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Review Article

Hyaluronic Acid: An Old Molecule with New Perspectives

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Abstract

Hyaluronic acid or hyaluronan was discovered 88 years ago and many scientist all over the world have investigated this interesting and multifaceted molecule. This article provides a short overview in the fields of wound healing, angiogenesis, drug delivery, tissue engineering, biomedical application in ophthalmology, eye pathology/surgery, osteorthrosis/cartilage repair, cancer therapy. Due to its exceptional rheological, hygroscopic and viscoelastic properties for decades HA was considered only a structural component of many tissues. The biosynthesis of this polysaccharide that occurs at the surface of cell membrane, the discovery of several specific cell receptors, the properties of small HA oligosaccharides to stimulate angiogenesis, the capacity of HA to initiate signal transduction in certain cell types changed dramatically the view of the role of this molecule. Furthermore the clinical use of HA is continually expanding in several fields such as skin repair, joints and eye pathologies, cancer therapy. This great potential in medicine stimulated the research on chemical modifications of this molecule with the aim to obtain new products and derivatives. Minor chemical modifications of the molecule, such as its esterification, have made possible the production of highly biocompatible materials in the form of gels, gauzes, nonwoven meshes, membranes and tubes. These biomaterials can be used as antiadhesive wound coverage and as scaffolds for in vitro and in vivo tissue engineering such as skin, cartilage, blood vessels. Also the association of HA with other substances such as collagen, elastin, lactose-modifies-chitosan, PLGA and poly-L-lysine allows the formulation of new compounds and scaffolds for several clinical applications.

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Introduction

In 1934 Karl Meyer and John Palmer isolated hyaluronic acid from the vitreous humor of the bovine eye [1]. After35 years it was possible to know its structure thanks to the work of Laurent in 1970 [2]. Hyaluronic Acid (HA) is a long, unbranched polysaccharide composed of repeating disaccharides of D-glucuronic and *N*-acetyl-D-glucosamine with Molecular Weight (MW) ranging from 0,1 x 10^6 up to 2 x 10^7Da. It reaches a great concentration in the vitreous body of the eye and in the umbilical cord [3]. In this embryonic district the MW of this molecule reaches the highest value as compared with other organs and tissues. Since at physiological pH, the carboxyl groups of the molecule are dissociated and can attract cations, such as Na^+, Balazs proposed the name "hyaluronan" as an alternative to "hyaluronic acid" [4]. The molecule is widely distributed in nature and it is present in many living organisms from bacteria to all vertebrates. It plays an important role in the Extracellular Matrix (ECM) of adult soft connective tissues where regulates hydration, tissue homeostasis and resistance to forces of compression such as in articular cartilage. In this tissue HA interacts with many proteoglycans giving rise to large molecule composites which in turn are responsible for the stabilization of ECM structure. High MW HA plays an important role as lubricant in the joints cavity. In addition to these mechanical properties, HA can play a more complex role forming a pericellular coat around most of the cells where behaves as a signaling molecule and regulates cell adhesion, migration and proliferation. It is present also inside the cells in various cytoplasmic structures [5]. By considering all these biological and structural properties HA plays a key role in many physiological and pathological conditions.

The biocompatibility, viscoelastic properties, and physiological activity of HA make it an ideal substance for several clinical applications, such as in ophthalmology, rheumatology, and dermatology. In addition esterification with benzyl alcohol of HA yields biocompatible and biodegradable HA-based biomaterials in the form of membranes, non-woven tissues [6,7], tubes and gauzes widely used for wound covering and for in vitro reconstruction of human tissues such as, dermis, epidermis, vascularized skin and cartilage.

Synthesis and degradation of HA

In1997 Weigel, et al. demonstrated that unlike others glycosaminoglycans HA is not synthesized in the Golgi apparatus but on the inner side of the cell membranes by three different synthetases [8], namely synthetase 1 (HAS 1), syntethase 2 (HAS 2) and synthetase 3 (HAS 3) [9]. After the synthesis the HA chain is then translocated to the extracellular space. During morphogenesis and in some pathological conditions the three enzymes are differently expressed and generate HA with different MW [10,11].

The degradation time of HA varies ranging from 10-25 hours in the skin to a few minutes in the blood stream by means of macrophages present in the lymph nodes and in the liver [12]. Six different hyaluronidases are present either inside and on the surface of the human cells while in tissues the degradation occurs during inflammatory process by Reactive Oxygen Species (ROS), superoxide, nitric oxide [13].

