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The Importance of Hyaluronic Acid in Biological Systems

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Abstract:

Hyaluronic acid (HA) is a crucial component of the extracellular matrix, found abundantly in connective tissues, skin, and synovial fluid. Its unique properties, including hydration capacity and viscoelasticity, play pivotal roles in tissue hydration, lubrication, and wound healing. Despite its ubiquitous presence, the specific mechanisms underlying its diverse biological functions remain the subject of ongoing research. Studies have elucidated HA's involvement in various physiological processes, such as cell proliferation, migration, and differentiation. Its interaction with cell surface receptors modulates signaling pathways implicated in tissue repair and inflammation regulation. Moreover, HA's rheological properties contribute to joint lubrication, facilitating smooth movement and preventing cartilage degradation. Understanding the multifaceted roles of HA holds significant implications for biomedical applications. Its therapeutic potential spans from skincare formulations to regenerative medicine and drug delivery systems. Targeting HA metabolism presents novel strategies for treating conditions like osteoarthritis, dry eye syndrome, and dermal aging. Continued exploration of HA biology promises exciting avenues for scientific advancement and clinical innovation. Emerging technologies, such as biomaterial engineering and nanomedicine, offer opportunities to tailor HA-based interventions for enhanced efficacy and targeted delivery. Additionally, investigating HA's interplay with the immune system could uncover new immunomodulatory therapies. In conclusion, the importance of hyaluronic acid in biological systems is indisputable, given its indispensable roles in tissue homeostasis and repair. By deciphering its intricate mechanisms of action, researchers pave the way for groundbreaking advancements in medicine and biotechnology. Harnessing the therapeutic potential of HA stands poised to revolutionize healthcare, offering solutions to a myriad of pathological conditions and enhancing quality of life.

Keywords: *Hyaluronic acid, Extracellular matrix, Rheological properties, Tissue hydration and Regenerative medicine.*

Introduction

Hyaluronic acid (HA) was first isolated in 1934 by Albert Meyer and John Palmer. It is widely used in medicine and skincare due to its biocompatibility and safety. Initially used in the food industry, HA has evolved into a structural molecule, lubricant, and modulator of inflammation, wound healing, and cancer. HA-based products dominate eye care, wound healing, drug delivery, and skin care (Narurkar et al., 2016). The human body's healing capabilities are limited, often requiring the use of foreign materials. Autografts, a procedure used in medical emergencies, can generate additional wounds and scarring. This has led to the development of tissue engineering and regenerative medicine (TERM), an interdisciplinary field that combines engineering and life sciences to generate and replace cells, tissues, or organs. Advanced wound healing relies on the proper use of biomaterials, such as hyaluronic acid (HA), which plays a crucial role in processes like cell differentiation and has been used in medical products for over three decades. HA's ability to directly and indirectly affect the wound healing process makes it a key component in regenerative medicine (Dovedytis, Liu, & Bartlett, 2020). Hyaluronic acid (HA), also known as Hyaluronan, is an anionic, non-sulfated glycosaminoglycan found in connective and epithelial tissues. It plays a crucial role in cell propagation and migration, and is responsible for some malignant tumors. Initially developed for ophthalmic surgery, HA has since been used in various diseases due to its long chain length and molecular weight (Vasvani, Kulkarni, &

