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The importance of interaction between hyaluronic acid and CD44 receptor

A importância da interação entre o ácido hialurônico e o receptor CD44

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ABSTRACT

Hyaluronic acid is one of the most used substances in dermatology. It presents structural roles in the extracellular matrix, binding to cells and biological components through specific and nonspecific interactions. The native ligand for hyaluronic acid is the transmembrane CD44 receptor, which interacts not only with hyaluronic acid but also with different growth factors, cytokines, and extracellular matrix proteins. We seek to review the interaction of the CD44 receptor with the various forms of hyaluronic acid in the skin to better understand its action and fully explore its use in dermatology.

Keywords: Rejuvenation; Hyaluronic acid; Skin

RESUMO

Ácido hialurônico é uma das substâncias mais utilizadas na Dermatologia. Apresenta tarefas estruturais na matriz extracelular, ligando-se às células e a componentes biológicos por interações específicas e inespecíficas. O ligante nativo para o ácido hialurônico é o receptor transmembrânico CD44, que interage não apenas com o ácido hialurônico, mas também com diferentes fatores de crescimento, citocinas e proteínas da matriz extracelular. Buscamos revisar a interação entre o receptor CD44 e as diversas formas de ácido hialurônico na pele, a fim de compreender melhor sua ação e explorar seu uso de forma mais completa na Dermatologia.

Palavras-chave: *Rejuvenescimento; Ácido hialurônico; Pele*

Review

Authors:

Carlos Roberto Antonio[1]

Lívia Arroyo Trídico[1]

[1] Faculdade de Medicina de São José do Rio Preto, Departmant of Dermatology, São José do Rio Preto (SP), Brazil.

Correspondence:

Lívia Arroyo Trídico

Email: latridico@terra.com.br / Alternative email: latridico@gmail.com

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INTRODUCTION

Hyaluronic acid (HA) is a natural biodegradable polymer. It is a non-sulfated, non-branched glycosaminoglycan composed of repeating disaccharide units (1.4 β-D-glucuronic acid and 1.3 N-acetyl-β-D-glucosamine). HA is a polyanion that can bind to each other and water molecules, forming a rigid and viscous structure similar to gelatin. HA is one of the main extracellular matrix (ECM) elements of vertebrate tissues, available in almost all body fluids and tissues. This biopolymer has a structural function, binding extracellular matrix molecules. Also, it is involved in several essential biological processes, such as regulation of cell adhesion and motility, in addition to acting in cell differentiation and proliferation and the mechanical properties of tissues.[1]

The HA characteristics, such as consistency, biocompatibility, and hydrophilicity, make it ideal for use in Aesthetic Dermatology. Also, its unique viscoelasticity and limited immunogenicity led to its use in various medical applications, such as osteoarthritis treatment (OA), eye surgery aid, and wound regeneration.[2] We will discuss the use of injectable hyaluronic acid as a dermal filler and its interactions with its primary receptor, CD44, to understand how it can promote rejuvenation through its biological interactions.

Hyaluronic acid metabolism in the skin

In the epidermis, HA content is especially high in the proliferating basal regions. It is in line with maintaining the undifferentiated and proliferative state of basal cells and corresponding observations during embryogenic development.[3] Histological findings suggest that basal layer keratinocytes contain intracellular HA, whereas extracellular HA prevails in the upper epidermal layers.[4] Extracellular HA is believed to maintain diffusion and open spaces to facilitate cell migration.[5]

HA's primary source in the dermis is fibroblasts, with higher HA synthesis activity in the papillary dermis. HA structures' high flexibility and hydrophilicity allow these molecules to fill any gaps in the ECM.[6] The multiple hydrogen bonds between adjacent disaccharides especially explain HA's large hydrodynamic volume, but these may also depend on the close interaction of HA with highly glycosylated proteoglycans. The viscoelastic properties resulting from HA in the dermis are responsible for supporting the dermal tissue architecture. Dermal HA has access to the lymphatic system, probably regulating the water content in the dermis. Both free HA crosslinked by proteins or proteoglycans and HA associated with the cell membrane facilitate cell migration, proliferation, and communication by interacting with cell receptors, grouping receptors, and subsequent signaling cascades.[7]

Specific enzymes called HA-synthase (HAS) synthesize the HA. They are membrane-binding enzymes that synthesize HA on the inner surface of the plasma membrane and then eliminate it through pore-like structures into the extracellular space. Three enzymes are responsible for HA synthesis: HAS-1, 2, and 3, which exhibit distinct enzymatic properties and synthesize HA chains of various lengths.[7,8]

