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Introduction to Lipid Biochemistry

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Introduction

Lipids are ancient and ubiquitous molecules. Among the three domains of life on our planet, differences are found in the lipid chemistry of the predominant building blocks (e.g., L-glycerol vs D-glycerol, ester vs ether linkages, among others) between life forms, but even many viruses possess lipid envelopes until they are shed inside the host cell. The evolution of an outer membrane composed of a complex mixture of lipids, proteins, and carbohydrates is one of the defining characteristics of an organism. Lipids are generated from two basic biosynthetic pathways [1]. The first involves the condensation of acyl carrier protein intermediates derived from malonyl-CoA and acetyl-CoA esters and a carbanion intermediate. This pathway leads to diverse classes of lipids that contain fatty acyl chains, including fatty acids, phospholipids, and glycerolipids. The polyketide biosynthetic pathway provides a similar pathway in plants. The second biosynthetic pathway involves the condensation of branched-chain five-carbon pyrophosphate intermediates and a carbocation intermediate. This latter pathway is the source of all lipid species identified in the Archaea domain as well as a number of species in the Bacteria and Eukarya domains, such as prenols, sterols, and arachaeal glycerolipids, glycerophospholipids, and sphingolipids. Appreciation of these biosynthetic sources has been suggested by some investigators to be a more enlightened definition of what molecules are lipids as opposed to classic definitions of solubility in an organic solvent (reviewed in Brown, H.A.; Murphy R.C. Nat. Chem. Biol.**2009**, 5, 602–606). It is clear that lipids evolved from these biosynthetic pathways to become involved in the multitudes of biological processes used by living organisms. The comprehensive counting of the total number of lipid molecular species in nature has yet to be fully tallied, but when one considers chirality, precise locations of double bonds, attachments of various head groups, carbohydrates, and amino acids, and other potential chemical diversity, the numbers are in the thousands or beyond [2].

In this thematic issue of Chemical Reviews, we seek to represent the diversity of species and functions in which lipids participate. We focus on lipid species and pathways in mammalian cells and emphasize classes of lipids where misregulation plays a role in human diseases. This issue is one of the most comprehensive collections of reviews on the subject of lipid biochemistry to date. The first section includes contributions on lipid species that are generated by the metabolism of polyunsaturated fatty acids, such as arachidonate and docosahexaenoic acid. Subsequent sections include the metabolism and signaling pathways of glycerolipids, sphingolipids, glycerophospholipids, and sterols. The enzymes that regulate these pathways, the functions of the lipid metabolites, and recent advances in developing chemical modulators are points of special emphasis in this thematic issue [3].

Enzymatic Substrate Oxygenation

Glycerophospholipids contain fatty acids esterified to the glycerol backbone at the sn-1 and sn-2 positions. In general, the sn-1 fatty acyl group is saturated whereas the sn-2 fatty acyl group is monounsaturated or polyunsaturated. Thus, there is an enormous concentration of unsaturated fatty acid residues in cellular membranes. The double bond geometries of the unsaturated fatty acids are nearly always cis, which introduces significant distortion into the membrane bilayer and contributes to its fluidity. Hydrolysis of the sn-2 ester releases polyunsaturated fatty acids that are substrates for multiple oxygenases, which introduce a single atom of oxygen, a single molecule of oxygen, or two molecules of oxygen into the carbon framework. Cyclooxygenases are hemeproteins that catalyze the double dioxygenation of arachidonic acid to form prostaglandin endoperoxides. The cyclic peroxide group of these products is converted to one of five different metabolites, each of which binds to one or more membrane-bound G protein coupled receptors. The prostaglandin or thromboxane products exert a broad range of biology through these receptors, and inhibition of cyclooxygenases by nonsteroidal anti-inflammatory drugs attenuates the production of these bioactive lipids. This is a major contributor to the pharmacological action of this important class of drugs. Smith, Urade, and Jakobsson describe the chemistry and enzymology of the cyclooxygenase cascade with focus on both the endoperoxide-generating cyclooxygenases and the endoperoxide-metabolizing isomerases and reductases. Of particular interest are the recent findings that cyclooxygenases act as functional heterodimers despite the fact that they are structural homodimers [4].

