**Leader**

**Synovial fluid phospholipase A₂s and inflammation**

**SUMMARY**  The activation of phospholipase A₂ is believed to have an important role in the inflammatory process owing to its induction of eicosanoids, platelet activating factor, and other mediators. Soluble phospholipase A₂ has been associated with exudates in different inflammatory conditions. In this review the general physiology and control of this enzyme and, in particular, the most recent findings on human synovial fluid phospholipase A₂s are discussed.

The phospholipases are a group of enzymes widely distributed throughout nature, whose generic name indicates their common property of catalysing the hydrolysis of phospholipids.¹ Figure 1 shows the classification of phospholipases based on their site of attack. The phospholipases A are classified according to their hydrolysis of the 1-acyl ester (phospholipase A₁) or the 2-acyl ester (phospholipase A₂). Phospholipase B hydrolyses both acyl groups, phospholipase C cleaves the glycerol phosphate bond, and phospholipase D removes the base group.¹ Phospholipase A₂ was the first of the phospholipases to be recognised over a century ago when Bokay found that phosphatidylcholine was degraded by a component of pancreatic juice²; which is now known to be the pancreatic phospholipase A₂. In mammalian cells phospholipase A₂ can be found as membrane associated and extracellular (soluble), thought to be released from lysosomal stores upon cell stimulation.³ Phospholipase A₂ has received much attention because of its putative involvement in the signal transduction process that enables leucocytes to effect a repertoire of responses crucial to the development of inflammation.¹ Therefore it may be implicated in tissue injury associated with various diseases, such as rheumatoid arthritis,⁴⁻⁷ psoriasis,⁸ and adult respiratory distress syndrome.⁹ Under normal conditions the cellular content of free arachidonic acid is low. It is stored within the cell membrane in sterified form almost exclusively at the 2 position of phospholipids. The liberation of arachidonic acid during the process of cell activation is widely believed to be the rate controlling step in the production of biologically potent eicosanoids by inflammatory cells.¹⁰ Free arachidonic acid is rapidly metabolised by cyclooxygenase to form prostanodins and thromboxanes or by lipoxygenase to form hydroxy fatty acids (hydroxyeicosatetraenoic acids) and leucotrienes.¹⁰⁻¹² Prostaglandin E₂ is a potent vasodilator and hyperalgesic agent that may cause erythema, oedema, and pain.¹³ It has also been implicated in bone resorption in rheumatoid arthritis.¹⁴ Leucotriene B₄, ¹²-hydroxyeicosatetraenoic acid, and 5-hydroxyeicosatetraenoic acid act as chemotactic agents for neutrophils and eosinophils and may contribute to the cellular migration into the rheumatic joint.¹⁵⁻¹⁶ Phospholipase A₂ itself may also have a role in inflammation; in rabbits purified exogenous phospholipase A₂ induces profound inflammatory lesions following intratracheal,¹⁷ intradermal,¹⁸ or intra-articular injection.¹⁹

**Fig. 1** Classification of phospholipases according to site of hydrolysis. AA = arachidonic acid.
A2 was a calcium requiring protein of molecular weight 11 000 with a neutral pH optimum. More recently, Gonzalez-Buritica and coworkers presented evidence for the presence of at least two phospholipase A2s in rheumatoid synovial fluid, one soluble or extracellular, present in the cell free fraction of synovial fluid and another, cell associated in mononuclear cells and neutrophils from synovial fluid. They suggested that a proinflammatory phospholipase A2 must be able to release arachidonic acid rather than other fatty acids from the labelled substrate. Another known mediator of inflammation, interleukin 1, which has been identified in rheumatoid synovial fluid, has the unique ability among interleukins to increase phospholipase A2 activity in chondrocytes and synovial cells. Therefore phospholipase A2 may act as a mediator of the inflammatory actions of interleukin 1. It has been reported that rheumatoid arthritis peripheral blood leucocytes contain more phospholipase A2 than those from healthy controls, and that serum concentrations of phospholipase A2 correlate with disease activity. It has not been shown, however, whether the leucocyte related phospholipase A2 belongs to the membrane bound or to the soluble variety.

The anti-inflammatory efficacy of certain steroidal and non-steroidal drugs may partially reside in their ability to inactivate extracellular phospholipase A2. The anti-inflammatory effect of corticosteroids has been explained by the induction of lipocortin synthesis, and lipocortin has been claimed to be a specific, non-competitive inhibitor of phospholipase A2. It has recently been reported that some patients with systemic lupus erythematosus and rheumatoid arthritis have antibodies against lipocortin. The possibility that inhibition of lipocortin leads to an increase of phospholipase A2 activity in arthritic patients should thus be considered. There is no conclusive evidence that aspirin and related non-steroidal anti-inflammatory drugs have effects on phospholipase A2, though indomethacin has been reported to inhibit phospholipase A2 through inhibition of calcium transport.