HA degradation is a gradual process that can occur through enzymatic or non-enzymatic reactions. Three types of enzymes (hyaluronidase, β-D-glucuronides, and β-N-acetylhexosaminidase) are involved in the enzymatic degradation of HA. These enzymes are found in several forms, in the intercellular space and serum. Hyaluronidase breaks high molecular weight HA into smaller fragments, while the other two enzymes degrade the fragments by removing non-reducing terminal sugars. In addition to the enzymatic mechanisms of HA degradation, it can be degraded by shear stress, heat, and chemical reactions, such as acid/alkaline hydrolysis and degradation by oxidants. These types of degradation occur at random, often resulting in disaccharide fragments.[1,9]

Skin aging and hyaluronic acid

The most dramatic histochemical change observed with aging skin is the marked disappearance of hyaluronic acid in the epidermis, while HA is still present in the dermis.[11] The reasons for the changes in HA homeostasis with aging are unknown, but it is known that the underlying dermis influences epidermal HA synthesis. A progressive reduction in the size of HA polymers in the skin due to aging has also been reported. Thus, the epidermis loses the main molecule responsible for binding and retaining water molecules, resulting in the loss of moisture from the skin. In the dermis, the main age-related change is the increasing avidity of HA for tissue structures and loss of HA extraction capacity. Also, there is progressive collagen crosslinking and loss of collagen extraction capacity with age. All of the above age-related phenomena contribute to the apparent dehydration, atrophy, and loss of elasticity that characterizes aging skin.[10]

The premature skin aging due to repeated and prolonged exposure to radiation results in an abnormal content of glycosaminoglycans and distribution compared to that found in scars, with decreased HA and increased chondroitin sulfate proteoglycans levels.[12] In dermal fibroblasts, this reduction in HA synthesis was attributed to collagen fragments, which activate αvβ3 integrins, resulting in reduced HA synthase expression (enzymes responsible for HA production).[12]

Injectable Hyaluronic Acid in Dermatology

Hyaluronic acid-based dermal fillers are currently one of the most commonly performed aesthetic procedures. HA injections into the skin promote a volume-filling effect and induce collagen synthesis, reversing the signs of aging skin.[13]

Compositional properties and rheological properties characterize the compositions of HA formulations used for tissue filling. The design of fillers includes concentration, size, and crosslinking particles (substances that generate intermolecular bonds that increase the stability and clinical durability of the filler). In contrast, rheological properties include elasticity (G') and viscosity (N'). Crosslinked HA (crosslinking particles) can be made with several chemicals (butanediol diglycidyl ether, divinyl sulfone, etc.). The increase in crosslinking particles and

concentration strengthens the fillers' resistance to enzymatic degradation. The polymerization of glycosaminoglycan chains and tension determine the particle size, which optimizes tissue lifting capacity. Elasticity and viscosity guarantee fillers the ability to resist compression and shear force, respectively. Another critical feature is hydrophilicity, that is, the filler's ability to attract water and expand.[14,15]

Each product consists of a unique combination of different characteristics, and understanding these differences allows treating appropriately other areas of the face. Softness and less viscosity are characteristics that make the filler ideal for surface wrinkles, lips, and eyelids. In contrast, denser and heavier fillers are better for deeper plane injection to increase volume.[16] Duration of corrective effect of HA fillers ranges from three to 24 months, predominantly depending on HA concentration, cross-linking (degree and type), treated area, and individual.[17]

In addition to replenishing volume, injectable HA acts as a skin remodeler because the filling effect persists for a time much longer than the filler's bioavailability. Studies have shown that HA can induce an increase in the production of collagen and elastic fibers, restoring the extracellular matrix by direct stimulation and/or mechanical stretching of fibroblasts.[18]

HA performs several structural tasks of ECM, as it binds to cells and other biological components through specific and non-specific interactions. Binding to HA stabilizes several ECM proteins. Specific molecules and receptors that interact with HA are involved in cellular signal transduction, such as the aggrecan, versican, and neurocan molecules, and the cellular receptors CD44, RHAMM, TSG6, GHAP, ICAM-1, and LYVE-1.[19] Among these receptors, CD44 (cell surface glycoprotein) deserves more attention as, due to its wide distribution and based on current knowledge, it is considered the primary HA receptor on most cell types.[1,20] We will address the importance of the CD44 receptor and its interactions with HA to promote rejuvenation.

