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Advances in Hyaluronic Acid-Based Therapies

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ABSTRACT

Hyaluronic acid (HA) is crucial in regulating stem cells and enhancing their therapeutic efficacy in chronic inflammatory diseases such as interstitial cystitis/bladder pain syndrome (IC/BPS). This study aimed to explore the potential of HA as a biomaterial for optimizing stem cell-based therapies in the treatment of IC/BPS. Due to its biocompatibility and bioactivity, HA serves as a supportive matrix that improves stem cell retention, survival, and function. Additionally, HA modulates stem cell behavior, promoting regeneration and anti-inflammatory response, which are essential for repairing the damaged bladder lining in animals. Its intrinsic anti-inflammatory properties further contribute to reducing inflammation and creating a favorable microenvironment for mesenchymal stem cells (MSCs). Furthermore, HA facilitates the controlled release of MSCs and other therapeutic agents, extending their benefits for chronic conditions like IC/BPS. The wide-ranging applications of HA in both animal models and human research underscore its potential as a therapeutic agent for various medical conditions. Preclinical studies have shown that HA supports tissue regeneration, reduces inflammation, and enhances stem cell retention, making it a valuable biomaterial for treating bladder inflammation, liver fibrosis, and cardiovascular disorders. In clinical settings, HA has been effectively applied in regenerative medicine, osteoarthritis management, wound healing, and drug delivery, demonstrating its biocompatibility and therapeutic effectiveness. These insights highlight HA's role in translating experimental findings into clinical applications, paving the way for improved treatment approaches for chronic and inflammatory diseases. Overall, HA holds significant potential in enhancing the efficacy and long-term therapeutic outcomes of MSC-based treatments for chronic bladder disorders.

Keywords: Hyaluronic acid, Interstitial cystitis, Matrix, Stem cell

INTRODUCTION

Hyaluronic acid (HA) is notable for interacting with stem cells via surface receptors, promoting differentiation (Meng and Chen, 2024). Uronic acid is one of the sugar components of HA, a naturally occurring linear polysaccharide with a high molecular weight that was first identified in the vitreous body of bovine eyes. The connective tissues, the umbilical cord, and the synovial and vitreous fluids are rich in HA. Its applications span ophthalmology, otology, and cosmetic surgery as a dermal filler, and it has gained attention in recent years as a preferred biomaterial for soft tissue reconstruction. The HA can be sourced from certain bacterial strains, such as Streptococci, as well as vertebrate tissues, with significant quantities found in human umbilical cords, and through bacterial fermentation (Chang et al., 2024).

The HA's unique structural composition and hydrophilic nature contribute to its biodegradability and metabolic processing, influencing its breakdown and clearance within the body. The lymphatic system is where HA largely breaks down, while the bloodstream carries the breakdown products to the liver. Enzymes called hyaluronidase mostly break the β1-4 glycosidic bond in HA while avoiding the β1-3 bond, which makes HA a biocompatible and biodegradable polymer appropriate for tissue engineering and regenerative medicine (Meng and Chen, 2024).

The HA plays a role in regulating cell migration and adhesion by engaging in complex cellular signaling pathways facilitated by proteins known as hyaladherins (Chang et al., 2024). Under biological conditions, HA functions both passively and as a signaling molecule. The passive function is linked to the molecular weight of hyaluronic acid, whereas the signaling function is mediated by interactions with specific binding proteins, including matrix and cellular hyaladherins. Key cellular hyaladherins include Cluster of Differentiation (CD44), the HA receptor for endocytosis (HARE), the receptor for HA-mediated motility (CD168 or RHAMM), toll-like receptors (TLRs), and lymphatic endothelial receptor-1 (LYVE-1; Gholamali et al., 2024).

The HA is essential in numerous biological processes, influencing both normal physiology and disease pathogenesis. It serves as a structural component in tissue regeneration by supporting the growth of blood vessels, fibroblasts, and inflammatory cells. It also helps in managing cellular behavior in the immune response. Notably, HA's interactions with

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stem cells, particularly hematopoietic and mesenchymal stem cells, suggest that it may be instrumental in tissue repair and regeneration, offering potential therapeutic avenues for treating injuries and diseases by targeting these pathways (Abdul Rahim et al., 2024).

