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Review article

Recent advances and prospects of hyaluronan as a multifunctional therapeutic system

Niranjan G. Kotla [a,1], Srinivasa Reddy Bonam [b,1], Swetha Rasala [a,1], Jitendra Wankar [a], Raghvendra A. Bohara [a], Jagadeesh Bayry [b,c], Yury Rochev [a,d,*], Abhay Pandit [a,*]

[a] CÚRAM, SFI Research Centre for Medical Devices, National University of Ireland Galway, H91 W2TY, Ireland
[b] Institut National de la Santé et de la Recherche Médicale, Centre de Recherche des Cordeliers, Equipe- Immunopathologie et Immunointervention Thérapeutique, Sorbonne Université, Université de Paris, Paris F-75006, France
[c] Indian Institute of Technology Palakkad, Palakkad 678 623, Kerala, India
[d] Sechenov First Moscow State Medical University, Institute for Regenerative Medicine, Moscow 119992, Russia

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ABSTRACT

Hyaluronan (HA) is a naturally occurring non-sulfated glycosaminoglycan (GAG), cell-surface-associated biopolymer and is the key component of tissue extracellular matrix (ECM). Along with remarkable physico-chemical properties, HA also has multifaceted biological effects that include but not limited to ECM organization, immunomodulation, and various cellular processes. Environmental cues such as tissue injury, infection or cancer change downstream signaling functionalities of HA. Unlike native HA, the fragments of HA have diversified effects on inflammation, cancer, fibrosis, angiogenesis and autoimmune response. In this review, we aim to discuss HA as a therapeutic delivery system development process, source, biophysical-chemical properties, and associated biological pathways (especially via cell surface receptors) of native and fragmented HA. We also tried to address an overview of the potential role of HA (native HA vs fragments) in the modulation of inflammation, immune response and various cancer targeting delivery applications. This review will also highlight the HA based therapeutic systems, medical devices and future perspectives of various biomedical applications were discussed in detail.

1. Introduction

Hyaluronan/Hyaluronic acid/Hyaluronate (HA) is a natural linear disaccharide polymer, the key constituent of the tissue extracellular matrix (ECM). It is a non-protein, non-sulfated glycosaminoglycan (GAG) of the GAG family, including chondroitin sulfate, dermatan sulfate, heparin, and keratin sulfate etc. [1,2]. Unlike other GAGs, HA is synthesized at the plasma membranes and released into the pericellular space [3]. Interestingly, the first assigned name was “hyaluronic acid” (derived from hyaloid [vitreous; vitreous humor of the bovine eye] and uronic acid) assigned in 1934 by Karl Meyer and John Palmer with the name “hyaluronan” being given in 1986, since then HA gained specific interest as a viscosupplement, and in various medical uses including in tissue regeneration, anti-aging, anti-inflammatory applications [4].

In the healthy physiological systems, native HA consists of 2000–25,000 disaccharide units, which correspond to 10^6–10^7 Da, length of 2–25 μm respectively. The number of repeating disaccharides in a long chain HA can be more than 10,000, which corresponds to ~4000 kDa (each disaccharide is about 400 Da). Average length of a disaccharide is about one nm, a HA molecule of 10,000 repeats may have a length of about 10 μm when stretched from end to end [5]. In native tissues, HA forms non-covalently assembled network with proteoglycans such as versican, neurocan, aggrecan and chondroitin sulfate etc. HA is endocytosed by the specific-cell surface receptors (explained in later sections) and non-specific macropinocytosis (especially in melanoma cells) mechanism [6].

Recently, the food and drug administration (FDA) has proposed to recommend reclassifying HA products as drugs by citing scientific evidence, i.e. HA achieves pain relief through chemical activities within the body. If reclassified, new HA products will face much more challenges before reaching the bedside [3]. The various stages of HA identification to structural analysis, synthesis and therapeutic application progress is

* Corresponding authors at: CÚRAM, SFI Research Centre for Medical Devices, National University of Ireland Galway, H91 W2TY, Ireland.
E-mail addresses: yury.rochev@nuigalway.ie (Y. Rochev), abhay.pandit@nuigalway.ie (A. Pandit).
[1] Authors contributed equally to the work

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depicted in Fig. 1. HA has multifaceted biological effects in the vertebrates, including but not limited to cell growth, cell adhesion, migration, proliferation, ECM organization, inflammation, embryonic development, joint lubrication, organ structural stability, tumor development and angiogenesis [7]. HA is mainly synthesized by fibroblasts, synoviocytes and chondrocytes, and distributes ubiquitously in the ECM of many tissues (about total 15 g/70 kg body weight) [2,3,8,9].

HA synthesis and degradation depend on the tissue microenvironment and regulated by intra and intercellular signaling factors [10]. The physiological concentrations of HA in tissues are essential to perform its regulatory functions, such as anti-inflammatory effects, immune tolerance, and others. Due to the aging or under induced oxidative stress conditions, reactive oxygen species (ROS) accumulate and affect the native HA content, thereby generating of HA fragments and causing inflammatory diseases. Nevertheless, molecular weight of the HA has been given prime importance while preparing the pharmaceutical products to obtain desirable biological functions. In contrast to native HA, HA fragments have entirely different effects (discussed in later sections). Irregularities in the synthesis, degradation, metabolism of these GAGs cause severe organ dysfunctionalities, and life-threatening diseases [11].

Considering the great interest in HA from different biomedical applications, the increasingly the number of studies and scientific results on this subject is noteworthy. The present article aims to give a clear picture of advanced findings on HA in the development process (including source), detailed mechanism of action (MoA), balancing the tissue homeostasis (synthesis, degradation and irregularities), involved biological pathways especially CD44 cell surface receptor interactions, and role of native HA and fragments in inflammation and cancer. Besides, we will discuss the applications in inflammatory diseases, cancer and immune responses specific to low molecular weight (LMW)-HA and high molecular weight (HMW)-HA.

2. Structural, physico-chemical, and degradation properties of HA

2.1. HA synthases and regulation

HA is synthesized as a large, elongated, unbranched structures and is tightly regulated by the HA synthase (HAS) 1, 2, and 3 enzymes. Each enzyme has its role in synthesizing the definitive size range of HA polymers. These three enzymes are regulated by levels of transcription, translation, and post-translation, including alternative splicing, subcellular localization and epigenetic processes [3]. Newly synthesized HA is released into the pericellular space by shuttling process because of inadequate handling of the HMW HA, however the intra/inter cellular availability, the release mechanism behind this process is still unclear (Fig.2). The deficiency of these synthase enzymes, especially HAS 2, causes cardiac and vascular defects at mid-gestation, followed by embryonic lethality [7,12]. Several cytokines and growth factors regulate the biosynthetic process of HA. For an example, under inflammatory diseases (like rheumatoid arthritis (RA) and osteoarthritis (OA)), these HAS enzymes in synovial fibroblasts display distinct expression pattern; HAS 1 is upregulated under the influence of transforming growth factor beta (TGF-β) and HAS 3 is upregulated by IL-1β and TNF-α. Also, various molecules and hormones differentially regulate the HA synthesis, e.g., phorbol esters (PMA), platelet-derived growth factors and glucocorticoids, which directly or indirectly, stimulate and inhibit HA synthesis respectively [9].

2.2. Hyaluronidases (HYAL) and associated downstream pathways

In the biological systems, native HA or HMW-HA is degraded into small fragments or LMW-HA and its dynamic degradation, turnover rate is associated with different methods (including enzymatic, non-enzymatic process). HMW-HA (large HA [lHA; >1–10 MDa] and sometimes intermediate HA [iHA; >100–1000 kDa]) can be degraded into small fragments as LMW-HA (majorly, oligomeric HA [oHA; 1–10 kDa] and in minor, small HA [sHA; >10–100 kDa]) and two different processes mediate its degradation: by hyaluronidase enzymes, HYAL 1–3 (specific) or by hydrolysis [14]. The acid hydrolysis of HA was found to be a spontaneous degradation process at all acidic pH levels, the degradation process is further accelerated by oxidative damage occurred due to ROS (non-specific process) [15–17] (Fig. 2). The different enzymes that facilitate HA degradation, such as hyaluronidases (i.e., HYAL 1–3 (genes encode; *HYAL1-3*, Karl Meyer coined the term "hyaluronidase" are endoglycosidases), PH20 ((genes encode; *SPAM1;* sperm adhesion molecule 1), and HYALP1 (hyaluronidase-like protein; hyaluronoglucosaminidase pseudogene 1), cleave the *β*-1,4 glycosidic bonds of HA. HYAL 1 regulates cell division, apoptosis and therefore it is abundantly available in cancers [9]. HYAL 2, which is located on the cell surface, cleaves the native HA into 25 disaccharide units (2×10^4 Da). Further, HYAL 2 helps the CD44 for the receptor-mediated endocytosis of HA fragments (Fig. 2). The endocytosed HA fragments are delivered to the endosome, followed by the lysosomes, further degraded by HYAL 1 (at low pH ~4.5–5.5) into tetrasaccharides or followed by *β*-D-glucuronidase and *β*-*N*-acetyl-D-hexosaminidase and released extracellularly via exocytosis [7,18]. Another process of HA degradation is by induction

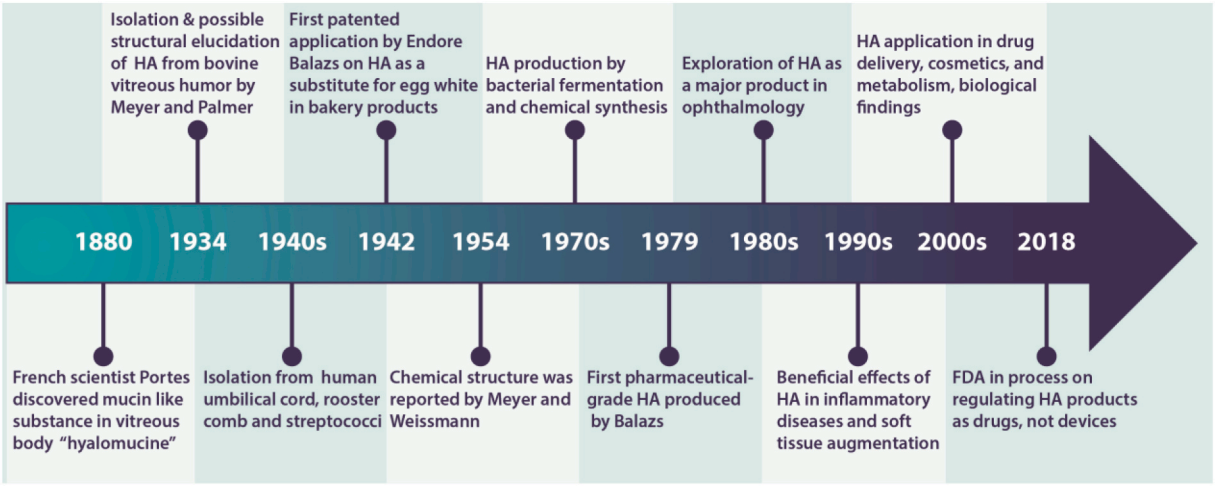

Fig. 1. Timeline of identification, characterization and therapeutic interventional progress of hyaluronan/hyaluronic acid/hyaluronate in various biomedical applications from first in ophthalmic, cosmetic application to recent biological findings.

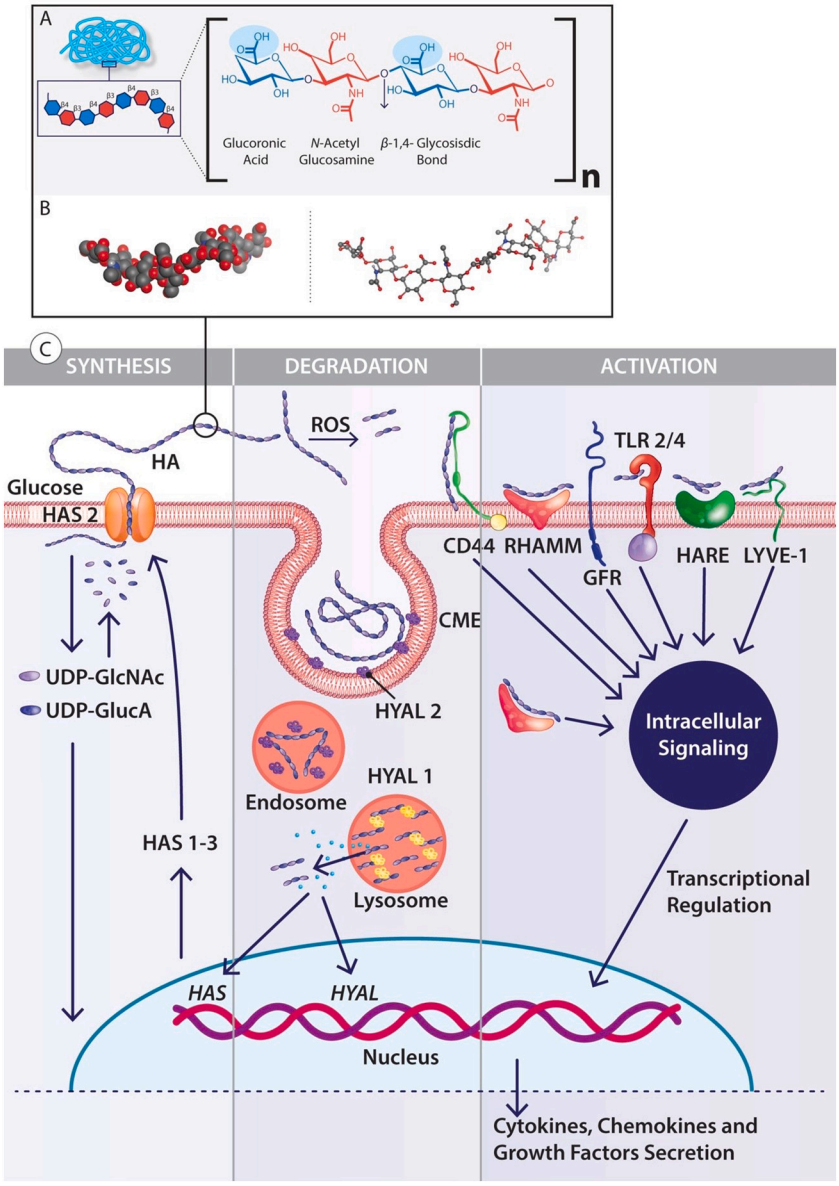

Fig. 2. Overview of HA synthesis, degradation, and activation of signaling pathways. A). Native form of long-chain coiled HA and its chemical structure. B). Structure of a fully extended helical, ball and stick structure of HA. Each monomer of HA has a carboxylic group on glucuronic acid, which provides a highly negative charge to the polymer (-COOH group is effectively deprotonated at physiological pH, giving rise to a polyanionic nature). A relatively negligible hydrophobicity is imparted from axial hydrogen atoms, and the equatorial side chains form a polar face (hydrophilic). These two aspects together form a twisted ribbon/coiled structures in the colloid form. C). Native HA ($\approx 10^7$ kDa) is synthesized by the enzymes called HA synthases, i.e., HAS 1–3, which are in the plasma membrane's inner face. HAS 1 and 2 produces HMW-HA (2×10^6 Da), whereas HAS 3 produces LMW-HA (2×10^6 Da). Of note, HAS 2 and 3 are more active isoenzymes than the one isoform. Synthesized HA is released into the pericellular space and exerts its effect via an autocrine and paracrine fashion. HA is degraded by the two mechanisms, one by hyaluronidases, i.e., HYAL 1–3 (well-characterized), or by free radicles (especially in the skin) function in a non-specific manner. HYALs are located in membrane (HYAL 2) and the lysosome (HYAL 1), and degrade HA into fragments (= ranging from $\approx 10^3$ to <6 mer). HYAL 2 (glycosylphosphatidylinositol (GPI)-anchored enzyme) degrades the HMW-HA into 20 kDa fragments and the end degradation of HA fragments (<3 kDa and tetrasaccharides) takes place in the lysosome by HYAL 1. Of note, however, the detailed characteristics of HYAL 3 is under investigation [13]. HA delivers signals through diversified receptors, such as CD44, Receptor for Hyaluronan Mediated Motility (RHAMM/CD168; first identified hyaloadherin), Lymphatic Vessel Endothelial Receptor 1 (LYVE-1, this is homologous to CD44 found primarily on lymphatic endothelial cells), toll-like receptors (TLRs), hyaluronan receptor for endocytosis (HARE; also known as Stabilin-2), layilin and others. Upon interaction with HA, these receptors induce intracellular signaling and regulate the transcriptional changes of cytokines, chemokines and growth factors.