CD44 receptor and hyaluronic acid

The native ligand for HA is the transmembrane receptor CD44.[21] HA binds to the N-terminal of CD44, which functions as a coupling site and is coated by a mixture of predominantly essential and hydrophobic amino acids.[22] The CD44 gene contains 20 exons, 10 of which can be regulated by alternative binding, leading to the generation of other variants (variant exons or 'v'), which are translated to a polypeptide of molecular weight 80-90kDa, depending on the binding. Biological functions, such as cell migration, adhesion, and structural integrity during anti-inflammatory processes, depend on the HA-CD44 interaction. The smallest CD44 isoform, standard CD44 (CD44s), is ubiquitous, whereas variant isoforms are expressed only in some epithelial tissues and cancers.[23,24]

The different forms of hyaluronic acid synthesized for medical use have common and distinct interactions with the CD44 receptor. Generally, HA-CD44 interactions can be altered according to HA extent modification, chemical group type used for that modification, and HA location where the alteration was made. Regardless of the peculiarities involving the different types of synthetic hyaluronic acid and CD44 receptor, we will globally address this receptor role in allowing HA action to go beyond simply filling tissues, mainly acting in tissue biomodulation.[25]

CD44 can also interact with different growth factors, cytokines, and extracellular matrix proteins, such as fibronectin.[26] The intracellular CD44 domain interacts with the cytoskeleton. Consequently, when its extracellular domain binds to the ECM's HA, it creates a link between the cytoskeleton structures and the polymer.27 Several intracellular signaling pathways are involved in the HA-CD44 interaction, and they act by controlling cellular biological processes: HA degradation and internalization, angiogenesis, cell migration, proliferation, aggregation, and adhesion to ECM components.[27,28,29]

HA concentration manipulations or HA-CD44 interactions can alter signaling pathways of many regulatory and adapter molecules, such as SRC kinases, Rho-GTPases, VAV2, and GAB1.[30] The binding of CD44 to hyaluronic acid can alter cell survival or proliferation by altering intracellular protein binding.[31] Also, HA can activate several receptor tyrosine kinases, and HA binding to CD44 can group and cooperate with growth factors.[32] It has also been shown that the CD44 receptor is involved in cellular uptake of extracellular HA.[33]

Kaya *et al.* (1992) demonstrated that CD44 is associated with the regulation of HA homeostasis in keratinocytes. The authors developed transgenic mice expressing an antisense CD44 cDNA triggered by the keratin-5 promoter. These mice do not show detectable CD44 expression on skin keratinocytes and corneal epithelium and exhibit abnormal HA accumulation in the superficial dermis and stroma of the cornea, morphological changes distinct from basal keratinocytes and cornea, and defective proliferation of keratinocytes in response to mitogen and growth factors. A decrease in skin elasticity, poor local inflammatory response and tissue repair, delayed capillary growth, and epidermal failure to undergo hyperplasia in response to the carcinogen reflect these changes. Therefore, they observed two main functions of CD44 in the skin: the regulation of keratinocyte proliferation in response to extracellular stimuli and the maintenance of local HA homeostasis.[34]

Vistejinova *et al.* (2014) conducted a study to compare the ability of high molecular weight (HMW) with low molecular weight (LMW) HA to stimulate the production of cytokines and chemokines by human dermal fibroblasts, associated with the importance of the CD44 receptor in this process. The study showed that dermal fibroblasts and their primary function of producing the extracellular matrix could respond to low molecular weight HA fragments via interaction with CD44 through the production of cytokines, suggesting that the LMW HA is implicated in an inflammatory signal that stimulates stromal fibroblasts.[35]

Studies have demonstrated that HA and CD44 on the outer surface of dermal fibroblasts act by regulating the physio-

logy of fibroblasts and stimulating the production of extracellular matrix.[36] Thus, it may be possible to alter the skin's collagen production by increasing or reducing the amount of HA.[37] In Wang *et al.* study (2007), 11 volunteers received injections of HA filler or vehicle and underwent biopsy at four and 13 weeks after the procedure. The results demonstrated that, compared to controls, skin treated with crosslinked hyaluronic acid injections revealed increased collagen deposition around the filler material, gene expression for types I and III procollagens, and various growth factors profibrotic, was also regulated between four and 13 weeks compared to controls. The authors concluded that the injection of crosslinked hyaluronic acid stimulates collagen synthesis, partially restoring the dermal matrix components lost in photoaged skin.[13]

