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The role of hyaluronan in the pathobiology and treatment of respiratory disease

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Submitted 28 May 2015; accepted in final form 5 January 2016

Garantziotis S, Brezina M, Castelnuovo P, Drago L. The role of hyaluronan in the pathobiology and treatment of respiratory disease. Am J Physiol Lung Cell Mol Physiol 310: L785–L795, 2016. First published January 8, 2016; doi:10.1152/ajplung.00168.2015.—Hyaluronan, a ubiquitous naturally occurring glycosaminoglycan, is a major component of the extracellular matrix, where it participates in biological processes that include water homeostasis, cell-matrix signaling, tissue healing, inflammation, angiogenesis, and cell proliferation and migration. There are emerging data that hyaluronan and its degradation products have an important role in the pathobiology of the respiratory tract. We review the role of hyaluronan in respiratory diseases and present evidence from published literature and from clinical practice supporting hyaluronan as a novel treatment for respiratory diseases. Preliminary data show that aerosolized exogenous hyaluronan has beneficial activity against airway inflammation, protects against bronchial hyperreactivity and remodeling, and disrupts the biofilm associated with chronic infection. This suggests a role in airway diseases with a predominant inflammatory component such as rhinosinusitis, asthma, chronic obstructive pulmonary disease, cystic fibrosis, and primary ciliary dyskinesia. The potential for hyaluronan to complement conventional therapy will become clearer when data are available from controlled trials in larger patient populations.

asthma; bacterial biofilm; chronic obstructive pulmonary disease; cystic fibrosis; hyaluronan; inflammation; respiratory tract diseases

HYALURONAN (also known as hyaluronic acid, hyaluronate, or HA) is a naturally occurring major component of the extracellular matrix (ECM) and is found in high concentrations in the mammalian connective tissue, including in the lung (3, 47).

There is emerging evidence that HA and its degradation products have an important role in lung pathobiology. Furthermore, HA supplementation may have beneficial effects in lung inflammation and airway hyperresponsiveness (AHR). The use of HA in the treatment of airway disease introduces a new class of therapeutic agents, which might be described as matrix modulators, and is therefore a very exciting development. The present article summarizes the available evidence and emerging data supporting a role of HA as a novel therapeutic in inflammatory airway disease (Fig. 1). The first half of this review provides a concise summary of available mechanistic data on the biological effects of HA in airway biology of the host (HA in inflammatory signaling and remodeling pathways) and the microbiome (HA in the formation of microbial biofilm). In the second half we detail the available evidence on the translational application of HA in the treatment of upper and lower respiratory tract diseases. Finally, we make suggestions about existing gaps in our knowledge of HA biology and therapeutic potential. In aggregate, we aim to provide the interested reader with a thoughtful bench-to-bedside review of HA biology, and hopefully stimulate further research into matrix biology of the lung.

HA Metabolism in the Respiratory Tract

HA is a linear polysaccharide polymer consisting only of simple repeating disaccharide units of D-glucuronic acid and N-acetylg glucosamine (47, 94). Unlike other glycosaminoglycan-
cans such as chondroitin, heparin, heparan sulfate, and keratan sulfate, HA is synthesized by HA synthases at the inner surface of the plasma membrane, rather than in the Golgi apparatus within the cell. It further differs from other glycosaminoglycans in that it is an unmodified polysaccharide and is not attached to a protein core or further modified after secretion (47, 86, 88, 94). HA has exceptional hydrophilic characteristics and can bind approximately a thousand times its weight in water. After it is extruded onto the cell surface or into the intracellular matrix it produces a highly viscous gel that has an essential role in tissue homeostasis and biomechanical integrity (94). HA interacts with cell surfaces in two ways: by binding to specific cell-surface receptors and inducing intracellular signal transduction and by creating a matrix coat around the cell that may protect it from the environment and that allows other interactions with the cell.

HA is a unique molecule with properties dependent on its size. There is a clear distinction between high-molecular-weight HA (>1 million), which is the physiologically available form, and short-fragment HA (150,000–350,000 Da), produced during inflammation. High-molecular-weight HA has anti-inflammatory and antiangiogenic properties and promotes cell survival, in contrast to short-fragment HA, which has proinflammatory and proangiogenic properties and promotes cell migration (24, 81, 94). The products of digestion through hyaluronidases, HA oligosaccharides (3,000–7,000), have mixed effects, promoting inflammation in some situations and having a protective effect in others.