of oxidative stress (i.e., chemical degradation) in which reactive oxygen/nitrogen species (RNS) (superoxide's, peroxides, peroxynitrites, nitric oxides etc.) cleave HA in a context-dependent manner. The reactive oxygen species (ROS) produced in the process of tissue injuries, infection or cancer, affect the physico-chemical properties of HA and to its glycosidic cleavage. Besides, the chemical degradation of HA is more prevalent in tissues with less hyaluronidase [9].

Defects in the HYALs- and other lysosomal enzymes-mediated HA degradation are implicated in mucopolysaccharidoses (lysosomal-storage disorders caused by the deficiency of enzymes degrade the GAGs) [11,19]. Mutations in the *HYAL 1* gene causes a deficiency of active hyaluronidase, which is unable to degrade the HA. This defect leads to the accumulation of HA, which causes mild craniofacial and haematological defects, referred to as Mucopolysaccharidosis (MPS) type IX (Natowicz syndrome) [20]. HYAL 2 deficiency also leads to an accumulation of unmetabolized HA, which causes abnormalities and progressive dysfunctioning of the cells. Studies in endothelial mesenchymal cells show that mice which are deficient in *HYAL 2* face the risk of heart failure [21]. Similarly, severe lung fibrosis is also observed in the mice, which lack *HYAL 2* [22]. In addition to the enzymatic and non-enzymatic degradation pathways mentioned above, two more HA catabolic pathways include turnover (internalization and degradation) and release from the tissue matrix for clearance. The HMW-HA and LMW-HA have diversified physicochemical (size, binding affinity, receptor interactions), different biological properties on immune cells, signaling processes which are compared and enumerated in Table 1.

3. Receptors associated with HA: therapeutic effects mediated via CD44

HA plays a key role in several biological functions by interacting with matrix elements, cell surface receptors and other biological tissue ECM components. HA has biological functionalities with specific proteoglycan molecules and receptors (cell surface to nucleus), and mediate cellular signal transduction, receptor-mediated phagocytosis and downstream pathway activities [30]. HA elicits its inherent pharmacological effects by binding predominantly to the CD44 receptor, and various other receptors including Receptor for Hyaluronan Mediated Motility (RHAMM/CD168), Lymphatic Vessel Endothelial Receptor 1 (LYVE-1, homologous to CD44 found primarily on lymphatic endothelial cells), Intercellular Adhesion Molecule 1 (ICAM-1), TNF-Stimulated Gene 6 (TSG6), Glial HA-Binding Protein (GHAP), layilin, and

Table 1
Various physico-chemical characteristics and functional properties of HMW-HA and LMW-HA[a].

Character	HMW-HA	LMW-HA
Physicochemical properties		
Size range	$>10^6$ kDa	<150 kDa
Binding affinity	K_d = 10–100 μM	Depends on the size
Biding capacity to CD44	Irreversible	Reversible
Physiological ionic strength	Polyanionic [23]	Polyanionic
Interactions with the immune system		
Immune tolerance	Yes	No proven defined fragments and related immune effects reported
Receptors	CD44, CD168/RHAMM, LYVE-1, TLRs, HARE, layilin. (acts as a CD44 agonist)	CD44 (CD44 antagonist-context dependent)
	CD44v6 and CD44v9 (on Tregs)	CD44v7 (at inflammation sites)
Proinflammatory response	–	Yes
Tissue repair	Colonic epithelial repair in murine colitis model and protects from T cell-mediated liver injury [24]	–
Anti-microbial	Human milk HA induces β-defensins in the gut [25]	35 kDa HA fragment produces β-defensins in the gut [26]
Anti-inflammatory	Yes	Mediator of inflammation [24]
Leukocytes migration	Yes	Yes
T cells motility and function	Yes	Yes
Activated TCR signaling is required to express active isoform of CD44	Yes	Not available
Stimulates innate immune receptors	?	TLR2 and TLR4 (especially tetrasaccharide fragments)
Angiogenesis	Anti-angiogenesis	Pro-angiogenesis
Pharmacokinetics		
Absorption	HA primarily transported by the lymphatic system and available in 15 min after oral administration [27]	–
Distribution	–	450 kDa size HA was observed in the liver after 5 min of IV administration [28]
Elimination	Renal	Renal

[a] LMW-HA presented here is context-dependent and not a fixed-sized fragment. LMW-HA has been considered based on the following nomenclature: large HA (lHA; >1–10 MDa), intermediate HA (iHA; >100–1000 kDa), small HA (sHA; >10–100 kDa), and oligomeric HA (oHA; 1–10 kDa). Partly intermediate, small, and oligomeric forms come under the LMW-HA fragments [29]. Abbreviations: CD44: Cluster of Differentiation 44; HARE: hyaluronan receptor for endocytosis; IV: intravenous; LYVE-1: Lymphatic Vessel Endothelial Receptor 1; RHAMM: Receptor for Hyaluronan Mediated Motility; TCR: T-cell receptor; TLR: toll-like receptor.

Hyaluronic Acid Receptor for Endocytosis (HARE; also known as Stabilin-2) [31–35].

CD44 plays a key role in HA-internalization, degradation of ECM components, angiogenesis, cell adhesion, proliferation, migration, particularly in the immune cells of the body. CD44 is also widely used as a marker for the antigen experienced effector and memory T cells [36]. CD44 exists in different isoforms (Fig.3) with multiple functions based on the alternative mRNA splicing and expression of 10 distinct exons [37]. Complete details of CD44 structures and immune tolerance are reviewed elsewhere [34]. Immune tolerance is regarded as a state of unresponsiveness of host-specific immune responses against self-antigens through inducing central and peripheral tolerance. It was found that native/ HMW HA (100 μg/mL) acts as an immunosuppressive agent via $CD4^+$ T cells [38]. In animals, especially in humans, the immune tolerance function is maintained by the $CD4^+$,$CD25^+$ T cell subpopulation, which expresses transcription factor forkhead box P3 (referred to as regulatory T cells [Tregs]); they secrete immunoregulatory cytokines such as TGF-β, IL-10, IL-35 [39,40]. The expression of FoxP3 correlates with the CD44 (CD44v6 and CD44v9; as a receptor for HA). Studies have found that native HA mediates its immunoregulatory functions by augmenting Tregs function(s) via CD44 (Figs. 3 & 4) [41]. Resting T cells express an inactive form of CD44, which does not bind to HA. Interestingly, T-cell receptor-stimulated Tregs exhibited an active form of CD44 (Fig. 3) [42]. Moreover, as with Tregs, HA-induced immunosuppression additionally requires the low doses of IL-2 and also does not requires inputs from antigen-presenting cells (APCs). In fact, abnormal HA-CD44 signaling has been implicated in different tumors [43].

3.1. CD44 and HA interaction in autoimmune diseases

CD44 and HA have been implicated in the activation, regulation of immune cell trafficking (rolling; primary adhesion), apoptosis and, importantly, in immunotolerance. As explained earlier, CD44 is expressed on a wide range of cells, including lymphocytes and its expression on activated lymphocytes helps in the primary adhesion (rolling) to the inflammatory sites in a HA-dependent manner. Likewise, secondary (firm) adhesion is provided by the α4β1 integrin, leukocyte ligand for endothelial vascular cell adhesion molecule-1 (VCAM-1; VLA-4) (Fig. 4) [44]. Remarkably, both processes are abrogated in the absence of CD44 cytoplasmic domain [45]. The former CD44 function was confirmed in different autoimmune diseases such as Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), and other Chronic Arthropathies [46–49]. In addition, the treatment of murine arthritis with anti-CD44 antibody causes a gradual depletion of CD44 and reduces the edema and leukocytes infiltration [50]. Analogous results with anti-CD44 antibody were observed in the collagen II-induced murine arthritis model [51]. Similarly, treatment with a monoclonal antibody against CD44 in the mice with experimental autoimmune encephalomyelitis (EAE) prevented the autoreactive T cell trafficking into the brain lesions [52]. CD44-deficient EAE mice have reduced levels of IFN-γ and IL-17 compared to the control mice [53]. Likewise, the abrogation of CD44 activation inhibited the trafficking of autoreactive $CD8^+$ T cells into the pancreas in the type 1 diabetic mouse model [54]. In a similar manner, inhibition/blocking of the CD44 variant isoforms (CD44v7) alleviated the disease severity in experimental colitis models [55,56].

Heterogeneity in the Tregs populations and their Tregs suppressive functions have been well documented [40,57]. Expression of different integrins (αEβ7, α4β1, and α4β7) and routine Treg markers (cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), glucocorticoid-induced TNFR-related protein (GITR), and lymphocyte-activation gene 3 (LAG-3)), which are also expressed in activated T cell populations do not have to distinguish the heterogeneity in Treg suppressive activities. One study has identified that Tregs, which are expressing an active form of HA binding receptor, CD44, display superior suppressive activity. In this study, it has been demonstrated that activated murine Tregs have a unique ability to upregulate the expression of HA-binding form of CD44. The expression of CD44 in Tregs was also associated with elevated mRNA levels of regulatory cytokines such as IL-4, IL-10, and TGF-β. Furthermore, Tregs, which express HA-binding form of CD44 have shown increased immune suppressive activity in vivo in graft-versus-host disease (GvHD) model [42]. These studies also strengthen the findings from the previous studies that soluble HA in the synovial fluid regulates the infiltration of the immune cells [48].

One of the β-galactoside-binding protein, galectin-9 (Gal-9) is shown to be crucial in the regulation of immune response, which can interfere

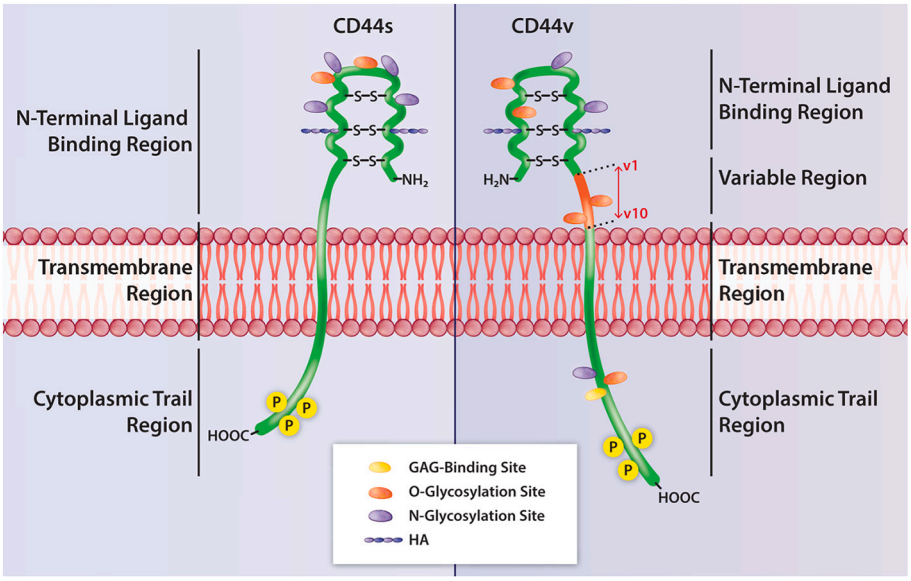

Fig. 3. CD44 and HA interaction. CD44 receptor existed in two forms (variant (CD44v) and standard (CD44s) form) and is composed of four segments of an *N*-terminal HA-binding loop (BX7B), a stem region, transmembrane domain, and cytoplasmic C-terminal domain. Abbreviations: CD44: Cluster of Differentiation 44.