Bhattacharya *et al.* (2017) demonstrated that alterations in HA structures modify its interaction with the CD44 receptor. They observed that both sulfation and deacetylation of HA in individuals are associated with lower interaction with CD44; thus, both modifications are necessary to reduce the HA-CD44 interaction. Therefore, the study suggests that it would be possible in future studies to regulate cell activation pathways through different forms of HA.[38]

Wang *et al.* (2019) assessed how different types of HA influence the binding of CD44 to HA hydrogels. HA-CD44 interactions can be altered when HA is modified to synthesize HA macromers, depending on the modification extent, chemical group type used for transformation, and the site used with HA for alteration. These effects are observable when HA macromers are presented to CD44 in soluble form and after crosslinking in hydrogels. Gene expression and long-term biochemical and histological analyzes of mesenchymal stromal cells encapsulated in HA hydrogels strongly suggest that levels of HA macromer modification influence cell-hydrogel interactions and chondrogenic differentiation. Notably, low and moderately modified HA hydrogels promote significantly higher binding to CD44 compared with inert molecules. Also, chondrogenesis and cartilage formation are regulated with HA hydrogels compared to inert polyethylene glycol hydrogel controls.[39]

Gruber, Holtz, and Riemer (2021) performed an in vitro evaluation on the influence of different molecular weights of HA on its binding to CD44. They showed that low molecular weight HA and a commercial complex with HA of three molecular weights (high, medium, and low) increased the CD44 protein expression in human epidermal keratinocytes. In contrast, medium and high molecular weight HA fractions didn't. Therefore, they concluded that HA can influence the expression of the CD44 protein and that this influence seems to be dependent on the molecular weight.[40]

CD44 receptor and carcinogenesis

It is known that the abnormal activation of the CD44 signaling cascade by HA and the CD44 overexpression and upregulation can result in the development of pathological lesions and malignant transformation since the HA-CD44 interaction is involved in cell processes such as cell proliferation and angiogenesis.[29,41] Therefore, CD44 is overexpressed in several solid tumors, such as pancreas, breast, and lung tumors.[42]

There is a complex communication between cancer cells and their microenvironment. Evidence indicates that the tumor microenvironment may regulate the capacity for tumor growth and metastasis.[43] HA provides cell support and hydrophilic matrix and also regulates cell-cell adhesion, cell migration, growth, and differentiation.[44] Thus, these properties make it a suitable candidate for involvement in pathological processes such as cancer. Furthermore, by forming pericellular layers, HA can protect tumor cells from immune attack.[45] Several tumor cells produce increased amounts of HA or induce the production of HA by releasing growth factors and cytokines. Likewise, fragmented HA induced by reactive oxygen species (ROS) also contributes to HA overproduction.[46] Tumor and stromal cells express HA isoforms and produce HA in the ECM, which accumulates in the tumor parenchyma and peritumoral stromal tissues, contributing to metastatic spread.[47] Also, HA overproduction in tumor cells can induce cancer cell-like epithelial changes toward a migratory fibroblastic phenotype.[48] HA-rich ECM can also mediate mesenchymal stem cells recruitment, which are progenitors of tumor-associated fibroblasts.[49]

HA interaction with CD44 could explain many HA tumor-promoting activities. There are three ways in which CD44 can interact with HA: binding with soluble extracellular HA molecules and ECM, interacting with receptor tyrosine kinases for anti-apoptosis and drug resistance, and binding of CD44 to actin cytoskeleton.[50]

Activated CD44 is overexpressed in solid tumors, but much less or almost none, in its non-tumorigenic counterparts. Adhesion of CD44 to HA induces upregulation of integrins that strengthen stem cell adhesion.[51] Tumor-derived cells express CD44 in a high-affinity state that can bind to and internalize HA. The binding affinity of CD44 to HA is essential for cell migration allowing CD44 to be incorporated into the leading edge of cells. CD44 can also react with other molecules, including collagen, fibronectin, osteopontin, growth factors, and metalloproteinases on tumor cells, but the functional roles of such interactions are less known.[50]

