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The hyaluronic acid–HDAC3–miRNA network in allergic inflammation

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We previously reported the anti-allergic effect of high molecular weight form of hyaluronic acid (HMW-HA). In doing so, HA targets CD44 and inhibits FcεRI signaling and cross-talk between epidermal growth factor receptor (EGFR) and FcεRI. We previously reported the role of histone deacetylases (HDACs) in allergic inflammation and allergic inflammation-promoted enhanced tumorigenic potential. We reported regulatory role of HA in the expression of HDAC3. In this review, we will discuss molecular mechanisms associated with anti-allergic effect of HA in relation with HDACs. The role of microRNAs (miRNAs) in allergic inflammation has been reported. We will also discuss the role of miRNAs in allergic inflammation in relation with HA-mediated anti-allergic effects.

Keywords: allergic inflammation, CD44, histone deacetylase-3, hyaluronic acid, micro RNA genes

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The Role of Hyaluronic Acid in Allergic Inflammation

Hyaluronic acid (HA), a major component of the extracellular matrix (ECM), plays a key role in regulating inflammation. HA enhances proteoglycan synthesis, reduces the production and activity of pro-inflammatory mediators and matrix metalloproteinases, and alters the behavior of immune cells (1). Inflammation is associated with accumulation and turnover of HA polymers by multiple cell types. Increased accumulation of HA has been demonstrated in joint tissue of rheumatoid arthritis (RA) patients (2); in lung disease, both in humans (3) and animal experimental models (4); in inflammatory liver disease; during vascular disease (5); in rejected kidney transplants (6) as well renal tissue of patients experiencing diabetic nephropathy (7); in the intestine of patients undergoing flares of inflammatory bowel disease (IBD) (8).

Circulating HA might be a marker of asthma control, as it correlates with airway resistance and has good sensitivity in the detection of impaired asthma control (9). The increased level of HA is correlated with asthma (10). In addition, HA appears to provide the scaffolding for inflammatory cell accumulation as well as for new collagen synthesis and deposition (10). HA deposition appears largely due to up-regulation of hyaluronan synthase 1 (HAS1) and hyaluronan synthase 2 (HAS2). HAS2 mRNA is markedly increased in asthmatic fibroblasts (11). In cases of inflammation, HA contains a variety of HA polymers with overlapping lengths and functions. HA exists as both a pro-and anti-inflammatory molecule *in vivo*, and these contradictory functions depend upon polymer length. High molecular weight form of hyaluronic acid (HMW-HA) elicits protective anti-inflammatory effects that protect lung epithelial cells from apoptosis and is protective against liver injury, acting to reduce pro-inflammatory cytokines in a T-cell-mediated injury model (12). HMW-HA inhibits macrophage proliferation and cytokine release, leading to decreased inflammation in the early wound of a preclinical post laminectomy rat model (13). HMW-HA exerts a negative effect on the activation of mitogen-activated protein kinase (MAPK) by allergic inflammation (14). HA with an average molecular mass <500 kDa can be considered a fragment. HA fragments with an average molecular weight of 200 kDa have been shown to stimulate chemokines, cytokines, growth

factors, proteases, and by macrophages (15–20). Organic contact sensitizers induce production of reactive oxygen species (ROS) and a concomitant breakdown of HA to pro-inflammatory low molecular weight fragments in the skin (21). Importantly, inhibition of either ROS-mediated or enzymatic HA breakdown prevents sensitization as well as elicitation of Chediak–Higashi Syndrome (CHS) (21). Mucus hyper secretion with elevated MUC5B mucin production is a pathologic feature in many airway diseases associated with oxidative stress (22). ROS-induced MUC5AC expression in normal human bronchial epithelial cells (NHBE) is dependent on HA depolymerization and epidermal growth factor receptor (EGFR)/MAPK activation (22). Although most of the work on low molecular weight HA (LMW-HA) fragments initially illustrated a pro-inflammatory response, a number of studies have shown that HA fragments can also be protective. In a murine model of colitis, intraperitoneal injection of HA <750 kDa protects colonic epithelium in a Toll-like receptor (TLR) 4-dependent manner (23). This functional difference between HAs of varying sizes is a matter of controversy since many studies have reported opposing results in regard to which type of HA can bring about cellular changes (24). These contradictory functions of HA, depending on the polymer length, may result from differential effects of these HA on HA receptors such as CD44 and receptor for HA-mediated motility (RHAMM). Exogenous HAs used in many studies are not homogenous with respect to size. Therefore, it is difficult to conclude that size alone determines the function of HAs of various sizes. These discrepancies may also be due to differences in experimental settings, purity of HA (25), and the possibility of diverse responses to HA depending on the cell type. Although many reports suggest anti-allergic effect of exogenous HA, the effect of endogenous HMW-HA on the allergic inflammation needs further investigation.