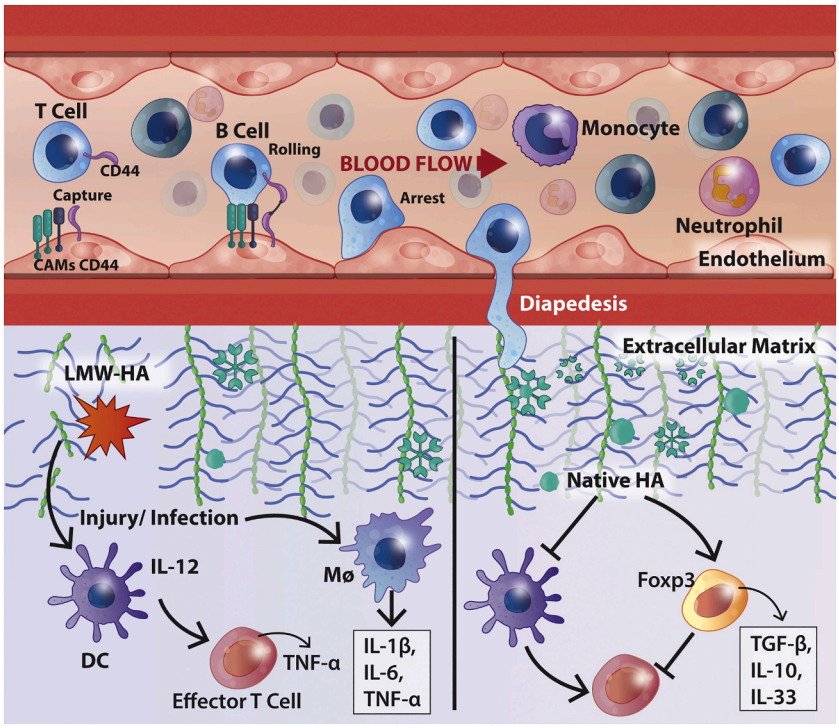

Fig. 4. The functions of different HA molecules on the immune system. As mentioned in the main text, native HA has anti-inflammatory, immune tolerance, wound healing, tissue regeneration, and other functions. However, fragmented HA, either by injury or infection, have diversified effects like immunostimulation, pro-inflammation, angiogenesis, and others. Fragmented HA facilitates proinflammatory function via matrix metalloproteinase (MMP), nitric oxide, plasminogen activator inhibitor, stimulation of macrophages, dendritic cells and endothelial cells to secrete cytokines and chemokines [62]. Abbreviations: CD44: Cluster of Differentiation 44; CAMs: cell adhesion molecules; Foxp3: Forkhead box protein P3.

with CD44-HA interactions on leukocytes by binding to CD44 and may therefore further regulate the extravasation of leukocytes to the inflammatory site. In addition, treatment with galectin-9 alleviated collagen-induced arthritis through increasing Treg numbers and inhibiting proinflammatory cytokine secretion. Of note, studies in galectin-9 deficient mice have demonstrated that galectin-9 promotes stability of induced Tregs through binding with CD44, which forms a complex with TGF-β receptor 1 on induced Tregs. This signaling enhances the induction, stability and functions of induced Tregs by activating Smad3 enhances the induction, stability and functions of induced Tregs by activating Smad3 and enhancing its binding affinity to conserved non-coding sequences (CNS) 1 region of FoxP3 locus [58].

Studies on HA implantations in bone regeneration confirmed the immunotolerance effect against inflammatory cartilage degeneration. Moreover, the addition of regulatory growth factors, such as insulin-like growth factor-1, and TGF-β3, bone morphogenetic protein (BMP)-2 to the HA hydrogel implants exhibited a synergic effect on matrix replacement and cartilage formation on bone respectively [59]. Despite of CD44 multifunctional activities, concerning autoimmunity, several questions need to be answered: 1) from where these activated T cells, which are expressing CD44, are arising from either superantigen-activated or autoantigen-activated (in the case of autoimmune diseases) or 2) the isoforms of CD44 (Fig.3) that is expressed on various T cell subtypes or 3) the type of HA (native or fragmented) that interacts

with CD44 on T cell subsets during pathophysiologies. Convincingly, the studies have found that HA on the endothelial cells is elevated by the influence of proinflammatory signals, such as TNF-α, IL-1β, IL-15 (Fig. 4) [60,61]. However, the CD44-HA-dependent lymphocytes trafficking into the inflammation site might be the cause for the regulation of inflammation. As such, the context-dependent role of CD44 towards CD4 and CD8 responses have been observed during the infections [36]. Besides, possible influence of other CD44 ligands in determining the final outcome of interaction between CD44 and HA need to be considered.

4. HA in inflammation and immune response

A variety of studies have shown that HA plays various immunological roles depending on its molecular weight, degradation, and turnover rate. It has been documented that HA of differing molecular weights may have various roles in inflammation, immunomodulation and cancer, however there is still crosstalk on molecular weight-dependent HA and its effects on inflammation, as to whether it imparts anti-inflammatory or proinflammatory cascades. Various HA formulations or devices are now applied worldwide in clinical usage, their MWs are very wide in range (500–6000 kDa), and the MW-dependent immune regulatory function of HA are reported elsewhere [63,64]. Besides, the large amount of HA present in the body is transported by lymph to the lymphatic vessels through which endothelial cells catabolize the HA [26]. The necessity for optimal HA synthesis and degradation into fragments followed by their clearance in the body is absolute since irregularities in their regular processes will lead to altered biological effects. Thus, targeting the lymphatic system, where the majority of unwanted material filters out (especially pathogens or cancer cells), with or without modified HA, is an attractive strategy in the drug discovery process against different diseases.

4.1. Anti-inflammatory effect of high-molecular-weight HA

HA has been recognized and approved by the FDA for the treatment of various inflammatory conditions including joint, ophthalmic applications. Of note, due to the non-toxic and therapeutic potential properties of native HA, it has long been used in Europe for the treatment of bacterial acute rhinopharyngitis [65]. An in-vitro model study has found that a synovial concentration of HA (4 mg/mL) inhibits the uptake of aggregated IgG by human peripheral blood polymorphonuclear leukocytes and also releases lysozyme/muramidase (potent antibacterial via hydrolyzing β-1,4 linkages between *N*-acetylglucosamine and *N*-acetylmuramic acid moieties of peptidoglycan present in bacterial cell walls) from these polymorphonuclear cells [66]. Moreover, HA has shown an inhibitory effect on prostaglandin E2 (PGE2) production from the IL-1β- stimulated [67]. Interestingly, the LMW- and less concentrated HA have not shown the effects mentioned above. Further, native HA restored proteoglycan content and prevented IL-1β -induced bovine cartilage explant damage. Hence, inhibition of proinflammatory signals and the production of prostaglandins by HA have proved to be protective and thus represents an attractive strategy in inflammatory joint diseases [67,68].

The anti-inflammatory ability of HMW-HA has been well established in osteoarthritis and also in a variety of other inflammatory conditions (i.e. intestinal inflammation, and wound healing). Several studies have examined the effect of HMW-HA on the expression of pro and anti-inflammatory cytokines by synoviocytes. HMW-HA was able to suppress the IL-1β levels in synoviocytes of osteoarthritis rabbit model [69]. Besides, in human synoviocytes following HMW-HA therapy, the IL-1-dependent expression of the matrix metalloproteinase (MMP)-1 and MMP-3 was also decreased. A large study conducted by Wang et al. has demonstrated the effect of HMW-HA on the gene expression of various inflammatory cytokines by human fibroblast-like synoviocytes (FLS) in patients with early-stage osteoarthritis, the proposed mechanisms include decreased IL-8 and inducible nitric oxide synthase gene expression in unstimulated FLS, and aggrecanase-2, and TNF-α gene expression in IL-1-stimulated FLS [70]. Further, Campo et al., reported that HMW-HA was able to significantly decrease the expression of various toll-like receptors (TLR) including TLR4 and TLR2, and the molecules implicated in TLR-signaling such as MyD88 (myeloid differentiation factor 88) and NF (nuclear factor)-kB expression and protein synthesis in synoviocytes in a murine model of osteoarthritis. The specific mechanism by which HMW-HA interacts with TLRs leading to inhibition of inflammatory cascades is not understood. The same group has also proposed that polymers of HMW-HA might mask the TLR2, TLR 4 and consequently prevent the stimulation [71].

4.2. Inflammatory effect of low-molecular-weight HA or fragments of HA

A highly coordinated immune system, which protects the tissues from injuries is essential for tissue homeostasis. The innate cellular clearance (e.g., autophagy pathways) is altered by inflammatory cascades during the tissue injury process [72], leading to the accumulation of undegraded cellular components and induction of several stimulatory signals. These signals further activate the immune system to regulate or produce a protective mechanism. During tissue injury, a surplus of ECM including HA is released and/or degraded. Interestingly, HA as a component in the ECM, gives different fragments upon degradation and most of these fragments produce effects that are opposite to those of native HA [41], such as cell migration, initiation of angiogenesis, and inflammation. The fragments of HA and their levels are correlated with the severity of different diseases, such as chronic obstructive pulmonary disease, allergic alveolitis, pulmonary fibrosis, sarcoidosis, and also different arthritis conditions [7]. HA fragments derived from the acute lung injury patient sera and also in-vitro generated HA fragments have stimulatory effects on macrophages via the release of macrophage inflammatory proteins (MIP)-2, MIP-1α and neutrophil chemotactic factor (KC). In addition, studies have indicated that HA fragments elevate the expression and production of numerous cytokines and inflammatory mediators, such as MMP-12, plasmogen activator inhibitor-1, MIP-1α, MIP-1β, monocyte chemoattractant-1, IL-8, and IL-12 by macrophages [73–75]. HA and their fragments bind to either specific-receptor CD44v7, or unidentified receptors, TLRs, and release chemokines, which help in the trafficking of leukocytes into the inflammatory site followed by the stimulation of protective inflammatory responses [76].

HA, especially fragments, also activate the innate immune signals via binding to TLR2-4, other conventional HA receptors on dendritic and endothelial cells, the interaction is anticipated because of the disaccharide moiety on the HA, which mimics the pathogen-associated molecular patterns (PAMP). Moreover, the above statement was confirmed based on the studies conducted in *Myd88*$^{-/-}$ and *Tlr2*$^{-/-}$*Tlr4*$^{-/-}$ macrophages. Nevertheless, the former report is context-dependent, and also, HA fragments have shown a synergistic effect with TLR2/3/5 ligands on mesangial cells [77]. In addition to the TLRs, HA also interacts with and has shown synergic effects with different components, such as chemokines, cytokines, growth factors, MMPs, and others [41]. Moreover, blocking of HA interaction with its cognate receptor, by HA-blocking peptide Pep-1, resulted in decreased leukocyte trafficking, increased apoptosis, and aggravated injury in lungs. Protective inflammatory responses by HA were confirmed using the transgenic mice that constitutively express *HAS2*, which delayed the bleomycin-induced lung injury. The mechanism behind the protective effect of HA on lung epithelial cells was the activation of NF-κB via TLR2 and TLR4-dependent manner. Additionally, alveolar macrophages and epithelial cells that lack a HA coat on their surface are more susceptible to apoptosis [78].

The role of HA immunosurveillance on lung homeostasis was studied extensively. Lung macrophages expressing CD44 have a protective mechanism in a HA-dependent manner. Mice deficient in CD44 exhibit a smaller number of alveolar macrophages than CD44 sufficient mice and increased lung inflammation, and lung cell apoptosis due to the

accumulation of HA. In addition, lipopolysaccharides (LPS)-induced inflammatory models revealed that alveolar macrophages expressing CD44 have a self-renewal capacity. During the recovery phase, from the inflammatory conditions, monocytes differentiated into alveolar macrophages with HA binding capacity. The former process is again essential to clear the aggregated or fragmented HA via CD44. Thus, it is clear that the lungs have a suitable environment for the maintenance of HA homeostasis. Once HA integrity in the matrix is restored, native HA provides the "all-clear" signal to the immune system. The granulocyte-macrophage colony-stimulating factor is one of the important factors within the lung environment that helps in the differentiation of monocytes (progenitor of different origin) into alveolar macrophages.

5. Role of HA in cancer progression and suppression

Among the HA synthases (explained in Fig. 2), HAS 2 has been implicated in the development of inflammation, cancer, and other diseases. Altered HAS expression followed by the synthesis of uncontrolled HA leads to the accumulation of HA and HA induced inflammation, which further progress into malignancies [24]. It is not clearly demonstrated in humans that the accumulated HA in the tumor environment is contributed by the healthy cells or tumor cells, for the protection from one another. Further, increased HA synthesis signals are corroborated with the tumor progression in many cancers. As explained earlier, increased HA synthesis and accumulation sometimes, but not invariably, are protective. An in-vivo study on ovarian carcinoma in murine models revealed that HA is antiangiogenic, and its function is reversed by the suppression of HA synthesis. Further, hormonal (gonadotropins) regulation plays a significant role in the augmentation of HAS and hyaluronidases [79]. The accumulation of a high content of HA is not always linked to the progress of malignancy or tumorigenesis because some non-aggressive cancers also found the elevated levels of HA in their microenvironment [80].

5.1. HA as a cancer-targeting agent

Different HA synthases and abnormalities in the synthesis process have a distinct role in cancer progression [23,80,83]. HYAL 1, which cleaves HA into LMW-HA (tetrasaccharides), had been reported to cause anti-angiogenic and tumor suppressor activity. In contrast, HYAL 2, which cleaves HA into HMW-HA fragments, had been reported for the proangiogenic and oncogenic activity [81]. Similarly, native HA, which helps in the cell motility and differentiation, however, inhibits angiogenesis, whereas LMW-HA stimulates the proinflammatory signals, which fuel the neovascularization. The same finding was confirmed by the detection of several early expressions of oncogenes, such as *c-jun*, *jun-B*, and *c-fos* upon HA fragment treatment. The above effect was, however, inhibited by the native HA in competition with fragment HA [9].

In many tumors, increased expression of CD44 has been observed where in HA binding and internalization are more significant [82]. This is particularly true of CD44v6, which is expressed in many cancer types and is inversely correlated with CD44s (Fig. 3). Thus, CD44v is a possible representative biomarker for advanced cancers (lung, liver, breast, pancreatic, colorectal etc). And also, the increase of CD44 on cancer cells is perhaps for the degradation of native HA, which in general prevents the angiogenesis or, conversely, it endocytoses HA and produces highly degradative products that are activators of inflammatory signals. An interesting study on breast cancer cells revealed that HA interaction with CD44 in cholesterol/ganglioside-containing lipid rafts activates the Na^+-H^+ exchanger (NHE1), which creates the acidic environment required for the degradation and/or modification of HA, augmenting cancer cell invasion [83].

5.2. HA as a cancer therapeutic agent

Several lines of evidence confirmed that tumor cells have an increased ability to synthesize HA and are followed by smaller fragments, which will stimulate the proinflammatory cytokines and growth factors to enhance tumor malignancy and progression. Involvement of different HA fragments, i.e. molecular size <600 kDa (larger molecular size in only exceptional cases) that have been involved in different types of cancer are reviewed elsewhere [23,24]. Strategies targeting the inhibition of HA production have shown beneficial effects on tumor growth. HA grafted with a cationic biodegradable polymer, poly (*N*-vinyl imidazole), has shown increased cytotoxicity on liver and breast cancer cells [84]. Targeting CD44, located at lipid rafts, is an effective strategy. For example, CD44 shedding decreased the migration of different cancer cells. In addition, lack of $CD44^{-/-}$ on $CD8^+$ T cells hindered the motility but not the localization.

