Work in our laboratory aims at understanding different aspects of the regulation of eicosanoid biosynthesis in cells of immunoinflammatory origin. The eicosanoids are a family of substances with strong pro-inflammatory activity that derive from the enzymatic oxygenation of arachidonic acid (AA). Prostaglandins, leukotrienes, lipoxins, are all members of the eicosanoid family. In cells, AA seldom occurs in free fatty acid form, and is almost always found esterified at the sn-2 position of glycerophospholipids. Thus, it has to be removed from there before any eicosanoid synthesis can occur. The enzymes involved in such a removal are the phospholipase A2s. Our laboratory devotes a special emphasis to understanding the regulation of phospholipase A2 in cells exposed to stimuli of the innate immune response.

Another family of enzymes that we are interested in is the cyclooxygenase family, of which there are only two members in mammalian cells. We are currently studying the one called cyclooxygenase-2, an enzyme whose expression is greatly induced during inflammation. Cyclooxygenase-2 catalyzes the addition of two oxygen molecules to AA, to form prostaglandin G2 first, and later prostaglandin H2. The latter is the universal precursor of all other prostaglandin molecules. We are particularly interested in the regulation of cyclooxygenase-2 induction by proinflammatory lipid mediators that are produced downstream of phospholipase A2 activation. To elucidate the different lipid mediators produced under the different conditions we utilize state-of-the-art mass spectrometry techniques.

Finally, our laboratory is also interested in the design, synthesis and assay of molecules with anti-phospholipase A2 activity. We study inhibitors of different chemical structures in an attempt to define structure-activity relationships. To this end we have developed specific assay systems and plan to utilize animal models as well.

In summary, our group utilizes a variety of experimental techniques, from cellular biochemistry and molecular cell biology to organic chemistry and mass spectrometry to study diverse pathophysiological situations that involve the participation of proinflammatory lipid mediators.

REFERENCES