Receptor tyrosine kinases (RTKs) are a subclass of cell surface growth factor (GFR) receptors with an intrinsic tyrosine kinase activity controlled by ligands. The HA-CD44 interaction has a general effect on activating anti-apoptotic cell survival proteins, initiated by association with the activation of tyrosine kinase receptors. Also, CD44 binds to cytoskeletal proteins, and this interface is modulated by the HA-CD44 interaction.[50]

Thus, given that HA levels and their interactions with CD44 can regulate cell differentiation (such as epidermal keratinocyte cornification and fibroblast differentiation), the modulatory capacity of regulated cell differentiation through the HA route could be used therapeutically, especially in Oncology. The fact that HA binding to CD44 can interact with several recep-

tor systems is very intriguing. If HA and CD44 interactions are necessary to lead to carcinogenesis and metastasis, then it is believed that manipulation of these interactions can be performed therapeutically.[37]

Since the first reports of HA liposomes targeting CD44 in 2001, researchers have devoted a great effort to using HA-mediated CD44 targets for disease and drug-delivery applications. Then, studies of HA nanomaterials have emerged as an effective way to improve drug delivery. In the future, it is believed that the straightforward structure and easy manufacturing process for HA nanomaterials may increase the possibility of success in clinical practice.[51]

CONCLUSION

There are numerous interactions between HA and its primary receptor, CD44. We know that they depend on several factors, including the type of HA involved. Studies show that HA-CD44 interactions occur not only with endogenous HA but also with topical and injectable HA. Therefore, we can conclude that exogenous HA acts with CD44 to cause cellular and molecular modulation in the site where it is applied, thus bringing results beyond the simple fact of filling the treated place. It mainly alters the environment through local interactions and improves skin quality. Also, several studies report the involvement of the CD44 receptor in carcinogenesis. Although further studies on this subject are needed, a better understanding of the role of the CD44 receptor can also positively influence the treatment of cancer in the future. ●

REFERENCES:

1. Fakhari A, Berkland C. Applications and emerging trends of hyaluronic acid in tissue engineering, as a dermal filler and in osteoarthritis treatment. Acta Biomater. 2013;9(7):7081-92.
2. Necas J, Bartosikova L, Brauner P, Kolar J. Hyaluronic acid (hyaluronan): a review. Veterinarni Medicina. 2008(8):397–411.
3. Pasonen-Seppänen S, Karvinen S, Törrönen K, Hyttinen JM, Jokela T, Lammi MJ, et al. EGF upregulates, whereas TGF-beta downregulates, the hyaluronan synthases Has2 and Has3 in organotypic keratinocyte cultures: correlations with epidermal proliferation and differentiation. J Invest Dermatol. 2003;120(6):1038-44.
4. Stern R, Maibach HI. Hyaluronan in skin: aspects of aging and its pharmacologic modulation. Clin Dermatol. 2008;26(2):106-22.