Based on the CD44-HA interaction strategy, different HA-based therapeutic systems including nano/micro carriers, hydrogels, conjugates, and liposomes have been developed and investigated (Table 2). Many of these formulations are most important for the selective delivery of the targeted drugs to the specific cancer tissue, and increase the local drug availability and efficacy with less off-targeted associated side effects [85]. Active targeting via CD44 glycoprotein which is overexpressed in most of the solid tumors provides a potential opportunity to make HA functionalized delivery systems, which might have a significant role in the ongoing clinical trials and future therapeutic developments. It has become increasingly apparent in recent years that drug discovery and delivery must work in concert to bring more effective, safe biopharmaceuticals.

6. Pharmacological effects of HA in neurological disorders

6.1. Role of HA in brain injuries and trauma

Brain injuries can cause the severe impact on the patients, due to the disruption of the brain intact structure and functional architecture that regulates the various body functions that leads to the disability. Cerebrospinal fluid (CSF) is rich in HA, levels of CSF HA that increase in patients with traumatic brain injury, cerebral infarction, haemorrhages, etc. [109]. The formation of blood clots/blockages creates a hypoxic condition in the brain that leads to the loss of the functional activity of neuron and endothelial cells, activation of the astrocytes/macrophages/oligodendrocytes, and secretion of various cytokines. Reactive astrocytes cause further damage to the brain by forming the scar tissue around the stroke region that inhibits the axon regeneration. This complex cascade mechanism stimulates the large immune response that leads to serious damage of the brain [110].

So far, there is only one therapeutic drug available for the clinical treatment of the stroke-recombinant tissue plasminogen activator and this needs to be administered within the 2–3 h of the stroke. This time limitation makes the drug ineffective in most cases of stroke because of the delay in the detection and, can benefit to only 5% patients [111]. Therefore, the development of advanced approaches to create the patient-friendly therapeutic modalities are under process. The biomaterial scaffolds, which mimic the intact tissue microenvironment and allow the regeneration using combinatorial approaches (using stem cells, growth factor, cytokines, and small molecules) were investigated. Multiple studies show that scaffolds made of HA provide an appropriate microenvironment for repair and regeneration in various neurological disorders (Table 3).

Lin et al., have shown the effect of the HA on the inhibition of the glial scar formation (Gliosis) in brain injury of rat [112]. Such type of scar is believed to be the reason for the development of epileptic focus resulting from the brain injury; inhibition of the scar condition could be a potential therapeutic approach to reduces the occurrence of the epilepsy. In this study, the authors explored the HA role in the cortical brain

Table 2
HA-based therapeutic delivery systems in cancer therapy.

Formulation	Composition	Target	Cancer Type	Proposed mechanism and outcome	References
Nanoparticles					
Catalase-Integrated HA-NPs	Catalase-encapsulated HA NPs loaded with adamantane-modified photosensitizer	CD44 activity and photodynamic therapy	Breast	Systemically administered HA CAT@aCe6 NPs in an MDA-MB-231 tumor bearing nude mice model shown that higher amount particles specifically aggregated at the tumor sites and lessen tumor hypoxia for an improved photodynamic therapy (PDT) application	[86]
Hydrophobically modified HA-NPs	5β-cholanic acid was used to modify HA for the self-assembly	CD44	Liver	Amphiphilic HA conjugate system has effectively shown higher accumulation (4-fold) at the tumor site than that of pure HA polymer in a SCC7 tumor-bearing mice model	[87]
HA-chitosan NPs	5-fluorouracil loaded HA-CS-NPs	MUC1	Colorectal	An aptamer (Apt) conjugated, MUC1 targeted HA-CS-NPs shown has higher toxicity than free 5-FU drug on colorectal cancer (MUC1(+) cell line) cells compared to normal cells	[88]
HA-Cur-NCs	HA modification on curcumin nanocrystals (Cur-NCs)	CD44	Breast	HA modified nanosystem shown enhanced intracellular uptake in MDA-MB-231 breast cancer cells (CD44 overexpressive), HA-Cur-NCs also shown increased anticancer activity than free drug in a murine 4 T1 orthotopic breast cancer model	[89]
AHNP/HA-hybrid NPs loaded with SN38 (7-ethyl-10-hydroxy-camptothecin)	Anti-Her2/neu peptide (AHNP) grafted HA (AHNP-HA-HAD) NPs	Her2 and CD44	Gastric	Intravenous administration of SN38-HA hybrid NPs has dual targeting ability by Her2& CD44 receptor interactions and shown a significant tumor growth inhibition in a HGC27 tumor xenografted in nude mice model	[90]
HA-RTX (raltitrexed) NPs	HA coated nanoparticle system encapsulating RTX (HARPs)	None	Colorectal	Combinatorial approach of HA-RTX NPs with radiation therapy (RT) has demonstrated improved CT26 cell uptake, and tumor growth inhibition in a colorectal cancer mice model	[91]
HA-Chitosan NPs	Raloxifene-loaded HA-decorated chitosan NPs	None	Lung	Raloxifene-loaded chitosan NPs decorated with HA (RX-HA-CS NPs) significantly suppress lung cancer A549 cell viability via NO level elevation leading to apoptosis	[92]
HA − SS − MTX NPs	Redox responsive HA disulfide methotrexate NPs	CD44 and folate	Different cancers	HA-SS-MTX NPs shown to be selectively uptaken/internalized in a model cancer cell line (HeLa) system by folate and CD44 receptors (dual targeting approach)	[93]
Nanocapsules					
An injectable hydrogel nanocapsule with a low molecular weight gelator	HA-polyglutamic Acid system loaded with C14-Gemcitabine	None	Gastric, pancreatic or oesophageal	Modified HA-nanocapsule system has shown an efficient anti-cancer activity against a few cancer cell lines (HCT 116, MIA PaCa-2, Panc-1 and Panc-1 GEM) in vitro with controlled drug release manner	[94]
HA-Protamine sulfate (HA/PS) nanocapsule	microRNA-34a (miR-34a) loaded HA/PS interpolyelectrolyte complex	CD44, Notch-1-signaling	Triple-negative breast cancer	The nanocomplex-assisted delivery of miR-34a has shown effective inhibition of cancer cells (MDA-MB-231) by CD44 targeting and Notch-1 signaling	[95]
HA-DCX (docetaxel) nanocapsule	Docetaxel-loaded hyaluronan (HA) nanocapsule	None	Lung	Hydrophobically modified HA (dodecylamide functionalized HA) shown to be effective in delivering docetaxel in the A549 lung cancer cell line system	[96]
Hydrogels					
A theranostic HA nanogel system	Graphene–doxorubicin conjugate in a HA hybrid nanogel	None	Lung	The fabricated theranostic nanogel scaffold shows simultaneous thermo-chemotherapeutic effects, enhanced drug release after laser exposure, shown higher cell inhibition rate in a A549 lung cancer cell line than non-cancerous cell (MDCK) system	[97]
HA–poly (β-amino urethane) hydrogel (injectable)	Doxorubicin (Dox)	None	For targeted cancer therapeutics	Doxorubicin was delivered at the tumors site through the subcutaneous route effectively and provided a durable and enhanced anti-tumor response in the B16/OVA melanoma model, in vivo	[98]
HA hydrogel-derived prostate cancer 3D model	Doxorubicin (Dox)-loaded polymer NPs (Dox-NPs)	None	Prostate	HA hydrogel scaffolds were used to culture LNCaP PCa cells in vitro and DOX-NPs were able to diffuse effectively and penetrate effectively in the LNCaP PCa tumoroid cells	[99]

(*continued on next page*)

Table 2 (*continued*)

Formulation	Composition	Target	Cancer Type	Proposed mechanism and outcome	References
3D Collagen-HA Composite	3D multicomponent composite HA- collagen hydrogel matrix	None	Glioblastoma multiforme (GBM) tumors	Examined single-cell morphology, distribution and migration of GBM cells into composites of 3D collagen−HA composite, potentially could be used to develop 3D brain simulating models	[100]
Liposomes					
HA-coated nanoliposomes	Paclitaxel, PTX loaded hyaluronan-targeted liposome (HA-Lipo/PTX)	None	Breast	Targeted HA-coated nanoliposomes shown high tumor accumulation and also adequate antitumor activity in 4 T1 tumor bearing mice model	[101]
PEGylated HA-coated liposome (PEG-HA-SF-Lip) formulation	Sorafenib	CD44	Breast	PEG-HA-SF-Lip showed successful inhibition of tumor growth by targeting CD44 receptor in MDA-MB-231 tumor xenograft mice model	[102]
HA-coated liposomes	Gemcitabine	CD44	Pancreatic adenocarcinoma	HA coating enables the recognition of liposomes by MiaPaCa2 cells (CD44+), and shown increased cellular uptake, inhibited more cell growth than plain liposomes	[103]
Oligohyaluronan−Lipid Conjugate	None	CD44	For targeted antitumor therapy	HA-lipid conjugates were integrated into liposomes and exhibited enhanced internalization in COS 7 cells which over express CD44 surface receptors which can be useful for CD44 targeted drug delivery/ imaging application	[104]
Conjugates and micelles					
HA-miR-34a nano conjugate probe	HA-based conjugate containing miR-34a beacons (bHNCs) nanoprobe	CD44	Multiple human cancer detection	A nanoscale vesicle device coupled with an endocytic targeting path, CD44, and a molecular imaging probe that allows for an effective detection of specific miRNAs in metastatic cancer	[105]
Curcumin (Cur)-HMW HA nanoconjugate system	High molecular weight HA functionalized- Cur loaded polymeric nanoconjugate system	None	Ulcerative colitis and associated cancer	HMW HA functionalized Cur NPs demonstrated that HA surface functionalization enhances the cellular interaction & uptake compared to uncoated nanoconjugates in a colon epithelial carcinoma (HT-29) cell line	[106]
HA-cisplatin conjugate	Cisplatin	CD44	Non-small cell lung cancer (NSCLC)	HA-conjugated cisplatin has high selectivity and shown enhanced anticancer effects in NSCLC cells that overexpress CD44 receptors	[107]
PMX-conjugated hyaluronan (HA-ADH-PMX)	Pemetrexed (PMX)	None	Malignant pleural mesothelioma (MPM)	Different molecular weights of HA based PMX conjugates shown to be effectively internalized into different MPM cell lines (MSTO-211H, AB22, MeT-5A), showed enhanced anti-cancer effect, in vitro; Single dose of HA-ADH-PMX didn't show the therapeutic effect compared to free PMX in a MPM mice model	[108]

Abbreviations: HA: Hyaluronan; CD44: Cluster of Differentiation 44; MUC1: Mucin 1, Cell Surface Associated; Her2: human epidermal growth factor receptor 2; AHNP: AntiHer2/neu peptide; RTX: raltitrexed; NO: Nitric oxide; NOTCH 1: Notch homolog 1; PEG: Polyethylene glycol; HMWHA: High molecular weight HA; NSCLC:Non-small cell lung cancer; ADH: adipic dihydrazide; PMX: Pemetrexed; MPM: Malignant pleural mesothelioma.

defect of the rats, where 3% HA was coated on the lesion created cortex region of the brain in a rat model. After 4, 8, and 12 weeks of treatment, HA reduced the proliferation of the glial cells followed by the scar formation around the damaged area, which prevent the axonal regeneration and thereby hamper the recovery of CNS after the brain injury. The scar thickness was significantly decreased in the HA treated animal compared to the control group. In another study by Lam et al., fabricated the HA hydrogel consisting of the arginine-glycine-aspartate-RGD as an adhesion peptide with neural progenitor cells (NPC) encapsulation to repair the tissue damage in a stroke NOD SCID gamma rat animal model by improving the NPCs cell viability and its differentiation [113]. Further, this study confirmed the differentiation of the transplanted NPC cell into the neuroblast in the brain stroke mice with polymer-based mechanical support with the HA hydrogel.

6.2. Role of HA in spinal cord injury

The spinal cord injury (SCI) is caused by permanent neurological damage to spinal cord and results in the loss of the neuronal function and its axonal growth around the lesion. This causes the permanent disability in the patient due to loss of the function of the neuron that communicates the information across the CNS to peripheral nervous system. So far, there is no standard treatment for spinal cord injury, and it is often managed by medication and surgical intervention. Interestingly, biomaterial systems were investigated for their supportive and inductive role for the regeneration of the axonal growth and endogenous cell migration to heal the lesion. During SCI, the immune system prompts the initial trauma, inflammation around the lesion that causes the formation of the fibrotic scar tissue, glial scar, and lesion cavity. Activated reactive astrocytes alter the composition of the ECM and forms the dense glial scar around the damaged lesion that restricts the movement of the infiltrating mononuclear cells, fibroblasts and alters the permeability of blood brain barrier. Moreover, glial and fibrotic scar severely inhibits the axon regeneration. To regain the neural function and heal the lesion cavity, it is imperative to focus on the regeneration of the axonal neuron and inhibit the scar formation that has caused the disability in the patients [120,121].

HA has significantly contributed to the treatment of the SCI through

Table 3
HA-based scaffolds and their neuro applications.

