Genetics Reveals Importance of Platelet Activating Factor in Asthma and Possibly Other Inflammatory States

Editorial

It is presently believed that multiple mediators and interactions among mediators are involved in the pathogenesis of asthma. How then is an important mediator identified? In the case of platelet activating factor (PAF), the history goes back a long way. PAF is a family of structurally related ether-linked phospholipids that are formed as a result of the action of phospholipase A_2 and acetyltransferase on membrane alkylacyl phospholipids. Its profound effects as a potent cause of airway microvascular leakage, bronchoconstriction, sustained increase in bronchial smooth muscle responsiveness, and pulmonary vasoconstriction share many features with clinical asthma and led to the suggestion that PAF could play an important role in the pathogenesis of asthma. Various cells in the airways produce PAF. In addition to airway cells, eosinophils, the major leukocytes that are recruited into asthmatic airways, are capable of producing large amounts of PAF. Furthermore, PAF causes the release of potent inflammatory mediators from eosinophils, and eosinophils from asthmatics exhibit a markedly increased sensitivity in their chemotactic response toward PAF compared with eosinophils from normal subjects. Finally, a significant increase in PAF receptors are reported in the lungs of asthmatic patients (1). These cascades suggest that important "positive feedback" mechanisms involving PAF may be at play in the "eosinophilic inflammation" that occurs in asthmatic airways.

Like many other inflammatory mediators, the proinflammatory actions of PAF are normally limited by the presence of PAF acetylhydrolase which catalyzes the degradation of PAF and related phospholipids, thus inactivating them and limiting their proinflammatory actions. A decrease in PAF acetylhydrolase would be predicted to exaggerate inflammatory and allergic responses involving PAF. Absent acetylhydrolase activity occurs in 4% of the Japanese population (2), and a report by Stafforini and associates in this issue of *The Journal* (3) shows that this inherited deficiency of PAF acetylhydrolase is the result of a point mutation in exon 9 and that this mutation abolishes enzymatic activity completely. This discovery has specific implications. First, it will allow rapid identification of a group of individuals predisposed to asthma. Second, it provides strong evidence that PAF plays a significant role in asthma. Early clinical studies with PAF receptor antagonists did not provide unequivocal evidence that PAF plays a pivotal role in asthma. Perhaps the clinical studies with PAF receptor inhibitors have not yet studied the appropriate group of patients. For example, when asthmatic patients die, pathological studies show thickening of the airways (from edema) and mucous plugs obstructing peripheral airways. PAF potently increases extravasation and causes hypersecretion, so it may be that this aspect of asthma is one on which to focus therapy with PAF antagonists.

Expression and secretion of inflammatory mediators is not obvious in healthy persons. Perhaps, a good experimental system for studying the role of PAF is in an animal with a knockout for the gene for PAF acetylhydrolase. Under these conditions, the role of PAF will be exaggerated and thus easier to define when inflammation is induced. Another method for exaggerating the effects of PAF is the administration of inhibitors to abolish enzymatic activity (4).

While a relatively small number of individuals of Japanese descent (4%) have a total absence of PAF acetylhydrolase activity, the heterozygous trait is present in 27% of the Japanese population (3). Even the smaller decrease in activity in heterozygotes could have significant physiologic effects in the presence of inflammatory bodily responses.

The enzyme deficiency in the Japanese study reported here has been implicated in asthma, but it is possible that PAF acetylhydrolase deficiency also plays a role in other diseases. PAF has been implicated as a mediator in adult experimental respiratory distress syndrome (ARDS), especially due to bacteremia (5). In experimental ischemia-induced reperfusion injury, PAF receptor antagonists have been shown to reduce lung injury after cardiopulmonary bypass (6). In pulmonary hypertension (7) and interstitial fibrosis induced by bleomycin (8), PAF receptor antagonists attenuate lung responses. Thus, there are a series of inflammatory diseases that need to be reexamined in the light of the present knowledge that genetic and acquired modifications of PAF acetylhydrolase could be important in the pathogenesis of pulmonary hypertension, pulmonary fibrosis, ARDS, and other inflammatory lung diseases. Similarly, diseases in other organs where PAF may play a role need to be reexamined with drug or "knockout" blockade of this enzyme that causes the inactivation of PAF.

One final comment: It is most interesting that the discovery of the importance of a molecule has been established definitively by identifying a limited population that genetically lacks the ability to break down this inflammatory mediator! It has opened a potentially profitable field of research of a molecule that has long been incriminated (but not previously definitively proven) to be important in various inflammatory states.

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