Rawtani, 2020). Hyaluronic acid (HA) is a crucial component of the cellular matrix and various tissues, with high moisture retention and viscoelasticity. It can be chemically modified to become a good drug carrier and play a non-negligible role in drug delivery. HA's unique physical and chemical properties, including viscoelastic and rheological properties, lay the foundation for its use as a tissue engineering material and drug carrier. HA can be extracted from various tissue cell stroma of vertebrates, but extraction is expensive, difficult to obtain, and complicated. HA can also be obtained through fermentation of bacteria, offering unlimited raw materials, low cost, and simple preparation processes (Huang & Chen, 2019). The evaluates joint lubrication by various substances and their effects on friction using dissipated energy, focusing on hyaluronic acid injections for mild osteoarthritis (Mederake et al., 2022). To develop a 3D biological construct for cartilage regeneration using natural extracellular matrix proteins and co-cultures of human AMSCs and adult chondrocytes, combining cell-based approaches for long-term regeneration (Amann et al., 2017). Hyaluronan (HA), a high-molar-mass linear glycosaminoglycan in the extracellular matrix, has anti-inflammatory, anti-proliferative, anti-angiogenic, and immunosuppressive properties, aiding tissue regeneration, wound healing, and epitheliogenesis (Valachová & Šoltés, 2021). Wounds, caused by external damage, can be acute or chronic, with healing involving haemostasis, inflammation, proliferation, and remodelling. Antimicrobial dressings, like HA, protect against infections and reduce bacterial adhesion (Della Sala et al., 2022). Hyaluronic acid (HA) is a natural, unbranched polymer with a simple chemical structure. It is present in intact tissues and is antiangiogenic and immunosuppressive. It has potential in therapy for inflammatory diseases, including benefits in joints, intestines, lungs, and heart (Marinho, Nunes, & Reis, 2021). Hyaluronic acid (HA) is a long, unbranched polysaccharide with a molecular weight of up to 2 × 107 Da. It is found in bacteria and vertebrates, particularly in the extracellular matrix. HA is negatively charged, hydrophilic, and has a key role in various physiological and pathological conditions. Its viscoelastic properties make it ideal for pharmacological applications, including wound covering and tissue engineering (Abatangelo et al., 2020). Hyaluronic acid (HA) is a naturally occurring linear polysaccharide with various biological properties, including space filling, antiangiogenic, and immunosuppressive functions. It is highly hydrophilic and plays a role in cell activity, proliferation, differentiation, and extracellular spaces (Di Mola et al., 2022). Hyaluronic acid (HA) is a linear glycosaminoglycan polymer found in vertebrate tissues and involved in various biological processes. It has gained interest due to its intrinsic properties and applications in cosmetics, surgery, and medicine. The global market for HA is expected to grow significantly, with a projected value of USD 16.8 billion by 2030. Optimizing HA production processes is crucial for maintaining high-quality standards and affordability (Iaconisi et al., 2023). Hyaluronan (HA) is a biomaterial found in all living organisms, found in synovial fluid, embryonic mesenchyme, vitreous humor, skin, and other organs. It interacts with growth factors, regulates osmotic pressure, and prevents or reduces post-operative inflammation. HA's non-immunogenic and non-toxic characteristics allow its use in various medical applications. It has been used in periodontology, aesthetic treatments, and as grafts and implants. HA could be a better choice than corticosteroids for relief of post-operative sequelae after third molar intervention, as it is widely used in medicinal applications and has no contraindications, side effects, or interactions with drugs (Shuborna et al., 2019). Human skin aging is a complex biological process resulting from two biologically independent processes: intrinsic aging, an unpreventable process, and extrinsic aging, the result of exposure to external factors, mainly ultraviolet (UV) irradiation, also known as photoaging. Intrinsic skin aging is influenced by hormonal changes with age, such as decreased production of sex hormones and the diminution of estrogens and progesterone associated with menopause. Deficiency in estrogens and androgens results in collagen degradation, dryness, loss of elasticity, epidermal atrophy, and wrinkling of the skin. Skin aging is also associated with loss of skin moisture, with the key molecule involved in skin moisture being hyaluronic acid (HA). HA belongs to the extracellular matrix (ECM) molecules and plays a role in angiogenesis, reactive oxygen species, chondrocytes, cancer, lung injury, immune regulation, and skin. Understanding the metabolism of HA in different skin layers and its interactions with other skin components can help modulate skin moisture in a rational manner (Papakonstantinou, Roth, & Karakiulakis, 2012). Cutaneous ageing, a complex biological process involving intrinsic and extrinsic ageing, is primarily caused by UV exposure, with hyaluronic acid playing a significant role (Tzellos et al., 2009). Also hyaluronic acid (HA) is a versatile, non-sulfated glycosaminoglycan used in tissue engineering and regenerative therapy. It regulates cell growth, migration, and differentiation, and is recognized by cell surface receptors. HA's versatility makes it ideal for various applications (Hemshekhar et al., 2016). Hyaluronic acid (HA) is a key biomolecule in skin moisture and viscoelastic properties, playing a crucial role in maintaining skin elasticity and structure. As a humectant, HA hydrates the stratum corneum and epidermis by drawing water from the dermis, bringing moisture and plumpness to the epidermal layers. However, HA concentration and synthesis decrease significantly in aging skin due to both exogenous and endogenous factors, including photoaging and HA metabolism. Reactive oxygen species (ROS) and other free radicals are a major driving force behind HA catabolism associated with photo- and chronic aging. This study evaluates antioxidant ingredients essential in the development of next-generation HA-based topical formulations aimed at leveraging HA's ability to maximize anti-aging properties. Two antioxidants, glycine saponin and glycyrrhetinic acid, were evaluated for stimulation of endogenous HA production and inhibition of endogenous hyaluronidase activity (Zeichner et al., 2024).

