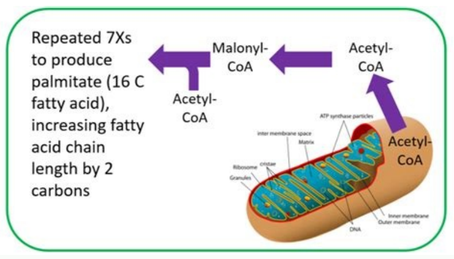
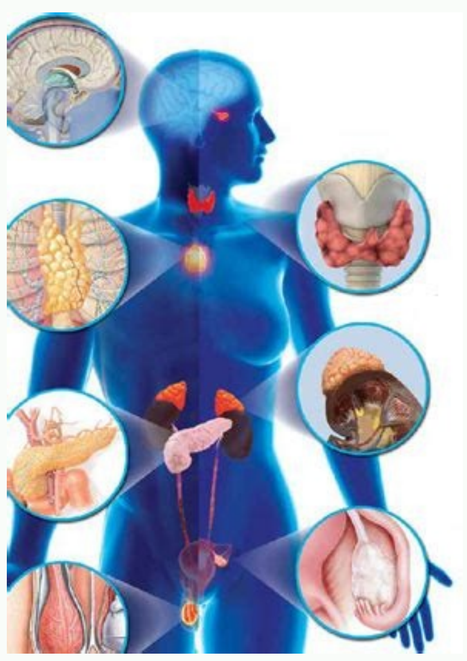
Biosynthesis of lipid pdf





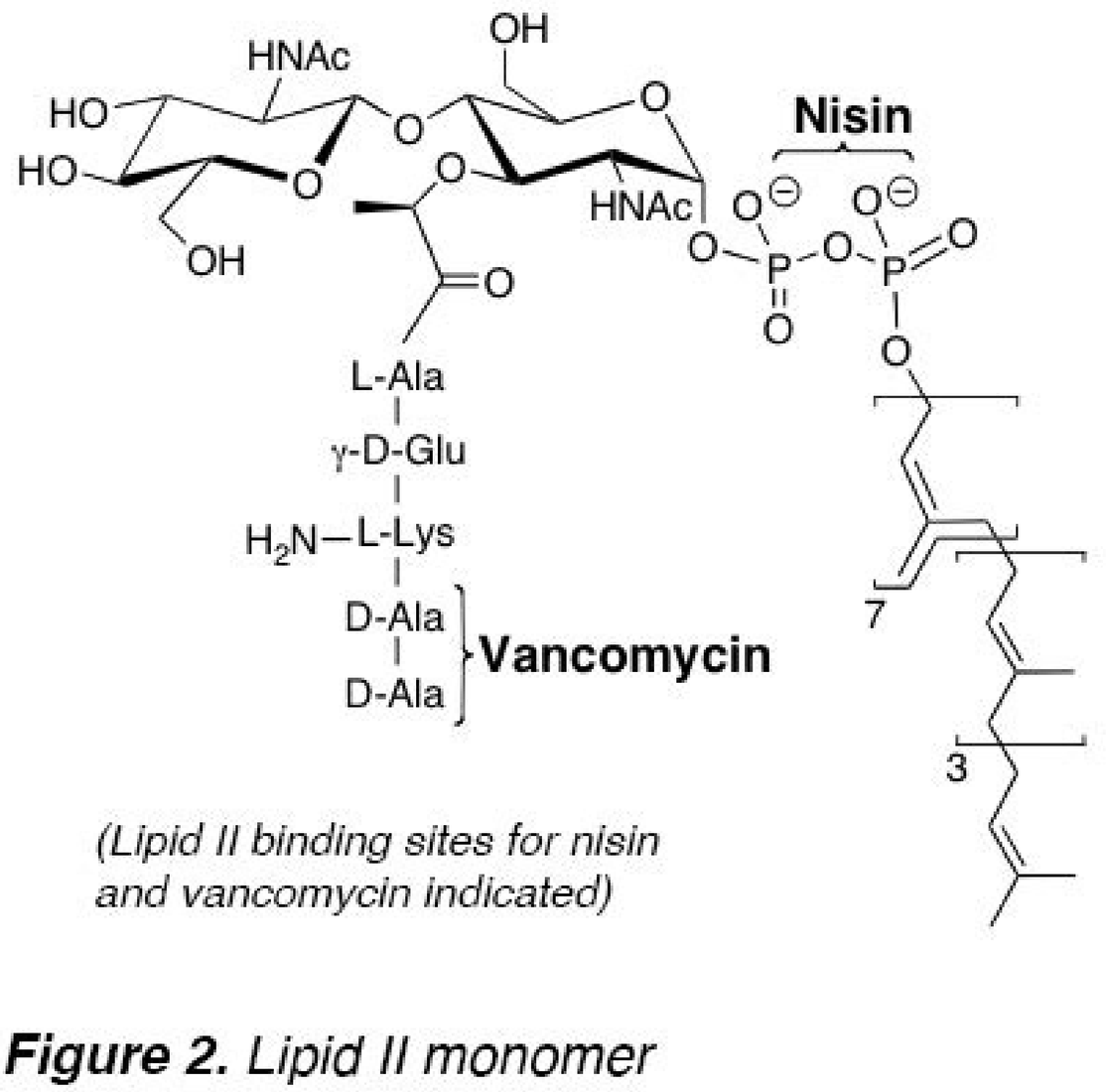
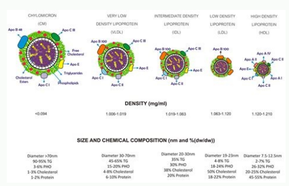
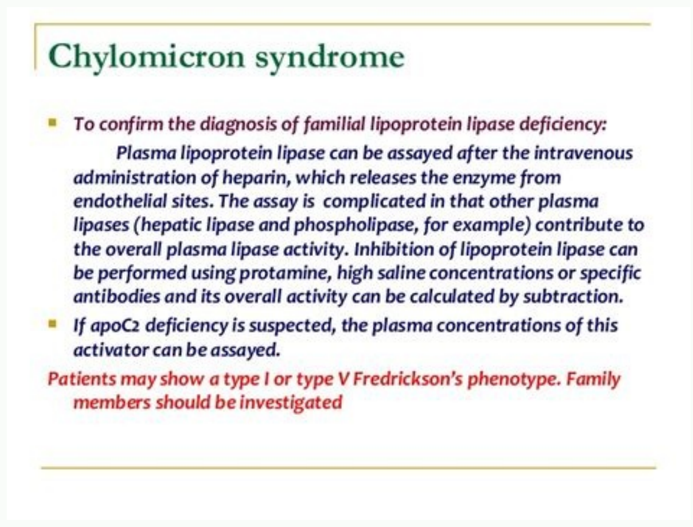


Figure 2. *Lipid II monomer*





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Many of the immune activating abilities of lipopolysaccharide can be attributed to the lipid A unit. Lipid A is a lipid component of an endotoxin held responsible for toxicity of Gram-negative bacteria. The synthesis of unsaturated fatty acids involves a desaturation reaction, whereby a double bond is introduced into the fatty acyl chain. In archaea, the mevalonate pathway produces reactive precursors isopentenyl pyrophosphate and dimethylallyl pyrophosphate from acetyl-CoA, while in plants and bacteria the non-mevalonate pathway uses pyruvate and glyceraldehyde 3-phosphate as substrates. lipid A: Lipid A is a lipid component of an endotoxin held responsible for toxicity of Gram-negative bacteria. It is the innermost of the three regions of the lipopolysaccharide (LPS, also called endotoxin) molecule, and its hydrophobic nature allows it to anchor the LPS to the outer membrane. endotoxin: Any toxin secreted by a microorganism and released into the surrounding environment only when it dies. lipogenesis: The biochemical production of fat, especially the conversion of carbohydrate into fat so that it may be stored as a long-term source of energy when food is scarce. Figure: Chemical structure of lipid A as found in E. coli: Chemical structure of lipid A as found in E. coli Lipids constitute a broad group of naturally occurring molecules that include fats, waxes, sterols, fat-soluble vitamins (such as vitamins A, D, E, and K), monoglycerides, diglycerides, triglycerides, phospholipids, and others. The main biological functions of lipids include energy storage, as structural components of cell membranes, and as important signaling molecules. Lipids may be broadly defined as hydrophobic or amphiphilic small molecules. The amphiphilic nature of some lipids allows them to form structures such as vesicles, liposomes, or membranes in an aqueous environment. Biological lipids originate entirely or in part from two distinct types of biochemical subunits or "building-blocks": ketoacyl and isoprene groups. Using this approach, lipids may be divided into eight categories: fatty acids, glycerolipids, glycerophospholipids, sphingolipids, saccharolipids, and polyketides (derived from condensation of ketoacyl subunits); and sterol lipids and prenol lipids (derived from condensation of isoprene subunits). Figure: Synthesis of the UDP-diacylglucosamine precursor of Lipid A: Synthesis of the UDP-diacylglucosamine precursor of Lipid AThe synthesis of unsaturated fatty acids involves a desaturation reaction, whereby a double bond is introduced into the fatty acyl chain. For example, in humans, the desaturation of stearic acid by stearoyl-CoA desaturase-1 produces oleic acid. The doubly unsaturated fatty acid linoleic acid as well as the triply unsaturated α-linolenic acid cannot be synthesized in mammalian tissues, and are therefore essential fatty acids and must be obtained from the diet. Triglyceride synthesis takes place in the endoplasmic reticulum by metabolic pathways in which acyl groups in fatty acyl-CoAs are transferred to the hydroxyl groups of glycerol-3-phosphate and diacylglycerol. Terpenes and isoprenoids, including the carotenoids, are made by the assembly and modification of isoprene units donated from the reactive precursors isopentenyl pyrophosphate and dimethylallyl pyrophosphate. These precursors can be made in different ways. In archaea, the mevalonate pathway produces these compounds from acetyl-CoA, while in plants and bacteria the non-mevalonate pathway uses pyruvate and glyceraldehyde 3-phosphate as substrates. Although humans and other mammals use various biosynthetic pathways to both break down and synthesize lipids, some essential lipids cannot be made this way and must be obtained from the diet. In animals, when there is an oversupply of dietary carbohydrate, the excess carbohydrate is converted to triglycerides. This involves the synthesis of fatty acids from acetyl-CoA and the esterification of fatty acids in the production of triglycerides, a process called lipogenesis. Fatty acids are made by fatty acid synthases that polymerize and then reduce acetyl-CoA units. The acyl chains in the fatty acids are extended by a cycle of reactions that add the acetyl group, reduce it to an alcohol, dehydrate it to an alkene group and then reduce it again to an alkane group. The enzymes of fatty acid biosynthesis are divided into two groups, in animals and fungi all these fatty acid synthase reactions are carried out by a single multifunctional protein, while in plant plastids and bacteria separate enzymes perform each step in the pathway. The fatty acids may be subsequently converted to triglycerides that are packaged in lipoproteins and secreted from the liver. One important reaction that uses these activated isoprene donors is steroid biosynthesis. Here, the isoprene units are joined together to make squalene and then folded up and formed into a set of rings to make lanosterol. Lanosterol can then be converted into other steroids such as cholesterol and ergosterol. Lipids are a key component of life. They play essential roles in membrane structure, cell signaling and energy production. Like other biomolecules, they undergo chemical modifications that expand their functional repertoire. One modification that has been steadily gaining attention is lipid oxygenation, with interest being attributed to two factors: advances in analytical methods that allow detection of oxygenated species, and the ever-growing body of literature implicating them in biological processes and disease. "Enzymatically oxidized lipids" constitute a large portion of known oxygenated lipid mediators, being bioactive lipids that are produced locally through specific biosynthetic pathways in response to extracellular stimuli. Those derived from oxygenation of polyunsaturated fatty acids (PUFA) such as arachidonic acid (AA) include prostaglandins (PG), thromboxanes and leukotrienes, which function in modulating inflammation, the immune response, and hemostasis, and are broadly termed "oxylipins" (1, 2). Oxylipins also include multiply oxygenated derivatives of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), of which specific enantiomers have been termed "specialized pro-resolving mediators" (SPM) for their proposed roles in the resolution of inflammation (3). SPMs derived from DHA include D-resolvins, maresins and protectin. On the other hand, E-resolvins are proposed to be generated from EPA but the enzymatic pathways are unclear and require further investigation. Oxylipins also constitute a core functional group on larger lipids including oxidized phospholipids (oxPL), endocannabinoids and cholesteryl esters (CE). Oxidized CEs are conversely associated with atherosclerosis progression (4), whereas enzymatically oxidized phospholipids (eoxPL) are pro-coagulant and promote a variety of innate immune actions in leukocytes and platelets (5).Enzymatically oxidized lipids are not limited to those containing oxygenated PUFA functional groups. Oxidized derivatives of cholesterol include steroid hormones, bile acids and their oxysterol precursors. Steroid hormones regulate multiple physiological processes including metabolism (e.g., glucose homeostasis by glucocorticoids), water retention, immune