



EDITORIAL



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Do NERDy eosinophils accelerate nasal polyp growth?

Since its description by Widal in 1922 and Max Samter in 1967, significant efforts have been made to understand the molecular underpinnings of NSAID-exacerbated respiratory disease (NERD), which comprises the pathognomonic triad of asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), and respiratory sensitivity to NSAID ingestion.¹ An intriguing aspect of this syndrome is that it is typically *acquired* in adulthood, and only a minority of patients with nasal polyps, asthma, or both conditions has sensitivity to NSAIDs. These observations would suggest the pathogenesis is neither a germ line metabolic syndrome nor a synergistic systemic manifestation of the component respiratory ailments. However, patients with NERD are well characterized as having more severe disease with rapid polyp regrowth after sinus surgery and more severe asthma. In this issue of *Allergy*, to identify differences between NERD nasal polyps and nasal polyps from aspirin tolerant individuals, Takabayashi et al utilized proteomic approaches to discover that L-plastin, a leukocyte-specific protein that cross-links actin filaments, was highly over-expressed in NERD. They further demonstrated that L-plastin was highly expressed by tissue-infiltrating eosinophils and down-regulation of L-plastin in an eosinophil cell line affected tissue factor surface localization as well as eosinophil transmigration.²

In prior work, it is well documented that patients with NERD, like many aspirin tolerant CRSwNP patients or severe asthmatics, exhibit elevated type 2 inflammation in their lungs or nasal tissue compared with control individuals without those conditions. However, when comparing NERD nasal polyps with those from aspirin tolerant CRSwNP, the levels of type 2 cytokines, epithelial-derived inducers of type 2 inflammation, and mast cell counts are not significantly different.³ In contrast, higher levels of eosinophil granule proteins have been reported in NERD than in aspirin tolerant CRSwNP—findings that had generally been interpreted as evidence that eosinophils were more highly activated in CRSwNP. In the paper by Takabayashi et al, they further demonstrated that L-plastin was highly expressed in eosinophils and correlated with eosinophil density. These results may thus suggest that L-plastin expression may reflect the enhanced eosinophil activation status in NERD nasal polyps.

Also increasingly recognized is the role that coagulation and fibrinolytic pathways play in the pathogenesis of these type 2 airway diseases. In prior work by Takabayashi, it was found that the stroma of a nasal polyp contains a dense fibrin mesh.⁴ Similarly in asthma, bronchiole lumen fibrin has been observed in patients who died of status asthmaticus and the activation of coagulation in the airway has been shown to enhance airway hyperresponsiveness.⁵ In their current article, Takabayashi et al demonstrate that the fibrin mesh density of NERD nasal polyps was denser than that observed

in non-NERD nasal polyps and was correlated with eosinophilia. To relate these findings to L-plastin, they utilized siRNA to modulate L-plastin expression in an eosinophil cell line and demonstrated that eosinophil surface localization of tissue factor by GM-CSF was dependent on the expression of L-plastin. Since tissue factor triggers the extrinsic coagulation pathway, the paper provides a mechanism by which eosinophil activation may fuel more aggressive nasal polyp growth or trigger airway hyperresponsiveness.

A central “hidden hand” in the mechanism proposed by Takabayashi et al is the role of GM-CSF which had previously found elevated in NERD nasal polyp tissue compared with those from aspirin tolerant CRSwNP.⁶ Furthermore, GM-CSF had independently been demonstrated to activate eosinophils through phosphorylation of L-plastin.⁷ Takabayashi et al further postulate that the source of GM-CSF in NERD nasal polyps may be the platelet-adherent leukocytes previously reported to be found at elevated levels in patients with NERD.⁸

What remains unclear from the current work is how it relates to the well-characterized derangements in systemic arachidonic acid metabolites that are measurable in NERD. Patients with NERD have systemic elevations in prostaglandin D2 (PGD2) along with reductions in the anti-inflammatory prostaglandin E2 (PGE2) and excessive production of pro-inflammatory cysteinyl leukotrienes, LTC4, LTD4, and LTE4. These eicosanoid mediators play important direct roles in bronchial constriction and vascular permeability through the prostaglandin receptors on smooth muscle in the lung and vascular system. They additionally have direct immune effects and play roles in the chemotaxis of important type 2 inflammatory cells such as eosinophils, mast cells, Th2 T cells, and innate lymphoid cells (ILC2) through their expression of CRTH2 (ligand PGD2). The source of these excess arachidonic acid metabolites has been attributed to inducible expression of prostaglandin synthetases in response to epithelial-derived initiators of type 2 inflammation like TSLP or IL-33 or to the paracrine effects of platelet-derived LTC4 synthase.⁹ Whether L-plastin expression and phosphorylation in eosinophils play a role in altering eicosanoid metabolism or may be induced by arachidonic acid metabolites will have to be further unraveled in the future.

Taken together, these studies are making progress in linking the immensely complex biological networks at the nexus of inflammation, coagulation, and lipid metabolism that mediate the distinct clinical phenotype patients with NERD exhibit (Figure S1). While the central inciting event(s) that cause eosinophils to upregulate L-plastin, platelets to adhere to leukocytes, and platelets to produce GM-CSF remain enigmatic, the human-based studies in this episode of *Allergy* and the highlighted studies provide insights into the pathologic underpinnings of this fascinating, though clinically vexing, condition.

CONFLICTS OF INTEREST

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