Hyaluronic acid levels are elevated in allergic animals and the increase correlates with the influx of inflammatory cells. This increase in HA levels is largely due to up-regulation of hyaluronidase-1 (HYAL-1) and hyaluronidase-2 (HYAL-2) (26). HYAL-1, -2, and -3 are expressed in airway epithelium and may operate in a coordinated fashion to depolymerize HA during allergen-induced asthmatic responses associated with up-regulation of tumor necrosis factor-alpha (TNF-alpha) and interleukin-1 beta (IL-1beta) (27). Degradation of HA by HYAL-1 primarily depends upon CD44 or other HA receptors to internalize HA fragments. Patients deficient in HYAL-1 have been reported with plasma HA levels at 40 times normal (28). The finding of HYAL-2 in complex with CD44 at the plasma membrane suggests that HA-binding proteins may enhance the activity of HA degrading enzymes, and CD44 binding may provide HYAL-2 with a preferable conformation of HA. IL-1beta exerts inflammatory activity via CD44 by the mediation of HA fragments derived from HA depolymerization (29).

CD44, a receptor for HA, expressed on CD4(+) T cells plays a critical role in the accumulation of antigen-specific Th2 cells, but not Th1 cells, in the airway and in the development of airway hyper-responsiveness (AHR) induced by antigen challenge (30). Airway fibroblasts from patients with asthma produced significantly increased concentrations of LMW-HA compared with those of normal fibroblasts (30). CD44, but not CD62L, is required for leukocyte extravasations during a Th2-type inflammatory response such as allergic dermatitis (31). HMW-HA inhibits interaction between IgE and FcεRI and between FcεRI and protein kinase C δ (PKCδ) during allergic inflammation (14). A role for CD44 in the regulation of allergic inflammation *in vivo* has been shown by studies in which anti-CD44 treatment inhibited the development of optimal contact allergic responses (32). CD44 has been shown to be responsible for the development of pulmonary eosinophilia (33). CD44-hyaluronan interaction is necessary for allergic asthma (34). The serum-derived hyaluronan-associated protein (SHAP)–HA complex has an inhibitory role in the development of airway hyper responsiveness and allergic airway inflammation which may be attributed, at least in part, to negative feedback mechanisms exerted by SHAP (35). It will be necessary to examine effects of HAs of various sizes on the expression and/or activity of CD44.

The Role of HDAC3 in Allergic Inflammation

Histone acetylation/deacetylation plays an important role in the regulation of inflammatory genes associated with allergic inflammation (36). Histone deacetylase-3 (HDAC3)-deficient macrophages are unable to activate almost half of the inflammatory gene expression program when stimulated with lipopolysaccharide (LPS) (37). Pulmonary inflammation is ameliorated in mice lacking HDAC3 in macrophages (38). The induction of cyclooxygenase (COX)-2, which occurs during allergic inflammation, is accompanied by degradation of HDAC1 (39). HDAC2 expression and activity are decreased in asthmatic subjects, smokers, and smoking asthmatic subjects (40). HDAC3, induced by antigen stimulation, interacts with FcεRI and is necessary for allergic inflammation both *in vitro* and *in vivo* (41). DNA methyl transferase I (DNMT1) acts as a negative regulator of allergic inflammation and the down-regulation of DNMT1 induces the expression of HDAC3 (42). HDAC3 is necessary for the induction of TNF-α, a cytokine increased during allergic inflammation, in cardiomyocytes during LPS stimulation (43). HDAC3 mediates allergic inflammation by regulating the expression of monocyte chemoattractant protein-1 (MCP1) (41). HMW-HA, but not LMW-HASs, decreases the expression of HDAC3 in human vascular endothelial cells to promote angiogenesis which is accompanied by allergic inflammation (44).