function, and development of sex characteristics (6–8). Bile acids, while traditionally known for aiding in fat digestion and bilirubin excretion, are also being increasingly revealed as signaling molecules and metabolic regulators (9, 10). Similarly, accumulating evidence is revealing oxysterols as more than just bile acid intermediates with functions in signaling (11).Enzymatic lipid oxidation is facilitated by a network of proteins that use PUFAs or sterols as substrates, specifically, lipoxygenase (LOX), cyclooxygenase (COX), and cytochrome P450 (CYP), all of which exist as several isoforms exhibiting broad substrate specificity (12–16). In general, PUFA oxygenation is initiated by COXs, LOXs, and to a lesser extent CYPs. For example, the biosynthesis of PGs is initiated by COXs, whereas the formation of leukotrienes begins with a LOX. Additionally, crossover between COX, LOX, and CYP is proposed to produce various SPMs. On the other hand, cholesterol oxidation is dominated by CYPs. For example, sidechain shortening during steroid hormone synthesis is catalyzed by CYP11A1 (P450scc). Bile acids are synthesized from cholesterol predominantly by two pathways: the neutral pathway starting with an endoplasmic reticulum resident enzyme CYP7A1, and the acidic pathway starting with CYP27A1 in mitochondria (17). CYPs account for many enzymes in both pathways, catalyzing the formation of oxysterols as well as oxygenated PUFAs. Last, aldo-keto reductases (AKR) and hydroxysteroid dehydrogenases (HSD) catalyze key redox reactions in bile acid and steroid hormone biosynthesis.By contrast, non-enzymatically oxidized lipids are produced through uncontrolled oxidation via free radical mechanisms. This involves the oxidation of lipids by free radicals, followed by chain propagation and ultimately termination. Notably, during oxygenation of PUFA, active site intermediates can escape to react in an uncontrolled manner, leading to some oxidized lipids forming due to non-enzymatic rearrangements of enzymatic pathway intermediates.Here, we provide an overview of major enzymes involved in lipid metabolism, including LOXs, COXs, CYPs and AKRs. Then we outline the biosynthetic pathways of oxylipins, oxPLs, oxysterols, bile acids and steroid hormones. Finally, we address outstanding questions and suggest directions for future work.Enzyme Families Involved in the Biosynthesis of Oxidized LipidsLipoxygenase (LOX)Human LOX: Isoforms and Tissue DistributionLipoxygenases (LOX) are a family of non-heme iron-containing dioxygenases. They catalyze the stereospecific addition of dioxygen to lipids containing a (1Z,4Z)-pentadiene group producing lipid hydroperoxides. The human genome contains six functional LOX genes, expressed in various tissues (Table 1). LOXs were traditionally named according to their positional specificity for arachidonic acid (AA). However, the latest characterized member eLOX3 has limited lipoxygenase activity (38), while some LOXs show preference for other PUFA. Sequence analysis of human LOXs (using UniProt entries (39)) shows that 12R-LOX (ALOX12B) is evolutionarily closer to 15-LOX-2 (ALOX15B; 48.2% identity) than 12S-LOX (ALOX12; 35.7% identity). Additionally, human 15-LOX-1 (ALOX15) exhibits dual positional specificity which is not reflected in the name (18). The lack of a robust naming system is a common cause of confusion. Thus, the use of gene names alongside enzyme names is recommended (14).Table 1 Human LOXs: Genes, substrates, and major expression sites.LOXs are typically constitutively expressed, except for 15-LOX-1 (ALOX15) which is inducible by IL-4 and IL-13 in monocyte-derived macrophages (28). Although 15-LOX-2 (ALOX15B) is constitutively expressed in the same cell type, its expression can be increased by cytokines, hypoxia, and lipopolysaccharide. It is possible that other constitutively expressed LOXs share this property.Structure and Membrane Association of Mammalian LOXsThere are a limited number of published crystal structures for mammalian LOXs. Available structures of 5- and 15-LOXs show a single polypeptide chain that consists of two domains: a small β-barrel N-terminal domain and a larger α-helix-rich C-terminal domain containing the catalytic non-heme iron (40–42). The coordination positions of the catalytic iron are occupied by three conserved His residues, the carboxyl group of the C-terminus Ile residue, a water molecule and one last variable ligand (water, His, Asn, or Ser). Studies on mammalian LOXs found that the N-terminal domain is not required for catalytic activity, but instead functions in membrane binding and regulation (43, 44). The N-terminal domain of mammalian 5-LOXs (ALOX5) was found to be important for the calcium-dependent translocation from the cytosol or nucleus (depending on cell type) to the nuclear envelope and enzyme activity (45, 46). Similar findings were reported for mammalian 15-LOXs, with the translocation from the cytosol to the cell membrane instead (47, 48). Unlike other LOXs, the activity of 5-LOX requires interaction with partner proteins 5-lipoxygenase activating protein (FLAP), coactosin-like protein (CLP) and cytosolic phospholipase A2 (cPLA2) (49, 50). Additionally, 5-LOX undergoes phosphorylation at multiple sites, regulating its translocation and activity, and is allosterically activated by ATP (51–53).On the other hand, 15-LOXs do not require accessory proteins for free FA oxygenation. Instead, 15-LOXs form a complex with a small scaffolding protein, phosphatidylethanolamine-binding protein 1 (PEPB1) (54). This complex facilitates 15-LOX activity on PL-esterified PUFA and is proposed to play regulatory roles in ferroptosis along with GPX. PEPB1 has been suggested to direct 15-LOX activity toward PL substrates when free AA is depleted (55). The crystal structure of human 15-LOX-2 (ALOX15B) revealed a hydrophobic loop in the N-terminal domain that is flanked by calcium binding sites, a feature that is absent in 5-LOX (42). Hydrogen-deuterium exchange mass spectrometry showed a decrease in H/D exchange for the hydrophobic loop, supporting a role in membrane hopping (48, 56). Both 5-LOX and 15-LOXs associate with membranes in a calcium-dependent process but they exhibit differences in activity, translocation and binding partners.Calcium-dependent membrane association has also been shown for platelet 12S-LOX (ALOX12), and more recently, 12R-LOX (ALOX12B), and eLOX3 (19, 57). The activity of 12S-LOX (ALOX12) is thought to be