HA (which was short-fragment HA whenever the size was analyzed) has been detected in a number of lung diseases, both in the airways (bronchoalveolar lavage fluid) (10, 30, 59, 62, 66) and in the parenchyma (mainly in the perivascular space) (4, 5, 87, 97, 100). HA deposition and metabolism are thus a major component of inflammatory lung disease development, progression, and resolution (19, 20).

**HA Signaling in the Airway**

HA is localized in the areas of the airways that contribute to the development of hyperresponsiveness and inflammation. Distal airway imaging shows that HA is limited to the subepithelial layer in healthy individuals, in contrast to a much expanded accumulation of HA in the subepithelial spaces of severely asthmatic airways, which contributes to chronic inflammation and airway remodeling (62). Data from mouse models of acute and chronic lung inflammation and from human studies in asthmatic vs. healthy subjects show that short-fragment HA is being produced during the inflammatory process, localized in the alveolar walls and airway smooth muscle cells and around alveolar macrophages (10, 27, 30, 31, 62).

Extensive research in the last 20 years has shown that short-fragment HA signaling through receptors CD44 and RHAMM contributes to the accumulation of immune cells in inflammatory sites (69, 84, 102); furthermore, short-fragment HA activates immune cells and leads to the release of proinflammatory cytokines and metalloelastases and the inhibition of plasminogen activation (39–45, 70, 71, 73, 79). Importantly, HA also mediates experimentally induced AHR, with a clear size-dependent response. Short-fragment HA, but not high-molecular-weight HA or oligosaccharides of HA, replicates the inflammatory changes and hyperresponsiveness in the airway (30). Indeed, instillation of high-molecular-weight HA protects against AHR in experimental models (30, 58).

Short-fragment HA signaling in the lung. The induction of airway inflammation, hyperresponsiveness, and remodeling by short-fragment HA appears to be mediated by interaction of short-fragment HA with a CD44 and Toll-like receptor 4 (TLR4) complex, leading to the activation of an intracellular signaling cascade involving, as far as is known, MyD88, TIRAP, and NF-κB and the release of proinflammatory cyto-

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**Fig. 1. Concept of hyaluronan (HA) actions after environmental lung injury.** Lung injury mediates the release of short-fragment HA, which activates innate immune receptors and leads to inflammation, remodeling, hyperresponsiveness, and clinical symptoms. Bacterial biofilms develop because of defective clearance in injury and compound the clinical presentation. The perpetuation of this vicious cycle can be broken by modulating short-fragment HA signaling, e.g., with high-molecular-weight HA.
kines and chemokines (31, 61). Extracellular proteins, such as inter-α-inhibitor (IαI) and TNF-α stimulated gene 6 (TSG-6), are involved in the receptor binding process. IαI is a complex protein found abundantly in serum but also expressed in many tissues including lung epithelia, fibroblasts, and airway smooth muscle and was originally described as a HA cross-linker that is necessary for the development of the cumulus oophorus in the ovaries (105). TSG-6 mediates the transfer of IαI heavy chains onto HA (72), which leads to better affinity of HA to its receptors (104). IαI is necessary for the development of AHR after ozone or chlorine exposure (30, 58), and the formation of a pathological HA matrix consisting of HA-IαI heavy chains is one of the hallmarks of asthmatic airway remodeling (57); on the other hand, genetic absence of IαI seems to exacerbate allergic asthma (103), suggesting complex interactions of IαI in the pathogenesis of allergic inflammation. TSG-6 itself is capable of cross-linking HA molecules (7); however, this is inhibited by IαI heavy chains (6), again underscoring the complex interactions and delicate balance of HA binding in the inflammatory matrix. Genetic absence of TSG-6 blocks the complexing of IαI heavy chains with HA and reduces inflammation and AHR in allergic asthma (90). HA [in association with IαI (104)] promotes the adhesion of activated lymphocytes onto the endothelial surface (51) and migration into the tissue, as well as persistence of immune cells such as eosinophils to apoptotic stimuli (74), which may be why HA deposition in asthmatic tissue correlates with influx of immune cells (19, 20). Short-fragment HA signaling through the involvement of IαI, TSG-6, CD44, and TLR4 leads to the activation of small GTPases (RhoA, Rho kinase) and calcium channels and, ultimately, AHR (Fig. 2) (58), while antibody neutralization of IαI or addition of high-molecular-weight HA inhibits these effects (30, 58). HA accumulation is also involved in the pathogenesis of acute and chronic airway rejection in transplantation (22, 89, 92, 93), wherein short-fragment HA activates innate and adaptive immunity (89, 92) while high-molecular-weight HA ameliorates immune activation in this condition (93). It is not clear at this point why different sizes of HA have disparate biological effects. It may be that short-fragment HA leads to its particular effects because it occupies the “Goldilocks” position for optimal receptor assembly, whereas high-molecular-weight and oligosaccharide HA competitively inhibit short-fragment HA effects by selectively occupying receptors but being unable to engage the full receptor complement. Other mechanisms may be at play as well. For example, HA oligosaccharides can “poach” IαI heavy chains away from higher-molecular-weight