Hydrogel	Composition	Key parameters evaluated	Major findings	References
HA-BDNF hydrogel	Brain-derived neurotrophic factor (BDNF) + neural cell (isolated from the striatum of rat fetus)	• Loading of Brain-derived neurotrophic factor (BDNF) in HA hydrogel using zinc chelate-crosslinking peptide chemistry (His–Zn (II)). • BDNF activity for neuronal differentiation (by evaluating the protein levels of β-tubulin III, GFAP).	• The survival rate of the neural cells in BDNF-HA hydrogel is significantly higher than in HA hydrogel without BDNF. • Mechanical properties of BDNF-HA hydrogel such as viscosity and binding sites provide the 3D environment for cell differentiation with less cytotoxicity.	[114]
Hyaluronic acid-collagen (HA–Coll) scaffold	HA-collagen (type I and II) and Neural stem cells (NSCs) isolated from the rat brain	• HA–Coll scaffold evaluated for morphological, mechanical behavior, water absorption capacity and cell differentiation.	• Collagen confers the mechanical strength (stiffness and slow degradation rate) to HA scaffold and also provides the binding sites for growth and regeneration of the neural stem cells (NSCs) • Desirable porous surface, mechanical properties and 3D environment of HA–Coll scaffold enhances the growth and differentiation of the neural stem cells (NSCs).	[115]
MAHA hydrogels	Methacrylic anhydride-HA hydrogel system with neural progenitor cells (NPCs) and spinal cord astrocytes (isolated from Ventral midbrains of mice)	• Photocrosslinkable hydrogel fabrication, mechanical properties, in vitro degradation. • Cell viability, differentiation studies using biomarker such as GFAP (astrocytes) and β-tubullin-III (neurons) by phase contrast microscopy and immunocytochemical staining.	• Biodegradable MAHA hydrogels support native brain like environment for the viability and differentiation of ventral mesencephalic NPCs into a mature neuronal phenotype. • Hydrogel enhances the outgrowth and length neurites in 3D environment that mimic the native tissue (brain for NPC cells) and (spinal cord for astrocytes). • Hydrogel scaffold allows the differentiation of NPC cells into dopaminergic neuron in vitro that can be a potential therapy for Parkinson's disease.	[116]
Laminin-HA (Lm-HA) hydrogel	Modified HA hydrogel with laminin (Lm-HA hydrogel)	• Fabrication of modified HA hydrogel with laminin, morphological and rheological characterization. • Implantation of Lm-HA hydrogel in lesion cavity created in left frontal region of the cortex of the rat and immuno-histological evaluation after 6 and 12 weeks.	• 3D Lm-HA hydrogel enhances the cell infiltration and axon growth with its biocompatible, multiple receptor binding sites with beneficial mechanical properties. • Helps in enhancing high integration with neural tissue around lesion cavity with angiogenesis capability. • Lm-HA hydrogel improves the cell adhesion, axonal regeneration, neurite extension and inhabit the glial scar formation around the implanted area.	[117]
Laminin-HA hydrogel	Thiolated HA- laminin (Lm) hydrogel conjugate- Neural progenitor/stem cells (NPSCs) (Isolated from medial and lateral germinal eminences of mice)	• Lm-HA hydrogel fabricated using thiolated HA conjugation with laminin and tested for mechanical, morphological properties. • Evaluated for the NPSC cell response in terms of the viability, cell density and chain length formation. • Hydrogel effect on temporal C-X-C Motif Chemokine Receptor 4 (CXCR4) expression, Chemotactic NPSC migration.	• Low MW HA-Lm hydrogel has mechanical properties close to the neural tissue (1.02 kPa storage modulus) that facilitate the NPSCs growth, high viability and density compared to high and moderate MW HA hydrogel. • Lm-HA hydrogel upregulated the expression of the CXCR4 protein expression which responsible for increased NPSC chemotactic migration due to injury induced chemokine SDF-1a. Also, Laminin enhance the adhesion and migration of NPSCs.	[118]
PLL/NgR-Ab modified HA hydrogel	Hyaluronic acid hydrogel, Nogo receptor antibody (NgR-Ab), poly-L-lysine (PLL) and Neural precursor cells (NPCs) (Isolated from the rat brain)	• The fabrication and characterization of the PLL/NgR-Ab modified HA hydrogel with NPCs cells. • Determining the effect on cell viability using MTT assay and its differentiation determined using immunostaining for differentiation biomarkers (antinestin, NF120, GFAP and Tuj 1).	• NgR-Ab and PLL modified HA hydrogel scaffolds increase the cell viability and differentiation of NPCs into the neurons and glial cells. • Immunofluorescence study of HA-PLL hydrogel exhibit the inhibition effect on the differentiation biomarker, β tubullin III and neurofilament cells whereas HA-NgR-Ab hydrogel shows a positive effect on NPCs differentiation through inhibiting the factor that restrict the axon outgrowth and also promote the cell attachment in scaffolds.	[119]

its supportive and stimulating role in regenerative medicine. Thompson et al., demonstrated the role of HA hydrogel containing the astrocytes derived with and without ECM to support the transplantation of mESC-derived V2a interneurons in a spinal cord injury rat model [122]. The authors have found that HA not only improves the level of the histological marker of the spinal injury recovery (GFAP and β-tubulin III) but also alters the behavior of the of neurons, astrocytes, and immune cells. Additionally, it also functioned a supportive matrix for the growth of the transplanted V2a interneurons in SCI lesion, which further improves the neuronal regrowth.

In a similar study by Kushchayev et al., investigated the neuroprotective effect of the HA hydrogels implanted in the lesion cavity of hemisected spinal cord of the rats [121]. HA was found to decreases the intensity of the secondary injury by reducing the lesion size and promoting the regrowth of the neurons and reduction of the scar tissue formation. Besides, Führmann et al., have explored the localised delivery of the brain derived neurotrophic factor (BDNF) using HA hydrogel [123]. The localised intrathecal injection of the chemically crosslinked HA hydrogel containing the bioactive BDNF in the lesion of SCI in rat model exhibit the controlled release of the bioactive BDNF,

which can increase the axonal outgrowth and induce the neuronal differentiation.

6.3. Role of HA in intervertebral disc (IVD) regeneration

Back and neck illness are the second most serious cause of disability and are due to degenerative intervertebral disc (IVD), with 60–80% of individuals between 20 and 50 years old being affected. The IVD soft structures are composed of the outer ring of collagen-rich annulus fibrosus (AF), which acts as central core for the proteoglycan-rich gelatinous nucleus pulposus (NP) that primarily offers the mechanical support to absorb compressive shock and provides flexibility for the movements. In chronic disc disorders, due to the loss of ECM component (AF and NP), results in inflammation and degeneration of the disc due to oxidative stress that leads to the painful condition [124]. Current surgical treatments for degenerative disc disease focus on relieving the symptoms of lower back hurting but won't direct the underlying causes of degeneration or promote disc regeneration. Patients with degenerative disc disease will often undergo a minimally invasive discectomy, which removes a small portion of the damaged disc without altering the stability of the spine. By removing this small portion, the pinched nerve will be released, and the symptoms of pain will be alleviated [125]. To overcome these challenges with current treatments, it is also important to develop new therapies with mesenchymal stem cells (MSCs), growth factors, glutathione, and biomaterials [126].

Our laboratory has extensively investigated the role of HA in the treatment of the degenerative IVD disease. An in-depth role of HA was studied in a symptomatic disc degeneration rat tail model. The surgically implanted HA hydrogel shows the decrease in the levels of thermal hyperalgesia and mechanical allodynia that reduces the nociceptive behavioral responses of the rat to noxious or innocuous stimuli in an IVD injury rat tail model through the suppression of spinal nociception markers (c-Fos and Tac1 as substance P encoders) and the inhibitory effect on sensory neuropeptide, and pro-nociceptive receptors (CGRP, Trk-A, and NGF, neurotrophic factors). HA also removed the injury induced elevation of the sialylation and galactosylation in the discs. In addition, HA exhibited an anti-inflammatory role in treating the injury induced inflammation that reduced the pro-inflammatory cytokines (IL-1β and IL-6) and increases the level of anti-inflammatory cytokines (IL-10) in AF and NP tissues and blood plasma. HA has also shown the inhibition of the GFAP (Glial fibrillary acidic protein) and NGF (Nerve growth factor), which is an essential factor for the axonal regeneration and neurite outgrowth of sensory nerves in disc region [127].

Moreover, the anti-inflammatory role of the HA in the IFNa2b signaling pathway in a bovine disc organ culture model was studied. HA down-regulates the caspase 3 p17 that suggests the modulation role of HA in apoptosis and also modulates the disc ECM matrix by increasing the synthesis of aggrecan and collagen I and down regulating the ADAMTS4 (ADAM metallopeptidase with thrombospondin type 1 motif 4) that are responsible for degradation of the ECM under inflammatory conditions. Thus, HA has an anabolic and an anti-inflammatory role that can be used in regeneration of the disc [128]. In another study, the crosslinked high molecular weight HA hydrogel was investigated as a potential therapeutic biomaterial for NP regeneration via reduction of the pro-inflammatory cytokines and modulation of ECM. It was found that HA has significant mechanical properties with negligible cytotoxicity on the NP cells, even after the 7 days. HA suppresses the inflammatory receptors, such as IL-1R1, MyD88, and down-regulates the expression of the *NGF* and *BDNF* gene. HA has shown its anti-inflammatory role through its interaction with an increased expression of CD44 receptor on the NP cells. Thus, HA can be utilized for the regeneration of the NP of the IVD [129].

7. Recent advances and commercially available HA-based systems in inflammatory disorders

7.1. HA physico-chemical cues towards wide-range biomedical applications

As HA is ubiquitously expressed throughout the body, it has been used either alone or in part in the treatment of many ailments and also used as a pharmaceutical aid in the different therapeutic formulations. Along with its remarkable physico-chemical properties and associated functionalities, HA also has very specific biological functions in the body. Unique characteristics of HA, such as water absorbing capacity (1000 times more than its weight), moisturizing property/hydrodynamic, ionic characteristics have made it as an excellent topical/dermal application product, like other effective lipid-based drug delivery systems reported elsewhere [130,131]. Moreover, because of its tunable viscoelastic properties, it is used as a viscosupplement in osteoarthritis treatment, ophthalmologic surgeries, wound dressing or healing material and in drug delivery systems [1,106]. In fluids, the physical nature of the HA polymeric networks does not exhibit a well-defined network structure and depends on the type of molecular weight of HA and its concentration [132]. HMW-HA ($>10^6$ kDa) forms an extended network even at very low concentrations (<0.01%). Besides, as the HA concentration, molecular weight increases the viscous/loss modulus (G") will also increase. Interestingly, under shear stress, HA behaves as a shear-thinning system, this unique nature of this material built to use as a viscosupplement in arthritis [4]. The rheological properties in an aqueous/colloidal system are influenced by pH, ionic conditions, and temperature [133]. Along with the aforesaid and biological properties, HA and modified HA has been extensively used in various biomedical applications.

7.2. HA in Intestinal inflammation

HA is an abundant component of the mucosal, epithelial, and ECM of the intestinal wall of the gastric tract. These GAG polymeric networks are located beneath the epithelial barrier of the gut in both healthy humans and rodents [134,135]. Variabilities in the gastro-intestinal factors and their effects on polysaccharide-based drug delivery systems degradation, release reviewed and reported elsewhere [136–138]. Göransson et al., demonstrated in rodent models that HA content in the colon is up to four times higher than that in the small intestine [139]. The major roles of HA and other GAGs in the intestinal barrier is to help in repairing the dysregulated mucosal/epithelial barrier, reducing inflammation in intestinal inflammation, enhancing the tissue homeostasis, enriching the commensal gut microbiota and antibacterial defense against harmful bacteria [138]. A cross-section of healthy mouse colon staining reveals the presence of HA in the ECM (green) with important roles in maintaining the gut barrier functions enumerated in (Fig. 5).

A recent study conducted by Xiao et al., shows an effective combinatorial HA functionalized formulation (SiCD98 with curcumin) that affords a promising method for a synergistic combination therapy of colitis. Where, HA-functionalized nanoparticles (NPs) able to release the loaded therapeutics to targeted colon cells, treatment with hydrogel encapsulated HA-siCD98/CUR-NPs inhibits the dextran sulfate sodium (DSS)-induced over-expression of the genes encoding CD98 and TNF-α in the colon [141]. In a similar study from Chiu et al., shown that a combined treatment of HA with 5-aminosalicylic acid accelerated wound healing and reduced inflammatory reaction in a rat colitis model [142]. A recent study by Xiao B group, explored the potential use of lysine-proline-valine (KPV), a naturally occurring tripeptide for colitis therapy using HA functionalized NPs to target intestinal epithelial cells and macrophages in colitis tissues. HA-KPV-NPs encapsulated in a hydrogel (chitosan/alginate) system after oral delivery showed a much stronger capacity to inhibit mucosa damage and downregulated TNF-α,

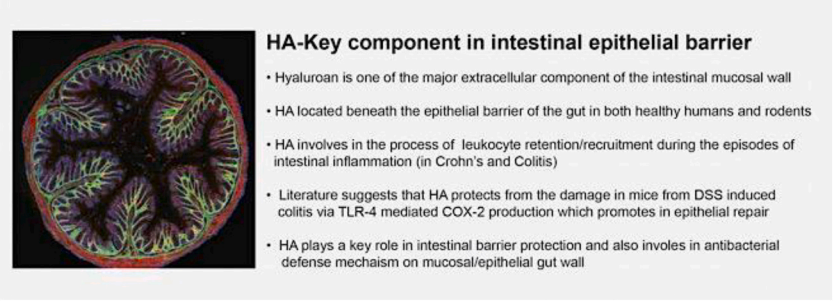

Fig. 5. A model representation of HA as a key component of the healthy mouse colon wall and HA-specific roles in maintaining the gut barrier functions (Reprinted from Ref [134, 140] with permission from Elsevier Group).

compared with a KPV-NP/hydrogel system alone in DSS colitis mouse model (Fig. 6) [143].

A similar study conducted by Kotla NG et al., shows the importance of HA functionalization on polymeric nano drug particles, where they used curcumin (Cur) as a model fluorescent drug and tested it in in vitro cell lines. Cur-HA NPs use on colon cancer (HT-29) monolayer cell cultures demonstrated the efficacy of HA functionalization, which enhanced the cellular interaction and uptake when compared to an uncoated nanoparticulate system. These findings signify that HA functionalized nano-hybrid particles are effective in delivering drugs orally to the lower gastrointestinal tract in order to treat local colonic diseases (Fig. 7) [106].