The amount and the molecular weight of the molecule depends on the equilibrium between HA synthesis and degradation. The resulting different molecular sizes can determine different and sometimes opposing biological actions [14]. While high MW HA exerts anti-inflammatory effects, the low MW molecules are pro-inflammatory and in addition promote angiogenesis and tissue repair in wound healing process [15,16]. Even though the mechanism of action remains largely unclear, high MW-HA, differently from low MW, inhibit tumor progression by slowing down cell motility [17].

HA Cell Surface Receptors

Several cell receptors for HA, the so called hyaladherins, have been identified [18,19], and their number is continuously growing. CD44 (Cluster of Differentiation 44), RHAMM or CD168 (Receptor for Hyaluronan Mediated Motility), LYVE1 (Lymphatic-Vessel Endothelial receptor 1) are specific cell membrane proteins while additional receptors are molecules present in the extracellular matrix, such as aggrecan and several proteoglycans. Binding of HA to hyaladherins promote several cell activities such as proliferation, differentiation and motility. CD44 and RHAMM are the principal cell membrane receptors that can trigger different cell responses [20]. CD44is the most studied receptor present in all human cell types. It is a glycoprotein expressed by a single gene that via alternative splicing gives rise to various isoforms with different functions and properties [21,22]. The HA receptor RHAMM, also known as CD168, promotes cell motility and migration by interacting with cytoskeletal proteins [23], with kinase protein complexes [24,25], mitochondria and microtubules [26,27]. The hyaladherin LYVE1 mediates the entry of leucocytes into lymphatic vessels and the traffic of HA from tissues to lymph [28,29].

Medical Applications of HA and its Derivatives

Osteoarthrosis and cartilage regeneration

One of the most widespread pathologies affecting senile and middle age population in the word is Osteoarthrosis (OA) that affects knee, hip and several minor body joints. Non Steroidal Drugs (NSAIDs) and corticosteroids are the most used drugs to relieve pain, even though they can cause undesirable side effects. For this reason several studies have been devoted to find alternative therapies and in 1971 Balazs proposed the visco-supplementation with HA for the treatment of osteoarthritis in human and horses [30]. The rationale of HA supplementation was the restoration of the rheological properties of the synovial fluid lost in OA where the MW of this molecule decreases as consequence of the hydrolytic effects of Reactive Oxygen Species (ROS) that in turn give rise to decreased fluid viscosity and cartilage erosion. In the last four decades several HA preparations have been proposed to protect articular cartilage and to relieve pain, such as Synvisc [31,32], Hyalgan [33,34]. Both HA preparations need multiple injections and are effective without side effects. In addition they last longer suggesting that do not restore only the rheological function of the synovial fluid but probably interact with cell membrane receptors.As demonstrated by Brun, et al. Hyalgan is able to protect chondrocytes from ROS damage and restore their survival and proliferation [35]. These effects are mediated by the interaction of HA with CD44 hyaladherin. To avoid repeated intra-articular injections a Hexadecylamide Derivative of HA (HYADD) has been proposed for intra-articular administration [36].

Furthermore, to improve the therapeutic effects a new formulation of HA has recently been proposed. Namely the mixture of HA and a lactose-modified chitosan (Chitlac®). This new compound has been tested either in human chondrocyte cultures and in experimentally induced osteoarthrosis in animals with encouraging results to promote clinical trials [37,38].

The progression of OA and mechanical injuries are the main causes that give rise to full thickness cartilage defects. The only effective therapy for this pathological condition is represented by the complex surgical procedure of autologous chondrocyte transplantation. An alternative possibility is represented by the use of three dimensional biodegradable scaffolds obtained by the total esterification of HA with benzyl alcohol (Hyaff-11®, Fidia, Italy) in the form of non-woven meshes. Human chondrocytes obtained by a simple biopsy of cartilage are successufully cultured inside these scaffolds and give rise to cartilage tissue [39-40]. This *in vitro* reconstructed cartilage can be then transplanted into the injured area of the joint and several clinical studies have demonstrated that after implantation the new tissue undergoes a regeneration with the formation of a hyaline cartilage [41-44].