Methods and Methodology

In researching this article, a meticulous approach was taken to gather information from reliable scientific and academic sources, as well as the latest research findings, to bring the topic of the importance of hyaluronic acid (HA) in biological systems to the forefront of investigation. By delving into peer-reviewed journals, textbooks, and reputable online databases, a comprehensive understanding of HA's molecular structure, physiological functions, and therapeutic applications was achieved. Special focus was directed towards elucidating HA's roles in tissue hydration, extracellular matrix dynamics, and cellular signaling pathways, alongside its interactions with specific cell surface receptors and implications in various pathological conditions. Data synthesis and analysis were conducted to highlight significant discoveries and identify research gaps, presenting a nuanced perspective on HA's multifaceted functions across diverse disciplines. This study aims to provide valuable insights into HA's pivotal role in physiological processes, offering implications for future research directions and therapeutic interventions.

Synthesis of Hyaluronic Acid (HA), Properties, and Degradation

Synthesis

Hyaluronic Acid (HA) is produced by a group of integral membrane proteins called HA synthases (HAS), comprising HAS1, HAS2, and HAS3 in vertebrates. These proteins elongate HA by continually adding glucuronic acid and N-acetyl-D-glucosamine groups to the sugar chain, extruding them through the cell wall via ABC-transporters. The synthesis of HA can be inhibited by 4-methylumbelliferone, offering a selective method for preventing tumor cell metastasis. Notably, Bacillus subtilis has been genetically engineered to produce HAs for human-grade products. Although any HAS protein is capable of HA production, the kinetic characteristics of HAS1, HAS2, and HAS3 influence the size of HA produced. HAS1 and HAS2 synthesize high molecular weight HA

(HMWHA), while HAS3 produces low molecular weight HA (LMWHA) due to its high activity. In humans, the half-life of HA varies across tissues, ranging from approximately 1 day in the skin to up to 70 days in the vitreous body of the eye. HA is utilized in animals, particularly horses, for treating joint dysfunctions and inflammatory disorders related to degenerative joint diseases.

Properties of HA

HA serves various structural functions within the extracellular matrix (ECM) through specific and nonspecific interactions with proteins and cellular receptors. CD44 is highlighted as a significant receptor due to its multifunctional presence on various cell types. HA is essential for cellular communication and tissue repair, with its molecular weight influencing wound healing and scar formation. While high molecular weight HA supports tissue integrity, low molecular weight HA plays a crucial role in growth processes.

HA-Receptor Interaction and Degradation

HA interacts with cell receptors such as CD44, RHAMM, and ICAM-1, contributing to various physiological events like cell adhesion, proliferation, and migration. Enzymatic degradation of HA occurs via hyaluronidases, while non-enzymatic degradation can be prompted by various stresses. The turnover of HA within tissues involves both local degradation and release into the lymphatic system (Vasvani, Kulkarni, & Rawtani, 2020).

Table 1. Summary of Using HA with Other Components in Engineering of Various Tissues

Applications	Components	Properties
Soft tissue engineering	Scaffold composed of collagen and HA	Improved resistance to collagenase and elastic mechanical properties, prevention of disintegration of collagen in aqueous medium, cytotoxic for Vero cells
Articular cartilage tissue engineering	HA and alginate bioink	Improved chondrocyte functionality
Articular cartilage tissue engineering	Methacrylated gelatin and methacrylated HA	Created cartilage models with varying chondrocyte densities, support of formation of cartilage ECM and recovery of chondrocyte phenotype
Tissue engineering	UV-crosslinkable HA and surface-modified nanodiamond hydrogels	Mechanically enforced compressive stress, a tunable buffering environment and facilitated interaction with long HA chains at molecular level
Articular cartilage tissue engineering	HA, hydroxyethyl acrylate and gelatin-methacryloyl bioprinting gel	Stable rheology properties and excellent biocompatibility, viability of bone cells in bioinks of the lattice-printed scaffolds
Articular cartilage tissue engineering	Silk-HA scaffold	Good biocompatibility with bone marrow mesenchymal stem cells, enhanced cellular proliferation, biodegradable, biomimetic nanofibrous structure
Bone tissue engineering	Hydrogel composed of arginine-based unsaturated poly(esteramide) and methacrylated HA	Better bone regeneration and expression of osteogenesis-related factors in rats
Vocal fold tissue engineering	Thiolated HA crosslinked with poly(ethylenglycol) diacrylate (PEGDA)	Increased mechanical properties of the hydrogels and reduced hyaluronidase degradation of HA and hydrogel swelling ratio, higher fibroblasts cell adhesion and spreading, viability of cells and synthesized new DNA through 21 days of culture
Tissue engineering	HA and halloysite nanotubes cryogel as scaffolds	Nonhemolytic materials, macroporous structure, high thermal and mechanical stability, good compatibility, template for cell proliferation, adhesion and the growth media
Tissue engineering	Carboxymethyl chitosan and partially oxidized HA hydrogel	Moderate swelling, good biocompatibility with embedded cells, sufficient viscosity for printing with good shape fidelity and structural integrity to retain the printed shape
Bone tissue engineering	Methacrylated HA gels	Good primary chondrocyte survival, excellent spontaneous osteogenic differentiation in vitro
Bone and cartilage tissue engineering	HA-polyethylenglycol hydrogel	High mechanical stability, enhanced metabolic activity and cell propagation