5. Kaya G, Rodriguez I, Jorcano JL, Vassalli P, Stamenkovic I. Selective suppression of CD44 in keratinocytes of mice bearing an antisense CD44 transgene driven by a tissue-specific promoter disrupts hyaluronate metabolism in the skin and impairs keratinocyte proliferation. Genes Dev. 1997;11(8):996-1007.
6. Evanko SP, Tammi MI, Tammi RH, Wight TN. Hyaluronan-dependent pericellular matrix. Adv Drug Deliv Rev. 2007;59(13):1351-65.
7. Prehm P. Hyaluronate is synthesized at plasma membranes. Biochem J. 1984;220:597-600.
8. Watanabe K, Yamaguchi Y. Molecular identification of a putative human hyaluronan synthase. J Biol Chem. 1996;271(38):22945-8.
9. Stern R, Kogan G, Jedrzejas MJ, Soltés L. The many ways to cleave hyaluronan. Biotechnol Adv. 2007;25(6):537-57.
10. Stern R, Maibach HI. Hyaluronan in skin: aspects of aging and its pharmacologic modulation. Clin Dermatol. 2008;26(2):106-22.
11. Röck K, Grandoch M, Majora M, Krutmann J, Fischer JW. Collagen fragments inhibit hyaluronan synthesis in skin fibroblasts in response to ultraviolet B (UVB): new insights into mechanisms of matrix remodeling. J Biol Chem. 2011 20;286(20):18268-76.
12. Bernstein EF, Underhill CB, Hahn PJ, Brown DB, Uitto J. Chronic sun exposure alters both the content and distribution of dermal glycosaminoglycans. Br J Dermatol. 1996;135(2):255-62.
13. Wang F, Garza LA, Kang S, et al. In vivo stimulation of de novo collagen production caused by cross-linked hyaluronic acid dermal filler injections in photodamaged human skin. Arch Dermatol. 2007;143(2):155-63.
14. Oliveira JD, Carvalho LS, Gomes AM, Queiroz LR, Magalhães BS, Parachin NS. Genetic basis for hyper production of hyaluronic acid in natural and engineered microorganisms. Microb Cell Fact. 2016;15(1):119.
15. Edsman K, Nord LI, Ohrlund A, Lärkner H, Kenne AH. Gel properties of hyaluronic acid dermal fillers. Dermatol Surg. 2012;38(7 Pt 2):1170-9.
16. Alam M, Tung R. Injection technique in neurotoxins and fillers: indications, products, and outcomes. J Am Acad Dermatol. 2018;79(3):423-35.
17. Muhn C, Rosen N, Solish N, Bertucci V, Lupin M, Dansereau A, et al. The evolving role of hyaluronic acid fillers for facial volume restoration and contouring: a Canadian overview. Clin Cosmet Investig Dermatol. 2012;5:147-58.
18. Trindade de Almeida AR, Sampaio GAA. Hyaluronic acid in the rejuvenation of the upper third of the face: review and update - Part 1. Surg Cosmet Dermatol. 2015;8(2):148-53.
19. Necas J, Bartosikova L, Brauner P, Kolar J. Hyaluronic acid (hyaluronan): a review. Vet Med. 2008;53:397-411.
20. Toole BP. Hyaluronan in morphogenesis. J Intern Med. 1997;242(1):35-40.
21. Gallatin WM, Weissman IL, Butcher EC. A cell-surface molecule involved in organ-specific homing of lymphocytes. Nature. 1983;304(5921):30-4.
22. Banerji S, Wright AJ, Noble M, Mahoney DJ, Campbell ID, Day AJ, et al. Structures of the Cd44-hyaluronan complex provide insight into a fundamental carbohydrate-protein interaction. Nat Struct Mol Biol. 2007;14(3):234-9.
23. Ponta H, Sherman L, Herrlich Pa. CD44: from adhesion molecules to signalling regulators. Nat Rev Mol Cell Biol. 2003;4(1):33-45.