Role of miRNAs in Allergic Inflammation

microRNAs (miRNAs) are small (20–23 nucleotides), single-stranded non-coding RNAs that play important roles in the post-transcriptional regulation of gene expression in mammalian cells by regulating translation. Upon binding of their 5′ extremity (seed sequence encompassing nucleotides 2–7 or 2–8) with a complementary site located most of the time in the 3′ un-translated region (3′UTR) of target mRNAs, miRNAs alter gene expression by translational repression or RNA degradation (45). Because miRNAs regulate the expression of transcription factors that regulate the expression of miRNAs themselves, miRNAs form feedback loops. miR-384 and HDAC3 form a negative feedback loop to regulate allergic inflammation [(46), **Figure 1A**]. This suggests the involvement of miR-384 in the anti-allergic effect of HA. Several

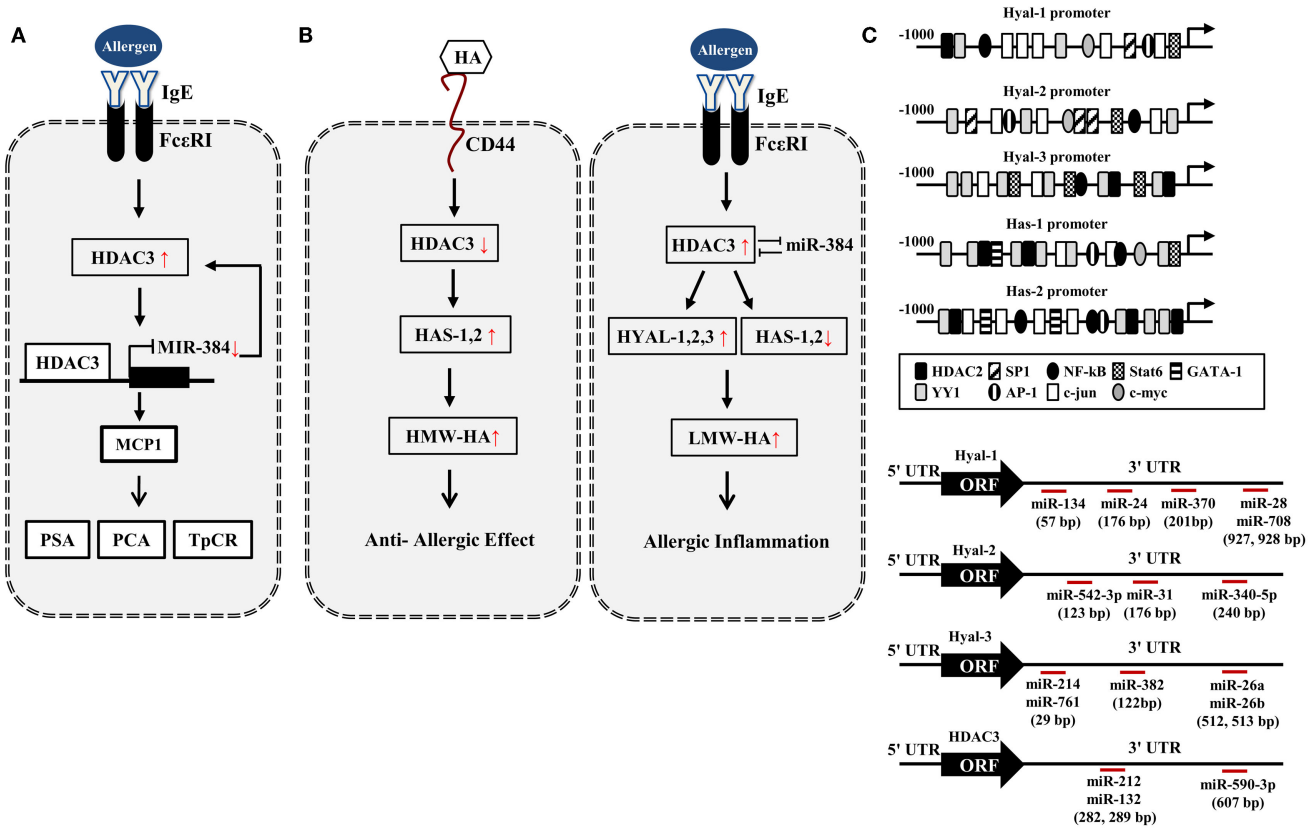

FIGURE 1 | HA–HDAC3–miRNA network in allergic inflammation. **(A)** Allergen activates FcεRI signaling and induces the expression of HDAC3. HDAC3, through forming a negative feedback loop with miR-384, regulates allergic inflammations *in vitro* and *in vivo*. PCA, passive cutaneous anaphylaxis; PSA, passive systemic anaphylaxis; TpCR, triphasic cutaneous reaction. **(B)** Potential effect of HA metabolism on allergic inflammation. HA fragments generated by HYALs may promote allergic inflammation while high MW-HA exerts anti-allergic inflammation by HASs. **(C)** Promoter analysis shows the binding of various transcriptional regulators to the promoter sequences of HYALs and HASs. Various miRNAs bind to the 3′-UTR of HYALs and HDAC3. UTR denotes un-translated region.

reports suggest role of HDACs in the expression regulation of miRNAs (47–50). miRNA let-7a regulates the expression of IL-13, a cytokine necessary for allergic lung disease (51). The down-regulation of miR-145 inhibits Th2 cytokine production and AHR (52). HA–CD44 interaction enhances the expression of miR-10b (53). miR-199a-3p and miR-34a miR-590-3p target CD44 (54, 55). Polymorphisms of CD44 3′UTR weaken the binding of miRNAs (55), suggesting that miRNAs regulate the expression of CD44. Given the fact that CD44 is involved in allergic inflammation, miRNAs may regulate HA-mediated anti-allergic inflammation.

The Regulation of HA Metabolism by miRNAs and HDAC3