During development, HA and its associated enzymes (HA synthases and hyaluronidases) have been found to play a role in the formation of critical structures in various organs (Meng and Chen, 2024). In animal models, for instance, the deletion of HA synthase 2 (HAS2) leads to severe defects in heart and limb development, indicating HA's significant influence on organogenesis. This is particularly evident in the skeletal system, where HAS2 modulates growth and joint formation through pathways such as the Sonic Hedgehog and BMP/transforming growth factor-beta1 (TGF-β1) signaling. Furthermore, HA plays an essential role in muscle cell differentiation, hematopoiesis, and intestinal epithelial proliferation, which highlights its extensive developmental influence (Øvrebø et al., 2024).

The HA precursors are synthesized by first phosphorylating glucose by hexokinase and then yielding glucose-6-phosphate, which is the main HA precursor. This process follows two routes, which are taken to synthesize UDP-n-acetylglucosamine and UDP-glucuronic acid, both reacting to form HA (Meng and Chen, 2024). HA also contributes to cell growth and differentiation in various tissues. In cancer cells, HA promotes tumor progression by enhancing resistance to apoptosis and facilitating growth via interactions with co-receptors such as CD44 (Gholamali et al., 2024). In fibrosis, HA supports fibroblast proliferation and transformation, which can lead to tissue scarring. Additionally, HA has complex roles in promoting or inhibiting differentiation across multiple cell types, depending on factors like cell type and environment. For instance, HA fragments can promote myofibroblastic, endothelial, and chondrogenic differentiation but may inhibit other pathways, such as osteogenesis, in certain contexts (Hejran et al., 2024).

In immune responses, HA regulates inflammation by influencing inflammatory cell behavior, promoting cytokine release, and controlling immune cell migration. HA interactions with the CD44 receptor on immune cells affect B-cell and T-cell activation, in addition to regulatory T-cell functions, thus modulating both innate and adaptive immunity (Gholamali et al., 2024). In particular, HA fragments activate dendritic cells and encourage their migration, impacting allergic responses and the immune system's reaction to injuries. In mouse models, HA-CD44 interactions are crucial for immune responses, as evidenced by impaired neutrophil recruitment and tissue inflammation in CD44-deficient mice (Gholamali et al., 2024).

The HA's involvement in cellular senescence is observed through its role in cellular aging and stress responses. HA fragments influence fibroblast senescence, contributing to skin aging, while reduced HA synthesis is linked to senescence in mesenchymal stem cells. Conversely, HA-based treatments have shown potential in mitigating oxidative stress-induced senescence, presenting an area for therapeutic research in aging-related diseases (Gholamali et al., 2024). HA also plays a role in apoptosis. It has been shown to protect lung and skin cells from stress-induced apoptosis while promoting apoptosis in immune cells, such as T cells and neutrophils. In lung injury models, high-molecular-weight HA has been shown to reduce inflammatory responses and protect against apoptosis in epithelial cells. Similarly, in conditions such as smoke-induced lung injury, HA shows protective effects, suggesting that targeting HA may offer therapeutic benefits in inflammatory and apoptotic regulation across various disease contexts (Vasvani et al., 2020). The present study aimed to explore the potential of HA as a biomaterial for optimizing stem cell-based therapies in the treatment of Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS).

LUNG FIBROSIS

The most common form of interstitial lung disease is idiopathic pulmonary fibrosis (IPF), characterized by chronic and progressive fibroproliferation that impairs gas exchange, often leading to respiratory failure and a poor prognosis of 2–5 years post-diagnosis. IPF patients exhibit elevated HA levels in their bronchoalveolar lavage (BAL) fluid, which correlates with disease severity. Studies show that fibroblasts from IPF patients secrete more HA, which supports TGF-β1-mediated fibroblast proliferation, a key factor in fibrogenesis. In humans, increased HA accumulates in lung tissue post-injury, intensifying fibrosis. However, hyaluronidases, when delivered via microparticles or intranasally, have shown promise in reducing fibrosis, likely by influencing mesenchymal stem cell-like populations in the damaged lung (Figure 1; Collum et al., 2017).