regulated by the availability of its substrates, which are supplied through the action of phospholipases. It is currently unknown whether 12S-LOX is regulated by other mechanisms. Research on the regulation of 12R-LOX and eLOX3 is also limited, although calcium has been shown to increase the activity of mouse 12R-LOX but not eLOX3 (58).Aside from the catalytic domain of 12S-LOX (ALOX12), no crystal structures are available for 12-LOXs or eLOX3. However, human platelet 12S-LOX (ALOX12) was characterized using small-angle x-ray scattering, showing its occurrence as a dimer in solution (59). This challenged the idea that all human LOXs exist and function as monomers. Human 15-LOX-2 displays full activity as a monomer but forms functional dimers as well, thought to exist in equilibrium (60). Similarly, rabbit 15-LOX-1 (ALOX15) undergoes ligand-induced dimerization in aqueous solutions, and molecular dynamics predicts stable dimers in the presence of substrate fatty acids (61). This supports the idea of monomer-dimer equilibria in LOXs. Human 15-LOX-1 (81.1% sequence identity to rabbit) likely exhibits the same property.In summary, all six human LOXs associate with membranes in a calcium-dependent manner. 5-LOX requires the help of protein partners for membrane translocation and activity, whereas 15-LOXs only require a partner protein to efficiently catalyze the oxygenation of PL-esterified PUFA. Less is known about the regulation of 12-LOXs and eLOX3. Dimerization and monomer-dimer equilibria have been observed in several LOX isoforms and represent a potential regulatory mechanism. Finally, complete crystal structures have yet to be reported for 12S-LOX, 12R-LOX, and eLOX3. In the case of 12S-LOX, a crystal structure would be beneficial in the rational design of inhibitors, as the enzyme is a potential therapeutic target. Mechanism of Lipoxygenase ReactionsFe(III) is not a strong enough oxidizer to abstract hydrogen directly. Thus, a mechanism involving proton-coupled electron transfer (PCET) has been proposed (62) (Figure 1A). In this, the electron is directly transferred to Fe(III) and the proton is picked up by the hydroxide ligand in a concerted mechanism (simultaneously), producing a lipid alkyl radical and ferrous iron (Fe(II)). This is followed by a rearrangement of the lipid radical into the more stable conjugated diene. After that, dioxygen is introduced onto the opposite side of the removed hydrogen (antarafacially), generating a lipid peroxyl radical. Finally, the lipid peroxyl radical is reduced by Fe(II) and protonated to form a lipid hydroperoxide, through PCET. This reforms Fe(III) for another round of catalysis.Figure 1 Reaction mechanisms of lipoxygenases (LOXs). (A) Dioxygenase activity. Hydrogen atom removal is conducted through a proton-coupled electron transfer mechanism (PCET), in which the transfer of electron and proton occur simultaneously (concerted mechanism), depicted separately for simplicity. (B) Lipohydroperoxidase activity. (C) Leukotriene synthase activity. (D) Activation of LOX by a hydroperoxide.The stereo and regio-specificity of lipoxygenation are determined by structural features which: (i) accommodate and position the substrate in a specific orientation, and (ii) direct radical rearrangement and oxygen insertion. These features include a U-shaped cavity that accommodates the substrate (63), a migration channel for oxygen (64), a glycine/alanine "switch" that determines stereospecificity by directing oxygen (65), and several amino acid residues that control positional specificity (66, 67). These properties are explored in-depth by Newcomer and Brash (68).In addition to classical dioxygenase activity, LOXs catalyze other reactions that involve free-radical processes like hydrogen abstraction, homolytic bond cleavage, and radical rearrangement (69).eLOX3 exhibits a hydroperoxide isomerase activity (lipohydroperoxidase activity) that converts hydroperoxides to epoxy-alcohols and ketones (70) (Figure 1B). eLOX3 has restricted dioxygenase activity (38), and its hydroperoxide isomerase activity is considered its primary catalytic reaction. Also, mammalian 5-LOXs and human 15-LOX-1 (ALOX15) possess leukotriene A4 synthase activity which produce epoxides from hydroperoxides (71–74). The mechanism involves the homolytic cleavage of a hydroperoxide into an alkoxy radical and hydrogen atom removal (via PCET) from a bis-allylic methylene carbon generating an allyl radical. The resulting biradical is stabilized by epoxide formation (Figure 1C) (75). [illegible] Cyclooxygenases (COXs)[illegible] There are two COX genes in humans: PTGS1 and PTGS2, which encode for COX-1 and COX-2, respectively. Traditionally, it was thought that COX-1 is constitutively expressed, whereas COX-2 is inducible in response to inflammatory signals. However, several studies suggest constitutive COX-2 expression in the brain, lungs, gut, thymus, kidneys, and blood vessels. [illegible] COX-1 is ubiquitous in the body, and its expression sites include blood vessels, platelets, stomach, resident inflammatory cells, smooth muscle, and mesothelium of many organs. On the other hand, COX-2 is inducible in many tissues including the immune cells (T-cells, B-cells, monocytes, and neutrophils), and is constitutively expressed in some tissues as previously mentioned. [illegible] Both COX isoforms are homodimers, and this quaternary structure is necessary for enzymatic activity. Each monomer consists of three domains: an N-terminal epidermal growth factor (EGF)-like domain, a membrane binding domain, and a large C-terminal catalytic domain. The EGF-like domain is located at the dimer interface and potentially facilitates dimerization. It is also thought to facilitate membrane binding. The membrane binding domain consists of four amphipathic α-helices that insert into one face of a membrane bilayer. Both COXs are found on the luminal face of the endoplasmic reticulum (ER) and the inner and outer nuclear membranes. However, COX-2 is also found in the Golgi apparatus. The catalytic domain (in both isoforms) contains separate cyclooxygenase and peroxidase active sites on opposite sides of the heme cofactor. [illegible] COXs undergo N-glycosylation at multiple asparagine residues. [illegible] COX-2 can also be S-nitrosylated by inducible nitric oxide synthase, which has been proposed to enhance its activity. [illegible] Although COXs are sequence homodimers, they are considered conformational heterodimers because one monomer functions as the catalytic subunit (Ecat) and the other as an allosteric regulator (Eallo). [illegible] Catalytic Mechanism of COXCOXs possess two enzymatic activities: a dioxygenase activity and a peroxidase activity. [illegible] Figure 2 Reaction mechanism of cyclooxygenases (COXs). [illegible] Cytochrome P450s (CYPs)[illegible] Figure 3 Reaction mechanism of cytochrome P450s (CYPs). [illegible] two hydroxylation steps on different carbons followed by a C-C bond cleavage (218). This reaction produces pregnenolone which is a key intermediate in the formation of androgens, estrogens, glucocorticoids and mineralocorticoids.CYP-mediated hydroxylation reactions are ubiquitous in cholesterol metabolism, leading to the formation of oxysterols, steroid hormones and bile acids. Key enzymes in the bile acid biosynthesis pathways are CYP7A1 (cholesterol 7α-hydroxylase), CYP8B1 (sterol 12α-hydroxylase), CYP27A1 (commonly named sterol 27-hydroxylase, but more correctly sterol (25R)26-hydroxylase) and CYP7B1 (oxysterol 7α-hydroxylase) (219, 220). Of these enzymes, CYP27A1 can both hydroxylate and carboxylate the terminal carbon of the sterol side-chain (221). Other enzymes involved in quantitatively minor bile acid biosynthesis pathways are CYP46A1 (cholesterol 24S-hydroxylase) which 24S-hydroxylates cholesterol (222, 223) and CYP3A4 which has 4β- and 25-hydroxylase activity (189, 224). CYP enzymes involved in steroid hormone biosynthesis include CYP11A (P450scc) (225), CYP17A1 (steroid 17α-hydroxylase) (226), CYP21A2 (steroid 21-hydroxylase), CYP11B1 (steroid 11β-hydroxylase), and 11B2 (aldosterone synthase) and CYP19A1 (aromatase) (198).Thus, CYPs play indispensable roles in the metabolism of both PUFA and cholesterol. However, some human CYPs like CYP2A7 and CYP20A1 have no assigned functions and remain orphan enzymes.Human Aldo-Keto Reductases (AKRs) and Hydroxysteroid Dehydrogenases (HSDs)AKRs: Nomenclature, Genes, and Tissue DistributionAldo-keto reductases (AKRs) are a superfamily of NADPH-dependent oxidoreductases. They catalyze the reduction of carbonyl groups to alcohols. A nomenclature system has been proposed for AKRs (227). Like CYPs, AKRs are grouped into families and subfamilies based on