In silico screening of expression data with predicted miR-23 target sites combined with *in vivo* testing, predicts HAS2 as novel direct target of miR-23 (56). miR-23a-3p in non-senescent fibroblasts leads to the decreased HAS2-mediated HA synthesis (57). This implies that miR-23 may regulate the production of HA during allergic inflammation. Based on our previous report (44), HA–CD44 may decrease the expression of HDAC3 (**Figure 1B**). Promoter analysis shows that HAS1 and HAS2 contain the binding sites for YY1, STAT6, NF-kB, and HDAC2 (**Figure 1C**), suggesting that the production of HA is under epigenetic regulation. Because HDAC3 shows an inverse relationship with HDAC2 (41), HDAC3 may regulate the expression of HASs to mediate allergic inflammation. Many reports suggest that HASs may increase the production of HMW-HA to exert anti-allergic effects (**Figure 1B**). Thus, the decreased expression of HDAC3 by HA–CD44 interaction may increase the expression of HAS1 and HAS2 to exert anti-allergic effect (**Figure 1B**). HDAC3, increased during allergic inflammation, may regulate the expression of HYALs and HASs differentially to increase the production of LMW-HA. This may result in allergic inflammation (**Figure 1B**).

Promoter analysis shows that HYAL-1, -2, and -3 contain binding sites for various transcriptional regulators including HDAC2 (**Figure 1C**), suggesting the role of HDAC3 in the expression regulation of HYALs. TargetScan analysis predicts the binding of miRNAs, such as miR-24,-28, -134, and -370, to the 3′-UTR sequences of HYAL-1 (**Figure 1C**). TargetScan analysis predicts the binding of various miRNAs to the 3′-UTR sequences of HYAL-2 and HYAL-3 (**Figure 1C**). These miRNAs may prevent the production of HA fragments by negatively regulating the expression of these HYALs. Thus, these miRNAs may mediate

allergic inflammation. TargetScan analysis predicts the binding of miR-212,-132, and -590 to the 3′-UTR of HDAC3 (**Figure 1C**). These miRNAs may exert anti-allergic effects by decreasing the expression of HDAC3. Taken together, miRNAs and HDAC3 may regulate allergic inflammation through their effects on HA metabolism.

Concluding Remarks and Perspectives

In this study, we show the possible involvement of miRNAs and HDAC3 in the regulation of HA metabolism. HA–HDAC3 –miRNA network described in this review may offer valuable mechanism for HA-mediated anti-allergic effects. For better understanding of HA-mediated anti-allergic effect, it will be necessary to identify downstream targets of HA. The downstream targets of HA would be valuable for the development of anti-allergic drugs. Identification of more miRNAs that regulate allergic inflammation in relation to HA and HDAC3 will be necessary for better understanding of HA-mediated anti-allergic inflammation.

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