Skin

For its hygroscopic and visco-elastic properties HA plays an important role in the skin, the largest organ of the body. It is associated with wound repair although the mechanism through which influences the process is not clear [45-47]. Several clinical studies demonstrate the positive effects of HA in promoting wound repair either in animal experimental models and in humans [48-50]. HA plays an important role in proliferative and inflammatory phases of wound repair as already demonstrated [51-53]. Recently many studies have been focused on the use of some HA-based biomaterials (Hyaff-11) for tissue engineering. These products have been demonstrated to be biocompatible, biodegradable and non toxic [54]. These biomaterials can be seeded either with fibroblasts and keratinocytes to obtain *in vitro* reconstructed skin substitutes. Dermal-like tissue was obtained by seeding non-woven meshes with dermal fibroblasts [55-57]. A Hyaluronic Acid membrane was used as delivery system for cultured keratinocytes either in wound and burns [58-62]. In order to provide the *in vitro* skin constructs with microvessels Tonello and coworkers obtained endothelialized skin substitutes by seeding fibroblasts and endothelial cells with Hyaff meshes [63,64]. Recently investigations have been conducted on HA based hydrogels and nanofibrous scaffolds synthesized either with chitosan and corn-stark and propolis [65-67]. Other interesting materials have been proposed for wound healing such as methacrilated gelatin and methacrilated hialuronic acid containing adipose derived stem cells [68].

Angiogenesis and vascular tissue

West and Kumar in 1989 demonstrated for the first time that low MW HA stimulated the angiogenesis in embryonic tissue [69]. Moreover HA was shown to be active also in promoting recruitment and activation of neutrophils and macrophages which in turn secrete

angiogenic factors [70]. For this role in angiogenesis HA derived biomaterialss (Hyaff-11) in the form of tubules have been utilized as small diameter vascular conduits. These tubular structures were grafted in rat abdominal aorta [71-73], in rat vena cava and in pig carotid artery as temporary absorbable guides to promote complete regeneration of vascular wall [74,75]. The experimental studies demonstrated the feasibility to create a biodegradable vascular guide for in vivo regeneration and reconstruction of small vessels.

Histological, immunohistochemical and ultra-structural analyses showed complete endothelialization of the tube's luminal surface, sequential regeneration of vascular wall and the biodegradation of the biomaterial four months after implantation. At this time new vessel remained to connect the artery stumps. In addition to monitor patency of vascular graft in pig carotid artery functional duplex scan studies after 1 and 5 months were performed confirming regular blood flow throughout the prosthesis and the new reconstituted artery tract [75] Given its high haemocompatibility additional studies have been performed on HA combined with other materials, such as chitosan based films. These composite structures when seeded with mesenchymal stem cells showed good biocompatibility and induced fibroblastic differentiation [76]. Another promising good material to be used as cardiovascular substitute is the expanded polytetrafluoroethylene treated with HA [77]. Also titanium microstrips coated with HA have been used for the co-culture of endothelial cells and smooth muscle cells with satisfactory results [78]. Low MW HA derivatives can be associated to hydrogels for fabricating dense tissues *in vitro* with a good capacity to promote endothelial cell motility [79]. HA has proven to exerts a potential role for the treatment of ischemia since it can remodel the tissue microenvironment and facilitate stem cell differentiation toward a vascular lineage, thus confirming its possible use for cell-based therapy [80].

Cancer therapy

The coniugation of antitumoral drugs with HA appears to be a potentially successful tool hoping that in the near future some technical difficulties will be resolved. The functions of HA, Hyaluronan Syntetases (HAS) and HA receptors in cancer cells undergo complex interactions [81]. Given the high biocompatibility and biodegradability HA has been suggested as an optimal drug carrier by considering also that cell CD44 receptors are able to internalize either HA and associated nanoparticles or liposomes [82-86]. Additional studies on the role of HAS and Hyaladerins in cancer biology may lead to improvements of their therapeutical usage. Indeed many cancer cells of solid tumors synthesize great quantity of HA with an increased cancer progression and metastasis [87]. It has been demonstrated that over-expression of HAS2 induces both progression of several tumors and chemiotherapy resistance [88-94]. On the other hand in some tumors the inhibition of HAS leads to inhibition of metastasis [95]. Fragmentation of HA due to over expression of hyaluronidases can be responsible of cancer progression [96,97]. However the role of HA, hyaluronidases and Ha syntetases in cancer appears controversial and clinical tests up to now are very few, even though the studies on these molecules can support their potential use in cancer therapy.

Ophtalmology

Eye vitreous body was the district from which hyaluronic acid was extracted for the first time by Meyer and Palmer in 1934 [1]. It is present also in conjunctiva, lacrimal gland and in the epithelium of cornea. Since during surgical ophthalmic procedures it necessary to replace the lost vitreous fluid, in 1980 HA was proposed by Balazs for viscosurgical supplementation in order to maintain either enough space for surgical manipulation and to protect from mechanical trauma [98]. In 1982 the first HA derivative commercially available for oftalmic applications was Healon® [99]. This preparation has been widely used as a therapeutic tool in many and different surgical operations performed on the eye. Later on other new cohesive ophthalmic viscosurgical devices were proposed for corneal protection and intraocular pressure [100]. For the treatment of dry eye syndrome, drops of aqueous HA solutions are also used as eye lubricant for the protection of corneal surface [101]. Recently additional HA preparation are available in ophthalmology such as Systane®, OptiveFusion™. Safety and effectiveness of these new products has been shown by several *in vivo* and *in vitro* studies [102-105]. Furthermore low MW HA solutions have recently been used to improve hydration of contact lens given its ability to prolong wettability [106,107]. HA has been also used as drug delivery substance for topical administration of ophthalmic drugs such as antibiotics and anti-inflammatory medicines. Indeed HA when combined with medicaments is able to slow down the delivery time and also can modulate the dose [108,109]. The proven properties of HA as drug delivery molecule can offer possibilities for additional investigations of pharmaceutical applications.