Interestingly, Lee et al., designed and reported an ROS-responsive and hyaluronidase-resistant, HA–bilirubin nanomedicine (HABN) that is formed by the nanoaggregation of an amphiphilic conjugate between HA and bilirubin. The HABN system efficiently accumulated in inflamed colonic epithelium and restored the epithelium barrier in DSS induced acute colitis mice model. The authors also concluded, surprisingly, that the HABN system modulated the gut microbiota, enhanced the overall richness, diversity, markedly augmenting the abundance of *Akkermansia muciniphila* and *Clostridium XIVα*, which are microorganisms with crucial roles in gut homeostasis. In addition, HABN associated with pro-inflammatory macrophages, regulated innate immune responses and exerted potent therapeutic efficacy against colitis. This work provides strong evidence of HA-based nanomedicine system on gut homeostasis, microbiome enrichment and associated innate immune responses for the

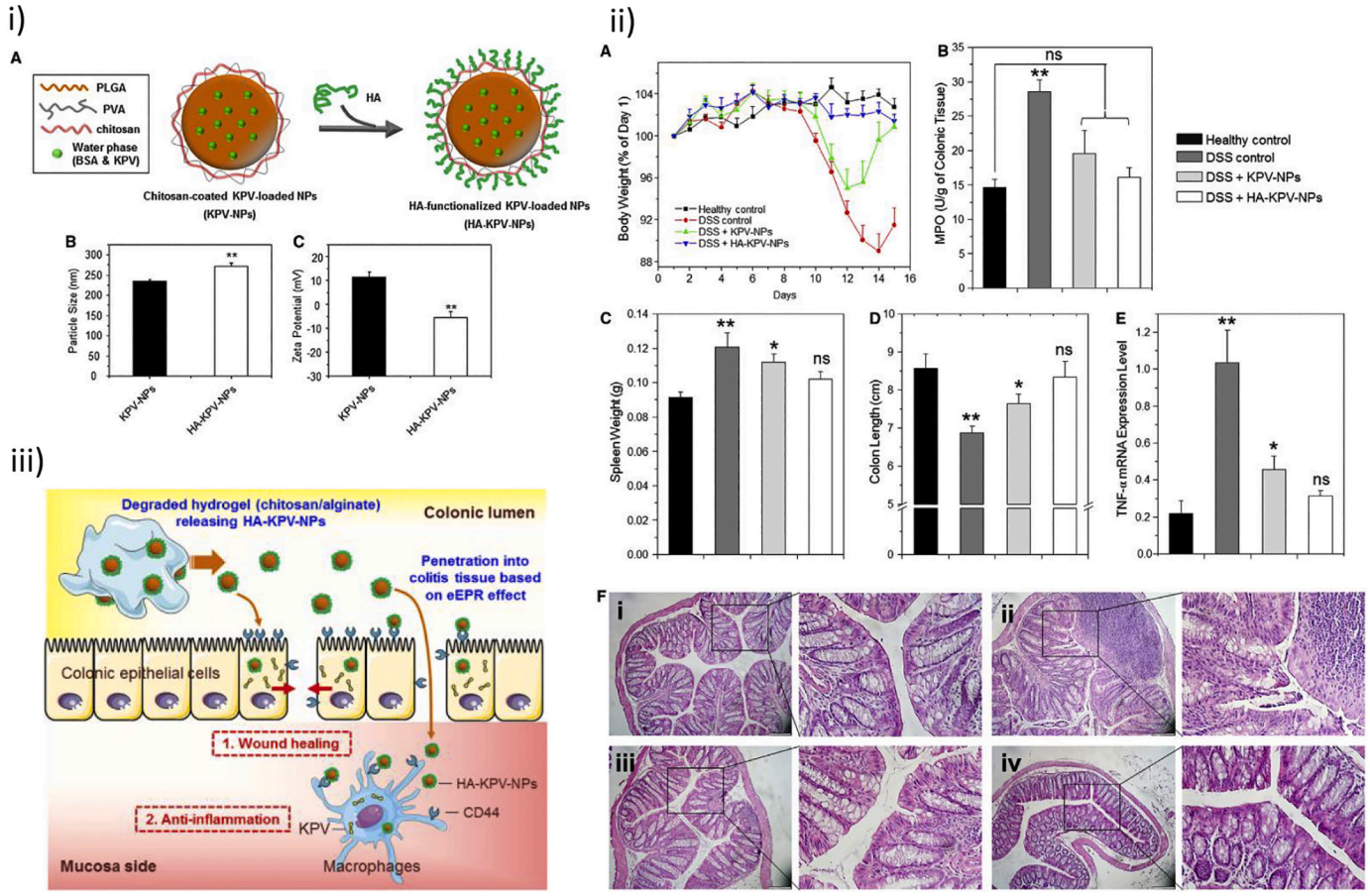

Fig. 6. Tripeptide loaded HA functionalized NPs for targeting intestinal epithelial cells and macrophages in colitis tissues, which the HA-KPV-NPs system accelerated mucosal healing and alleviated inflammation of a dextran sulfate sodium (DSS)-induced ulcerative colitis mouse model compared to one without HA functionalization. (Reprinted from Ref [143] with permission from The American Society of Gene and Cell Therapy Group).

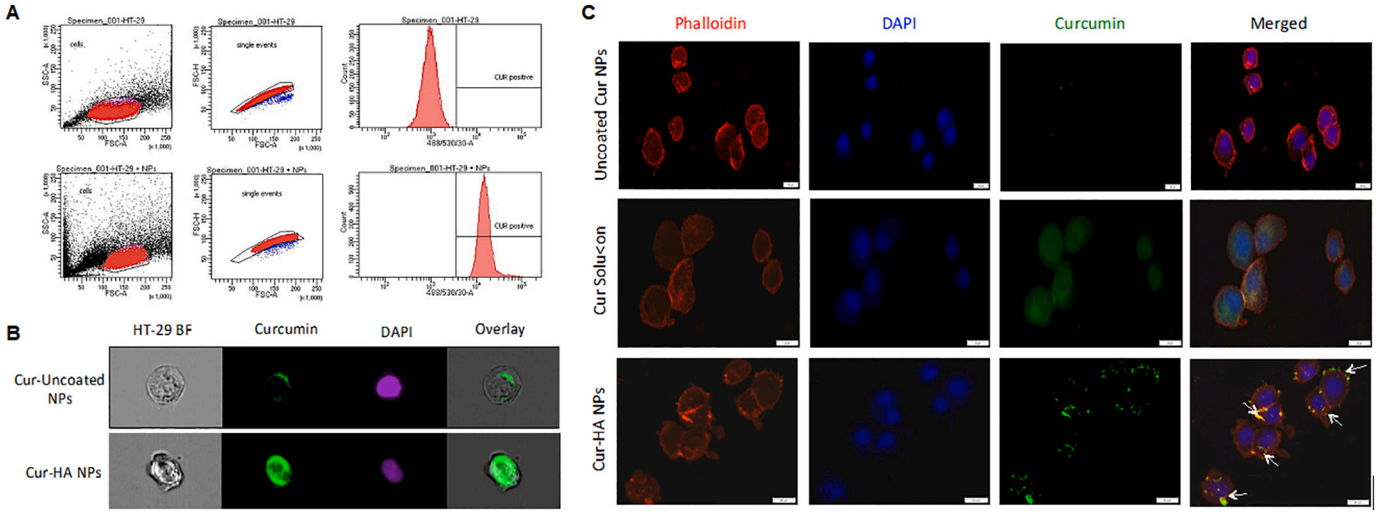

Fig. 7. HA functionalization increases the fluorescent drug curcumin loaded nanoparticles interaction, uptake in HT-29 cells, in vitro. The uncoated Cur NPs, Cur solution, and Cur-HA NPs after 3 h incubation, HA functionalized NPs showing more cellular interactions and uptake compared to uncoated NPs; nuclei (blue) stained with DAPI, cytoskeleton (red) stained with rhodamine-phalloidin, curcumin (green) from Flow cytometry histogram, ImageStream flow cytometry images and Representative slide scanner images. (Reprinted from Ref [106] with permission from Nanomaterials, MDPI). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

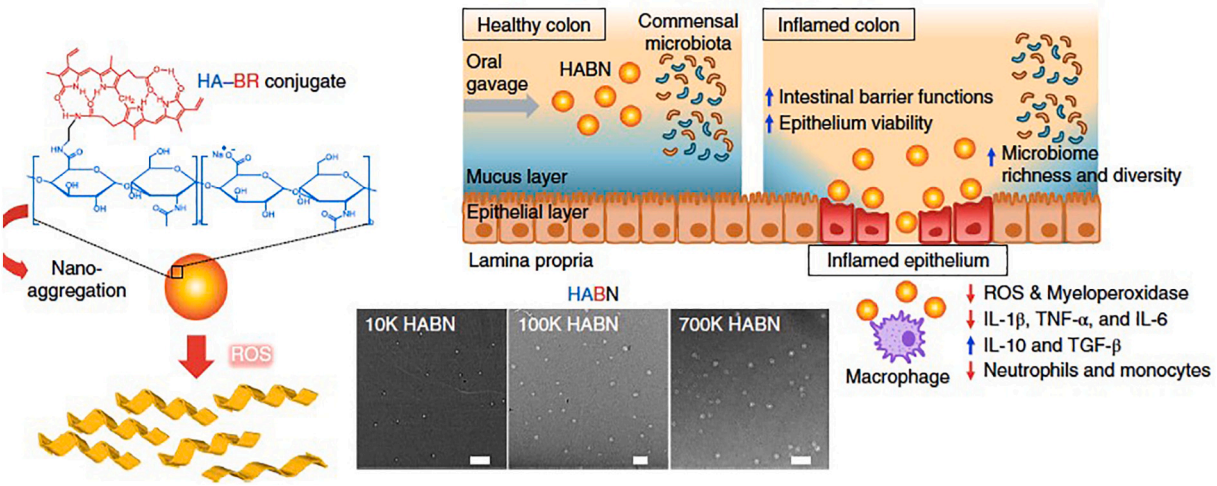

Fig. 8. Schematic synthesis and the proposed mechanism and therapeutic potential of HABN self-assembled nano aggregates targeted to inflamed colon and exerted therapeutic effects against DSS acute colitis model. (Reprinted from Ref [144] with permission from *Nature* Group).

treatment of colon inflammatory diseases (Fig. 8) [144].

In addition to the anti-inflammatory, microbiota enrichment properties of HA in intestinal inflammatory disorders, a few research reports revealed that HA has a role in decreasing the permeability by enhancing the tight junction proteins. These proteins are critical in maintaining homeostatic intestinal permeability in multiple intestinal inflammatory diseases, including Crohn's and colitis. Kim et al., reported that HA 35 kDa treatment increases ZO-1 (Zonula occludens-1, a tight junction protein) expression in mouse intestinal epithelial organoids, whereas large HA 2000 kDa is not internalized into the cells, and also layilin is an important HA receptor that mediates the effect of oral HA (35 kDa) treatment on intestinal epithelium [34]. In addition to the research investigations of HA, there are a few commercial products available in the market on maintaining the dysregulated intestinal epithelial barrier, repairing the mucosal layer, and maintaining the tissue homeostasis and gut microbiota. Products, such as TRUD™, Mucosamin®, Proktis-M® (Table 4) have LMW- or HMW-HA or in combination, which are given intrarectally with specific benefits (LMW-HA facilitates mucosal healing, HMW-HA provides protective barrier effect and also HA hydrates and lubricates the colorectal tissue and enhances would healing).

7.3. HA in urological disorders

Interstitial cystitis (IC) also known as painful bladder syndrome (PBS), a chronic urological disease with pelvic pain, increased urinary frequency and discomfort [145]. The bladder wall is composed of urothelial cells, which form a tight, impermeable, protective barrier composed of GAGs and sulphated forms (sGAGs) [146]. One of the most common therapies for IC is intravesical sGAG (intravesical route) based systems, which form a physical barrier coating and helps in process. Several GAG based treatments are available for the treatment of IC, mainly composed of HA solutions, CS solutions or a combination of HA and CS. HA has been shown to decrease the secretion of inflammatory cytokines as a cost-effective medication for cystitis [147,148]. Rooney et al., reported the mechanistic role of HMW-HA in the treatment of IC (Fig. 9) [148], where, HA significantly decreased the cytokine secretion,

Table 4
Commercially available hyaluronan-based products used for various inflammatory disorders.

Product	HA composition	MW	Dose Regime	Route of Administration	Approved Indications	Proposed Mechanism
HA in intestinal inflammation						
TRUD ™	Mixture of 1.8×10^6 Da & 0.35×10^6 Da	LMW^+ HMW-HA	Daily	Rectal enema	Mild to moderate Ulcerative Colitis	• LMW-HA facilitates mucosal healing • HMW-HA provides protective barrier
Mucosamin®	HA with synthetic amino acids	NA	Once or several times a day	Rectal gel	Rectal mucositis	• Improves mucosa tropism • Acts as a protective layer on the rectal mucosal layer (rectal mucositis)
Proktis-*M*®	HA	NA	Once daily	Rectal suppository	Hemorrhoids, fissures, and in radiation-induced acute proctitis	• HA hydrates & lubricates the colorectal tissue and enhances would healing process
HA in urological disorders						
Hyacyst®	120 mg & 40 mg HA Solution	LMW^-HA	Weekly	Intravesical/Non-surgical catheterisation	Interstitial cystitis/bladder inflammation	• Repairs & regenerates the dysregulated urothelium • Replaces the deficient GAG layer
Cystistat®	40 mg HA Solution	HMW^-HA	Weekly	Intravesical	Interstitial cystitis	• Temporarily replaces the deficient GAG layer on the bladder wall
IAluril®	Mixture of 800 mg/50 mL HA (1.6%), 1 g/50 mL chondroitin sulfate (2%)	NA	Weekly	Intravesical	-Interstitial cystitis -Painful bladder syndrome -Urinary tract infections	• First combined intravesical GAG replacement therapeutic • Repairs and restores the dysfunctional GAG layer of the bladder
INSTYLAN®	80 mg HA/50 mL (0.16%)	NA	Weekly	Intravesical by urological catheter	Hemorrhagic cystitis (HC)	• Creates a viscoelastic membrane on the mucosal surface of bladder • Regenerates and protects the damaged GAG
Instillamed®	Mixture of 800 mg HA & 1000 mg chondroitin sulfate/50 mL	NA	Weekly	Intravesical	Interstitial and chronic cystitis	• Temporary replacement of the GAG layer
HA Cran Chewable Lozenge	Mixture of HA (10 mg), VitaCran® and Vitamin C	NA	Daily	Oral	Supports for healthy urinary tract	• Maintains urinary tract health
Hyaluronan in Ocular inflammation						
HYLO®-TEAR	0.1% HA	NA	Daily	Topical (eye)	Dry eye syndrome	• Eye lubricant
Vismed®	0.18% HA (0.3 mL/vial)	NA	Daily	Topical (eye)	Superficial keratitis, Sjögren's syndrome or primary dry eye syndrome	• Lubricates the eyes in case of sensation of dryness, burning and ocular fatigue
Lubristil®	0.15% HA (0.3 mL/vial)	NA	Daily	Topical (eye)	Dry eye syndrome	• Eye lubricant
HYLO®-CARE	0.1% HA + 2% Dexpanthenol	NA	Daily	Topical (eye)	Severe dry eye and for outside layer of the cornea injuries	• Provides intensive moistening and to aid healing in a damaged or injured cornea especially after eye surgery
HYLO®-DUAL	0.05% HA and 2% Ectoin	NA	Daily	Topical (eye)	Allergy related dye eye	• Provides protection against environmental allergens and relief for itching, burning eyes
Hyaluronan in Osteoarthritis						
Hyalgan®	1% HA	500–730 kDa	weekly	Intra-articular injection	Osteoarthritis (OA) of knee	• Viscosupplement to patients who have failed to respond adequately to analgesics
Supartz®	10 mg/mL	620–1170 kDa	Weekly	Intra-articular injection	Osteoarthritis (OA) of knee	• Viscosupplement
Orthovisc®	15 mg/mL	1 to 2.9 mDa	Weekly	Intra-articular injection	Osteoarthritis	• Acts at the joint space as a shock absorber and lubricant
Euflexxa®	1% HA	2.4 to 3.6 MDa	Weekly	Intra-articular injection	Osteoarthritis (OA) of knee	• Provides tissue lubricant effect and modulates the interactions between adjacent tissues
Synvisc® (hylan GF 20)	Crosslinked HA (10 mg/mL)	6 MDa	Weekly	Intra-articular injection	Osteoarthritis	• Acts as a temporary replacement/ supplement for synovial fluid
DUROLANE®	2% HA	1000 kDa	Weekly	Intra-articular injection	Osteoarthritis	• Acts at the joint space as a shock absorber and lubricant
Fermathron®	1% HA	NA	Weekly	Intra-articular injection	Osteoarthritis	• Viscosupplement for knee, hip, ankle, and shoulder synovial joints

permeability and increased sulphated GAG production.