24. Toole BP, Wight TN, Tammi MI. Hyaluronan-cell interactions in cancer and vascular disease. J Biol Chem. 2002;277(7):4593-6.
25. Kwon MY, Wang C, Galarraga JH, Puré E, Han L, Burdick JA. Influence of hyaluronic acid modification on CD44 binding towards the design of hydrogel biomaterials. Biomaterials. 2019;222:119451.
26. Vigetti D, Karousou E, Viola M, Deleonibus S, De Luca G, Passi A. Hyaluronan: biosynthesis and signaling. Biochim Biophys Acta. 2014;1840(8):2452-9.
27. Knopf-Marques H, Pravda M, Wolfova L, Velebny V, Schaaf P, Vrana NE, et al. Hyaluronic acid and its derivatives in coating and delivery systems: applications in tissue engineering, regenerative Medicine and Immunomodulation. Adv Healthc Mater. 2016;5(22):2841-55.
28. Girish KS, Kemparaju K. The magic glue hyaluronan and its eraser hyaluronidase: a biological overview. Life Sci. 2007;80(21):1921-43.
29. Toole BP. Hyaluronan: from extracellular glue to pericellular cue. Nat Rev Cancer. 2004;4(7):528-39.
30. Toole BP, Wight TN, Tammi MI. Hyaluronan-cell interactions in cancer and vascular disease. J Biol Chem. 2002;277(7):4593-6.
31. Morrison H, Sherman LS, Legg J, Banine F, Isacke C, Haipek CA, et al. The NF2 tumor suppressor gene product, merlin, mediates contact inhibition of growth through interactions with CD44. Genes Dev. 2001;15(8):968-80.
32. Misra S, Toole BP, Ghatak S. Hyaluronan constitutively regulates activation of multiple receptor tyrosine kinases in epithelial and carcinoma cells. J Biol Chem. 2006;281(46):34936-41.
33. Culty M, Nguyen HA, Underhill CB. The hyaluronan receptor (CD44) participates in the uptake and degradation of hyaluronan. J Cell Biol. 1992;116(4):1055-62.
34. Kaya G, Rodriguez I, Jorcano JL, Vassalli P, Stamenkovic I. Selective suppression of CD44 in keratinocytes of mice bearing an antisense CD44 transgene driven by a tissue-specific promoter disrupts hyaluronate metabolism in the skin and impairs keratinocyte proliferation. Genes Dev. 1997;11(8):996-1007.
35. Vistejnova L, Safrankova B, Nesporova K, Slavkovsky R, Hermannova M, Hosek P, et al. Low molecular weight hyaluronan mediated CD44 dependent induction of IL-6 and chemokines in human dermal fibroblasts potentiates innate immune response. Cytokine. 2014;70(2):97-103.
36. Webber J, Jenkins RH, Meran S, Phillips A, Steadman R. Modulation of TGFbeta1-dependent myofibroblast differentiation by hyaluronan. Am J Pathol. 2009;175(1):148-60.
37. Maytin EV. Hyaluronan: More than just a wrinkle filler. Glycobiology. 2016;26(6):553-9.
38. Bhattacharya D, Svechkarev D, Souchek JJ, Hill TK, Taylor MA, Natarajan A, et al. Impact of structurally modifying hyaluronic acid on CD44 interaction. J Mater Chem B. 2017;5(41):8183-92.
39. Gruber JV, Holtz R, Riemer J. Hyaluronic acid (HA) stimulates the in vitro expression of CD44 proteins but not HAS1 proteins in normal human epidermal keratinocytes (NHEKs) and is HA molecular weight dependent. J Cosmet Dermatol. Epub 2021 Apr 28.
40. Kwon MY, Wang C, Galarraga JH, Puré E, Han L, Burdick JA. Influence of hyaluronic acid modification on CD44 binding towards the design of hydrogel biomaterials. Biomaterials. 2019;222:119451.
41. Girish KS, Kemparaju K. The magic glue hyaluronan and its eraser hyaluronidase: a biological overview. Life Sci. 2007;80(21):1921-43.
42. Mattheolabakis G, Milane L, Singh A, Amiji MM. Hyaluronic acid targeting of CD44 for cancer therapy: from receptor biology to nanomedicine. J Drug Target. 2015;23(7-8):605-18.
43. Bissell MJ, Radisky DC, Rizki A, Weaver VM, Petersen OW. The organizing principle: microenvironmental influences in the normal and malignant breast. Differentiation. 2002;70(9-10):537-46.
44. Laurent TC, Fraser JR. Hyaluronan. FASEB J. 1992;6(7):2397-404.
45. McBride WH, Bard JB. Hyaluronidase-sensitive halos around adherent cells. Their role in blocking lymphocyte-mediated cytolysis. J Exp Med. 1979;149(2):507-15.
46. Stern R, Jedrzejas MJ. Hyaluronidases: their genomics, structures, and mechanisms of action. Chem Rev. 2006;106(3):818-39.
47. Knudson W, Biswas C, Toole BP. Interactions between human tumor cells and fibroblasts stimulate hyaluronate synthesis. Proc Natl Acad Sci USA. 1984;81(21):6767-71.
48. Itano N, Zhuo L, Kimata K. Impact of the hyaluronan-rich tumor microenvironment on cancer initiation and progression. Cancer Sci. 2008;99(9):1720-5.
49. Zhu H, Mitsuhashi N, Klein A, Barsky LW, Weinberg K, Barr ML, D, et al. The role of the hyaluronan receptor CD44 in mesenchymal stem cell migration in the extracellular matrix. Stem Cells. 2006;24(4):928-35.
50. Misra S, Hascall VC, Markwald RR, Ghatak S. Interactions between hyaluronan and its receptors (CD44, RHAMM) regulate the activities of inflammation and cancer. Front Immunol. 2015;6:201.
51. Choi KY, Han HS, Lee ES, Shin JM, Almquist BD, Lee DS, et al. Hyaluronic acid-based activatable nanomaterials for stimuli-responsive imaging and therapeutics: beyond CD44-mediated drug delivery. Adv Mater. 2019;31(34):e1803549.

AUTHORS' CONTRIBUTION:

Carlos Roberto Antonio ORCID 0000-0001-9243-8293
Approval of the final version of the manuscript; study design and planning; active participation in research orientation; critical literature review; critical revision of the manuscript.

Lívia Arroyo Trídico ORCID 0000-0002-7743-4195
Study design and planning; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.