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 discovered¹ and identified². 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 processes³-⁵. 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 others⁵-⁷, while it was blocked by glucocorticoids⁸. 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 mechanisms⁴,⁵,⁹-¹¹, and (2) discovery of other PLA₂¹²-¹⁸.

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 hydrolysis⁹, 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 transduction¹¹,¹³,¹⁸.

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 humans¹⁶. Some of these, mainly types V¹⁷, X¹², and III¹⁵, almost certainly play a role in inflammatory processes, with marked similarity in function of sPLA₂ IIA, V, and X¹³,¹⁴,¹⁸. Genes coding for those enzymes are almost all located in the gene cluster on chromosome I 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 factor¹⁰.

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)²⁰. 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 activity²¹. This study, further expanded to 212 RA patients in a prospective double-blind fashion²², 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 source²,²³-²⁵.

Further, experimental studies have shown that an inflammatory reaction similar to RA synovitis can be induced by injections of sPLA₂ into animal joints²⁶,²⁷ and subcutaneous air pouches²⁸. Several types of cells found to produce and secrete sPLA₂ participate in a pathogenic articular process; they include osteoblasts, chondrocytes, macrophages²⁹-³¹, 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 process³¹,³².

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-

See A randomized, double-blinded, placebo-controlled clinical trial of LY333013, a selective inhibitor of group II sPLA₂, in RA, page 417
imum of 12 weeks. All patients were receiving a variety of disease modifying antirheumatic drugs and nonsteroidal antiinflammatory drugs, and many were also receiving low dose steroids. The authors concluded that sPLA₂ inhibitor did not significantly affect RA activity.

Does this mean we have reached the end of the road? It seems to me that this is just the beginning. The authors correctly state that the bioconcentration of the inhibitor was possibly insufficient to inactivate sPLA₂ IIA in synovial fluid. In fact, in their study, inhibitor concentration in synovial fluid was not reported. One can envisage different avenues to study inhibitors of sPLA₂ IIA. The concentrations of sPLA₂ in the blood and synovial fluid versus various concentrations of inhibitor can be studied in experimental animal arthritis. Some in vivo studies have already been published. Experimental autoimmune encephalomyelitis in rats and mice was ameliorated by sPLA₂ inhibitor. It also suppressed the production and secretion of lipopolysaccharide-induced sPLA₂, prostaglandin E₂, and nitric oxide by glial cells. More relevant to the studies of Bradley, et al was the report that sPLA₂ inhibitory peptide markedly reduced severity of synovitis, bone erosion, and cartilage destruction in the human tumor necrosis factor transgenic mouse model of arthritis. The inhibitor also normalized high levels of circulating sPLA₂ detected in untreated mice.

It would be useful to conduct the clinical trial in patients with RA not treated with other agents that may inhibit either sPLA₂ and/or eicosanoids. The patients with RA should be 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 PLA₂. It is quite possible that along with sPLA₂ IIA these proinflammatory PLA₂ 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