Similar clinical research conducted by Scarneciu et al., reported that intravesical HA instillations to 30 urinary tract infection (UTIs) and 24 bladder pain syndrome (BPS)/IC patients showed substantial progress (75% patients showed a complete response) in reducing urinary bladder pain in UTI patients [149]. In another study, Lee et al., demonstrated the positive effect of HA (modulating inflammatory responses, improving the urothelial-lining defects) in a ketamine-induced interstitial cystitis (Fig. 10) [150].

The bladder instillation therapies for cystitis/bladder inflammation are classified as devices by the regulatory bodies with various therapeutic options. Some of the key therapeutic systems include-pentosan polysulphate sodium (PPS) (Elmiron®) and dimethyl sulfoxide (Rimso-50®). PPS is an oral GAG replacement treatment studies shown minimal therapeutic effect for patients [151,152]. Gepan®, Uracyst® are CS based products, which demonstrated no effect compared to placebo in two double, blinded, multicentre, randomised, parallel group studies [153,154]. Hyacyst®, Cystistat®, iAluRil®, INSTYLAN®, Instillamed® are HA-based products (Table 4), which demonstrated the repair and regeneration of dysregulated/altered urothelium and replaces the deficient GAG layer [155].

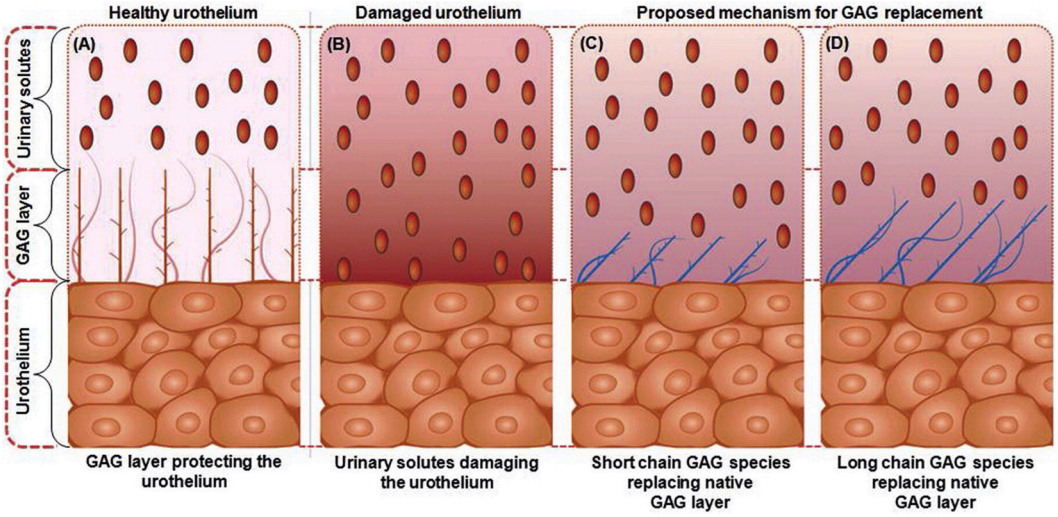

Fig. 9. Mechanistic illustration of the role of HA (GAG) coating, repair on the damaged urothelium via GAG replacement therapy for interstitial cystitis. (Reprinted from Ref [148] with permission from Elsevier Publishing Group).

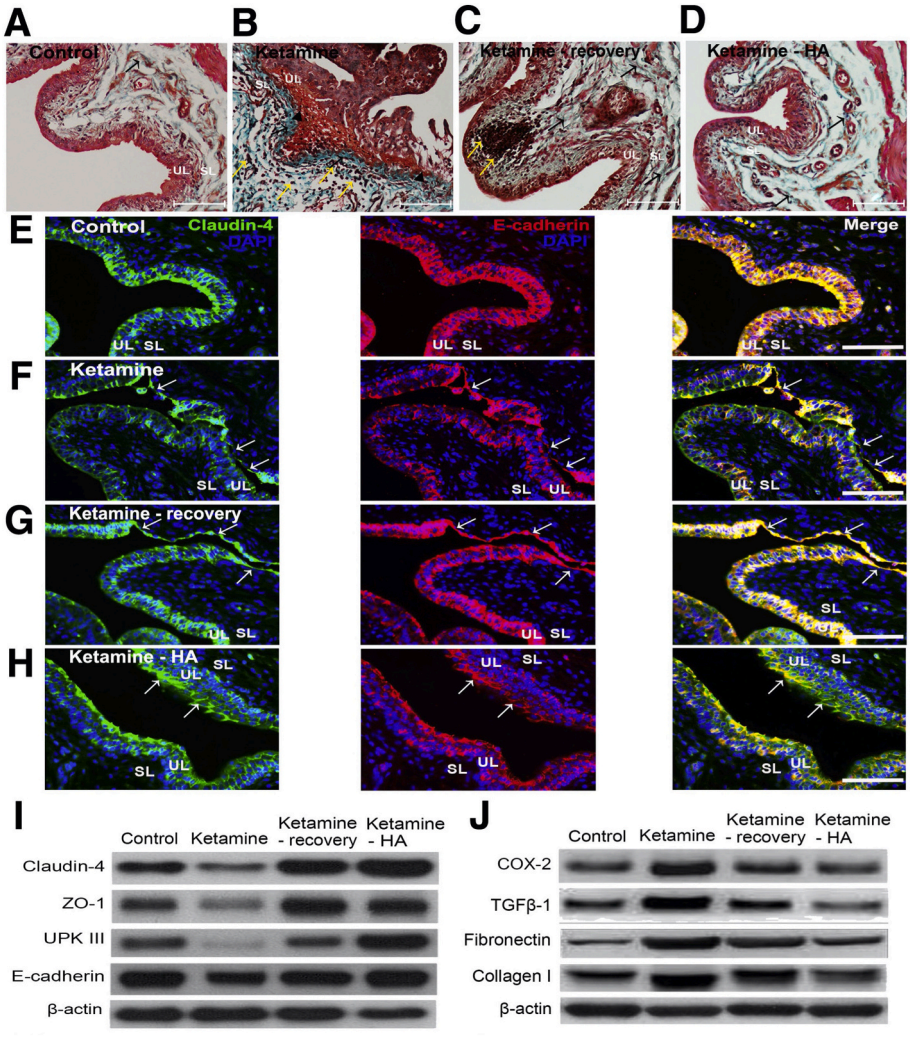

Fig. 10. HA based system improves the ketamine-induced cystitis histological features and junctional protein expression. (Reprinted from Ref [150] with permission from Elsevier Publishing Group).

7.4. HA in ocular, osteoarthritis applications

HA based systems efficiently lubricate the ocular cavities and used for dry eye-related indications and in specific surgical procedures. HA solutions are the most commonly used viscosurgical devices to protect and lubricate the eye [156]. Along with lubricant property, a few HA-based studies also showed elevating the drug concentrations in ocular drug delivery application. The first (approved by FDA in 1980) ophthalmic viscosurgical device containing HA is still marketed under the trademark Healon® (Abbott) and HA based other products DropStar® (Bracco) and Lubristil® (Eyelab) are mainly used for dry eye syndrome [157,158], and as artificial tears [159–161]. Recently, novel derivatives of HA (HA-cysteine ethyl ester) [162] and (urea-crosslinked HA, HA-CL) [163] are being investigated to enhance the delivery system ocular residence time.

Synovial joints filled with clear/faint yellowish synovial liquid (~2 mL in knee joints), which is composed of GAGs of which the majority is the combination (chondrotin-4-sulfate-2% and HA-98%) [164]. In conditions like, osteoarthritis, knee impairment or upon aging, synovial fluid loss the critical viscoelastic properties under dynamic mechanical conditions, allows the cartilage contact, increases the chances of joint surface fissures [165,166]. Intra-articular treatment with naïve HA (noncrosslinked HA) and hylans (crosslinked HA) has recently been accepted for osteoarthritis [164,167]. Currently, FDA-approved products, such as Hyalgan® (noncrosslinked HA), Orthovisc® (noncrosslinked HA), and Synvisc® (hylan GF 20) used in osteoarthritis as viscosupplements. The low viscous products (Hyalgan®, Orthovisc®) have lower viscosity, ease to administer but are not as effective as Synvisc® (crosslinked HA) (Table 4). Several clinical trials demonstrated that intraarticular injections of the aforementioned products provide knee pain relief up to six months [168,169].

8. Recent advances in protein and peptide delivery using HA based systems

HA with a simple linear structure exerts several biological functions. HA and modified-HA derivatives have been reported for target-specific long-acting intracellular delivery of protein, peptide therapeutics. HA-based bioconjugated systems have been used to develop various macromolecules delivery, as HA functionalization increases cellular uptake, receptor-mediated endocytosis, and enhances transcriptional activities. Besides, hydrophilic HA or modified-HA derivatives (hydrogels, crosslinked systems) are well established as a depot for the long-acting/sustained release of peptides or protein agents without denaturation [170]. *Even though HA has been successfully commercialized, various techniques have been devised to increase the residence time, biomechanical properties* via *different chemical modification techniques (modifying carboxyl and hydroxyl groups, esterification of HA, and crosslinking HA with divinyl sulfone, glycidyl ether, or dialdehyde* etc.*). In this section, we focus on some HA-based systems for peptides and proteins delivery for enhanced therapies (Table 5).*

Human serum albumin nanoparticles (HSA NPs) with numerous benefits such as non-immunogenic, high drug loading capacity, the possibility for surface modification, which have been regarded as an ideal platform to deliver various agents, including synthetic drugs, nucleic acids, and proteins.

Table 5
HA-based macromolecules (protein, peptide) therapeutic delivery systems.

Type of the protein or peptide	Composition of the delivery system	Applications	Advantage or biological outcome	References
Insulin (oral)	Hyaluronic acid (HA) coated CaCO3-based composite nanocarriers (NCs)	Diabetes	Oral administration of insulin in HA-CaCO3 nanocarriers to the diabetic rats showed enhanced hypoglycemic effect compared with insulin delivery via the subcutaneous route	[177]
Bone morphogenetic protein 6 (BMP-6)	HA-based hydrogel system by linking thiolated heparin via PEGDA	Multiple myeloma	BMP-6 functionalized HA-hydrogels signify as a potential biopolymeric hydrogel system for local treatment of myeloma-induced bone disease by inducing the differentiation of MSCs	[178]
Bovine serum albumin (BSA)	HA hydrogels with different molecular weights (5 kDa, 100 kDa, 1 MDa) effect on the skin permeability or absorption	Barrier-deficient skin/dermal application	In barrier-deficient skin, HA hydrogels limited the transport of biomacromolecules (BSA) to the stratum corneum and viable epidermis, suitable for topical drug delivery	[179]
Connexin43 mimetic peptide (Cx43 MP)	Targeted delivery of Cx43 MP by HA-coated human serum albumin (HSA) nanoparticles	Retinal inflammatory conditions	HA-coated HSA NPs with Cx43 MP displayed enhanced cellular uptake and retinal penetration (ex vivo) via HA-CD44 receptor mechanism with targeted, sustained release of the payload	[171]
Intracellular protein drugs, cytochrome *c* (CC) and granzyme B (GrB)	HA nanogel (HA NG) system: (HA-cystamine methacrylate (HA-Cys-MA) and HA-lysine-tetrazole (HA-LysTet) with CC and GrB protein drugs	Anti-cancer (Breast and lung tumor models)	CC and GrB-loaded HA NGs able to target, release both loaded proteins to MCF-7, A549 cancer cells (via CD44), with enhanced antitumor effects, in vivo	[180]
Bovine serum albumin (BSA)	HA-coated BSA NPs	Anti-cancer (lung tumor models)	HA-coated BSA NPs showed enhanced pharmacokinetics and pharmacodynamic properties when compared to Taxol^{R} by suppressing the proliferation of metastatic lung melanoma at a relatively low dosage	[181]
Bovine serum albumin (BSA)	HA-coated albumin nanocomposite via conjugation of BSA with Au nanoclusters (AuNC) and Indocyanine green (ICG), which is read as AuNC@cBSA-ICG@HA	Photothermal therapy for anti-cancer targets	HA shell endowed AuNC@CBSA-ICG@HA with actively targeting ability and hyaluronidase-dependent drug release as compared to other formulations	[182]
Human serum albumin nanoparticles (HSA NPs) and Connexin43 mimetic peptide (Cx43 MP	Connexin43 mimetic peptide (Cx43 MP) MP was loaded into HSA NPs via two methods, adsorption and incorporation.	Retinal ischemia	HA-coated albumin NPs rapidly diffused through the vitreous and specifically targeted the retina after intravitreal injection, exhibiting enhanced retention and thus sustained therapeutic action as compared to free Cx43 MP	[183]
Lysozyme	Dopamine-conjugated HA (HADA)/ polydopamine (PDA) complexes	Combinatorial protein delivery	HADA/PDA complexes were prepared by one-pot synthesis, where HA provided a synergistic effect for both PDA and protein with an efficient protein delivery application	[175]
Hyaluronic acid and human serum albumin nanosystem	Erlotinib (ERT) was loaded in HA modified human serum albumin (HAS) particles (ERT-HSA-HA NPs)	Lung cancer	HA/HSA co-modified erlotinib albumin nanoparticles have the potential to become a new strategy in the treatment of lung cancer	[184]

In one recent study, transmembrane proteins called Connexins (Cx) play an essential role in cellular communication as subunits of hemichannels and gap junctions. The isoform of this is Cx43 was loaded into HSA NPs and further coated with HA to achieve active targeting to CD44 positive retinal cells. In vitro *cell viability, cellular uptake, and Cx43 hemichannel blocking with various NP formulations were investigated using human RPE cells (Fig.11). The results showed that compared to uncoated HSA NPs, HA coating resulted in higher* in vitro *cellular uptake and enhanced retinal tissue penetration* via *ligand-receptor interactions between HA and CD44 receptors. Overall, the HA functionalized HSP-based delivery platform achieved specific cell targeting and can potentially treat various retinal inflammatory disorders* [171].