Bone and cartilage tissue engineering	HA with methacrylated glycol chitosan hydrogel	Increased propagation and extra deposition of cartilaginous ECM
Cartilage tissue engineering	Water-based polyurethane based photosensitive materials with HA	Nontoxic, high printing resolution, good cytocompatibility, facilitated chondrocyte adhesion, proliferation and differentiation
Cartilage tissue engineering	HA-adipic dihydrazide and the oligopeptide grafted oxidized pectin hydrogel	Facilitated chondrogenesis, tissue compatibility by using a mouse subcutaneous implantation model
Heart valve tissue engineering	Collagen type I and HA scaffold	Mimics fibrosa layer in the aortic valve leaflet ECM, potential to be developed into the trilayer structure of the leaflet, mimics the entire aortic root, cell material system for valve repair
Soft tissue engineering	Aerogel sponges of silk, fibroin, HA and heparin	High swelling degree and porosity; lower biodegradation; adequate mean pore diameter and connectivity for cells and a soft texture close to that of the brain
Periodontal tissue engineering	Chitosan-HA scaffold	Increased viability of NIH3T3 and MG63 cell lines, high CD44 expression, physico-chemical parameters without significant morphology changes
Bone tissue engineering	HA/corn nanosilver-silk β-tricalcium phosphate hydrogel	Antibacterial activity, mesenchymal stem cells high bone differentiation, enhanced physical, mechanical properties, cell binding affinity and tissue compatibility
Bone tissue engineering	Collagen/HA oligosaccharides/hydroxyapatite and chitosan/HA oligosaccharides in D,L-lactic-co-glycolic acid solution	Stimulation of osteogenesis and endothelialization, promotion of the attachment of endothelial cells, promotion of osteogenic differentiation of MC3T3-E1 and BMSCs cells, ideal biocompatibility and tissue regenerative capacity
Salivary gland tissue engineering	HA-catechol conjugates	Enhanced cell adhesion, vascular endothelial and progenitor cell proliferation, and branching of cultured embryonic submandibular glands in vitro
Abdominal tissue regeneration	Chitosan/HA hydrogel	In rats, sufficient extracellular matrix exposition and marked neovascularization were found compared to the control group

Source: (Valachová & Šoltés, 2021).

Biology of Hyaluronan (HA)

Presence of HA in Living Organisms and its Distribution in the Human Body

Hyaluronan (HA) is ubiquitously found in various organisms including humans, animals like rabbits, bovines, roosters, certain bacteria such as Streptococcus species, algae like Chlorella sp. infected by Chlorovirus, yeasts like Cryptococcus neoformans, and mollusks. However, it is notably absent in fungi, plants, and insects. In humans, HA content averages around 15 grams in a 70-kilogram adult. It is predominantly located around cells, forming a coating, and in the extracellular matrix (ECM) of connective tissues. Approximately half of the HA in the body is found in the skin, while significant amounts are also present in synovial joint fluid, eye vitreous body, and the umbilical cord. The turnover rate of HA is rapid, about 5 grams per day, and is tightly regulated through enzymatic synthesis and degradation.

Synthesis of HA in the Human Body

HA synthesis occurs via three transmembrane glycosyltransferase isoenzymes known as hyaluronan synthases (HAS): HAS1, HAS2, and HAS3. These enzymes synthesize HA as a free linear polymer, with their catalytic sites situated on the inner side of the plasma membrane. The synthesized HA chains are extruded onto the cell surface or into the ECM. Although the HAS isoforms share similarities in structure and function, they exhibit differences in gene location, expression, activity regulation, and biochemical properties. Dysregulation of HAS genes can lead to abnormal HA production, influencing various physiological and pathological processes including cancer.

Degradation of HA in the Human Body

HA degradation in the body occurs through specific enzymatic mechanisms mediated by hyaluronidases (HYAL) and nonspecific oxidative damage caused by reactive oxygen species (ROS). Approximately 30% of the total HA is locally degraded by HYAL and ROS, while the remaining 70% undergoes systemic catabolism. HYAL enzymes play a crucial role in HA metabolism by predominantly degrading HA. The expression and activity of HYAL are tissue-specific, and their dysregulation can contribute to pathological conditions. Additionally, ROS-induced degradation of HA occurs during inflammatory responses and tissue injury, impacting various physiological processes.