Lipoxygenases introduce a single molecule of O_2 into the carbon framework of polyunsaturated fatty acids, and the hydroperoxide products are transformed into a multiplicity of metabolites. In the case of arachidonic acid, this includes an epoxide called leukotriene A_4 that is hydrolyzed to leukotriene B_4 or conjugated with glutathione to form leukotriene C_4. Unique receptors exist for these products that contribute to the inflammatory response and allergic hypersensitivity. Haeggström and Funk review the chemical biology of this pathway of lipid mediator generation. The structures of the enzymes in this pathway are fascinating because the lipoxygenases are nonheme iron proteins structurally unrelated to cyclooxygenases; the leukotriene A hydrolase is a Zn^{2+} containing enzyme that also exhibits aminopeptidase activity; and the leukotriene C4 synthase is a glutathione transferase structurally related to a lipoxygenase-activating protein that lacks enzymatic activity.

Much of the focus of lipid oxygenase biochemistry has been on the oxidation of free fatty acid substrates. However, over the past 15 years a number of laboratories have reported that unsaturated fatty acid esters and amides are also substrates for oxygenation. The oxygenation products are similar to those produced from the free fatty acids, but their biological effects appear to differ. 2-Arachidonoylglycerol and

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2-arachidonoylethanolamide are two such alternate substrates that are biologically interesting in their own right. They are the first known endogenous ligands for the cannabinoid receptors and are referred to as endocannabinoids. They are naturally occurring analgesic and anti-inflammatory compounds that are metabolized by hydrolysis to arachidonic acid or by oxygenation to prostaglandin- and leukotriene-related derivatives. Rouzer and Marnett review the biochemistry of endocannabinoid oxygenation by cyclooxygenase, lipoxygenases, and cytochromes P450 and the signaling properties of these novel metabolites [5].

The pharmacology of nonsteroidal anti-inflammatory drugs and their ability to inhibit cyclooxygenase enzymes has inferred that oxidized lipids are important mediators of inflammation. Indeed, there is significant prostaglandin production during the development of inflammation in various animal models and high levels of prostaglandins are found in inflamed tissue. However, oxidized lipids are also important mediators of the resolution of inflammation as reviewed by Serhan and Petasis. Multiple classes of pro-resolving lipids exist including resolvins, protectins, and maresins. These are polyhydroxylated derivatives of arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid that are formed by sequential oxygenation by multiple lipoxygenases. They exert extremely potent pro-resolving activity and may account for the beneficial effects of the ω-3 fatty acids found in fish oil.

Nonenzymatic Fatty Acid Oxidation

The elegant chemical transformations that give rise to prostaglandins, leukotrienes, and resolvins inter alia borrow heavily from the autoxidation of polyunsaturated fatty acids. In fact, one can consider their biosynthesis by cyclooxygenases and lipoxygenases as enzyme-controlled autoxidations. The fundamental chemistry of fatty acid autoxidation is reviewed by Yin, Xu, and Porter. They not only articulate the chemical precedents for enzyme catalysis but also highlight the destructive potential of lipid autoxidation with regard to membrane integrity and cellular homeostasis. Lipid autoxidation is an efficient radical chain process that is optimal when the fatty acids are arrayed in a monolayer, as they are in cell membranes. Interruption of these radical changes underscores the importance of vitamin E as the principal membrane-bound antioxidant.

Autoxidation of arachidonic acid was found in the 1960s to produce small amounts of prostaglandins that lacked the stereochemical control displayed by enzyme catalysis. This fact was rediscovered in the early 1990s but in the context of living tissue. These nonenzymatic oxygenation products, called isoprostanes, were found to be present in extracts from intact animals and healthy humans. This discovery unequivocally established that lipid oxidation occurs spontaneously in human beings and that it can be modulated by pro- or antioxidants. Milne, Yin, Hardy, Davies, and Roberts review the occurrence of lipid autoxidation products in animal models and humans, the biological effects of these novel metabolites, and their use as biomarkers of diseases associated with oxidative stress including inflammation and cardiovascular disease [6].

The spontaneous autoxidation of polyunsaturated fatty acids not only generates isoprostanes but also yields molecules (e.g., α,β-unsaturated aldehydes and ketones) that are electrophiles and couple to intracellular nucleophiles. Covalent modification of nucleic acid produces adducts that block DNA replication, cause cell toxicity, and induce genetic mutations. Covalent modification of DNA or protein induces changes in cell signaling that enable a cell to respond productively to a low-level challenge or commit suicide at high levels of modification. In addition to electrophilic fatty acids produced by autoxidation, electrophilic fatty acid derivatives can be produced by coupling to reactive nitrogen species to form nitro or nitroso fatty acids. Schopfer, Cipollina, and Freeman outline the pathways of electrophile generation and the cellular responses that they induce. This relatively new branch of lipid oxidation-dependent cell signaling is an interesting complement to the well-characterized signaling by lipid mediators through G protein coupled or nuclear receptors.

Acknowledgement

None

Conflict of Interest

None

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