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Hyaluronan biology: A complex balancing act of structure, function, location and context

Stavros Garantziotis, **Rashmin C. Savani**

Division of Intramural Research, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

Center for Pulmonary & Vascular Biology, Division of Neonatal-Perinatal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

Abstract

Cell-matrix interactions are fundamental to many developmental, homeostatic, immune and pathologic processes. Hyaluronan (HA), a critical component of the extracellular matrix (ECM) that regulates normal structural integrity and development, also regulates tissue responses during injury, repair, and regeneration. Though simple in its primary structure, HA regulates biological responses in a highly complex manner with balanced contributions from its molecular size and concentration, synthesis *versus* enzymatic and/or oxidative-nitrative fragmentation, interactions with key HA binding proteins and cell associated receptors, and its cell context-specific signaling. This review highlights the different, but inter-related factors that dictate the biological activity of HA and introduces the overarching themes that weave throughout this special issue of *Matrix Biology* on hyaluronan.

Keywords

Hyaluronan; Structure; Synthesis; Degradation; Receptors; Signaling

Introduction

The extracellular matrix (ECM) plays pivotal roles in cell self-renewal, fate, death, and signaling to regulate diverse functions including migration, proliferation, differentiation, tissue patterning, inflammation, and angiogenesis, among other homeostatic and pathological processes [1–3]. The complexity of ECM biology derives, in part, from the heterogeneity of its components, which participates in extraordinarily dynamic interactions with each other as well as with resident and migrating cells [4–6]. One of the most fascinating ECM components is hyaluronan (HA), a ubiquitously expressed glycosaminoglycan. While HA structure is deceptively simple with repeating disaccharide

Correspondence to Rashmin C. Savani: Department of Pediatrics – Mail Code 9063, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75390-9063, USA. rashmin.savani@utsouthwestern.edu.

Conflicts of interest

RCS is a co-founder of Eravon Therapeutics, Inc. that is focused on RHAMM-HA-based therapeutics. RCS also holds the William Buchanan Chair in Pediatrics at University of Texas Southwestern Medical Center. Neither author have any conflicts of interest related to this work.

chains of *N*-acetyl-glucosamine and glucuronic acid, its biology is wonderfully complex [7–10]. This special issue will lend insights into the cornucopia of mechanisms of HA biology and its biological diversity.

HA plays important roles in almost all areas of biology. Its interactions with cell receptors or other extracellular binding partners are important in cell and organ development, the response to tissue injury and inflammation, cell migration, cancer formation and resistance. A puzzling aspect of the existing literature is that, depending on context, HA has differing and sometimes contradictory effects on many biological functions; for example, pro- or anti-inflammatory, promoting and inhibiting either migration or cell proliferation. Research over the past several years has begun to shed light into the underlying mechanisms that explain these disparate effects. There are at least four key mechanisms by which HA function and activity are regulated (Fig. 1): 1) physical properties, size and molecular weight distribution; 2) chemical modifications, binding partners, crosslinking patterns, and macromolecular structure; 3) metabolism of HA synthesis and degradation, as well as regulation by the microenvironment; and 4) receptor engagement and downstream signaling. These mechanisms are not mutually exclusive. For example, HA metabolism alters size, distribution, and physicochemical properties, while microenvironmental regulation may affect crosslinking patterns and binding partner engagement. Thus, HA biology is best understood by determining how its individual effects contribute to a dynamic process that directs biology at the cellular, organ, and organismal levels.