LIVER FIBROSIS

Chronic hepatitis and cirrhosis patients often show elevated serum HA levels, which may help monitor liver fibrosis non-invasively. Studies on rats indicate that low molecular weight (LMW) HA supports liver resistance against certain inflammatory injuries, while HA interactions with CD44 impact inflammation based on disease progression. However, HA as a sole biomarker in liver fibrosis remains unreliable due to variability in disease pathology (Figure 1; Gudowska et al., 2017).

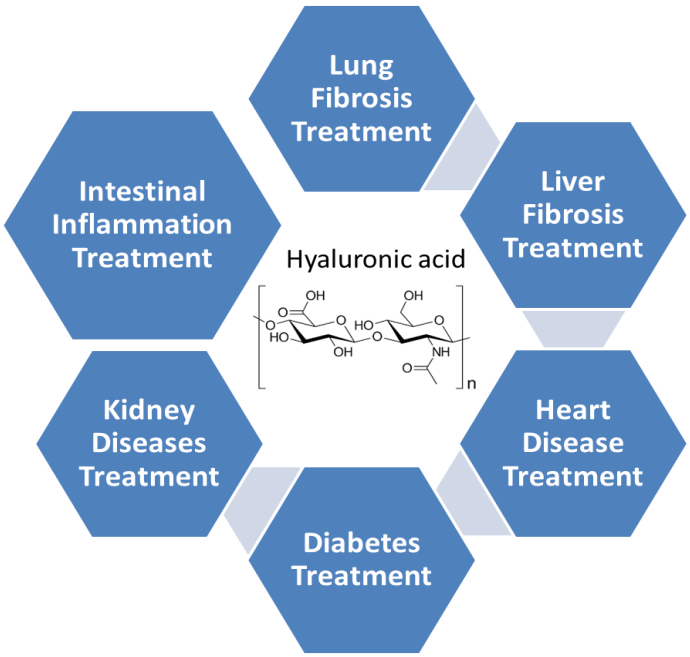

Figure 1. The beneficial effects of hyaluronic acid in animals

HEART DISEASES

In heart conditions such as atherosclerosis, HA is expressed in aortic layers and associated with vascular smooth muscle cells, promoting vascular remodeling and leukocyte adherence. The HA synthase inhibitors, which may prevent HA accumulation, must be carefully used to avoid disrupting the protective endothelial glycocalyx. Additionally, CD44 has been found to facilitate leukocyte and vascular cell activation, promoting atherosclerosis through various mechanisms in rat models (Medina-Leyte et al., 2021).

DIABETES

The HA levels are often higher in diabetic patients, correlating with poor glucose control and diabetic complications. HA production under hyperglycemic conditions contributes to vascular and tissue alterations, such as mesangial cell proliferation and changes in vascular smooth muscle cells (Prashanth et al., 2019). Blocking the CD44-HA interaction has shown potential in rat models, suggesting a role for HA in diabetes development (Figure 1; Gudowska et al., 2017).

RENAL DISEASES

In kidney diseases, particularly nephritis and renal insufficiency, HA accumulation is linked to tissue fibrosis and inflammation (Agarwal et al., 2020). High serum HA levels are observed in patients with lupus nephritis and renal failure, with elevated levels often indicating poor survival rates. HA-CD44 interactions also contribute to immune cell recruitment and tissue damage in rat models of kidney disease, while specific HA inhibitors may help preserve renal function by reducing inflammatory infiltration (Figure 1; Kaul et al., 2022).

INTESTINAL INFLAMMATION

In inflammatory bowel disease disorders like Crohn's disease, HA regulates intestinal and colonic growth and accumulates in nonvascular spaces, attracting leukocytes (Madurga Patuel et al., 2022). Experimental models indicate that HA deposition precedes inflammation, promoting leukocyte infiltration. The HA interactions with CD44 and other receptors support immune cell adherence and TLR4-mediated epithelial protection. Furthermore, HA may support intestinal epithelium repair in response to injury in animal models, though its roles in inflammation and epithelial protection require further investigation (Vasvani et al., 2020).

In tissue engineering, hydrogels, particularly those containing HA, are crucial for enhancing cell attachment, growth, and overall tissue regeneration. HA-based hydrogels simulate the extracellular matrix (ECM), facilitating growth factor delivery and surface modifications that improve the regenerative potential of tissues (Madurga Patuel et al., 2022). For instance, HA can promote cell adhesion and tissue repair while serving both anti-aging and therapeutic purposes (An et al., 2023). Products like Hylase Wound Gel®, an HA-based gel, showcase the benefits of HA in wound care for humans by aiding in the healing process (Sekar et al., 2023).