amino acid sequence. Families have 40% sequence identity, whereas subfamilies are defined by 60% sequence similarity. The nomenclature consists of the root "AKR" followed by a number for family, a letter for subfamily and finally a number as a unique gene identifier. The nomenclature has also been expanded to accommodate multimers (228). The older (trivial) names of AKRs are still heavily in use, which could lead to confusion. Thus, it is advised to follow the nomenclature system proposed by Jez et al. (227).There are 15 AKRs in the human genome spanning three families and seven subfamilies. Human AKRs have variable expression and accept a wide range of substrates (Table 3). They are involved in the metabolism of sugars, prostaglandins and sterols, as well as the detoxification of carbonyl compounds like lipid peroxidation products. Additionally, members of family 6 (AKR6A3, AKR6A5, and AKR6A9) are constituents of voltage-gated potassium channels (250). All human AKRs have either established or proposed roles in lipid metabolism except for AKR1E2.Table 3 Human AKRs: Genes, expression sites, and example substrates.Human AKRs are generally cytosolic with some exceptions. AKR1B15 is found in mitochondria (236). Members of the AKR1C subfamily in the lung (1C1, 1C2 and 1C3) are also secreted in pulmonary surfactant (256). AKR1B10 is present in lysosomes and is secreted into the intestinal lumen by epithelial cells (257). AKR6 members form a complex with a plasma membrane voltage channel on the cytosolic side. Finally, rat AKR7A2 associates with the Golgi apparatus (258). Human AKR7A2 contains a similar N-terminal amphipathic sequence and likely associates with the Golgi apparatus.Mammalian AKRs: Structure and EnzymologyCrystal structures have been solved for many mammalian AKRs. They comprise of a triosephosphate isomerase barrel motif (α/β)8 which has alternating α-helices and β-strands repeating eight times. The α-helices surround an internal β-barrel formed by the β-strands. The active site is located at the base of the barrel, in which the substrate and the nicotinamide head group of NADPH (cofactor) are proximally positioned for the reaction, while three flexible loops form the back of the barrel and control substrate specificity (259, 260). The structure also contains two additional helices that are not part of the barrel motif. Family 1 AKRs are monomeric, whereas families 6 and 7 form tetramers and dimers, respectively (258, 261).AKRs catalyze the stereospecific reduction of carbonyls into alcohols. They can also catalyze the reverse oxidation reaction. However, the reducing direction is generally favored due to the abundance of reduced cofactor in the cellular environment. AKRs can use both NADPH and NADH, but NADPH is the preferred cofactor for most known AKRs as they interact with the phosphoryl group present in NADPH but not NADH (262, 263). The stereospecific nature of the reaction is due to the orientation of the NADPH and the substrate in the active site. The NADPH is bound in the anti-conformation (with respect to the ribose ring) which promotes the transfer of the 4-pro-R hydride (264), and the substrate is positioned perpendicular to the cofactor.The reaction of AKRs follows an ordered bi-bi mechanism in which the NADPH cofactor binds first and leaves last. The active site of AKRs contains a highly conserved catalytic tetrad of Tyr, Lys, Asp and His. The hydride transfer is facilitated by acid-base catalysis involving the protonation state of Tyr and the other catalytic residues. In the reduction direction, the protonated form of Tyr acts as an acid by participating in proton relay with His (259) (Figure 4A). This polarizes the carbonyl group of the substrate, allowing it to accept a hydride ion from the cofactor. In the oxidation direction, the phenolate form of Tyr (generated through proton relay with Lys and Asp) acts as a base and abstracts a proton from the alcohol group of the substrate, facilitating hydride transfer to the cofactor (259) (Figure 4B).Figure 4 Catalytic mechanism of aldo-keto reductases (AKRs) in the: (A) Reduction direction and (B) Oxidation direction. (C) 5β-Reduction of steroid double bond by AKR1D1.AKR1D subfamily members catalyze the irreversible 5β-reduction of sterol double bonds into single bonds, instead of the reversible reduction of carbonyls typical of AKRs (Figure 4C). They possess an altered catalytic tetrad with Glu replacing His (265). This substitution allows the substrate to penetrate deeper into the active site pocket, positioning C5 close to the 4-pro-H of NADPH (259). The catalytic Glu residue is thought to act as a superacid, facilitating the enolization of the steroid double bond and allowing hydride transfer to C5 (259, 265).Human AKR1B1 catalyzes the isomerization of PGH2 to PGD2 in the absence of cofactor, as well as the reduction of PGH2 to PGF2α in the presence of cofactor (266). Curiously, both of these reactions are reported to be facilitated by a catalytic triad of Lys, His and Asp, without the involvement of Tyr in catalysis, although Tyr is still required for the p-nitrobenzaldehyde reductase activity of the enzyme (266). Thus, both Tyr and His can participate in acid-base catalysis, at least in AKR1B1.Involvement of Human AKRs in Lipid MetabolismHuman AKRs play roles in the detoxification of reactive carbonyls. Several AKRs metabolize lipid peroxidation-derived aldehydes like acrolein and 4-HNE (Table 3). Additionally, some AKRs (1A1, 1B1, 1B10, 6A5) can reduce oxidized phospholipids, particularly phospholipid aldehydes (229, 251). These activities mitigate the cytotoxicity of reactive carbonyls (240, 267–269), and in the case of family 6 AKRs are also thought to function in redox sensing (251).Both AKR1B1 and AKR1C3 exhibit prostaglandin F synthase activity (270, 271). AKR1B1 catalyzes the reduction of PGH2 to PGF2α. AKR1C3 catalyzes the same reaction as well as the reversible reduction of PGD2 to 9α,11β-PGF2 (241). Furthermore, AKR1B1 catalyzes the isomerization of PGH2 to PGD2 exclusively in the absence of NADPH as noted previously. However, the biological relevance of this activity is not clear as this isomerization reaction is also catalyzed by two prostaglandin D synthases (272), and the cellular redox status favors the reduction reaction. Both PGF2α and its isomer 9α,11β-PGF2 promote uterine contractions during labor (237).Six of the 15 human AKRs are involved in sterol/steroid metabolism: AKR1B15, the four members of the AKR1C subfamily (also grouped as hydroxysteroid dehydrogenases; HSDs), and AKR1D1. AKR1B15 catalyzes the 17β-reduction of androgens and estrogens (236). AKR1C1 (20α-HSD) catalyzes the 20α-reduction of progesterone inactivating it (273), whereas AKR1C2 (Type 3 3α-HSD) possesses a 3α-dehydrogenase activity and deactivates 5α-dihydrotesterone (259). AKR1C3 (Type 5 17β-HSD) exhibits 17-ketoreductase activity and produces testosterone and estradiol from their respective precursors.AKR1D1 and AKR1C4 (Type 1 3α-HSD) catalyze key steps in bile acid biosynthesis. AKR1D1 catalyzes irreversible 5β-reduction of a double bond in 3-ketosterols. This modification changes the geometry of the steroid nucleus from flat to twisted, with a bend in the A/B ring junction. Next, AKR1C4 catalyzes the 3α-reduction of the ketosteroid, resulting in a 3α,5β-configuration, a characteristic feature of bile acids.Other HSDs Belong to the Short-Chain Dehydrogenase/Reductase (SDR) FamilySome HSDs belong to a different family of enzymes: the short-chain dehydrogenases/reductases (SDR). SDRs exhibit key differences from AKRs