Physical properties, size, and molecular weight distribution

High molecular weight (HMW) HA is a hydroviscous substance, a characteristic that dictates many of its macromolecular effects. Given its extremely hydrophilic nature, HA can bind up to 1000× its weight in water, thus forming a very voluminous, expanded random-coil structure in aqueous physiological solutions. Interestingly, however, the structure of HMW HA varies with the context in which it is found. Thus, the glycocalyx of vascular endothelial cells consists of a brush-like border [11], the HA surrounding the cumulus cells around the oocyte is tightly bound and circular [12], and when surrounding chondrocytes, HA gives rise to a biomechanical structure that protects cartilage [13]. These variations of HMW HA likely arise from the macromolecular structure imparted by interacting HA-binding proteins and proteoglycans. Thus, HA most likely acts as an insulating coat or spatial buffer, permitting lowmolecular-weight molecules such as electrolytes and nutrients to diffuse, but blocking high-molecularweight proteins or even cells from reaching the cell surface, as elegantly demonstrated in the red blood cell exclusion assay [14]. Further, the endothelial HA glycocalyx prevents inflammatory cells from directly interacting with the endothelium by maintaining a nonadhesive surface and, in platelets, HA prevents adherence and degranulation [15]. Degradation of HA, however, reduces its barrier function thus making the HA matrix much more permeable and accessible to cell interactions.

HA size is one of the major determinants of its activity. Several studies have demonstrated that HA >1 MDa is anti-inflammatory and promotes epithelial cell homeostasis and survival. Thus, HA, at doses of 1 mg/ml or greater in its HMW form, inhibits inflammatory cell chemotaxis, phagocytosis, elastase release, and respiratory burst activity [16–19]. HMW HA

also acts as an anti-inflammatory and anti-fibrotic agent in rheumatoid and osteoarthritis [20] and in the repair of tympanic membrane perforations [21]. Additionally, HMW HA accelerates cutaneous wound healing [22] and reduces adhesion formation after intra-abdominal surgery [23]. On the other hand, at lower concentrations and at lower molecular weights, fragmented HA (LMW HA) promotes monocyte maturation into macrophages as measured by production of insulin-like growth factor-1 [24] and IL-1β [25,26]. HA is also significantly increased during inflammatory conditions such as myocardial infarction, arthritis, and during transplant rejection [27–29]. Removal of HA by early treatment of myocardial infarction with hyaluronidase results in reduced myocardial fibrosis and infarct size [30]. HA fragments consist of LMW HA (<~500–700 kDa), and much smaller HA oligosaccharides (8–30-dimer lengths). Collectively, these fragments increase the expression of proinflammatory chemokines and iNOS in macrophage cell lines as well as in alveolar macrophages from injured lungs [25,31,32]. On the other hand, a hyaluronan tetrasaccharide blocks TLR2 activation and protects against ischemic brain injury [33]. The reasons for this pronounced sizedependency are not entirely clear. Several factors, including receptor clustering and engagement, cellular uptake, intra- *vs* extracellular signaling, and interactions with HA ligands such as heavy chains of inter-α-inhibitor (IαI), potentially related to linear or globular structures of different-sized HA chains, likely play a role.

HA modifications, binding partners, crosslinking patterns and macromolecular structure

The HA matrix can be best viewed as a canvas that is continually woven, unraveled, and decorated by dynamic patterns of hyaladherins which help shape HA-specific effects. Several ECM proteins interact directly with HA that significantly expand the repertoire of HA interactions with ECM components, and contribute to the diversity of HA responses. One of the best characterized examples is TSG-6. Heavy chain transfer from IαI to HA, as catalyzed by TSG-6, and further macromolecular stabilization by PTX3 change the conformation of HA [34]. The IαI heavy chains and PTX3 can also bind ECM proteins such as complement [35], and vitronectin [36], to indirectly attach these molecules onto the HA matrix complex. The decoration of HA with IαI heavy chains alters the adhesive properties of HA to invading cells, as do aggrecan and versican, which confers pro-and antiinflammatory activity. Importantly, the association of HA with these proteins changes dynamically during tissue injury, inflammation, and organ development, thus lending great plasticity and versatility to the biological properties of HA matrices. Importantly, these HA binding partners have significant functions beyond HA binding, thus vastly expanding the spectrum of HA matrix activity. These HA modifications can modulate their own interactions with these proteins. For example, the IαI heavy chain transfer onto HA chains is reversible with HMW HA, but irreversible when the heavy chains are transferred onto HA oligosaccharides [37]. Therefore, the evolution of HA sizes in response to injury may itself affect the interaction with proteins and may be a clearing mechanism for HA and HAassociated proteins.

