Minireview Article

In Search Of Bioactivities Of Hyaluronan And Its Fragments: A Mini-Review

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ABSTRACT

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| Hyaluronic acid (HA) is a biopolymer widely distributed in the extracellular matrix, synovial fluid, and other tissues, where it plays a key role in hydration, cell signaling, and wound healing. High-molecular-weight HA (HMWHA) is primarily produced through microbial fermentation, while enzymatic degradation has become the preferred method for obtaining low-molecular-weight HA (LMWHA) due to its high purity and scalability. The biological functions of HA are strongly influenced by its molecular weight. HMWHA remains localized due to limited permeability, whereas LMWHA, particularly HA35, penetrates tissues more effectively, interacts with receptors and ion channels, and exhibits potent anti-inflammatory and analgesic properties. The presence of high levels of HA in the naked mole rat has been linked to its advantages in cancer resistance, longevity, and reduced pain sensitivity, significantly expanding its clinical applications. Furthermore, the development of high-dose oral HA therapies has opened new avenues for clinical use. As research continues, the therapeutic potential of LMWHA is expected to become increasingly prominent, reinforcing its role in modern medicine and biotechnology. This review provides a comprehensive overview of HA’s historical development, molecular characteristics, and recent scientific and industrial advancements, highlighting its expanding contributions to biomedical innovation. |

*Keywords:* *Hyaluronic acid (HA); Low molecular weight HA (HA35); Cancer resistance; Anti-inflammation; Pain relief*

1. INTRODUCTION

HA is a naturally occurring polysaccharide composed of repeating disaccharide units of D-glucuronic acid and N-acetylglucosamine, linked by β-1,4 and β-1,3 glycosidic bonds (Hargittai et al., 2010; Gallo et al., 2019). It is widely distributed in the extracellular matrix, synovial fluid, and other biological tissues, playing a crucial role in tissue hydration, cell signaling, and wound healing (Hargittai, 2010; Johnson et al., 2021). HA is primarily sourced from animal-derived materials, such as rooster combs, and microbial fermentation. Due to its higher purity and scalability, bacterial fermentation using *Streptococcus* species has become the predominant production method (Necas et al., 2008).

 Over the past three decades, the applications of HA have expanded beyond ophthalmic surgery, arthritis treatment, and aesthetic dermatology to include drug delivery, wound healing, and regenerative medicine (Hynnekleiv et al., 2022; Xu et al., 2024), with its potential applications continuing to grow.The broad applications of HA are largely attributed to its molecular weight-dependent biological activities (Iaconisi et al, 2023). Pharmacokinetic studies indicate that HA is rapidly degraded by hyaluronidases into smaller fragments within a specific size range (Jia et al., 2023), which enhances tissue permeability and facilitates receptor binding in vivo (Chaudhry et al., 2021). Its pharmacodynamic effects are further supported by its interactions with key receptors such as cluster of differentiation 44 (CD44), receptor for hyaluronan-mediated motility (RHAMM), and lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1), contributing to its diverse medical and clinical applications (Diaz-Salmeron et al., 2023).

With the growing aging population and increasing focus on global health, the discovery that the “ageless” naked mole rat exhibits cancer resistance, longevity, and pain insensitivity due to its high endogenous HA levels (Zhang et al., 2023) has accelerated interest in non-invasive and non-pharmacological therapies, including orally administered HA with enhanced tissue permeability. This review provides a comprehensive overview of HA research, covering its sources, molecular characteristics, biological activities, and clinical applications. Special attention is given to advances in LMWHA with enhanced tissue permeability, particularly its roles in cancer resistance, inflammation control, and pain relief, emphasizing its expanding impact in disease treatment and biomedical innovation.