![Fig. 2. Theoretical model of HA-induced airway hyperresponsiveness (AHR) at the airway smooth muscle level. Short-fragment HA (sHA) engages CD44 and Toll-like receptor 4 (TLR4) (and perhaps other receptors as well) and activates RhoA, Rho kinase, and ERK in the cell. RhoA activation also leads to calcium influx into the cell. All components are necessary for the development of smooth muscle contraction and hyperresponsiveness. High-molecular-weight HA (HMW-HA) and inter-α-inhibitor (IαI)-blocking antibodies (Anti-IαI Ab) inhibit this process. oHA, oligosaccharide HA.]
HA, thus inhibiting the development of pathological HA matrix and binding of HA to its receptors (56). Although the exact mechanisms for the airway effects of HA are not completely understood, it is becoming apparent that short-fragment HA is overexpressed in lung injury, whether from asthma, pollution, inflammation, infection, or remodeling processes (4, 5, 10, 12, 19, 20, 26, 30, 32, 59, 101), leading to activation of receptors and downstream signaling pathways that directly affect lung function. This cycle of hyperresponsiveness and remodeling can be ameliorated by high-molecular-weight HA or HA oligosaccharides.

**High-molecular-weight HA signaling in the lung.** Studies in animal models of inflammatory lung conditions and in patients with asthma suggest a potential role for high-molecular-weight HA as a treatment for airway disease (16, 46, 77), including amelioration of inflammatory hyperresponsiveness, decreased expression of proinflammatory cytokines in a mouse model of allergic asthma (Fig. 3) (Garantziotis S, unpublished data), and protection against acute lung injury-induced inflammatory responses in mice (46). One possible mechanism is that high-molecular-weight HA promotes regulatory T-cell activity and suppression of adaptive immunity (8, 9), but high-molecular-weight HA also has stabilizing effects on airway myocytes and prevents repolarization and calcium flux-mediated contraction as well (58). In mouse models of chronic obstructive pulmonary disease (COPD), aerosolized HA protects endogenous HA in lung tissue against degradation by cigarette smoke-generated reactive oxygen species and produces significant reductions in air space enlargement and mitigation of elastic fiber injury, a marker for loss of alveoli (16). In humans, HA protects against exercise-induced AHR in patients with bronchial asthma (77).

Finally, high-molecular-weight HA applied to the airways may also protect the lung via interactions with the airway epithelium. Epithelium-expressed high-molecular-weight HA supports epithelial integrity in a lung injury model (46) through TLR2-4 signaling and thus reduces lung injury and remodeling. HA promotes ciliary beating through the engagement of RHAMM (28, 68). HA further interacts with the cystic fibrosis transmembrane conductance regulator (85) and may act as an airway carrier for IL-10, which blocks epithelial sodium channel activation, thus promoting mucus fluidity (59). The net effect of these actions, in addition to the shear hydrophilic potential of HA, may significantly improve airway clearance. HA also modifies epithelial immunity and the microbiome composition of the organism, which may also have relevance to the lung. For example, ingested HA isolated from human milk is a substrate for commensal bacteria (33) and enhances the innate intestinal epithelial antimicrobial defense, including protecting against *Salmonella enteritis*, by engaging with TLR4 and CD44 (38).

