Phospholipase A2: quo vadis?

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The Journal of Rheumatology is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
Phospholipase A₂: Quo Vadis?

About a quarter of a century ago, the first human secretory nonpancreatic phospholipase A₂ (sPLA₂) was discovered and identified. sPLA₂ is a calcium-dependent, low molecular weight (13.99 kDa) enzyme that is highly cationic (pI > 10.5) and optimally active at neutral pH. It contains 124 amino acids preceded by a 20-residue membrane translocation signal. Gene coding for sPLA₂ is located on chromosome 1.

From early studies it became obvious that sPLA₂, which is expressed in a wide variety of cells, plays an important role in inflammatory processes. Expression of sPLA₂ was found to be enhanced by a variety of cytokines and mediators, including interleukin 1 (IL-1), tumor necrosis factor, IL-6, cAMP, and others, while it was blocked by glucocorticoids. In the last 2 decades, these discoveries have led to extensive studies. It is beyond the scope of this editorial to describe them in detail, but investigations can be divided artificially into 2 groups: (1) the physiologic and pathologic roles of sPLA₂, cellular origin, and controlling mechanisms, and (2) discovery of other PLA₂.

Briefly, the first sPLA₂, now called sPLA₂ IIA, was found to catalyze hydrolysis of the sn-2 position in glycerophospholipids, liberating free fatty acids, mainly arachidonic acid and lysophospholipids. These in turn convert into potent proinflammatory lipid mediators. Human lipoproteins were found to be good substrates for sPLA₂ IIA hydrolysis. sPLA₂ IIA also potentiates the antimicrobial activity of bactericidal/permeability-increasing protein. Subsequent studies further defined the roles of sPLA₂ IIA in systemic and acute inflammatory processes, host defense mechanisms, and signal transduction.

Initially limited to type IIA of sPLA₂, these studies have since expanded with the discovery of another type of sPLA₂. At present, there are at least 11 groups of PLA₂, including 7 identified in humans. Some of these, mainly types V, X, and II, almost certainly play a role in inflammatory processes, with marked similarity in function of sPLA₂ IIA, V, and X. Genes coding for those enzymes are almost all located in the gene cluster on chromosome 1 along with the genes for PLA₂ C, D, and E.

The above studies suggested that PLA₂ may be an attractive target for drug discoveries, since PLA₂ inhibition may lead to suppression of prostaglandins, leukotrienes, and platelet activating factor.

In this issue of *The Journal*, Bradley, et al describe the first oral use of a selective inhibitor of sPLA₂ IIA in 251 patients with active rheumatoid arthritis (RA). There were compelling reasons to initiate such a study. It was reported in 1988 that circulating sPLA₂ was markedly elevated in 25% of 51 patients with RA and that synovial fluid contained high levels of sPLA₂ activity. This study, further expanded to 212 RA patients in a prospective double-blind fashion, in fact showed marked correlation of high sPLA₂ to joint count, swollen joints, Lansbury index, low hemoglobin, and erythrocyte sedimentation rate. PLA₂ found in the circulation of patients with RA was purified and characterized using rheumatoid synovial fluid as a source.

Further, experimental studies have shown that an inflammatory reaction similar to RA synovitis can be induced by injections of sPLA₂ into animal joints and subcutaneous air pouches. Several types of cells found to produce and secrete sPLA₂ participate in a pathogenic articular process; they include osteoblasts, chondrocytes, macrophages, and others. Further, synovial fluid contains lipoproteins, which were found to be a good substrate for the hydrolysis by sPLA₂ IIA, V, and X. Thus, it was postulated that sPLA₂ may play a pathogenic role in the rheumatoid inflammatory process.

Bradley, et al reported that inhibitor LY 315920 given intravenously to patients with active RA alleviated their inflammatory condition. This was a short-term and probably unpublished study. On the other hand, the authors concentrated on an orally administered inhibitor, LY 333013, which in vivo converted into the bioactive compound. Various dosages were given to 251 patients for the maxi-
substantial interest to synthesize and test sPLA2 inhibitors. It would be of equal interest to address the issue of biocompatibility needs that inhibit type IIA and type V equally well. Such inhibitors divided into 2 groups, namely those with normal versus high sPLA2 in circulation. Penetration of the inhibitor into synovial fluid should be studied. Finally, one should remember that the inhibitor used by the authors had very weak inhibitory activity against sPLA2 group V and X and was inactive against cytosolic PLAs. It is quite possible that along with sPLA2 IIA these proinflammatory PLAs play an important role in RA inflammation. Thus, it would be of substantial interest to synthesize and test sPLA2 inhibitors that inhibit type IIA and type V equally well. Such inhibitors do exist. For example, LY 311727 inhibited both enzymes equally well. Certainly the issue of biocompatibility needs to be addressed.

Thus the importance of the article by Bradley, et al is not limited to presentation of original observations, but gives us seminal ideas on the direction of research on the role of sPLA2 in inflammation. Only then will we know: Quo vadis.

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REFERENCES