HA metabolism (synthesis and degradation) and microenvironmental regulation

HA metabolism is intriguing in that one third of the body's HA undergoes turnover daily [38]. The balance of HA synthesis and breakdown of HA either by hyaluronidases or oxidative and nitrative stresses define HA content and form. HA production is regulated at multiple levels including enzyme expression, post-transcriptional control by micro-RNAs and antisense HAS expression, and/or posttranslational modifications. HA is synthesized by at least three distinct, apparently functionally redundant synthases. However, the HASs appear to have different biological roles depending on specific contexts [39] The relative functions of each HAS have been investigated using knockout mice. Global ablation of *Has2* is embryonic lethal and is associated with cardiac cushion defects. Conditional *Has2* knockout mice demonstrate a wide variety of functions including activity in lung epithelia to support resilience after injury, in lung fibroblasts to support invasiveness and fibrosis [40], and in bone marrow to support hematopoiesis [41]. On the other hand, *Has1* and *Has3* knockout mice are phenotypically less dramatic. *Has1* deficiency is associated with a failure to form the retrocalcaneal bursa [42], whereas *Has3* loss results in a migratory defect in vascular smooth muscle cells that results in decreased neointimal formation following endothelial injury [43], as well as abnormal neuronal activity and seizures [44]. Interestingly, the combined deficiency of *Has1* and *Has3* deficiency is associated with increased inflammation and accelerated wound closure of full thickness wounds [45]. Of particular interest, the naked mole rat has a unique *Has2* sequence, and concomitantly decreased hyaluronidase expression, resulting in HMW HA accumulation which is associated with longevity and greatly reduced tumorigenesis [46]. Pharmacologically, four-methylumbelliferone (4-MU) inhibits HA synthesis by depleting intracellular pools of UDP-glucuronic acid and decreasing *HAS2* and *HAS3* expression [47]. This tool has been used to determine the role of HA in tumor growth, inflammation, and autoimmunity [48].

HA catabolism is still incompletely understood. Several hyaluronidases have been identified; however, recent studies have cast doubt on the specificity or potency of the hyaluronidase activity of some of these proteins [49]. Among the most studied are Hyal1, Hyal2, and PH20. Hyal1 is an endoglycosidase that is active at an acidic pH and is found within lysosomes, serum, and extravascular space. A rare, genetically-induced deficiency in Hyal1 leads to the lysosomal storage disorder mucopolysaccharidosis IX and arthritis in children [50]. Conversely, in the skin, Hyal1 triggers adaptive immunity by generating HA oligosaccharides which activates TLR4 and CD44, the HA receptor, that leads to increased allergic inflammation via dendritic cell trafficking and improved clearance of bacterial skin infections [26,51–53]. Hyal2, a GPI-anchored protein with an acidic pH, hydrolyzes HMW HA into intermediate length HA that is internalized for further degradation by Hyal1. Hyal2 deficiency leads to high pre-weaning mortality as well as long-term cardiopulmonary dysfunction by 3 months of age. Additionally, Hyal2 is necessary for thrombopoiesis [15]. PH20 (or SPAM1), initially characterized as a hyaluronidase active at neutral and acidic pHs, is critical for fertilization of the oocyte by sperm. Subsequent studies demonstrated that this protein is also GPI-anchored and possesses signaling properties [54]. Pathologically, all three hyaluronidases are elevated in a variety of cancers and have been proposed as tumor