In summary, HA naturally occurs in the mammalian body, and its biology is strongly size dependent. Short-fragment HA is generated during tissue injury and mediates the inflammatory response, whereas high-molecular-weight HA ameliorates inflammation and lung injury in multiple models of respiratory disease. HA may therefore have potential as a novel treatment option in lung diseases where one or more of the following pathways are present: inflammation, epithelial survival, remod-
eling, or the microbiome. This suggests a possible role in asthma, COPD, cystic fibrosis (CF), primary ciliary dyskinesia (PCD), and other diseases with inflammation or epithelial dysfunction.

Role of HA in Bacterial Colonization and Biofilm Production

The biofilm is a complex microbial community protected by a self-produced polymeric matrix composed of polysaccharides, nucleic acid, and proteins (80). Biofilms firmly adhere to the surfaces of many materials used in a clinical setting. This is of particular relevance to airway infections, when biofilms occur on tracheostomy, endotracheal and tympanostomy tubes, sinus drainages, stents, valves, ossicular prostheses, and cochlear implants, but is also an issue with orthopedic prostheses, dental implants, catheters, and heart valves.

Role of the biofilm in infections. The role of biofilms in chronic infections is well established; ~65–80% of microbial infections in the body, including almost all chronic infections, involve bacterial biofilms (23). The principal biofilm-producing bacteria responsible for respiratory tract infections are *Streptococcus pneumoniae*, *S. pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa* (37, 95, 98). In studies of children with chronic or recurrent otitis and sinusitis media, there was evidence of mucosal biofilm formation in 54–95% of cases (21, 48).

Biofilm resistance to antimicrobials is an important issue for clinicians. Bacteria embedded in biofilms are significantly more resistant to antimicrobials, as the biofilm protects bacteria embedded within the matrix against antibiotics (23, 80, 99). Thus strategies to reduce or prevent bacterial colonization and biofilm formation are essential.

Interfering with the biofilm: antiadhesive and antibiofilm activity of HA. Evidence that HA has bacteriostatic activity against pathogens of the oral cavity (17, 78) prompted the evaluation of the in vitro antiadhesive and antibiofilm properties of HA against bacterial species responsible for respiratory tract infections. A proprietary preparation of HA 0.3% was tested at full strength and diluted to 50% for antibiofilm activity against *S. aureus*, *M. catarrhalis*, *H. influenzae*, and *S. pneumoniae* (25). The effect of HA on bacterial adhesion was assessed in Hep-2 cells, while antibiofilm activity was assessed by spectrophotometry following incubation of bacterial biofilms with HA. The study demonstrated that HA was able to interfere with bacterial adhesion to a cellular substrate, particularly at full strength. Biofilm produced by *S. aureus* was more sensitive to the antibiofilm action of HA than *H. influenzae* or *M. catarrhalis* (25) (Fig. 4). Thus HA has notable antiadhesive properties and moderate-to-high antibiofilm activity. “As bacterial adhesion to oral cells is the first step for colonization, these results further sustain the role of hyaluronic acid in the prevention of respiratory infections” (25).

Clinical Use of HA

There is increasing evidence that administration of aerosolized exogenous HA may be useful for the prevention of recurrent chronic rhinosinusitis and may have an anti-inflammatory and protective effect in COPD, asthma, CF, and other respiratory conditions. We address current experience with the use of high-molecular-weight HA in the clinical setting below.

HA as Treatment in the Upper Airways

The mucociliary system is among the primary defense mechanisms of the airways, and impairment of mucociliary clearance predisposes to chronic airway infections. Chronic rhinosinusitis is characterized by a marked decrease in mucociliary clearance. In addition to its anti-inflammatory activity and ability to promote bacterial biofilm disruption, recent evidence
that HA promotes mucociliary transport and helps to prevent the recurrence of chronic rhinosinusitis suggests a possible role for HA in diseases of the upper respiratory tract (18, 35, 65).

