Possible involvement of platelets in patients with aspirin-exacerbated respiratory disease

Excessive production of cysteinyl leukotrienes (cysLTs) is a known contributor to the clinical symptoms experienced by patients with aspirin-exacerbated respiratory disease (AERD). Laidlaw et al (Blood 2012, doi:10.1182/blood-2011-10-384826) investigated the role of platelet-adherent leukocytes in cysLT overproduction in patients with AERD. Increased percentages of circulating neutrophils, eosinophils, and monocytes with adherent platelets were found in the blood of patients with AERD when compared with those seen in aspirin-tolerant control subjects. The adherent platelets resulted in higher levels of cysLT production by activated granulocytes. In fact, the platelets were responsible for the majority of the cysLTs produced by granulocytes. Further findings demonstrated a strong correlation between a marker of systemic cysLT production and the frequency of circulating platelet-adherent granulocytes, supporting a pathogenic role for increased numbers of platelet-adherent leukocytes in patients with AERD. Thus the authors speculate that antiplatelet therapies might be efficacious as treatment for AERD.

We asked lead author Tanya Laidlaw, from Brigham and Women’s Hospital, Boston, some questions about this article:

**JACI:** Your findings demonstrate a disturbance in the homeostasis of interactions between platelets and leukocytes that result in increased inflammatory cell accumulation and likely contribute to the overproduction of cysLTs in AERD. Do you think the interaction between platelets and leukocytes has a role in other inflammatory diseases? Is there a role for this interesting partnership in maintaining good health?

Dr. Laidlaw: Increases in circulating platelet-adherent leukocytes have been found in connection with several other inflammatory states, including acute myocardial infarction and inflammatory bowel disease, so we suspect that these platelet-leukocyte interactions in general are not unique to AERD. Although small numbers of platelet-adherent leukocytes are present in the circulation of healthy individuals as well, there is currently no evidence that the interactions of these adherent cells have a role in the maintenance of good health.

**JACI:** The mechanism for the increase in platelet-adherent leukocytes in AERD remains undetermined. What’s next in terms of your research in an effort to identify the mechanism?

Dr. Laidlaw: Our work will now focus on elucidating the underlying cause of the platelet-leukocyte adherence, in order to determine whether the primary abnormality lies on the side of the platelet, the leukocyte, or both. This information would help in guiding us to develop new treatments for AERD, perhaps aimed at suppressing platelet-leukocyte interactions.

Proteases from intraepithelial mast cells can enhance or inhibit airway hyperresponsiveness

Mast cells have a key role in the pathogenesis of allergic asthma, but the mechanisms by which they regulate airway narrowing in vivo remain to be elucidated. In mice deficient in the epithelial integrin αvβ6, a critical activator of latent TGF-β, Sugimoto et al (J Clin Invest 2012;122:748-58) discovered increased numbers of bronchial intraepithelial mast cells at baseline, yet the β6-deficient mice were protected from airway hyperreactivity in a model of allergic asthma. The protection was determined to result from increased expression of murine mast cell protease (mMCP) 4, a functional homolog to human chymase. The authors’ findings revealed an important role for TGF-β in regulating expression of mast cell proteases that can either enhance (mMCP-1) or inhibit (mMCP-4) airway contractility. The authors propose that delineation of the mechanism of chymase’s inhibitory activity could lead to novel treatment strategies in asthmatic patients.

Senior author Dean Sheppard, from the University of California, San Francisco, gave us this comment about the results:

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Climate change affects allergic respiratory diseases

In a review from the World Allergy Organization’s Special Committee on Climate Change and Allergy (WAO Journal, July 2011), D’Amato et al report that local climate changes coupled with air pollution and altered weather patterns might have a significant effect on the frequency and severity of allergic respiratory diseases. Climate changes have affected local plant growth, as well as pollen production and dispersion, resulting in earlier and longer pollination seasons that potentially could lead to increased duration of symptoms in sensitized subjects. Alterations in local vegetation and airborne allergens caused by climate change can result in new pollen sensitization and increased prevalence of allergic respiratory disease. Editors’ note: For those readers interested in this topic, further articles on the relationship among climate change, air pollution, and allergy can be found in the January 2012 issue of the Journal of Allergy and Clinical Immunology.

Committee chair Gennaro D’Amato, from High Specialty Hospital A. Cardarelli, Naples, Italy, commented on the importance of this topic: “Strategies to reduce climatic changes and air pollution are political in nature, but citizens and in particular health professionals and societies must raise their voices in the decision process to give strong support for clean policies on both national and international levels.”

Identiﬁcation of a common subgroup of patients with persistently noneosinophilic asthma

Subphenotyping of asthma is vital to improved understanding of disease pathogenesis and development of novel therapies. A cross-sectional analysis of pooled data from 995 asthmatic patients enrolled in multiple clinical trials conducted by the Asthma Clinical Research Network (McGrath et al, Am J Respir Crit Care Med, 20 Jan 2012) identiﬁed a large subgroup of participants with mild-to-moderate asthma and persistently noneosinophilic sputum samples over time but no evidence for a distinct neutrophilic subgroup. Although this noneosinophilic subgroup showed good response to bronchodilators, they responded poorly to intense combined anti-inﬂammatory therapy. Cluster analysis of the clinical characteristics of the persistently noneosinophilic subgroup revealed 3 distinct clusters, including a novel phenotype composed of nonobese male patients with childhood-onset asthma and Alternaria species sensitization. Because this common subgroup of patients with persistently noneosinophilic asthma responds poorly to current standard controller medications, McGrath et al propose that characterization of the eosinophilic phenotype in subjects enrolled in clinical studies might lead to better understanding of the disease mechanism.

News items are written by Patricia C. Fulkerson, MD, PhD.

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