Advanced HA-based formulations have furthered medical applications, such as an injectable HA gel blended with carboxymethyl hexanoyl chitosan that enables sustained drug release and protection of cartilage cells (Vasvani et al.,

2020). This gel supports joint health by preventing cell apoptosis and holds promise for intra-articular drug delivery. In treating tendinopathy, HA hydrogels, enhanced with antioxidants, have been effective in mitigating oxidative stress and promoting faster recovery (Jabbari et al., 2023).

In regenerative medicine for brain tissues, overcoming the blood-brain barrier (BBB) remains challenging. HA-based nanomaterials show potential in this regard due to their ability to simulate ECM and transport therapeutic agents across the BBB. Injectable and bulk hydrogels serve specific roles in regenerating tissues by transforming them at the injury site to provide structural support and a healing-promoting environment (An et al., 2023).

The development of HA with varied molecular weights allows tailored applications, from skin regeneration to anti-inflammatory uses. Clinical studies reveal HA's versatility in applications such as facial correction treatments, wound healing, and the prevention of post-surgical adhesions. In animal trials, HA has shown effectiveness in reducing pain and postoperative adhesions in gynecologic surgery, as well as enhancing outcomes in bladder cancer treatment when combined with Bacillus Calmette-Guerin (BCG) in rats. This ongoing research and clinical validation underscore HA's therapeutic impact across regenerative medicine, from aesthetics to cancer treatment, and its role in advancing minimally invasive, effective medical solutions (Figure 1; Antoszewska et al., 2024).

STEM CELL FATE CONTROL AND DELIVERY

CD44 and RHAMM have been the most investigated hyaladherins due to their critical role in mediating HA bioactivity. Numerous cellular processes, such as adhesion, activation, migration, and proliferation, are linked to the CD44 receptor. Additionally, these receptors are essential for the breakdown of HA (Vasvani et al., 2020). Through PI3K/Akt signaling, CD44 receptors on the surface of human placenta mesenchymal stem cells (hPMSCs) have been shown to enhance multidrug resistance. Furthermore, human adipose-derived mesenchymal stem cells (hAD-MSCs) and human bone marrow mesenchymal stem cells (hBM-MSCs) are directed to areas of inflammation or damage by CD44 expression (Agarwal et al., 2020). Additionally, CD44 is known to modulate the differentiation capacity of neural stem cells and preserve their quiescence. On the other hand, the RHAMM hyaladherin is present in the cytosol, nucleus, and cell surface. It facilitates cell migration, especially in fibroblasts and smooth muscle cells, and coordinates cellular processes triggered by growth factors (Nikitovic et al., 2013).

When HA interacts with CD44 and other receptors, including RHAMM, it activates multiple signaling pathways, such as tyrosine kinase, protein kinase C, phosphatidylinositol 3-kinase (PI3K), nuclear factor kappa B (NF-κB), and mitogen-activated protein kinase (MAPK). Moreover, cell division and death have been connected to HA binding to CD44. Since p185-HER2 and c-Src kinase are two tyrosine kinases that are closely linked to CD44, HA can increase the activity of the CD44-linked p185-HER2 tyrosine kinase, which in turn stimulates the proliferation of tumor cells (Nikitovic et al., 2013). Research on the use of stem cells (SCs) with HA for tissue regeneration and repair shows that the physicochemical characteristics of HA can improve the regenerative capacity of SCs. Thus, HA affects stem cell activity and may enhance stem cell regeneration capacity (Agarwal et al., 2020).

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS)

The precise cause of IC/BPS has remained unclear, though several contributing factors, such as inflammation, bladder lining dysfunction, and tissue abnormalities, have been implicated. IC/BPS is a painful disorder that affects the bladder and urethra, leading to symptoms such as urinary frequency, urgency, and pelvic pain. In recent years, HA, a naturally occurring glycosaminoglycan, has emerged as a potential therapeutic agent for IC/BPS due to its ability to restore and protect the bladder lining in animal studies (Madurga Patuel et al., 2022).