In a recent study, 75 children with recurrent upper respiratory tract infections were treated with aerosolized HA (0.3% solution in normal saline) or normal saline alone (64). HA improved the symptoms of rhinitis compared with saline alone (55.3% vs. 10.8%), postnasal drip (26.3% vs. 8.1%) and nasal dyspnea (31.6% vs. 10.8%), and reduced the presence of mycetes (26.3% vs. 8.1%) and biofilm (42.1% vs. 5.4%) (64). At 4 mo of treatment, ciliary motility was significantly improved in the HA group and adenoid hypertrophy, bacterial cell counts, and neutrophils were significantly reduced.

There is also evidence that aerosolized HA is beneficial in the postoperative management of patients with chronic rhinosinusitis by minimizing nasal crusting and edema and reducing the risk of infection, promoting restoration of the epithelium, mucociliary transport, and disruption of the microbial biofilm. In patients with nasal polyposis undergoing sinus surgery who were treated with HA (0.3% solution in saline) for 30 days from day 2 after surgery there were improvements in mucociliary clearance at 1 mo, and recipients of HA experienced a significantly lower incidence of rhinorrhea, lower nasal obstruction scores, and a lower presence of exudate on endoscopic examination (35). In another study of patients undergoing endoscopic sinus surgery for rhino-sinus remodeling, patients received HA (0.3% solution) nasal washes or saline alone for 15 days/mo over 3 mo. At the end of that period, HA was associated with significantly greater improvement in nasal dyspnea, mucociliary motility, presence of mycetes and appearance of nasal secretions and nasal mucosa, improvement in patency of the sinus ostia, reduction in mucosal edema, reduction in scarring, and improvement in the presence of biofilms (65). Finally, intranasal HA (0.3% solution) significantly improved short-term quality of life after sinus surgery for chronic rhinosinusitis with nasal polyposis, with improvements in both general and ENT-specific health status (13).

Although these studies suggest a useful role for aerosolized HA 0.3% solution in the management of chronic rhinosinusitis, further studies with larger patient numbers are needed to confirm these findings. A large, randomized study that plans to enroll at least 320 patients to investigate the use of HA in the postoperative period after functional endoscopic sinus surgery for chronic rhinosinusitis is currently underway in Germany, Italy, and Switzerland.

HA as Treatment in the Lower Airways

In addition to its role in the upper airways, HA has a functional role in various aspects of the bronchopulmonary pathology of the lower airways. Almost 20 years ago, simultaneous administration of HA was shown to reduce the number of infectious acute exacerbations in patients with chronic bronchitis (96). Since then, various preclinical studies in animal models and lung tissue have found increased levels of HA degradation products in the disease and demonstrated a protective effect for exogenous high-molecular-weight HA, mostly when administered as inhaled HA (30, 60). Beneficial effects of HA have been cited in the literature in connection with asthma, COPD, emphysema, CF, PCD, extrinsic allergic alveolitis, interstitial lung disease, sarcoidosis, idiopathic pulm-

AJP-Lang Cell Mol Physiol • doi:10.1152/ajplung.00168.2015 • www.ajplung.org
tients underwent 40 days of alternate-day inhalatory administration of HA. If the patient was receiving a prescribed mucolytic, this was omitted on the day of inhalation; all other medications remained unchanged. Seven of ten patients showed clinically relevant improvements in lung function parameters, with increases in forced expiratory volume in 1 s (FEV₁) of up to 10 percentage points in PCD patients and up to 25 percentage points in patients with CF (Fig. 5). Further study in a larger patient population would be very useful in elucidating the therapeutic potential of exogenous HA in CF.

Gaps in Our Knowledge and New Research Directions

Although our understanding of HA biology has dramatically increased over the past decade, many gaps remain to be filled. Furthermore, the clinical research into applications of HA in human disease is only now starting. Therefore, there are many outstanding questions still to be elucidated.

As mentioned above, high-molecular-weight HA and short-fragment HA share the same molecular structure and appear to engage the same receptors. It is therefore important to understand what drives the different signaling behaviors. Are there differences in the affinity to receptors? Does size affect compartmentalization of HA or affinity to Iot1 or TSG-6 and thus dictate the differential effects? A related question, for clinical applications, is the ideal size of HA as a treatment agent. A common, and reasonable, concern about the application of high-molecular-weight HA in inflammatory disease is that it will be degraded to short-fragment HA, thus “adding fuel to the fire” in the intermediate or long term. Yet there is no evidence of this effect in either animal models or human studies that employed high-molecular-weight HA over several weeks. Additionally, although short-fragment HA does not protect from exercise-induced hyperresponsiveness in human asthma, and induces inflammation in naive mice, it seems to protect from the development of COPD in animal models and is being currently tested in clinical COPD trials. Thus it appears that we still do not fully understand the scope of HA signaling or effects in disease. It may be that pharmacological application of HA through the airway reaches a different compartment than short-fragment HA released in the interstitial space in inflammation, and this may account for the observed differences. Alternatively, it could be that short-fragment HA has adverse effects in naive tissues but acts as an antagonist to stronger inflammatory triggers, such as endotoxin and cigarette smoke. However, these hypotheses are yet to be experimentally tested.