2. Advancements in HA Research: From Molecular Insights to Clinical Applications

* 1. History of HA and HA Structure

Thorbjörn Laurent (1930–2009) was a pioneering Swedish scientist who made groundbreaking contributions to the study of HA, particularly in elucidating its chemical structure (Hargittai., 2010). HA is abundantly distributed in human tissues, with concentrations reaching as high as 80% in the eyes and umbilical cord (Gallo et al., 2019). However, its large molecular size significantly limits its ability to penetrate deep tissues, restricting its bioactivity primarily to localized applications (Beasley et al., 2009; Gantumur et al., 2024; Snetkov et al., 2020). This limitation has prompted researchers to explore novel approaches to enhance the tissue permeability and bioavailability of HA, expanding its potential applications in medicine.

* 1. Advances in Medical Applications of HA and Large-Scale Production of HA

Endre A. Balazs, a scientist from the United States, revolutionized the medical use of HA by extracting it from chicken combs and developing injectable formulations for treating arthritis and as protective agents in ophthalmic surgeries. Together with his collaborators, he developed six major HA-based products, including low-dose (20 mg) joint cavity injections (Marshall et al., 1998), ophthalmic surgery formulations (Huerta et al., 2021), dermal fillers (Beasley et al., 2009), adhesion prevention products for abdominal surgeries (Kramer et al., 2002), treatments for bladder pain syndrome (Sherif., 2018; Diaz-Salmeron et al., 2023), and eye drops for dry eye syndrome (Hynnekleiv., 2022). Initially, medical-grade HA was predominantly extracted from bovine eyes and chicken combs. However, with the rising global demand, researchers began exploring more efficient production methods. In this regard, Dr. Peixue Ling from Shandong University in China played a pivotal role in advancing large-scale fermentation techniques for producing HA from Streptococcus bacteria (Sheng et al., 2015). This advancements contributed to China's emergence as a leading producer of HA, with the country now supplying a significant portion of the global market. Shandong, in particular, has become a key hub for HA production, reflecting its strong influence on the industry.

* 1. HA Receptors and Biological Activity

Although HMW-HA has limited tissue permeability, its biological activity in vivo remains a subject of extensive research. Studies have demonstrated that HA and its continuously degrading fragments (Laurent et al., 1991; Fraser et al., 1997; Lebel et al., 1991) interact with multiple cell surface binding proteins and receptors, including CD44 (Chaudhry et al., 2021), LYVE-1 (Johnson et al., 2021), RHAMM (Messam et al., 2021), Hyaluronic Acid Receptor for Endocytosis (HARE, Stabilin-2) (Pandey et al., 2015; Harris et al., 2020), Siglec-9 (Mei et al., 2023), Toll-like receptor 2 (TLR2) (Jiang et al., 2015), Cell migration-inducing and hyaluronan-binding protein (CEMIP) (Domanegg et al., 2022), and Transmembrane Protein 2 (TMEM2) (Tobisawa et al., 2021). The widespread distribution of these receptors suggests that HA plays a crucial role in various biological processes, including inflammation regulation, immune response, and cell migration. However, due to the deep localization of many HA receptors within tissues and the poor penetration of HMW-HA, its in vivo biological activity has not been definitively confirmed. To address this limitation, scientists have turned to animal models to better understand HA’s potential biological functions. Among these, the naked mole rat has emerged as a particularly intriguing subject of study.

