The Eicosanoids, a Family of Bioactive Compounds

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The eicosanoids are a family of bioactive compounds that derive from the enzymatic oxygenation of arachidonic acid (AA). Prostaglandins, leukotrienes, thromboxane, lipoxins, are all members of the eicosanoid family. The eicosanoids are biomedically important because they mediate all four signs of inflammation, namely heat, redness, swelling and pain. Controlling the formation of eicosanoids has been found to be of great benefit for the treatment of acute and chronic inflammatory diseases.

(Results & Publications sections, up to 2011 – The Eicosanoid Research Division – www.balsinde.org)

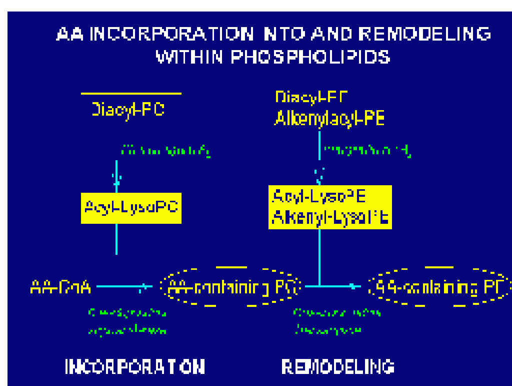
AA seldom occurs in free form in resting cells. It is mostly found esterified at the sn-2 position of cellular phospholipids. This is so because in resting cells the mechanisms for AA incorporation into phospholipids dominate over the hydrolytic mechanism for AA release. Thus, due to the very low level of free AA, unstimulated cells produce only modest amounts of eicosanoids.

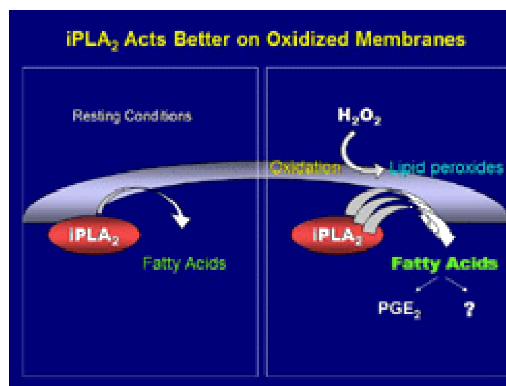
AA incorporation into phospholipids is critically dependent on the availability of lysophospholipid acceptors, particularly lysophosphatidylcholine (lysoPC). Once the AA is initially incorporated into lysoPC by the action of CoA-dependent acyltransferases, it is then transferred to certain lysophospholipids, particularly the ethanolamine lysophospholipids (lysoPE). Thus, for the AA to be efficiently incorporated into phospholipids, two kinds of lysophospholipid acceptors should be readily available. These acceptors are provided by intracellular phospholipase A_2 (PLA_2) enzymes. A particular PLA_2 form, called Group VIA calcium-independent PLA_2 (iPLA_2-VIA), appears to play a key role in regulating the steady-state level of lysoPC in some cells. These include phagocytes, which are the cells we work with. In recent years it has become clear that, in addition to iPLA_2-VIA, other PLA_2s may also be involved in the control of lysophospholipid formation. We are currently trying to determine the molecular nature of these PLA_2s. We are also interested in dissecting other regulatory aspects of lysophospholipid-limited AA incorporation into membrane phospholipids, as well as in delineating the general role of iPLA_2-VIA in homeostatic phospholipid metabolism.

Apart from its homeostatic functions, iPLA_2-VIA may also play other roles in cells. For instance, recent evidence suggests the participation of this enzyme in the destruction of membrane phospholipid subsequent to the cells entering apoptosis (programed cell death). Apoptosis occurs in response to many factors, and one of them is oxidative damage. This is a condition that frequently accompanies a variety of inflammatory states. Phagocytic cells produce substances with high oxidant capacity during inactivation and phagocytosis of invading pathogens. An uncontrolled production of these substances may negatively impact on phagocytic cell function and compromise the resolution of inflammation.

Oxidative damage results in the loss of significant quantities of free fatty acids from cells. We have shown that in U937 phagocytic cells, iPLA_2-VIA mediates phospholipid hydrolysis and fatty acid release in response to hydrogen peroxide exposure. We are currently trying to elucidate the molecular mechanisms leading to augmented iPLA_2-VIA activity during oxidative stress and the ensuing apoptotic response. The ultimate goal of these studies is to provide clues to understand the molecular processes involved in oxidative damage, which in turn may help uncover new molecular targets with possible therapeutic potential.

On the other hand, exposure of phagocytic cells to immunoinflammatory stimuli that act through cell surface receptors results in the tightly-controlled activation of another intracellular PLA_2, the Group IVA cytosolic $PLA_2\alpha$ ($cPLA_2\alpha$). Under these conditions, the rate of AA liberation clearly exceeds that of reincorporation into phospholipids; hence, net accumulation of free AA occurs that is followed by its conversion into different classes of eicosanoids. In many instances, a third PLA_2 form participates in the process, usually acting to amplify the $cPLA_2\alpha$-regulated AA mobilization response. This is the inducible secreted PLA_2 ($sPLA_2$), of which there are several group types. The most prominent with regard to AA release are those of Groups IIA and V. Interestingly, cross-talk appears to exist between $cPLA_2\alpha$ and $sPLA_2$ during cellular activation. We are currently characterizing different molecular aspects of this cross-talk in phagocytes, and have also begun studies to localize the intracellular sites of action of all these PLA_2s during cellular stimulation by different agonists.





Cyclooxygenase-2 (COX-2) is an inducible enzyme that initiates the biosynthesis of prostaglandins by converting free arachidonic acid into the precursor prostaglandin H2. COX-2 plays important roles in inflammation and, more recently, has also been demonstrated to play a role in tumor progression by regulating angiogenesis. Our previous studies established that in murine macrophages, COX-2 gene expression is dependent upon the activity of another inducible enzyme, the aforementioned Group V PLA_2. The molecular mechanism implicated in the regulation of COX-2 expression and activity by Group V PLA_2 remains unknown. Defining such a mechanism is another of the goals of our current research efforts.

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