biomarkers [55]. Indeed, the growing evidence of HA accumulation within the tumor stroma and its contribution to cancer progression has prompted the development of PEGylated PH20 as an anti-cancer therapeutic currently undergoing clinical trials [56]. Recent evidence demonstrates that HA degradation *via* hyaluronidases can be used therapeutically in inflammatory and infectious diseases as well, thus vastly expanding the spectrum of effects of HA metabolism [57]. More recently, HYaluronan Binding protein Involved In HA Depolymerization (HYBID), also known as KIAA1199, is a deafnessassociated gene established as a hyaladherin with *endo*-β-N-acetylglucosaminidase-dependent HA degradation activity [58]. Increased HA degradation in synovial fibroblasts was dependent on HYBID thereby implicating it in inflammatory arthritic synovium [58]. Subsequent studies have noted that HYBID is associated with the endoplasmic reticulum and regulates cancer cell migration [59], and is responsible for the generation of HA fragments in Crohn's disease fibroblasts [60]. HYBID is highly expressed in the brain and HYBID knockout mice show memory dysfunction concurrent with an accumulation of HA in the hippocampus [61].

In addition to enzyme-mediated degradation, HA can be fragmented by reactive oxygen and nitrogen species. Oxygen radicals degrade HA *in vitro* [62–64], and activation of neutrophil myeloperoxidase can do the same *in vivo* [65]. Thus, HA fragments become part of the front-line defense to injury by activating innate and adaptive immunity.

Changes at the microenvironmental level also contribute to HA modification and activation of signaling pathways. For example, CD44, Hyal2 and the Na^+/H^+ exchanger (NHE1) are in close approximation in lipid rafts. Binding of HA to CD44 results in phosphorylation and activation of NHE1 to acidify the local environment which stimulates Hyal2 and Cathepsin B to modify HA and promote cell invasion [66].

HA receptor engagement and signaling

Several cell-associated HA receptors have been described and characterized in some detail. Differential expression of both content and timing, localization, functions, and unique activation pathways mediated by these receptors greatly expand the spectrum of HA action. CD44, the best characterized of all HA receptors, is a ubiquitous family of non-kinase, type 1 cellular hyaladherins with many described functions. CD44 mediates cell motility, inflammation, lymphocyte homing, and cell growth including tumorigenesis, but also participates in HA clearance and injury resolution. CD44 consists of 10 consistent exons and nine alternatively spliced exons resulting in a multitude of CD44 isoforms with distinct functions that remain incompletely elucidated. CD44 is promiscuous in its binding partners that include osteopontin, collagen, and fibronectin in addition to HA [67]. These properties result in the diverse function of CD44 in homeostasis and pathobiology.

The scavenging receptor Stabilin 2 or Hyaluronic Acid Receptor for Endocytosis (HARE) is a sinusoidal endothelial cell surface receptor in the liver, spleen, and lymph nodes that is responsible for the rapid clearance of HA, chondroitin sulfate and heparin from circulation [68,69]. Interestingly, ligand binding to Stabilin 2 activates intracellular signaling pathways including NFκB [70,71], and blocking Stabilin 2 is associated with a substantial increase in serum HA concentrations and an inhibition of tumor metastasis [72]. Most recently, Stabilin

2 has been implicated in the recycling of VWF and Factor VIII complex to regulate serum concentrations and modulate immune responses [73].

LYVE-1, structurally similar to CD44, is a marker for lymphatic *versus* blood endothelial cells, mediates dendritic and other inflammatory cell egress to the lymphatic lumen, and is necessary for antigen-specific T cell responses [74,75]. The unraveling of LYVE-1 functions reveals new horizons of HA-LYVE-1 interactions that may influence diverse actions including inflammation, transplantation, and drug delivery [76,77].