* 1. HA in Naked Mole Rats and Its Biological Significance

Professors Vera Gorbunova and Andrei Seluanov from the University of Rochester have spent the past 15 years investigating HA levels in naked mole rats (Tian et al., 2013; Takasugi et al., 2020; Taguchi et al., 2020). Certain tissues in these remarkable animals contain HA concentrations as high as 6% (6 grams per 100 grams of tissue), significantly higher than those found in other mammals. With an average lifespan of 32 years, naked mole rats are often referred to as “immortal creatures” and exhibit extraordinary traits, including lifelong cancer resistance, pain insensitivity, a lack of major inflammatory diseases, and minimal subcutaneous fat deposition. These characteristics suggest that highly concentrated HA may have biological activities or therapeutic effects related to cancer prevention (Zhang et al., 2023), anti-inflammation (Tian et al., 2013), pain relief (Lewin et al., [2021](https://pmc.ncbi.nlm.nih.gov/articles/PMC10329625/#CR30)), and inhibition of subcutaneous adipogenesis (Zhang et al., 2023). Building on these findings, researchers transferred the HA synthase gene from naked mole rats into laboratory mice. Under the regulation of the strongest known chick β-actin promoter, these transgenic mice expressed relatively high levels of HA in their tissues (Zhang et al., 2023). The results demonstrated that HA-enriched mice exhibited notable resistance to cancer and inflammation, alongside cosmetic benefits (Zhang et al., 2023). Consequently, the HA synthase gene from naked mole rats has been designated as a longevity gene. The work of Professors Gorbunova and Seluanov further indicates that gene transfer techniques—such as the use of viral or mRNA vectors combined with potent gene promoters—could overcome the limited tissue permeability of HMW-HA. These methods may facilitate the effective delivery of HA into human tissues, enabling interactions with various HA receptors to produce significant biological activities and therapeutic effects in clinical applications. This strategy opens new possibilities for HA-based therapies in medicine.

* 1. HA, the Lymphatic System, and Immune Cell Movement

Professor David Jackson from Oxford University was the first to identify LYVE-1, a key HA receptor in the lymphatic system, and its role in facilitating the return of leukocytes, including lymphocytes, to the bloodstream (Johnson et al., 2021; Jackson, 2019; Stanley et al., 2020). This discovery laid the foundation for further research on HA’s influence on immune cell circulation. Building on Jackson’s work, Dr. Matthew Hui, a graduate of the University of Toronto, demonstrated that HA35, with a size of less than 220 nm, rapidly diffuses through the lymph nodes and spleen before re-entering systemic circulation (Jia et al., 2023). Moreover, HA35 was shown to enhance leukocyte mobility, potentially reducing the accumulation of inflammatory cells in affected tissues (Gantumur et al., 2024; Hui et al., 2024). These findings suggest that HA35 may have significant implications in regulating immune responses, reducing chronic inflammation, and potentially alleviating inflammatory disorders.

* 1. HA’s Role in Pain and Itch Regulation

Expanding the scope of HA research, Professors Elvira de la Peña and Carlos Belmonte from Spain demonstrated that high concentrations (400 µg/mL) of HMW-HA inhibit the pain-related calcium channel TRPV1 (Caires et al., 2015; de la Peña et al., 2016). Given that HA interacts with multiple ion channels, it is plausible that both HA35 and HMW-HA at similar concentrations may also influence TRPA1, another pain-related calcium channel. If confirmed, this dual modulation of TRPV1 and TRPA1 could lead to a synergistic and potent analgesic effect. Moreover, Liu et al. proposed that itch and pain share largely overlapping receptors, including TRPV1 and TRPA1 (Liu et al., 2013). These findings suggest that HA35, as a potential modulator of TRPV1 and TRPA1, may not only contribute to pain relief but could also be effective in alleviating itch caused by mosquito bites, gingivitis, and senile eczema, thereby expanding its therapeutic applications in dermatology and pain management.

