Phospholipase A\(_2\): Quo Vadis?

About a quarter of a century ago, the first human secretory nonpancreatic phospholipase A\(_2\) (sPLA\(_2\)) was discovered\(^1\) and identified\(^2\). sPLA\(_2\) 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 sPLA\(_2\) is located on chromosome 1.

From early studies it became obvious that sPLA\(_2\), which is expressed in a wide variety of cells, plays an important role in inflammatory processes\(^3^-^5\). Expression of sPLA\(_2\) 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\(^5^-^7\), while it was blocked by glucocorticoids\(^8\). 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 sPLA\(_2\), cellular origin, and controlling mechanisms\(^4,5,9^-^11\), and (2) discovery of other PLA\(_2\)\(^12^-^18\).

Briefly, the first sPLA\(_2\), now called sPLA\(_2\) 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 sPLA\(_2\) IIA hydrolysis\(^9\). sPLA\(_2\) IIA also potentiates the antimicrobial activity of bactericidal/permeability-increasing protein. Subsequent studies further defined the roles of sPLA\(_2\) IIA in systemic and acute inflammatory processes, host defense mechanisms, and signal transduction\(^11,13,18\).

Initially limited to type IIA of sPLA\(_2\), these studies have since expanded with the discovery of another type of sPLA\(_2\). At present, there are at least 11 groups of PLA\(_2\), including 7 identified in humans\(^16\). Some of these, mainly types V\(^17\), X\(^12\), and III\(^15\), almost certainly play a role in inflammatory processes, with marked similarity in function of sPLA\(_2\) IIA, V, and X\(^13,14,18\). Genes coding for those enzymes are almost all located in the gene cluster on chromosome I along with the genes for PLA\(_2\) C, D, and E.

The above studies suggested that PLA\(_2\) may be an attractive target for drug discoveries, since PLA\(_2\) inhibition may lead to suppression of prostaglandins, leukotrienes, and platelet activating factor\(^10\).

In this issue of *The Journal*, Bradley, et al describe the first oral use of a selective inhibitor of sPLA\(_2\) 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 sPLA\(_2\) was markedly elevated in 25% of 51 patients with RA and that synovial fluid contained high levels of sPLA\(_2\) activity\(^21\). This study, further expanded to 212 RA patients in a prospective double-blind fashion\(^22\), in fact showed marked correlation of high sPLA\(_2\) to joint count, swollen joints, Lansbury index, low hemoglobin, and erythrocyte sedimentation rate. PLA\(_2\) found in the circulation of patients with RA was purified and characterized using rheumatoid synovial fluid as a source\(^23^-^25\).

Further, experimental studies have shown that an inflammatory reaction similar to RA synovitis can be induced by injections of sPLA\(_2\) II into animal joints\(^26,27\) and subcutaneous air pouches\(^28\). Several types of cells found to produce and secrete sPLA\(_2\) participate in a pathogenic articular process; they include osteoblasts, chondrocytes, macrophages\(^29^-^31\), and others. Further, synovial fluid contains lipoproteins, which were found to be a good substrate for the hydrolysis by sPLA\(_2\) IIA, V, and X. Thus, it was postulated that sPLA\(_2\) may play a pathogenic role in the rheumatoid inflammatory process\(^31,32\).

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-
Quo vadis. Substantial interest to synthesize and test sPLA2 inhibitors important role in RA inflammation. Thus, it would be of do exist. For example, LY 311727 inhibited both enzymes that inhibit type IIA and type V equally well. Such inhibitors have 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 PL2. It is quite possible that along with sPLA2 IIA these proinflammatory PL2 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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