to flavonoids, with an additional activity of potent inhibitor of the enzyme aromatase. Aromatase is the enzyme responsible for the conversion of testosterone into estrogen or DHT, it is present in adipocytes and pre-adipocytes, influencing the distribution of the fat tissue. This way, it is indicated for the treatment of cellulite and localized fat, reducing the inflammatory process and improving the venous return, aiding in the drainage of edemas.[50,51]

Mesoglycan: sulphated polysaccharide compound initially used in vascular disorders associated to thrombotic risk. It acts inhibiting the proliferation of smooth muscle cells of the tunica intima of the endothelium, stimulating the enzyme lipoprotein lipase and inhibiting platelet adhesion, therefore acting as antiatherogenic. It has antithrombotic activity by activation of antithrombin III and heparin cofactor II. It reduces capillary permeability and also has fibrinolytic activity by the induction of systemic fibrinolysis through the stimulation of the tissue plasminogen activator, reducing fibrotic processes. This fibrinolytic mechanism is responsible for its use in aesthetic medicine for the treatment of cellulite, for it allows dissolution of the nodules that cause skin deformity.[50, 51]

Sodium deoxycholate: is a salt derived from bile acids that have lipolytic activity over adipocytes. It acts rupturing adipocyte plasma membrane and emulsifying the fat released, making it excretion possible. It is capable of promoting cellular lysis with irreversible destruction of the adipocyte membrane, what explains its increased action in the fat tissue, when compared to other tissues.[54]

Phosphatidylcholine: is an extract derived from soy, with different functions such as: emulsification of fat through activation of liver enzymes (lipases), breaking them down into fatty acids and glycerol; improvement of hepatic fibrosis and fat build up; regulation of the cholesterol metabolism, because it favors the uptake and transport of cholesterol into the liver, reducing the levels of LDL and triglycerides and increasing HDL. Besides, it is the main plasma membrane phospholipid, with an important action in cell apoptosis, and a precursor of Ach, which when in high concentrations decreases laxity and muscle tone.[50,55]

Tranexamic acid

Tranexamic acid is a plasmin inhibitor used to prevent fibrinolysis, in order to reduce blood loss. It is a synthetic derivative of the amino acid lysine, which effect is to reversibly block the binding sites of lysine in the plasminogen molecule, therefore inhibiting plasminogen activator (PA) from converting plasminogen into plasmin. In dermatology, it has been used for the treatment of melasma in various presentations: oral, topical and intradermal injection. Although plasminogen also exists in the human epidermal basal cells, and it is known that cultivated human keratinocytes produce PA, there is a basic explanation that tranexamic acid could affect keratinocyte functions and interactions.[56]

Ultraviolet radiation (UV) induces the synthesis of plasminogen activator and increases plasmin activity in keratinocytes. As a result of plasmin activity, there is intracellular release or arachidonic acid, a precursor of prostanoids, and elevation of the alpha-melanocyte stimulating hormone. These two substances can activate melanin synthesis. Therefore, the antiplasmin activity of tranexamic acid is considered to be the main mechanism of this agent's bleaching effect.[56]

Precursors of plasmin-activated secretory phospholipase take part in the production of arachidonic acid, which is a prostaglandin E2 and leukotriene LK precursor, involved in melanogenesis. Plasmin also participates in the release of basic fibroblast growth factor (FGF), which a potent melanocyte growth factor. Therefore, it is believed that tranexamic acid inhibits plasmin activity in the keratinocyte activated by UV radiation, inhibiting plasminogen binding to the keratinocyte, resulting in a reduced ability of prostaglandin production and subsequent reduction of melanogenesis.[57]

Furthermore, tranexamic acid is similar to tyrosine, partly because of its structure, and can competitively inhibit the activity of the enzyme tyrosinase. There was a significant reduction of tyrosinase activity, of the protein related to tyrosinase TRP1/2 and melanin content in melanocyte culture after 48 hours after adding tranexamic acid in the culture medium irradiated with UVB.[58]

In the study by Kim *et al* (2016), suppression of the paracrine melanogenic factor ET-1 was demonstrated with tranexamic acid, which is increased in melasma patients. ET-1, believed to be secreted by keratinocytes, is a well-known melanogenic factor that induces pigmentation and tanning response to radiation.[59]

Literature reports also suggest that tranexamic acid reduces erythema in melasma skin, because it is associated to a reduce number of vessels in the dermis; therefore, the antiangiogenic effect of tranexamic acid is also considered. The number of vessels and the expression of vascular endothelial growth factor are reduced after using tranexamic acid.[59]

Mast cells are related to many histological changes associated to melasma. Repetitive UV radiation increases the number of mast cells and mast cell tryptase, and tryptase degrades type IV collagen. Mast cells also perform an important role in the development of solar elastosis, one of the histological features of melasma. The amount of elastin in the skin exposed to UV radiation correlates to the mast cell count. Besides, rats with no mast cells do not develop solar elastosis after repetitive UV radiation. Moreover, mast cells can also induce vascular proliferation secreting many angiogenic factors, such as VEGF, FGF-2 and transforming growth factor beta. Tranexamic acid was capable of reducing the activity and number of mast cells in melasma patients.[60]

CONCLUSION

Understanding the mechanisms involved in cell biomodulation is fundamental to understand the use of substances in dermatology with a broader view. Till present, what we know is very limited in view of the magnitude that encompasses biomodulation, a field with recent and growing discoveries. This way, with this review, we aimed at bringing information on this new way of understanding dermatology: biomodulation. ●

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