Biological Functions of HA in Relation to its Molecular Weight

The balance between HA synthesis and degradation regulates its biological functions, which are influenced by its molecular weight (MW). High molecular weight (HMW) HA exhibits anti-inflammatory, lubricating, and tissue-protective properties, while low molecular weight (LMW) HA can have pro-inflammatory and pro-angiogenic effects. HA fragments of different sizes can exert diverse physiological and pathological actions depending on the tissue context. Further research is necessary to fully understand HA's biological roles and its potential for therapeutic applications (Fallacara et al., 2018).

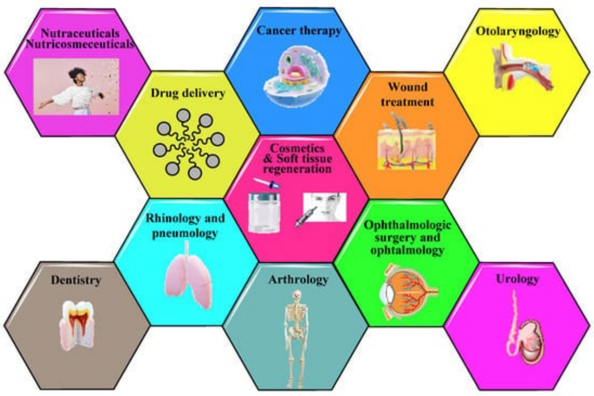

Figure 1. HA functions
Source: Iaconisi et al., 2023

Mechanism of actions of HA

Hyaluronic Acid (HA) exerts its biological effects through two primary mechanisms. Firstly, it functions both as a passive structural component and as a signaling molecule, with its actions being influenced by its size and molecular weight. Secondly, HA regulates tissue hydration, osmotic balance, and the physical properties of the extracellular matrix (ECM), which serves as a hydrated and stable environment crucial for maintaining cellular integrity, collagen structure, elastin fibers, and other ECM constituents. The interaction between HA and various proteins dictates contrasting actions, including both pro-inflammatory and anti-inflammatory activities, promotion or inhibition of cell migration, and modulation of cell division and differentiation. Within the ECM, HA primarily exists in the hyaluronate form and is distributed in various tissues such as the lung, kidney, brain, and muscle, as well as in regions experiencing friction such as joints, tendons, sheaths, pleura, and pericardium. The average lifespan of HA is approximately 2 to 3 days, with elimination occurring through metabolism in the liver, local metabolism in the skin and joints, and lymphatic drainage. In the bloodstream, the liver eliminates the majority of HA (approximately 85-90%), with a smaller portion processed by the kidneys and a minimal amount excreted in urine. HA is characterized as a hygroscopic, viscoelastic, biocompatible, and non-immunogenic substance with anti-inflammatory, anti-edematous, and antioxidant properties. Studies have confirmed its lack of cytotoxicity and good biocompatibility. HA maintains structural homogeneity across species and exhibits minimal interaction with blood components. Neurotoxicity studies have ruled out concerns associated with epidural-administered HA in animal models. Various tumors, including epithelial, ovarian, colon, stomach, and acute leukemia tumors, exhibit overexpression of HA-binding receptors CD44 and RHAMM, resulting in enhanced binding and internalization of HA. Correlations have been observed between HA and HA synthases (HAS) with cancer progression. Excessive HAS activity leads to increased HA levels, stimulating tumor growth and metastasis. However, exogenous algometric HA has been found to inhibit tumor xprogression, potentially through competition with endogenous polymeric HA Figure 1. (Shuborna et al., 2019).

Applications of Hyaluronic Acid

Taking into account its biological actions, physico-chemical properties, its biocompatibility or safety profile, HA has multiple applications. Figure 02 depicts the utilization of HA and its derivatives in: medical (arthrology, cancer therapy, pneumology, odontology, ophthalmology, otolaryngology, rhinology, soft tissue regeneration, urology, wound treatment, etc.), pharmaceutical (e.g., drug delivery systems), nutritional (nutraceuticals, nutricosmeceuticals), or cosmetic field Figure 02 (Juncan et al., 2021).