in structure, kinetics, catalytic mechanism, and reaction stereochemistry (reviewed in (274)). Of note, HSDs of the SDR family work as either ketosteroid reductases or hydroxysteroid oxidases, depending on their preference for the corresponding forms of NADP(H) or NAD(H). This contrasts with HSDs of the AKR1C family which operate in the reduction direction using (primarily) NADPH (274). Like CYPs and AKRs, a systematic nomenclature has been proposed for SDRs (275). However, the old names (especially for HSDs) remain heavily in use. HSDs of the SDR family have important functions in sterol/steroid metabolism (Table 4).Table 4 Human SDR-HSDs and their substrates/reactions.Biosynthetic Pathways of Oxidized LipidsOxygenated PUFA and Oxidized PhospholipidsClassification of Oxygenated PUFA as Eicosanoids and DocosanoidsThe term "oxylipin" refers to oxygenated PUFA derivatives. It encompasses a wide range of oxidized lipids like hydroxy-, epoxy-, oxo-FAs, and endoperoxides. Oxylipins can be classified according to their precursor into eicosanoids (C20) or docosanoids (C22), etc., and this system will be used from here on. Following the classification system of the LIPID MAPS consortium, eicosanoids include prostaglandins, leukotrienes, thromboxanes, lipoxins, hepoxilins, E-resolvins, as well as hydroxy-, hydroperoxy-, epoxy-, and oxo-eicosanoids (286). Likewise, docosanoids include D-resolvins, protectins, maresins, hydroxy-, hydroperoxy-, epoxy-, and oxo-docosanoids. Structures of these lipids are available on the LIPID MAPS database (287).Here, we focus on the biosynthesis of eicosanoids derived from AA and EPA, and docosanoids derived from DHA, as they are the most studied. Due to the broad substrate specificity of enzymes involved in lipid oxidation, PUFAs with shorter chains or different number of double bonds also undergo similar reactions. Similarly, oxygenation of endocannabinoids occurs on the PUFA moiety and follows the enzymatic mechanisms described here. Further aspects of oxygenated endocannabinoids are discussed in other reviews (216, 288).Release of PUFA from Membranes for Oxylipin BiosynthesisIntracellular concentration of free PUFA is tightly regulated through conjugation with coenzyme A (CoA) and subsequent esterification into lysoPL forming PL or shuttling into other pathways (like β-oxidation). PUFAs are abundant in membrane PLs, typically esterified at the sn-2 position. The classical pathway of oxylipin biosynthesis involves the release of PUFA from membrane PL via the action of lipases like phospholipase A2 (PLA2), phospholipase C and diacylglycerol lipase (289, 290). PLA2 enzymes are classified into six types: secreted (sPLA2), cytosolic (cPLA2), calcium-independent (iPLA2), platelet-activating factor acetylhydrolases (PAH-AH), lysosomal (LPLA2), and adipose (AdPLA), and these are further divided into groups and subgroups (291, 292). cPLA2α is localized in the cytosol but translocates to intracellular membranes upon calcium activation, and exhibits selectivity for phospholipids containing AA at the sn-2 position (293, 294). On the other hand, the release of DHA from the membrane can be facilitated by iPLA2β (295, 296). Last, sPLA2 enzymes are involved in the release of AA, EPA and DHA (297, 298). PLA2 enzymes are extensively reviewed by Murakami (299).Biosynthesis of EicosanoidsArachidonic acid is a substrate of eicosanoids produced through the actions of COXs, LOXs, CYPs, and other downstream enzymes (Figure 5A). The most established of these are mono-oxygenation products of AA, DHA, and EPA and classic prostaglandins, leukotrienes, and thromboxane from COXs, LOXs, and CYPs. Most of these were described from the 1950s–90's in seminal studies, with many conducted at the Karolinska Institute in Stockholm by Sune Bergstrom, Bengt Samuelsson and colleagues. Indeed, the Nobel Prize for Physiology and Medicine was awarded for discovery of prostaglandins and related biologically active substances in 1985 to Bergstrom, Samuelsson and John Vane. More recently, research has focused on characterization of multiply oxygenated PUFAs from AA, EPA, and DHA including several which are proposed to form from transcellular sequential oxygenation by various enzymes. However, for many of these, their specific biosynthetic pathways, enantiomeric composition and biological actions in tissues are not well understood and the levels formed are extremely low in comparison to classic PGs and monohydroxy-oxylipins. Furthermore, their bioactions often require amounts of lipids that are considerably higher than levels detected in cell and tissue samples, and thus could be considered pharmacological.Figure 5 Biosynthesis of eicosanoids derived from: (A) Arachidonic acid and (B) Eicosapentaenoic acid. HETE, hydroxy-eicosatetraenoic acid; Hp, hydroperoxy; Ep, epoxy; LTA4H, leukotriene A4 hydrolase; LTC4S, leukotriene C4 synthase; GGT, γ-glutamyl transpeptidase; DPEP2, dipeptidase 2; sEH, soluble epoxide hydrolase; 12-HEDH, 12-hydroxyeicosanoid dehydrogenase; PGES, prostaglandin E synthase (m: microsomal, c = cytosolic); PGDS (prostaglandin D synthase (L: lipocalin type, H: hematopoietic); 15-PGDH, 15-hydroxyprostaglandin dehydrogenase; PG-9KR, prostaglandin 9-ketoreductase; EET, epoxyeicosatrienoic acid; DiHETrE, dihydroxy-eicosatrienoic acid; HEPE, hydroxy-eicosapenatаenoic acid.COXs convert AA into PGG2 which is reduced into PGH2 (Figure 5A). From there, PGH2 functions as substrate for classic PGs and thromboxane, generated by tissue-specific enzymes. CYP5A1 (thromboxane synthase) is expressed in several cell types and tissues (platelets, macrophages, lung, kidney, liver) and catalyzes the isomerization of PGH2 into thromboxane A2, a potent vasoconstrictor and activator of platelet aggregation (300, 301). CYP5A1 also catalyzes the cleavage PGH2 into malondialdehyde and 12-hydroxyheptadecatrienoic acid. CYP8A1 (prostacyclin synthase) is widely expressed (abundant in ovary, heart, lung, skeletal muscle, and prostate) and catalyzes the isomerization of PGH2 into prostacyclin (PGI2), a vasodilator and inhibitor of platelet aggregation (302).PGH2 can also be converted into PGD2 through the action of AKR1B1 or PGD synthases, of which there are two isoforms: lipocalin-type PGD synthase (in the central nervous system, male genitalia, heart, cerebrospinal fluid and plasma) and hematopoietic PGD synthase (in antigen-presenting cells, mast cells and megakaryocytes) (266, 303). PGD2 plays roles in the regulation of body temperature, sleep cycle, pain perception and the immune response (304). In the uterus, AKR1C3 catalyzes the reduction of PGD2 into 9α,11β-PGF2, which promotes uterine contractions (237). Similarly, AKR1C3 and AKR1B1 catalyze the reduction of PGH2 into PGF2α, which also promotes uterine contractions (305). Finally, PGH2 can be converted into PGE2 via the action of PGE synthases, of which there are three isoforms: an inducible microsomal isoform (mPGES-1), a constitutive microsomal isoform (mPGES-2) and a constitutive cytosolic isoform (cPGES) (306). PGE2 is abundant in the body and plays a complex role in immunity and inflammation (307). Additionally, PGE2 is reduced into PGF2α by prostaglandin 9-ketoreductase (PG-9KR) (308).COXs also produce 11R-, 15R-, and 15S-HpETEs as side products, all three of which can be reduced into their corresponding alcohols by peroxidase activity, which are in turn reduced into oxo-ETEs by 15-hydroxyprostaglandin dehydrogenase (15-PGDH). Bioactivities of HETEs and oxo-ETEs are extensively reviewed by Powell and Rokach (309).5-LOX converts AA into 5S-HpETE (Figure 