Adipose tissue

HA-based scaffolds have been investigated by several authors for adipose tissue engineering [110]. There is an important need of in vitro reconstructed fat for the correction of dermis defects in plastic and reconstructive surgery. Several HA materials have been used for adipocyte cultures to be implanted *in vivo* [111]. Tan, et al. injected thermo responsive HA gel in athymic mouse and showed in situ gel formation [112]. Generally a rapid resorption of HA has been observed after *in vivo* implantation of cultured adipocytes [113,114]. Instead when HA-based (Hyaff-11®) pre-adipocyte seeded scaffold was grafted in patients the graft survival was longer and lasted for up to 16 weeks [115]. Fan et al. demonstrated that adipocyte growth was stimulated when HA hydrogel was functionalized to obtain release of dexamethasone [116]. Along this line of research magnetic HA nano-sphere were developed in order to release dexamethasone and *in vitro* studies showed increase viability of adipocytes [117]. Other scaffolds have been developed for adipose tissue *in vitro* reconstruction. Collagen with cross-linked HA scaffolds seeded with adipocytes were able to induce increased gene expression of adipsin [118]. Furthermore scaffolds made up by the combination of elastin and collagen have been investigated and the results demonstrated a good cell proliferation and adhesion [119]. Engineered constructed made by gelatin-HA scaffolds seeded with Adipose Stem Cells (ASC) were implanted in murine and porcine animal models and compared with acellular gels. Specific gene expression of leptin, a P2, PPAR-g and LPL, were greater in the adipocyte containing gels as compared with a cellular scaffolds [120]. From all the cited works in this section it appears evident that HA has been tested either alone or combined with other materials for adipose tissue reconstruction with the aim to promote fat reconstruction to be used for the correction of skin defects.

Peripheral nerve

Another interesting field of investigation is represented by the widespread use of HA in peripheral nerve tissue engineering. In particular HA hydrogels showed to be a good material for the survival rate and proliferation of neuronal precursors with the possibility to

have a role both in nerve regeneration and in central nervous system therapy [121-126]. Furthermore HA hydrogels are able to promote proliferation and differentiation of nervous cells precursors that could open a new approach for the therapy of neurodegenerative diseases [127-129]. Also the association of chitosan and HA either in the form of conduits [130] and injectable hydrogels were successfully used in peripheral nerve regeneration [131]. Other biodegradable polymers, such as PLGA and poly-L-lysine have been combined with HA to obtain composite materials useful for the controlled delivery of drugs for axonal growth either *in vitro* and *in vivo* [132,133]. More complex structures were investigated by Wang in order to decrease inflammatory response in the field of tissue engineering of nervous tissues [134]. The Author developed porous scaffold with HA doped-poly (3,4-ethylenedioxythiophene)/chitosan/gelatin nanoparticles into chitosan-gelatin matrix. The biological property of this construct supported adhesion, proliferation, and synapse growth in nerve tissue regeneration.

From all the above mentioned experimental works it is reasonable to assess that HA used in the form of hydrogel or in association with other substances can play an important and promising role also in the nervous tissue engineering.

Conclusion

In this article we reported a short overview on the several aspects of HA starting from its discovery to the last chemical and biological new findings. This molecule is used for several clinical applications such as eye surgery, osteoarthrosis, wound repair. From its chemical modification several new products have been obtained. Synvisc®, Hyalgan®, Hyadd®, Arty-Duo®, Healon®, Systane®, OptiveFusion™, Hyaff-11®,various Hydrogels associated with HA are the main HA formulations and derivatives widely used for the treatment of several pathologies and for tissue engineering of skin, cartilage, small caliber vessels, peripheral nerve conduits. However, these new generations of biocompatible and bio-reabsorbable products should be further developed to improve their therapeutical performances. Drug release, cancer therapy, tissue hydration and dermal augmentation are the main candidates for the application of innovative HA based pharmaceutical formulations.

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