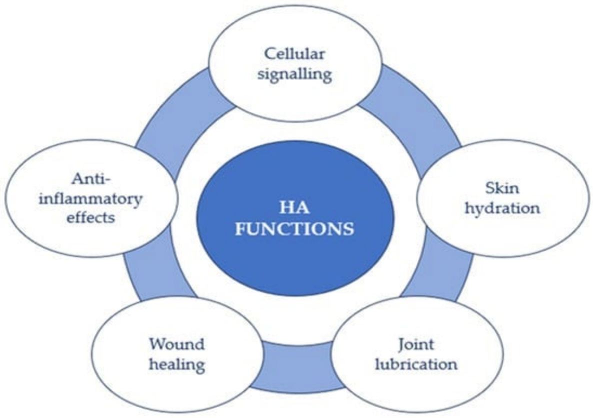

Figure 2. Cosmetic, pharmaceutical, and medical applications of HA and its derivates. Source: Juncan et al., 2021

Applications of HA-based Biomaterials

Initially used for joint lubrication and stress reduction in osteoarthritis, hyaluronic acid (HA) has expanded its applications to ophthalmology, otology, and beyond. Despite initial limitations due to rapid degradation, chemical modifications and crosslinking have extended its therapeutic potential to dermal fillers, tissue regeneration, and drug delivery. HA's anti-inflammatory properties make it attractive for various clinical uses. In tissue engineering, HA supports cell survival, proliferation, and stemness, offering promise for stem cell encapsulation and controlled differentiation. Its versatile chemistry allows for precise tuning of biophysical properties, enabling the development of tailored biomaterials for diverse applications. Crosslinking HA with other polymers further enhances its functionality. Overall, HA-based biomaterials represent a versatile platform for addressing various biomedical challenges (Wolf & Kumar, 2019).

Future Directions Top of Form

Drug Delivery in Periodontics

The distinctive properties of HA have led to numerous applications for drug delivery utilizing this polysaccharide. One intriguing possibility is the use of HA membranes for drug delivery, particularly in periodontics. Periodontal disease is a prevalent global issue, with reported prevalence as high as 50% worldwide. It is characterized as a chronic state of inflammation resulting from interactions between bacterial biofilm and the host's immune system. Current treatment methods involve biofilm and calculus removal through debridement, followed by antimicrobial treatments such as chlorhexidine, tetracycline, or metronidazole. However, systemic antibiotic treatment has faced significant criticism due to the escalating battle against antimicrobial resistance (AMR). Because of AMR, there is a need for more localized administration of antibiotics. HA has demonstrated anti-inflammatory properties at high molecular weights, making it a suitable medium for the local delivery of antibiotics to treat periodontal pockets post-cleaning, thereby preventing periodontal infections. Clinical trials are currently investigating the use of HA for furcation or bone defects resulting from periodontal disease.

Hyaluronic Acid as Nanocarriers

Another application of HA under investigation is the delivery of nanoparticles. Many materials used for nanocarriers pose toxicity risks.

However, by coating the nanocarrier with a biocompatible and bioactive substance like HA, this toxicity can be mitigated, enabling targeted delivery to tissues. HA can be utilized for various applications, from HA-drug conjugates exploiting HA's functional groups to HA-based micelles, nanoparticles, and HA coatings for nanocarriers. The primary goal is to alleviate or modulate drug toxicity. For instance, metallic quantum dots, used in biological imaging and tumor visualization, often elicit a strong immune response and systemic toxicity. By shielding or modulating the release of these quantum dots, potential toxicity may be reduced. Similarly, HA-coated nanocarriers are being explored for the delivery of chemotherapy agents to alleviate systemic toxicity associated with cancer treatment. Clinical trials are underway for the delivery of paclitaxel, a common chemotherapeutic agent, using HA-based drug delivery systems.

Injectable Hyaluronic Acid Hydrogels

Another rapidly evolving area is injectable HA hydrogels. Clinical trials have examined their use in treating osteoarthritis, with mixed results. Now, the focus is shifting towards using injectable HA drug carriers for sustained delivery of anti-proliferative chemotherapeutic agents for inflammatory arthritis treatment. Similar to nanoparticle delivery, toxicity is tightly controlled and localized to the treatment area. Injectable HA hydrogels come in various forms, including macroscopic hydrogels and alternatives like microgels, nanogels, and cryogels. These alternatives offer benefits such as increased surface area, enhanced resilience to degradation, and improved solubility of pharmaceuticals. They show promise for controlled and extended drug release, as well as potential applications in cartilage repair and imaging techniques like magnetic resonance imaging (MRI). The versatility of HA in drug delivery presents a broad range of possibilities, from modulating systemic drug cytotoxicity to providing lubrication and sustained release. The future holds much promise for this unique polymer, with ongoing exploration into its diverse administration routes (Buckley et al., 2022).