5A), which is reduced into 5S-HETE through the action of a peroxidase (e.g., GPX) or converted into leukotriene A4 (LTA4) through the leukotriene synthase activity of 5-LOX. Various immune cells (neutrophils, monocytes, platelets) express 5-hydroxyeicosanoid dehydrogenase (5-HEDH) which converts 5S-HETE into 5-oxo-HETE, a potent chemoattractant for eosinophils (310). On the other hand, LTA4 serves as a precursor for LT peptide conjugates (LTC4, D4 and E4) and lipoxins (A and B). LTC4, D4, and E4 are synthesized from LTA4 through LTC4 synthase (a gluthathione-S-transferase), γ-glutamyl transpeptidase (GGT) and dipeptidase 2 (DPEP2). Leukotrienes exhibit pro-inflammatory properties and are implicated in asthma and allergic reactions (311). On the other hand, lipoxins are thought to be synthesized by 12S-LOX through a transcellular pathway which involves interactions between two cell types (312). Lipoxins exhibit anti-inflammatory properties and are proposed to play a role in wound healing and tissue homeostasis (313). Alternatively, LTA4 can be hydrolyzed by leukotriene A4 hydrolase (LTA4H) into LTB4, which attracts neutrophils (314).15-LOXs converts AA into 15S-HpETE (Figure 5A), which can be reduced into 15S-HETE then oxidized into 15-oxo-ETE. 15S-HpETE and 15S-HETE are also substrates for 5-LOX, which produces a 5S,6S epoxy intermediate that can be hydrolyzed into lipoxins by unidentified hydrolases. Additionally, 15S-HpETE is proposed to be a precursor for eoxin A4 (a 14,15 leukotriene), which is converted into peptide conjugates (eoxin C4, D4, and E4) similar to leukotrienes (315). Conversion of eoxin A4 into C4 is thought to involve LTC4S. Enzymes that catalyze the following two steps leading to eoxin D4 and E4 are unidentified, presumably a GGT isoform and DPEP2. Eoxins are produced in eosinophils, mast cells and airway epithelial cells, and have been shown to possess pro-inflammatory properties (316).12S-HpETE and 12R-HpETE are produced by 12S-LOX and 12R-LOX, respectively (Figure 5A). These hydroperoxides can be reduced to their corresponding alcohols via a peroxidase, and both alcohols further oxidized into 12-oxo-ETE by 12-hydroxyeicosanoid dehydrogenase (12-HEDH) (309). Both hydroperoxides are also precursors for hepoxilins, which are epoxy-alcohols. eLOX3 in skin converts 12R-HpETE into either hepoxilin A3 or 12-oxo-ETE. On the other hand, 12S-HpETE can be converted into hepoxilin A3 or B3 by either 12S-LOX or eLOX3, but eLOX3 also generates 12-oxo-ETE (70, 317). Hepoxilins A3 and B3 are hydrolyzed by sEH into trioxilins A3 and B3, respectively (318). Hepoxilin A3 can also be conjugated with glutathione via LTC4S producing hepoxilin A3-C, which can be converted into a hepoxilin A3-D by GGT (319). The occurrence of hepoxilin A3-E (cysteinyl conjugate) has also been proposed but not confirmed. Hepoxilin A3 is proposed to regulate mucosal inflammation by recruiting neutrophils across the epithelial junction into the gut lumen (320).CYPs generate various midchain R- and S-HETEs as well as 20-HETE through hydroxylation of AA (Figure 5A). Alternatively, epoxyeicosatrienoic acids (EET) are produced from AA through epoxidation of its double bonds. Major mammalian CYP epoxygenases include CYP2C8, CYP2C9, and CYP2J2 (15). EETs are further metabolized by sEH (and potentially other epoxide hydrolases) into dihydroxyeicosatrienoic acids (DiHETrE). Note that EPA and other PUFA are also targets of CYP-mediated reactions, which generate the corresponding hydroxy-, epoxy-, and dihydroxy- derivatives."E-resolvins", another class of eicosanoids, are proposed to be generated from EPA (Figure 5B). COX-2 and CYPs have both been proposed to act on EPA to produce 18R-hydroxyeicosapentaenoic acid (18R-HEPE), which is in turn a proposed precursor for lipids termed resolvins E1, E2 and E3 (E-resolvins). It is known that the acetylation of COX-2 shifts its activity into favoring the lipoxygenase-type reaction over the cyclooxygenase activity, and that acetylated COX-2 generates 18R-HEPE from EPA (321). However, acetylated COX-2 is not a physiologically relevant form, and 18R-HEPE could be potentially generated through other means. COX-2 is theoretically capable of generating 18R-HEPE from EPA in a lipoxygenase-type reaction followed by peroxidase activity. However, whether the generation of 18R-HEPE from EPA occurs in vivo and in sufficient amounts without COX-2 acetylation is unknown. Microbial CYPs have also been proposed as sources of 18R-HEPE during infection. E-resolvins are proposed to be produced through a transcellular mechanism involving microbial and mammalian cells (322). Alternatively, mammalian CYPs are also potential sources of 18R-HEPE, although the exact isoforms involved are unknown.18R-HEPE can be metabolized by 5-LOX into a 5S-hydroperoxy intermediate and further into a 5S,6S-epoxy intermediate (323). The former is proposed to be converted into resolvin E2 by a peroxidase, whereas the latter is proposed to be hydrolyzed into resolvin E1 by LTA4H (324). 18S-analogues of resolvin E1 and E2 have also been described and are proposed to be generated from 18S-HEPE through a similar pathway (Figure 5B), although the enzymatic sources of 18S-HEPE (aside from acetylated COX-2) are also unknown. 18R-HEPE is also proposed to be a precursor to two stereoisomers collectively called resolvin E3 generated by 15-LOX-1 (325). E-resolvins are proposed to exhibit anti-inflammatory effects and promote the resolution of inflammation (325, 326).Both lipoxins and E-resolvins have been classified as specialized pro-resolving mediators (SPMs), a term which currently describes families of oxygenated PUFA metabolites with proposed roles in the resolution of inflammation and tissue regeneration generated at extremely low levels in biological samples.Biosynthesis of DocosanoidsOxygenation of DHA by LOXs and CYPs forms oxygenated docosanoids (hydroxy-, epoxy-, and dihydroxy derivatives). DHA is also the precursor to several classes of multiply oxygenated docosanoids, including additional SPMs which have been named maresins, D-resolvins, and protectins (Figure 6). Maresin biosynthesis has been proposed to start with action of 12S-LOX, generating 14S-hydroperoxy-DHA (14S-HpDoHE) then a 13S,14S-epoxy intermediate. Hydrolysis of this epoxy intermediate by sEH or an unidentified hydrolase is proposed to generate maresin 2 and maresin 1, respectively (93, 327). The biosynthesis of protectin and D-resolvins both begin with 15-LOX-1 which generates a 17S-hydroperoxide (17S-HpDoHE). Further conversion of this hydroperoxide into a 16S,17S-epoxy intermediate by 15-LOX-1 followed by hydrolysis (unidentified hydrolase) is proposed to generate protectin D1 (328). Alternatively, 17S-HpDoHE could be reduced into an alcohol by a peroxidase, which then serves as a precursor for D-resolvins. In this route, 5-LOX is proposed to generate two distinct products hydroperoxides (4S or 7S), which undergo further transformations leading to several D-resolvins (Figure 6). Additionally, epoxide intermediates in the previously described pathways are proposed to undergo glutathione conjugation by LTC4S, generating peptide conjugates of maresin, protectin and D-resolvin named MCTR1, PCTR1, and RCTR1, respectively (CTR = conjugate in tissue regeneration). These conjugates are proposed to be metabolized by GGT and DPEP2, similar to leukotrienes (329).Figure 6 Biosynthesis of specialized pro-resolving mediators (SPMs) derived from docosahexaenoic acid. HDoHE, hydroxy-docosahexaenoic acid; Hp, hydroperoxy; Ep, epoxy; CTR, conjugate in tissue