The Receptor for HA-Mediated Motility (RHAMM) or CD168 was first isolated as a 56–58 kDa protein from the supernatant of non-confluent embryonic chick heart fibroblasts and shown to regulate their ruffling and migration [78]. A number of critical functions, including the motility of thymocytes, lymphocytes, hematopoietic progenitor cells, malignant B lymphocytes, fibroblasts, smooth muscle cells, endothelial cells, and macrophages, as well as the regulation of MAP kinasemediated proliferative responses and cellular transformation have been ascribed to RHAMM [79–83]. Binding of HA to membrane RHAMM results in a transient burst of protein tyrosine phosphorylation, focal adhesion turnover [82], and regulation of the ERK kinase cascade through *Ras* [84]. A number of reports are consistent with a role for RHAMM in inflammatory and endothelial cell migration, thereby contributing to wound healing, *in vivo* angiogenesis and acute lung injury [79,85–87].

Layilin is a transmembrane, talin-binding protein homologous to C-type lectins that bind HA [88,89]. Layilin is key in maintaining gut epithelial integrity by regulating ZO-1, a tight junction protein, in response to a specific 35 kDa HA that is orally anti-inflammatory [90].

As noted above, HA interacts with CD44 and innate immune receptors such as TLR4 to activate the NLRP3 inflammasome [26,51–53,91]. HA signaling is thus dependent not only on the gene expression of specific receptors in a given cell, but also on receptor clustering and cell-specific intracellular signaling pathways activated downstream of the receptors. Many of these pathways remain to be mechanistically defined in more depth.

Organ development and injury responses

The ECM plays a pivotal role in organ development and cell differentiation [92,93]. A number of recent studies focused on the role of HA in organ and tissue differentiation, as well as in responses to tissue injury. These constitute a number of distinct processes that ultimately define the mechanisms of a disparate set of diseases that all appear to be influenced by HA. Indeed, HA regulates disease progression by regulating the inflammatory process and common themes are discernable that will likely lead to therapeutic approaches to ameliorate these conditions that carry high rates of morbidity and even mortality.

Therapeutic applications

The discovery that HMW HA had highly viscoelastic properties led to the development of clinical grade HMW HA as a therapeutic intervention for a wide array of therapeutic modalities including ophthalmic surgery, visco-supplementation for joint arthritis and pain control, wound healing, surgical adhesions, and tissue augmentation. HMW HA also serves

as a scaffold for tissue engineering, as a drug delivery vector, and cosmetic uses as fillers for skin wrinkling [94–99].

Using the primary and secondary structures of HA-binding proteins and receptors, a variety of probes and therapeutic interventions have been developed. Employing a phage display library, Mummert and colleagues developed Pep1, a 12-mer HA-binding peptide for curtailing inflammatory responses to skin hypersensitivity [100] as well as a biotinylated Pep1 to localize HA in tissue sections [101]. In addition, peptides that bind to HA and block their interactions with CD44 reduce inflammation, neovascularization, and cancer metastasis [102–104]. These studies provide proof of concept that limiting HA function in injured tissues is a viable approach for restraining inflammation.

Various domains within RHAMM have been proposed. However, the best characterized are the two HA-binding domains near the carboxy terminus of the protein [105]. Site-directed mutagenesis of these HA-binding domains indicates that the minimum binding requirement for HA is represented by B (X_7)B where B represents the basic amino acids arginine or lysine and X represents any non-acidic amino acid [106]. Identification of this HA-binding motif has allowed the creation of synthetic peptides with varying affinities for HA to competitively inhibit cell locomotion *in vitro* [106] and inflammation and fibrosis *in vivo* [107].

Knowledge gaps

There has been tremendous progress in HA biology over the past few years, as the contents of this Special Issue make abundantly clear. However, much remains to be elucidated. Below are some examples of “known unknowns” which may further explain the observed effects of hyaluronan:

- What are the precise polymer-receptor interactions of HA? It is still unclear how HA fragment size influences receptor activation. Sophisticated experiments suggest that tertiary or quaternary interactions of HA receptors with the HA matrix may be invoked to explain these interactions [108–110]. These studies pave the way for future studies.
- How are pro- or anti-inflammatory functions of LMW and HMW HA mediated and can contamination be safely ruled out as a contributing factor? Although in general LMW HA has pro-inflammatory properties, recent reports have questioned this, suggesting that contaminants such as LPS may, in fact, account for the previously discovered pro-inflammatory effects [111]. On the other hand, carefully conducted studies have demonstrated the pro-inflammatory functions of oligomeric HA [16]. The truth is likely somewhere in between. It is likely that some reports are confounded by contaminants, and it is equally possible that a lack of cell-specific receptors may account for negative results – ultimately, the effect of HA is likely to be the result of complex interactions between receptors, intracellular mediators, and the pathologic mechanisms being studied.
- Analysis of HA interactions with its receptors and effects on signaling at the microdomain level. It is very likely that the divergent effects of HA are partly

due to different receptor clusters with which it interacts, as well as their interactions with ECM binding partners of HA. Recent research is shedding light on these interactions, but much remains unknown.

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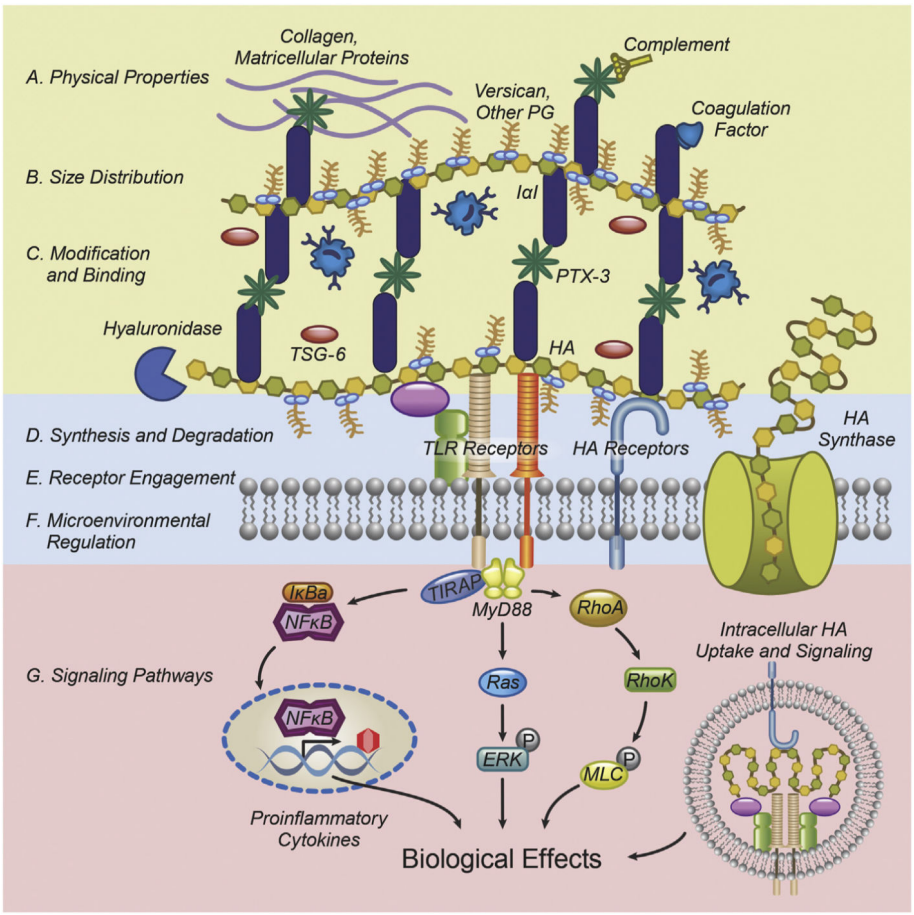

Fig. 1.

HA function and activity depend on key properties: physicochemical parameters, size, distribution, functional modifications and binding partners in the ECM; synthesis and degradation, microenvironmental regulation and receptor engagement in the vicinity of the plasma membrane; and intracellular signaling pathways. The complex interaction of these mechanisms manifests as distinct biological effects at the cell, organ, and organismal level.