In another study, a multilayered hydrogel film system based on hyaluronic acid–cysteamine (HA-Cym) and polyvinylalcohol (PVA) was fabricated, which provided a drug-impermeable backing layer for a controllable unidirectional insulin release. The fabricated film provided mucoadhesive property with controlled insulin release [172]. *Altiok EI* et al. *reported the possibility of improving the intravitreal half-life of the anti-VEGF drug (VEGF decoy receptor sFlt-1) by multivalent bioconjugation sFlt-1 grafting to linear hyaluronic acid (HyA) chains. The reported approach of multivalent conjugation substantially minimized the enzymatic degradation, improved the drug residence time in the eye for enhanced diabetic retinopathy therapy* [173]. *In another study, a tunable localised hydrogel system was developed to study the encapsulation and release of model proteins using the HA-Tyr (Hyaluronic acid-tyramine) hydrogel system. The mechanical strength of the hydrogel and charge (negatively charged α-amylase showed sustained release, positively charged lysozyme undergone rapid release) controlled the release rate of proteins. Such an injectable hydrogel system can reduce patient discomfort by forming a protein-hydrogel depot with a single injection dose with the long-term release of the payload* [174].

The development of self-organizing complexes of HA and polydopamine (PDA) to encapsulate and release proteins for combinatorial protein delivery applications has also been reported. The complexes were prepared with HA of different molecular weights (20 kDa and 200 kDa) and various molar ratios of dopamine using lysozyme as a model protein. Dopamine-conjugated HA (HADA)/PDA complexes were prepared by one-pot synthesis by relying on the self-polymerization of dopamine (Fig.12). Here, HA provided a synergistic effect for both PDA and protein by serving as a binding factor and a backbone; polymeric networks provided beneficial insights for other protein-based delivery formulations [175]. *Combining proteins and peptides on HA provides abundant functional groups and high affinity hydrophobic binding sites, binding ligands and drugs. Therefore, these combinations have become an ideal carrier and have been widely used to encapsulate various therapeutic agents with HA, facilitating the receptor-mediated uptake* [176]. *Thus, the combination of HA with proteins or small peptides overcomes HA delivery limitations.*

9. Challenges and limitations associated with HA and modified-HA systems

There has been massive progress in using HA-based medicinal products in clinical use for over 40 years. However, there are a few detrimental effects, including contradictory outcomes of high to low MW HA or fragments, susceptibility to invivo degradation, poor mechanical properties, unpredicted effects in the disease environment (fibrosis, cancer). The HA-based systems intended to use for in vivo *applications undergo rapid degradation by*

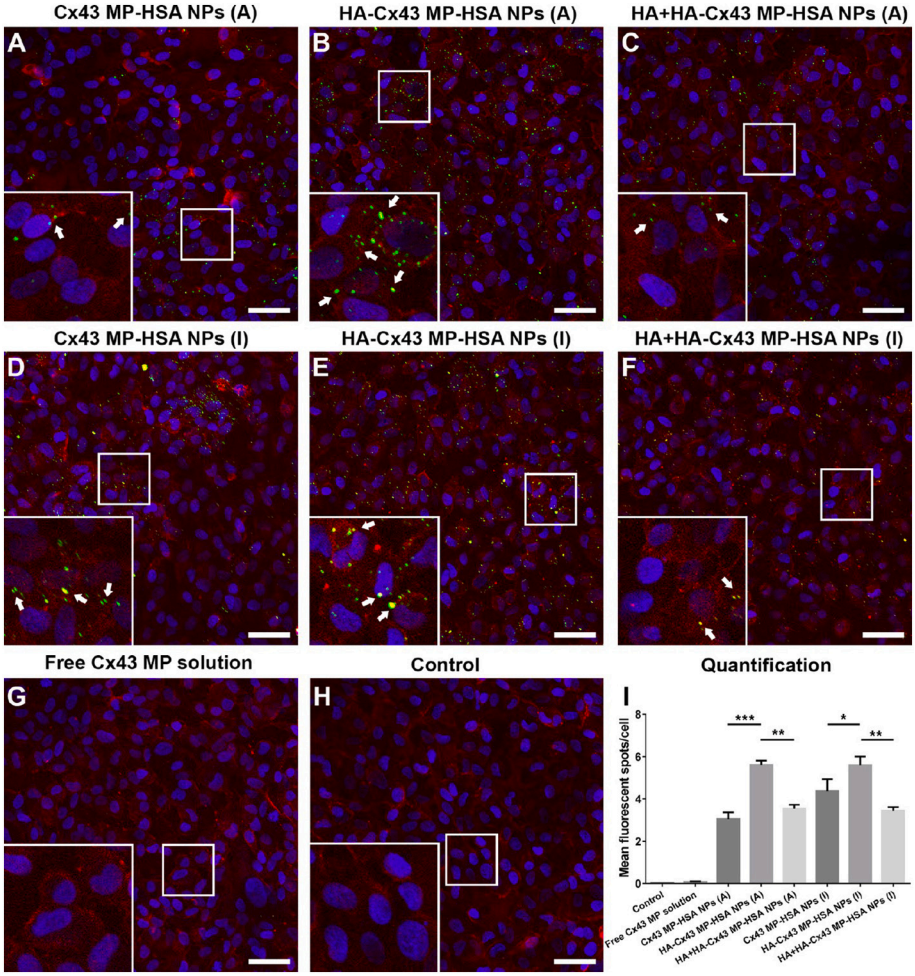

Fig. 11. *Representative confocal micrographs of ARPE-19 cells without any treatment (control) (H), with incubation of free FITC-Cx43 MP solution (G), FITC-Cx43 MP-HSA NPs prepared by adsorption (A) and incorporation (D), HA-FITC-Cx43 MP-HSA NPs prepared by adsorption (B) and incorporation (E), and cells pretreated with free HA (10 mg/mL) together with HA-FITC-Cx43 MP-HSA NPs prepared by adsorption (C) and incorporation (F). (Green fluorescence- internalized FITC-Cx43 MP; DAPI, blue- nuclei; WGA-Texas Red-X, red- cell membranes). Scale bar = 50 μm. A representative magnified area is displayed in the bottom left corner of each image with white arrows pointing towards internalized NPs. (I) Quantification of average green fluorescent spots per cell was performed using ImageJ software (data points represent mean values ± SD, n = 3). (Adapted from Ref with Permission* [171]). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

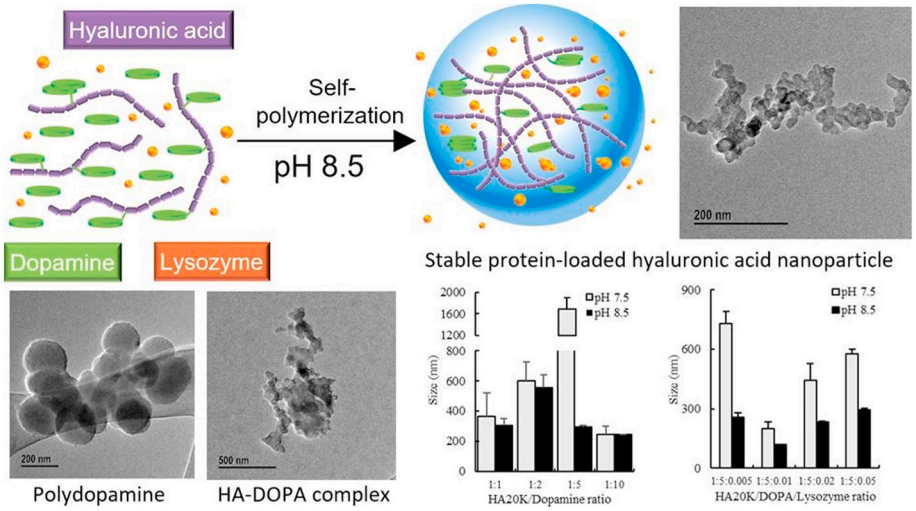

Fig. 12. *Schematic illustration of the one-pot synthesis of HADA/PDA/lysozyme complexes for combinatorial protein delivery application. Representative TEM images and particle size distribution of various formulations of dopamine-conjugated HA (HADA)/PDA complexes (Adapted from Ref with Permission* [175]*).*

enzymatic, ROS and hydrolysis mechanisms [16]*; the excessive swelling ability of the HA polymer chains also affects the biochemical functionality for cell growth with weak mechanical stability* [185]*. As a result, numerous investigations are reported/ongoing to tune the mechanical strength, degradation* via *chemical crosslinking, conjugation approaches. Various strategies exist for modifying the HA biopolymer to increase its mechanical stability and control degradability; however, such a high degree of modifications also influence its cellular, biological functionalities. These chemical modifications/crosslinking strategies still face challenges to produce the biological tissue matrix mimicking HA alone or combinatorial scaffolds.*

As mentioned before, HA plays diverse biological roles depending on its molecular weight, degradation, and turnover rate. Based on the type of application used, one must consider the molecular weight of modified or naïve HA. Numerous studies have indicated that low molecular weight HA levels or fragments are correlated with the severity of different diseases (including pulmonary fibrosis, allergic alveolitis, and cancer) [7,24]*. Hence, the presentation of HA to the disease target should be dependent on the disease tissue matrix associated events. Despite its broad applicability, care must be taken in selecting the HA, formulation type, route of administration, disease application, and others. Besides, an Appropriate Use Criteria (AUC) should be adopted for the use of HA in all disease types,* e.g.*, intra-articular HA therapy (for osteoarthritis), injection of HA dermal filters (for cosmetic dermatology practice), and others. Several studies have documented the elevated HA levels in autoimmune and inflammatory diseases* [186]*; however, we don't know the increased HA level due to either a protective mechanism or one of the causative factors. Use of HA-based products in autoimmune diseases (such as systemic sclerosis, cutaneous lupus erythematosus, psoriatic arthritis, and others) is not advised because of their innate immune-stimulating properties, which amplify the disease conditions* [187–190].

Few investigations aim to study the molecular mechanisms of native HA and modified HA and its derivatives in immunomodulation, tissue remodelling and repair strategies. However, defined mechanistic aspects, organization of ECM, signaling mechanisms remain largely unexplored. Moreover, the source and purity of HA also alter its biological functionalities, the large-scale production (either animal or microbial fermentation) of high purity HA for clinical use is still challenging due to high polydispersity, associated impurities while production, which should be monitored carefully to avoid excess inflammatory reactions [185,191]*. Besides, the sterilization of naive HA or modified HA-based products may also degrade the polymer, influencing its immunological responses. However, advanced HA-based products for biopharmaceutical applications are challenged by multiple factors with numerous product development technological issues, suggesting that various barriers must be overcome to advance the novel HA-based systems into clinical settings.*

9.1. Conclusion and future perspectives of HA as a therapeutic transition

Hyaluronic acid has shown tremendous success over the last few decades because of its numerous, unique physical and biological properties not limited to mucoadhesivity, viscoelasticity and receptor interactions. Numerous in vitro and in vivo findings have shown various therapeutic effects of HA, which supported the development of a high number of HA-based commercial products especially for inflammatory diseases. Besides, the broad spectral chemical modifications of HA allow the development of tunable derivative systems with specific tissue engineering, drug delivery and in medical device applications. Although hyaluronan offers potential biological applications, further exploration and technological advances are essential. This is because some questions still need to be answered specific to HA metabolism, fragmentation, the quantity of HA (particularly dosage regimen) to use for various therapeutic responses, mechanisms and associated downstream pathways. Additional understanding is needed to know the relation between size of HA polymer, localization, degraded HA fragments and the downstream mechanistic signaling effects. The understanding of all these mechanisms could provide further opportunities to advance HA based, HA-modified systems in pharmaceutical, biomedical, tissue engineering, and cosmetic products.

As explained above, physiological (native) high molecular weight HA is beneficial to the host. However, its mechanism depends on the physicochemical state of the HA, the type of receptor it binds and its expression, affinity, and signaling molecules that are attached to receptors, tissue microenvironment and environmental cues present. The HA degradation process in different tissues has different kinetics, hence targeted therapies should evaluate their effects, also consider HA kinetic properties. Any injured/pathogen infected cells release the fragmented HA, which may have functions that differ from those of native HA. Native-HA in higher doses produces immune suppressor effects on T cells and has also shown a synergistic effect with Tregs. Due to this suppressive effect, native HA inhibiting activation of innate immunity is dependent on the adaptive immune response. Considering the anti-inflammatory and immune tolerance properties, the native HA has been regarded as an attractive therapeutic component in the autoimmune diseases.

It is a fact that CD44 expression, on activated T cells, enhances their survival and functional activity, and long term autoreactivity of T cells after HA-based therapies should always be monitored. The researchers should precisely identify the central receptor that is activating in their experimental conditions as HA has wide receptors (mentioned above)

with different biological functions. Because of HA-containing formulations interact with CD44, TLRs and other HA associated receptors in vivo, which also interact with other ligands, such as MMPs, collagens, osteopontin, and others may have undesirable effects if their native functions are altered. We anticipate that HA degradation process in different tissues has different kinetics, so targeted therapies should evaluate their effects beyond the self-life of HA. Moreover, additional understanding is required to assess whether there is a relationship between HA size, length, localization and how signaling can be modulated by the concomitant use of different HA sizes, which is remain largely unexplored. Understanding these mechanisms with holistic approaches may provide opportunities to expand and enhance the application of HA-based drug/formulation therapeutic improvements, tissue engineering, and cell-based therapies. Furthermore, establishing the safety, mechanistic roles of molecular weight dependant HA in various ECM (especially brain, lung, eye, mucosal epithelial surfaces) using high throughput analysis (proteomics, glycomics) will help in further translation as a therapeutic. While preparing the development of HA-based formulations for biomedical applications, we urge researchers to consider the above important molecular weight, physicochemical, biological aspects for the safe and efficient therapies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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