Another related question with translational implications is whether other HA sizes, such as oligosaccharides, or HA analogs such as heparosan may play a role in the modulation of airway inflammation or remodeling. A potential benefit of these molecules is that they are not further degradable, thus bypassing questions of metabolite actions and also potentially prolonging the half-life time of the drug. HA oligosaccharides have been proposed as anticancer therapy agents (reviewed in Refs. 49, 63), and companies are developing both oligosaccharides and heparosan for human use. Thus new medical-grade compounds may soon be available for study.

With reference to compounding, it will also be interesting to investigate possible application routes. Notably, one of the first studies to investigate HA in human airway disease used a subcutaneous delivery to reduce exacerbations in patients with chronic bronchitis (96). Currently, HA is only available as a solution of nebulization in Europe. However, dry powder and systemic application may alter bioavailability, tissue delivery kinetics, and ease of use and are worth considering as HA-based drug formulations are developed.

Finally, it is worth noting that much of HA biology has focused on inflammatory cells or remodeling but there are significant HA effects on other cells, e.g., endothelia (52, 83, 87, 91) and platelets (1, 36, 75). Thus a role for HA in diseases of endothelial dysfunction or coagulation disorders, as they occur in sepsis and multiorgan dysfunction, is very probable. With it, therapeutic applications could be also envisioned.
Even within the role of HA in remodeling, there are potential roles in vascular as much as airway remodeling. Indeed, HA metabolism and signaling have been found to play a role in pulmonary hypertension development (4, 5, 50, 55, 76). Thus it seems likely that therapeutic applications of HA may be expanded to the vascular compartment as well.

Summary and Conclusions

HA is a naturally occurring glycosaminoglycan macromolecule component of the ECM in the mammalian body, where it participates in a number of important biological processes, including water homeostasis, cell-matrix signaling, tissue healing, inflammatory processes, angiogenesis, and cell proliferation and migration. The physiological activity of HA is closely related to its molecular weight, and there is evidence that short-fragment HA, which is generated during tissue injury, augments inflammatory responses while high-molecular-weight HA may exert an anti-inflammatory and protective effect.

The anti-inflammatory, analgesic, and protective effects of exogenous HA are established in osteoarthritic conditions, where HA supplementation is widely accepted in clinical practice for the relief of pain and inflammation. Now there is increasing evidence that HA and its degradation products have an important role in the pathobiology of the respiratory tract and that the administration of aerosolized exogenous HA has beneficial activity against airway inflammation, protects against bronchial hyperreactivity and remodeling, and disrupts the biofilm associated with chronic infections. Exogenous HA may therefore be a novel treatment option to complement conventional medical or surgical therapy in diseases of the upper and lower respiratory tract that involve inflammation, epithelial survival, remodeling, and/or the microbiome, such as rhinosinusitis, asthma, COPD, CF and PCD, ARDS, or pulmonary hypertension. This role will become clearer when data are available from controlled trials in larger patient populations.

GRANTS

S. Garantziotis’ research is funded by the Division of Intramural Research, National Institute of Environmental Health Sciences, National Institutes of Health (NIH).

DISCLOSURES

Some of the information in the present article was presented as scientific talks at the symposium “The Role of Hyaluronan in Respiratory Diseases” at the 2014 European Respiratory Society Meeting, in Munich, Germany, sponsored by IBSA Farmaceutici Italia Srl. M. Brezina, P. Castelnuovo, and L. Drago received an honorarium as reimbursement for their participation in the symposium. In accordance with NIH regulations, no speaker fee was provided to S. Garantziotis.

AUTHOR CONTRIBUTIONS


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