regeneration (M: maresin, P: protectin, R: resolvin); sEH, soluble epoxide hydrolase; LTC4S, leukotriene C4 synthase; GGT, γ-glutamyl transpeptidase; DPEP2, dipeptidase 2.Oxygenation of Esterified PUFA and Biosynthesis of Oxidized PhospholipidsThe classical pathway for the biosynthesis of oxidized phospholipids starts with the release of PUFA from membranes through the action of PLA2. PUFA are then oxygenated by the enzymes discussed earlier. This is followed by acylation of oxygenated PUFA with CoA and esterification into a lysoPL via the action of an sn-2 acyltransferase.The generation of PL-esterified eicosanoids is well-documented in mammalian cells such as epithelial, endothelial and immune cells (330). HETE-PLs are acutely generated by activated neutrophils, platelets and monocytes (331–333). Similarly, PGD2 and PGE2 generated from COX-1-derived PGH2 in activated platelets are rapidly incorporated into PE-lysoPLs (334). Also, EET-PLs have been detected in rat liver (335). For most of these, the mechanism of formation requires endogenous generation of an oxylipin, which is then rapidly esterified into membrane PL pools (e.g., on a timescale of minutes) via Lands cycle enzymes (336).15-LOXs also contribute to the formation of oxPL by two other pathways. The first involves direct oxygenation of membrane PLs (331, 337). In the second pathway, 15-LOXs oxygenate the PUFA moiety of CEs, then hydrolysis of oxygenated PUFA from CE liberates oxygenated PUFA which can be esterified to lysoPL (87).Recent studies found that COX-2, 15-LOX-2, and platelet 12S-LOX can catalyze the oxygenation of 2-AA-lysoPL released by iPLA2γ in response to calcium ionophore stimulation (88, 94). These reactions generate 2-eicosanoid-lysoPLs which are proposed to be a source of free eicosanoids as well as acting as signaling mediators themselves. 2-eicosanoid-lysoPLs can also be converted into oxPLs through the action of sn-1 acyltransferase (338). Cytochrome c has been recently been identified as a plasmalogenase, and is proposed to be a source of 2-eicosanoid-lysoPLs under conditions of oxidative stress (339). These findings describe novel pathways for the biosynthesis of oxPLs (Figure 7). Further research is required to assess the contribution of these pathways to the formation of oxPLs and other mediators in vivo.Figure 7 Biosynthetic pathways of oxidized phospholipids. (1) The classical pathway involves the action of PLA2 on membrane phospholipids, releasing sn-2 PUFA which are oxygenated by cyclooxygenases (COXs), lipoxygenases (LOXs), and cytochrome P450s (CYPs) then re-esterified. *Oxygenated PUFA can be also be esterified with plasmalogen lysophospholipids (2) Direct oxygenation of membrane phospholipids by 15-LOXs. (3) 15-LOX-mediated oxygenation of PUFA in cholesteryl esters followed by hydrolysis of oxygenated PUFA provides substrates for the classical pathway. (4) An alternative pathway involves the action of PLA1, forming 2-PUFA-lysophospholipids which are oxygenated by COX-2, 12S-LOX, and 15-LOXs then re-esterified with FA. (5) Cytochrome c releases 2-PUFA-lysophospholipids by cleaving the vinyl ether bond in plasmalogen phospholipids, providing substrates for the alternative pathway. PLA, Phospholipase A; oxPUFA, oxygenated PUFA; ACS, acyl-CoA synthase; CE, cholesteryl ester; CEH, neutral cholesterol ester hydrolase; FA, fatty acid/acyl; lysoPL, lysophospholipid.Biosynthesis of Oxysterols, Bile Acids, and Steroid HormonesOxysterolsOxysterols are formed in the first steps of cholesterol metabolism: they are oxidized forms of cholesterol and also of its precursors (340). 7α-Hydroxycholesterol (7α-HC) is formed from cholesterol by CYP7A1 and represents the first metabolite in the neutral pathway of bile acid biosynthesis (Figure 8) (219, 220). (25R)26-Hydroxycholesterol (26-HC), more commonly called 27-hydroxycholesterol, and 3β-hydroxycholest-5-en-(25R)26-oic acid (3β-HCA) are both formed from cholesterol by CYP27A1 and are the first members of the acidic or alternative pathway of bile acid biosynthesis (219–221). While CYP7A1 is an endoplasmic reticulum and liver specific protein, CYP27A1 is mitochondrial and expressed in many tissues. CYP46A1 is almost exclusively expressed in neurons, its function is to maintain cholesterol balance in the brain, converting cholesterol from a molecule unable to pass the blood brain barrier to 24S-hydroxycholesterol (24S-HC), a more polar molecule which can cross the barrier (222, 223, 341). CYP11A1, like CYP27A1, is a mitochondrial inner membrane protein. It is highly expressed in steroidogenic tissue and will oxidize cholesterol to pregnenolone in a three step process involving 22R-hydroxycholesterol (22R-HC) and 20R,22R-dihydroxycholesterol as intermediates (20R,22R-diHC) (342, 343) (Figure 9). The pathways of bile acid biosynthesis are discussed in more detail below.Figure 8 A simplified view of the major bile acid biosynthesis pathways. The "neutral" pathway (highlighted in blue) starts with 7α-hydroxylation of cholesterol by CYP7A1, the "acidic" pathway with (25R)26-hydroxylation then (25R)26-carboxylation of cholesterol by CYP27A1. In the "acidic" pathway (highlighted in red) CYP7B1 is the 7α-hydroxylase.Figure 9 Simplified view of steroid hormone biosynthesis. Highlighted in red are the classical steroid hormones, progesterone, aldosterone, cortisol, testosterone, and 17β-estradiol.While most "primary" oxysterols are formed from cholesterol in CYP catalyzed reactions, cholesterol 25-hydroxylase (CH25H), the dominating enzyme that generates 25-hydroxycholesterol (25-HC) is an exception, in that is not a CYP, but a member of a family of enzymes that utilize di-iron cofactors to catalyze the hydroxylation (344). CH25H is expressed in activated immune cells and 25-HC has both anti-bacterial and anti-viral activities (345–348). 25-HC is metabolized by CYP7B1 to 7α,25-diHC, a ligand to the GPCR Epstein Barr virus induced gene 2 (EBI2 or GPR183). 7α,25-diHC acts as a chemoattractant to GPR183 expressing immune cells (349, 350). An alternative route to 7α,25-diHC production is through CYP3A4 oxidation of 7α-HC (190), while the same enzyme has also been reported to act as a second cholesterol 25-hydroxylase and also a 4β-hydroxylase of cholesterol (189, 351).Oxysterols can also be formed from cholesterol precursors in reactions catalyzed by CYP enzymes (202, 352). These reactions may be important in patients suffering from inborn errors of cholesterol biosynthesis such as Smith-Lemli-Opitz syndrome (SLOS, 7-dehydrocholesterol reductase deficiency) and desmosterolosis (3β-hydroxysterol-Δ24-reductase deficiency) or where there is very high expression of sterol hydroxylases, e.g., CYP7A1 in cerebrotendinous xanthomatosis, where CYP27A1 is deficient.Bile Acid BiosynthesisThere are two quantitatively major and at least five minor pathways of bile acid biosynthesis and all pathways involve multiple oxidation reactions (219, 220, 353–358). Besides CYP enzymes, key oxidation reactions are carried out by hydroxysteroid dehydrogenase (HSD) members of the short chain dehydrogenase/reductase (SDR) family and reductions by aldo-keto reductases (AKR) enzymes. One of the minor pathways that results in the formation of 3β,5α,6β-trihydroxycholan-24-oic acid involves of cholestane-3β,5α,6β-triol which is likely formed via the cholesterol peroxidation product 5,6-epoxycholesterol (219, 354).While the acidic pathway may be most important in infants (359), at later stages of life the neutral pathway is dominant. This is initiated by CYP7A1 oxidation of cholesterol to generate 7α-HC in