On the other hand, hydroxychloroquine and meperidine, two antimalarials used with some success in the treatment of systemic lupus erythematosus and rheumatoid arthritis, among other actions, inhibit phospholipase A2 activity and perhaps that explains part of their anti-inflammatory actions. In the search for the physiological control of phospholipase A2 two new developments seem to have relevance—namely, the calpactins or calcium dependent phospholipid and actin binding protein and, secondly, the phospholipase A2 activating protein. The calpactins inhibit phospholipase A2 by sequestering the phospholipid substrate, whereas the phospholipase A2 activating protein activates phospholipase A2 through an unknown mechanism. Free arachidonic acid also inhibits phospholipase A2, acting as a negative feedback.

Our knowledge of the mechanisms of inflammation and the treatment of inflammatory diseases is likely to increase substantially in the next few years. New insights into the biochemistry and the pharmacological modulation of the process should open new avenues and a promising future in the prevention and treatment of the so called autoimmune diseases.

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References

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12. Hamberg M, Samuelsson B. Prostaglandin endoperoxides
    n cerebral transformation of arachidonic acid in human platelets.
    arachidonate cyclooxygenase products by rheumatoid and non-
    rheumatoid synovial lining in non-proliferative organ culture.
    production by rheumatoid synovial cells: stimulation by a factor
    399-404.
15. Serhan C N, Smolen J E, Korchak H M, Weissmann G.
    Leukotriene B4 is a complete secretagogue in human neutrophils:
    calcium translocation in liposomes and kinetics of
    neutrophil activation. In: Samuelsson B, Paoletti R, Ramwell
    P, eds. Advances in prostaglandin, thromboxane and leukotriene
    Textbook of immunopharmacology. London: Blackwell Scien-
17. Shaw J O, Roberts M F, Ulevitch R J, Henson P, Dennis E A.
    Phospholipase A2 contamination of cobra venom factor prepa-
18. Pruzanski W, Vadas P, Fornasier V. Inflammatory effect of
    intradermal administration of soluble phospholipase A2 in
19. Vadas P, Pruzanski W, Fornasier V, Kim J. Acute inflamma-
    tion induced by intradermal and intraarticular injection of
20. Gonzalez-Buritica H, Smith D M, Turner R A. Characterisa-
    tion of pro-inflammatory phospholipases A2 in rheumatoid
    Difference in substrate specificity for synovial fluid phospholi-
    pase A2 in rheumatoid and osteoarthritis. Arthritis Rheum
    1988; 31: S60.
22. Gonzalez-Buritica H, Smith D M, Turner R A. Characterisa-
    tion of soluble and cell associated phospholipase A2 from
23. Chang J, Gilman S C, Lewis A J. Interleukin 1 activates
    phospholipase A2 in rabbit chondrocytes: a possible signal for
    Ebsworth N M, Russell G G. In vitro activation of human
    chondrocytes and synoviocytes by a human interleukin-1 like
    necrosis factor and interleukin 1 both stimulate human synovial
    cell arachidonic acid release and phospholipid metabolism.
    P. Phospholipase A2 correlates with disease activity in rheuma-
    autoantibody for phospholipase inhibitory protein, lipomodu-
    lin, in patients with rheumatic diseases. Proc Natl Acad Sci USA
    L, Persico P. Macrocortin: a polypeptide causing the antiphos-
    R J. Anti-lipocortin autoantibody responses in severe RA
    patients treated with pulse intravenous methylprednisolone. Br
    J Rheumatol 1987; 26 (suppl 2): 76.
30. Franson R C, Eisen D, Jesse R, Lanni C. Inhibition of highly
    purified mammalian phospholipases A2 by non-steroidal anti-
    inflammatory agents. Modulation by calcium ions. Biochem J
    Evidence that antimalarial drugs act as phospholipid analogue
    inhibitors of key pathways of phospholipid metabolism in
32. Davidson F F, Dennis E A, Powell M, Glenney J R. Inhibition of
    phospholipase A2 by lipocortins and calpactins. J Biol Chem
33. Bomalaski J S, Baker D, Brophy L, Resurreccion N V, Clark
    M L. A phospholipase A2 activating protein (PLAP) isolated from
    rheumatoid synovial fluid stimulates human neutrophil
    release of lysosomal enzymes and superoxide, and erythrocyte
34. Ballou L R, Cheung W Y. Human platelet phospholipase A2,
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