Hyaluronic acid has shown promise as a therapeutic option for IC/BPS due to its ability to restore the bladder's protective GAG layer and promote healing of the bladder lining. The primary mechanisms by which HA may benefit IC/BPS patients include its ability to restore the GAG layer, thereby reducing bladder irritation and inflammation. The HA can help prevent irritants from penetrating the bladder wall, which may reduce symptoms such as pain and urgency. Furthermore, HA has been shown to possess anti-inflammatory properties in animals, which may help modulate the inflammatory response in the bladder, potentially alleviating symptoms of discomfort and pain associated with IC/BPS. Additionally, HA promotes tissue repair by enhancing cell migration and regeneration, which could aid in healing the damaged urothelium in IC/BPS patients (Polisini et al., 2024).

BLADDER HEALTH

The urothelium, or bladder lining, is made up of protective glycosaminoglycans (GAGs), including hyaluronic acid. These GAGs form a protective barrier on the bladder wall that helps maintain its integrity and prevents harmful substances from penetrating the tissue. In patients with IC/BPS, this protective GAG layer is often defective or damaged,

leading to increased bladder permeability, irritation, and inflammation. This dysfunction of the bladder lining is thought to contribute to the characteristic symptoms of IC/BPS, such as pain, urgency, and frequent urination (Tsai et al., 2021).

CLINICAL EVIDENCE AND APPLICATIONS

There is substantial clinical evidence supporting HA as a treatment for IC/BPS. One of the most common methods for administering HA in IC/BPS patients is through intravesical instillation, where HA is delivered directly into the bladder via a catheter. Clinical studies in animals have shown that this form of treatment can significantly reduce symptoms of IC/BPS, such as pelvic pain, urinary frequency, and urgency (Jabbari et al., 2023). In many studies, patients have reported long-lasting symptom relief following intravesical HA treatment. Furthermore, some research suggests that combining HA with other agents, such as heparin or dimethyl sulfoxide (DMSO), may enhance the therapeutic effects. The safety profile of intravesical HA is generally favorable, with minimal side effects. Some patients may experience mild discomfort during the procedure, as well as transient urinary urgency or frequency, but these side effects are typically short-lived. Hyaluronic acid presents a promising treatment option for IC/BPS due to its ability to restore the protective barrier of the bladder, reduce inflammation, and promote tissue healing. Intravesical HA instillation has shown positive clinical outcomes, with many patients experiencing significant improvement in their symptoms and quality of life (Plotti et al., 2024).

CONCLUSION

Hyaluronic acid stands out as a highly versatile biomaterial, especially valuable in stem cell-based therapies aimed at treating inflammatory and degenerative diseases. Its unique biocompatibility, biodegradability, and bioactivity properties make it an ideal candidate for supporting stem cell survival and directing cellular behavior at the target site of IC/BPS. Through interactions with cellular receptors like CD44 and RHAMM, HA not only enhances cellular retention but also influences key signaling pathways that promote tissue repair and anti-inflammatory responses. The diverse applications of HA in both animal models and human studies highlight its therapeutic potential across various medical conditions. Preclinical studies in animals have demonstrated HA's ability to enhance tissue regeneration, reduce inflammation, and improve stem cell retention, making it a promising biomaterial for conditions such as bladder inflammation, liver fibrosis, and cardiovascular diseases. In human studies, HA has been successfully utilized in regenerative medicine, osteoarthritis treatment, wound healing, and drug delivery systems, confirming its biocompatibility and clinical efficacy. These findings emphasize the role of HA in bridging experimental research and clinical applications, offering improved therapeutic strategies for chronic and inflammatory diseases. Future research on HA's molecular interactions and applications will further unlock its therapeutic potential, advancing the efficacy of regenerative medicine in chronic diseases.

DECLARATIONS

Availability of data and materials

All original data presented in the article are available upon reasonable request from the corresponding author.

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Competing interests

The authors declare no conflicts of interest.

Authors' contributions

Mahmoud Abdel-Maboud played a key role in the study design and supervision. Nada A. Elhossieny significantly contributed to the study design, data analysis, interpretation, manuscript drafting, and final manuscript preparation. Nashwa Barakat contributed to the study design, data analysis, interpretation, and manuscript drafting. All authors read and approved the final version of the manuscript.

Ethical considerations

All authors adhered to ethical considerations, including plagiarism, publication consent, research misconduct, data fabrication, and duplicate submission or publication.

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