Discussion

HA is a biocompatible and biodegradable compound with significant potential for addressing various physiological and pathological conditions, particularly musculoskeletal rehabilitation. Its abundance in connective tissues, particularly joints, lubricates joints, mitigates friction, and enhances flexibility. HA's properties make it an effective therapeutic compound for musculoskeletal diseases, and its use in physical therapy and rehabilitation exercises can enhance treatment outcomes (Iaconisi et al., 2023). Hyaluronan, a versatile material, is increasingly being explored for its potential in biomedical applications like drug delivery and regenerative medicine due to its biodegradability, biocompatibility, and ease of chemical functionalization (Valachová, Hassan, & Šoltés, 2024). Skin aging is a complex biological phenomenon influenced by intrinsic and extrinsic factors. It leads to deep wrinkles, uneven skin tone, laxity, dullness, and roughness, affecting collagen and elastin levels. Hyaluronan (HA), a key molecule in skin moisture, is affected by aging. A study found that a stabilized retinol formulation stimulated HAS genes and induced HA production, leading to increased HA accumulation and wrinkle reduction (Li et al., 2017).

Bioactive materials (HA) are attractive for various research and technological applications due to their bioactivity and versatility. HA signaling influences cells and tissues, and its mechanical properties, adhesivity, and degradability are central. HA MW has implications for biophysical signaling, with HMW HA associated with homeostasis and LMW HA associated with tissue remodeling. Various strategies exist to modify HA's biophysical cues, but none capture the complexities of HA organization with other matrix factors. As HA biology expands, future work should focus on incorporating critical features of HA into biomaterial design and characterization of downstream effects. More attention should be given to HA MW, the biological importance of HA organization within the ECM, and the role of HA degradation in biomaterial performance (Wolf & Kumar, 2019).

A study has found that HA, CD44, and RHAMM play functional roles in embryonic myogenesis. The research used a mouse model with GFP+ myoblasts and GFP- forelimb cells. HA is widely expressed in the developing forelimb, while CD44 and RHAMM are expressed by myoblasts and surrounding connective tissue cells. Knockdown of HA in vitro and antibody blocking of CD44 and RHAMM induced differential effects on cell behavior, suggesting different complexes may be associated with these receptors depending on cell type. The study also found changes in HAS and Hyal gene expression in skeletal muscle during forelimb development (Leng et al., 2019). Hyaluronan (HA) biology has made significant progress, but much remains to be elucidated. Some "known unknowns" include the precise polymer-receptor interactions of HA, the pro- or anti-inflammatory functions of LMW and HMW HA, and the complex interactions between receptors, intracellular mediators, and pathologic mechanisms. Recent studies suggest that tertiary or quaternary interactions of HA receptors with the HA matrix may explain these interactions. Additionally, the divergent effects of HA are likely due to different receptor clusters and their interactions with ECM binding partners of HA (Garantziotis & Savani, 2019). The study shows that both HMW and LMW IA HA formulations induce a mild-to-moderate inflammatory response in healthy equine joints. The exact mechanism of this response is unknown and requires further research. The adverse effects may outweigh the beneficial effects of HA in the diseased joint. Further research is needed on the effects of different HA molecular weights and formulations on normal and inflamed equine joints (Johnston et al., 2020).

Osteoarthritis (OA) management can be effectively managed through multidisciplinary non-surgical approaches, but challenges remain like patient adherence and heterogeneity. Personalized patient-centered strategies, caregiver involvement, and sustainability of multidisciplinary programs are crucial. Virtual reality and augmented reality systems can provide immersive experiences, while future research should explore the synergy of HA injections in multidisciplinary care (Lippi et al., 2023). HA, a biodegradable, biocompatible, nontoxic, and nonimmunogenic polysaccharide, is widely used in medical applications like OA surgery, ocular surgery, plastic surgery, and drug delivery, particularly for target-specific, long-acting therapeutics (Sudha & Rose, 2014). The intercellular matrix is a complex network of macromolecules, including proteins and polysaccharides like hyaluronan (HA), which maintains skin elasticity and acts as a selective filter. In cartilage tissue, the extracellular matrix occupies a large volume and plays connective tissue functions, including spring function. It contains strong collagens, elastins, adhesive proteins, and proteoglycans, which regulate connective tissue regeneration. The fibrillar network of cartilage matrix is composed of types II, IX, and XI collagen, providing strength. The extracellular matrix of bone tissue is characterized by high mineralization, with 50% inorganic compounds, 25% organic compounds, and 25% water (Selyanin et al., 2015).