* 1. Human Studies and Applications of HA35

In the United States, researchers Carol de la Motte and Laura Nagy were among the first to identify the biological activity of the HA35 fragment in human colostrum (Kessler et al., 2018; Saikia et al., 2017). They also conducted initial human safety studies for HA35 (Bellar et al., 2019), providing a foundation for its clinical use. Inspired by these findings, Dr. Matthew Hui and his collaborators developed a uniform injectable formulation of HA35 using sperm acrosome hyaluronidase PH20 (B-HA injection, 100 mg/5 mL, L20200708MP07707, Ministry of Health, Mongolia; EP3479830; US11839625B2; US11826380B2; US11826381B2; CA3049286; AU2017255833). Through a series of clinical studies, Dr. Hui demonstrated that high-dose HA35 injections (100 mg) are highly effective in managing various pain conditions, including inflammatory, neuropathic, wound-related, and cancer-related pain (Hui et al., 2024; Dashnyam et al., 2023; Xu et al., 2024; Treger et al., 2024; Zhang et al., 2024; Purevsuren et al., 2025). Beyond pain relief, HA35 injections have been shown to significantly reduce inflammation-related redness and swelling while accelerating wound healing (Hui et al., 2024; Treger et al., 2024). Further research by Dr. Hui revealed that both HMW-HA and HA35 exhibit comparable effects in cell culture studies, where tissue permeability is not a limiting factor (Jia et al., 2023; Gantumur et al., 2024). This finding suggests that HA’s receptor-binding capacity is primarily derived from its disaccharide units, meaning that both forms interact with the same receptors to modulate inflammatory responses (Huang et al., 2014; Huang et al., 2015). Moreover, Dr. Hui’s latest study suggests that different LMWHA fragments (within the 100 kDa range and capable of passing through a 220 nm filter) exhibit varying affinities for red blood cell surfaces, influencing their ability to induce erythrocyte aggregation (Guo et al., 2022). The study ranks their affinity as 24 kDa > 35 kDa > 70 kDa. This finding indicates that, similar to influenza virus hemagglutinin, different molecular weights of low molecular weight HA can trigger red blood cell aggregation, potentially inhibiting influenza virus hemagglutinin activity. These insights could open new possibilities for HA in antiviral research (Skehel et al., 2000).

* 1. HA35 in Oral Applications and Fat Metabolism Regulation

In addition to injectable HA formulations, Dr. Hui successfully commercialized a food-grade beverage containing a high dose (5 grams) of 35kDa molecular weight HA fragments. These fragments, measuring <220 nm, are rapidly absorbed through the mesenteric lymphatic system, offering an effective alternative to high-dose HA35 injections. Clinical studies have demonstrated the beverage’s efficacy in treating various diseases and conditions (PCT priority patent application 2024113443177.7, submitted from China). This innovation highlights the potential of HA-based nutraceuticals for systemic health benefits. Furthermore, Dr. S. Bahram Bahrami from Lawrence Berkeley National Laboratory discovered that the expression of the HA receptor RHAMM inhibits subcutaneous adipogenesis, suggesting that HA may play a role in regulating fat accumulation (Bahrami et al., 2017). This hypothesis is further supported by observations in naked mole rats, where high HA concentrations are associated with minimal subcutaneous fat deposition (Zhang et al., 2023). These findings suggest that HA may have applications in metabolic health and fat regulation, potentially influencing future obesity-related treatments.

3. Conclusion

Hyaluronic acid (HA) has undergone significant advancements in both fundamental research and clinical applications. From its early structural characterization to modern large-scale fermentation production, HA has become a crucial biomedical material. Studies on naked mole rats have provided insights into its roles in cancer resistance, pain modulation, and inflammation control, while research on HA receptors has deepened our understanding of its diverse biological functions. The development of LMWHA, such as HA35, has further expanded its therapeutic potential, demonstrating enhanced tissue permeability and efficacy in pain relief and wound healing. Recent breakthroughs in gene transfer techniques and innovative HA-based formulations, including high-dose oral and injectable therapies, highlight promising avenues for future medical applications.

Despite these advancements, challenges remain. The pharmacokinetics and pharmacodynamics of different molecular weight HA formulations require further investigation to optimize their therapeutic efficacy. Additionally, the long-term safety of high-dose HA treatments and potential immunogenic responses need to be thoroughly evaluated. The industrial production of HA also faces scalability and cost-efficiency challenges, particularly in developing novel bioengineered formulations. Future research should focus on overcoming these limitations by improving targeted delivery systems, enhancing HA’s bioavailability, and exploring its synergies with other biomaterials and therapeutic agents. As research continues to bridge the gap between academia and industry, HA-based therapies may soon lead to groundbreaking medical innovations with significant clinical and commercial impact. By fostering collaboration between these two fields, it aspires to drive breakthroughs that could achieve prestigious recognitions such as the Lasker Award or the Nobel Prize in Medicine within the next decade.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

Disclaimer (Artificial intelligence):

Author hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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