the liver. Further oxidation may occur at C-12 by CYP8B1 to generate 7α,12α-dihydroxycholesterol (7α,12α-diHC), which may be preceded or succeeded by oxidation and isomerization of the 3β-hydroxy-5-ene structure to a 3-oxo-4-ene by HSD3B7, giving 7α-hydroxycholest-4-en-3-one (7α-HCO) and 7α,12α-dihydroxycholest-4-en-3-one (7α,12α-diHCO), respectively (Figure 8). A general feature of bile acid biosynthesis is that many of the enzymes involved in the pathways accept multiple substrates resulting in variations in the order of reactions depending on the tissue in which they proceed (360). The next steps involve A-ring reductions which may be succeeded or preceded by (25R)26-hydroxylation and (25R)26-carboxylation to ultimately give 3α,7α,12α-trihydroxy-5β-cholanestan-(25R)26-oic acid. The A-ring reductions are carried out by AKR1D1 and AKR1C4, while CYP27A1 carries out the (25R)26-oxidations. Side-chain shortening of the cholestanoic acid proceeds in the peroxisome through the CoA-thioester formed by bile acid Co-A synthetase (BACS, SLC27A5) or very long chain acyl-CoA synthetase (VLCS, SLC27A2). Following C-25 racemization by α-methylacyl-CoA racemase (AMACR) the next oxidation involves the introduction of Δ24 double bond by the enzyme acyl-CoA oxidase 2 (ACOX2). The Δ24 double bond is then hydrated by D-bifunctional protein (DBP), which then oxidizes the C-24 hydroxy to a C-24 ketone via HSD17B4 activity. The resulting product 3α,7α,12α-trihydroxy-24-oxo-5β-cholestan-(25R)26-oyl-CoA is then oxidized by the enzyme peroxisomal thiolase 2 (SPCx) to the thioester of cholic acid ready for conjugation with glycine, taurine, or hydrolysis to the free acid by peroxisomal acyl-CoA thioesterase (ACOT) (219, 220).The acidic pathway starts with (25R)26-hydroxylation and (25R)26-carboxylation of cholesterol by CYP27A1 and this and many other steps may proceed extrahepatically (Figure 8). Most of the enzymes involved in the neutral pathway are also involved in the acidic pathway although not in the same order (361). An exception is CYP7A1, which is replaced by CYP7B1 as the 7α-hydroxylase in the acidic pathway. CYP7B1 is expressed in many tissues, not just liver (362, 363), and unlike CYP7A1 uses side-chain oxysterols as its substrate. The acidic pathway mostly generates chenodeoxycholic acid rather than cholic acid, so CYP8B1 has minor involvement. The order of A-ring reduction and side-chain cleavage can be reversed in the acidic pathway with the formation of bile acid intermediates possessing 3-oxo-4-ene or 3β-hydroxy-5-ene functions.Steroid Hormone BiosynthesisThe classical steroid hormones aldosterone (mineralocorticoid), cortisol (glucocorticoid), testosterone (male sex hormone) and 17β-estradiol (female sex hormone) are all formed from cholesterol through multiple oxidation reactions (Figure 9) (364, 365). Pregnenolone formed via CYP11A1 oxidation of cholesterol represents an intermediate between oxysterol and steroid hormone biosynthesis. It is oxidized by HSD3B2 to progesterone on the pathway to aldosterone or by CYP17A1 to 17α-hydroxypregnenolone on the route to cortisol. Both these pathways use CYP21A2 as a C-21 hydroxylase and CYP11B enzymes as the 11β-hydroxylase. Note, HSD3B1 is the enzyme which generates progesterone from pregnenolone in the placenta, when progesterone acts as the hormone of pregnancy. Further oxidation of 17α-hydroxypregnenolone by CYP17A1 leads to dehydroepiandrosterone on the road to testosterone and17β-estradiol. In this pathway additional oxidations and reductions are carried out by HSD3B2 and HSD17B3, respectively, while CYP19A1 is required to generate estrogens. Besides being synthesized in the adrenal gland and sex organs it is noteworthy that steroids can be synthesized in the brain and are then named neurosteroids (366, 367). A more general term for brain steroids which may be synthesized in the brain or imported from the periphery and exert rapid non-genomic effects is neuroactive steroids. It is beyond the scope of this review to discuss steroid hormone biosynthesis and metabolism in greater detail and the reader is directed to the excellent reviews of Shackleton and colleagues (364, 368–370).Concluding RemarksEnzymatically oxidized lipids are derivatives of PUFA or cholesterol with critical functions in cellular and physiological processes as signaling mediators and hormones. Their biosynthesis is highly regulated and carried out by enzymes that include LOXs, COXs, CYPs, and AKRs. Advances in our understanding of these enzymes have led to the discovery of novel lipid mediators and their biosynthetic routes. Many functional aspects of these enzymes and their products remain unclear, requiring further investigation. These include elucidating the function of 15-LOX-2 (ALOX15B) in macrophages, the regulatory mechanisms of 12-LOXs and eLOX3, the mechanistic details of transcellular biosynthesis, the origin of 18-HEPE required for E-resolvin biosynthesis, the biological functions of orphan CYPs, and the bioactivities/functions of oxygenated endocannabinoids. The relative physiological importance of some multiply oxygenated PUFA mediators, which are generated in extremely low amounts, also needs to be further clarified. This is also true for multiply oxygenated derivatives of cholesterol.Research on oxygenated PUFA and oxysterols has been carried out largely in parallel, and both areas have benefited greatly from advances in analytical methods. However, there are still major questions to be answered in terms of their proposed roles in human disease including atherosclerosis and neurodegeneration. Here, we presented biosynthetic pathways of oxygenated PUFA and oxysterols, highlighting their (known) functions to show the diversity of products but also to draw connections between the two groups. An integrated approach encompassing the analysis of both lipid groups could be useful in examining the etiology of disease. Despite their involvement in the progression of disease such as atherosclerosis and neurodegenerative disease, the two lipid groups are rarely analyzed together. We propose that oxygenated PUFA and oxysterols are more connected than previously thought, especially as 15-LOX is being increasingly recognized as a regulator of cholesterol metabolism. The immune and nervous systems are both of particular interest as major sites of cholesterol metabolism and 15-LOX expression. Further work on the enzymology of 15-LOX with cholesteryl substrates could lead to the discovery of novel oxidized lipids. For example, 15-LOX oxygenation of PUFA esters of oxysterols could generate novel lipids that link both classes directly in cell types that possess the enzymatic machinery for oxysterol and oxylipin biosyntheses (e.g., macrophages). An alternative biosynthetic route could be through the esterification of oxylipins with free oxysterols. That said, the detection of these proposed molecules could be challenging due to low abundance and sensitivity to alkaline conditions commonly used in analysis. Finally, the substrate promiscuity of many of the enzymes involved in production of oxidized lipids provides a technical challenge for dissection of (patho)physiological function of specific oxidized lipids. Clearly, there is plenty of scope for ongoing exploration of the molecular, cellular, and physiological functions of oxidized lipids.Author ContributionsAH planned the manuscript. AH, WG, and YW wrote the manuscript with input from AF and VO. All authors contributed to the article and approved the submitted version.

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