The cosmetic industry is focusing on active cosmetic products and cosmeceuticals, with hyaluronic acid (HA) and its derivates having numerous applications. The efficacy of HA depends on its molecular weight, with effects like hydrating, regenerating, and anti-aging. Recently, commercially available cosmetic formulations incorporate HA or HA derivates, with sodium hyaluronate being the majority. These formulations also include plant extracts, vitamins, amino acids, peptides, proteins, saccharides, probiotics, and gold or malachite extracts. (Juncan et al., 2021). Natural beautifying items are increasingly popular for healthcare purposes, with a growing interest in everyday beauty care. These products contain herbal elements like bleaching agents, oils, and plant fabrics. They are effective in sidelining synthetic ingredients and are used for cosmetic purposes and disease treatment. Proper control measures are crucial for their protection (Goyal et al., 2022). Hyaluronic acid production using microorganisms is a complex process that involves selecting the appropriate substrate, supplements, and culture conditions. Alternative sources like agricultural waste and industrial waste can be used, but the most suitable substrate depends on the microorganisms and production scale. The optimal culture conditions include temperature, pH, aeration, agitation, and substrate concentration. Fermentation is a widely used process for hyaluronic acid production, but challenges include limited production due to high viscosity, competition for precursors, accumulation of by-products, and inhibition of production. Researchers are exploring alternative culture media and downstream strategies to achieve high purity hyaluronic acid for medical applications. Despite the challenges, achieving low dispersity and achieving low costs remain a priority for hyaluronic acid production (Serra et al., 2023). Hyaluronan (HA) is used in various medical, pharmaceutical, cosmetic, and dietary applications due to its unique properties. Its chemical modifications enable the development of long-lasting drug delivery and anti-inflammatory effects. However, further research is needed to understand its biological actions and potential applications. Next-generation products like crosslinked derivatives and polymer-drug conjugates are needed for high biocompatibility and long-lasting drug delivery (Fallacara et al., 2018). In brief, hyaluronic acid (HA) is versatile in medical, pharmaceutical, and cosmetic industries due to its biocompatibility. It's used for transdermal delivery (low molecular weight) and sustained release (high molecular weight) formulations. HA-based products enhance permeation and sustained release through various mechanisms, with future focus on simplifying manufacturing for large-scale production (Zhu et al., 2020).

Conclusion

In conclusion, the comprehensive examination of scientific literature and recent research findings unequivocally underscores the pivotal role of hyaluronic acid (HA) in biological systems. HA stands as a multifunctional molecule whose significance permeates across diverse domains of biology and medicine. Its contributions to tissue hydration, extracellular matrix integrity, and cellular signaling pathways are foundational to numerous physiological processes. Moreover, HA's rheological properties and interactions with cell surface receptors underscore its versatility in facilitating tissue homeostasis, wound healing, and immune modulation. From skincare formulations harnessing its moisturizing effects to regenerative medicine applications exploiting its regenerative potential, HA emerges as a cornerstone of therapeutic interventions. Additionally, insights into HA's involvement in pathologies such as osteoarthritis and dermal aging shed light on its diagnostic and therapeutic relevance in treating a spectrum of medical conditions. Nevertheless, despite substantial advancements, gaps in understanding persist, urging further exploration into HA's intricate mechanisms and therapeutic potential. Future research endeavors hold promise for unveiling novel insights, innovative technologies, and targeted interventions that leverage HA's inherent properties for improved healthcare outcomes. Thus, the significance of HA in biological systems remains enduring, beckoning continued investigation and innovation to unlock its full spectrum of possibilities in advancing human health and well-being.

Highlights

- Foundational Role: Hyaluronic acid (HA) serves as a foundational molecule in biological systems, playing crucial roles in tissue hydration, extracellular matrix integrity, and cellular signaling pathways.

- Versatility and Adaptability: HA's rheological properties and interactions with cell surface receptors highlight its versatility and adaptability in facilitating tissue homeostasis, wound healing, and immune modulation.

- Therapeutic Potential: HA's multifunctional nature underpins its therapeutic potential, with applications ranging from skincare formulations harnessing its moisturizing effects to regenerative medicine interventions exploiting its regenerative capabilities.

- Clinical Relevance: Insight into HA's involvement in pathologies such as osteoarthritis and dermal aging underscores its diagnostic and therapeutic relevance in treating various medical conditions.

- Ongoing Research: Despite significant advancements, gaps in understanding persist, driving the need for continued exploration into HA's intricate mechanisms and therapeutic potential.

- Promise for the Future: Future research endeavors hold promise for unveiling novel insights, innovative technologies, and targeted interventions that leverage HA's inherent properties for improved healthcare outcomes.

- Enduring Significance: The enduring significance of HA in biological systems beckons continued investigation and innovation to unlock its full spectrum of possibilities in advancing human health and well-being.

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