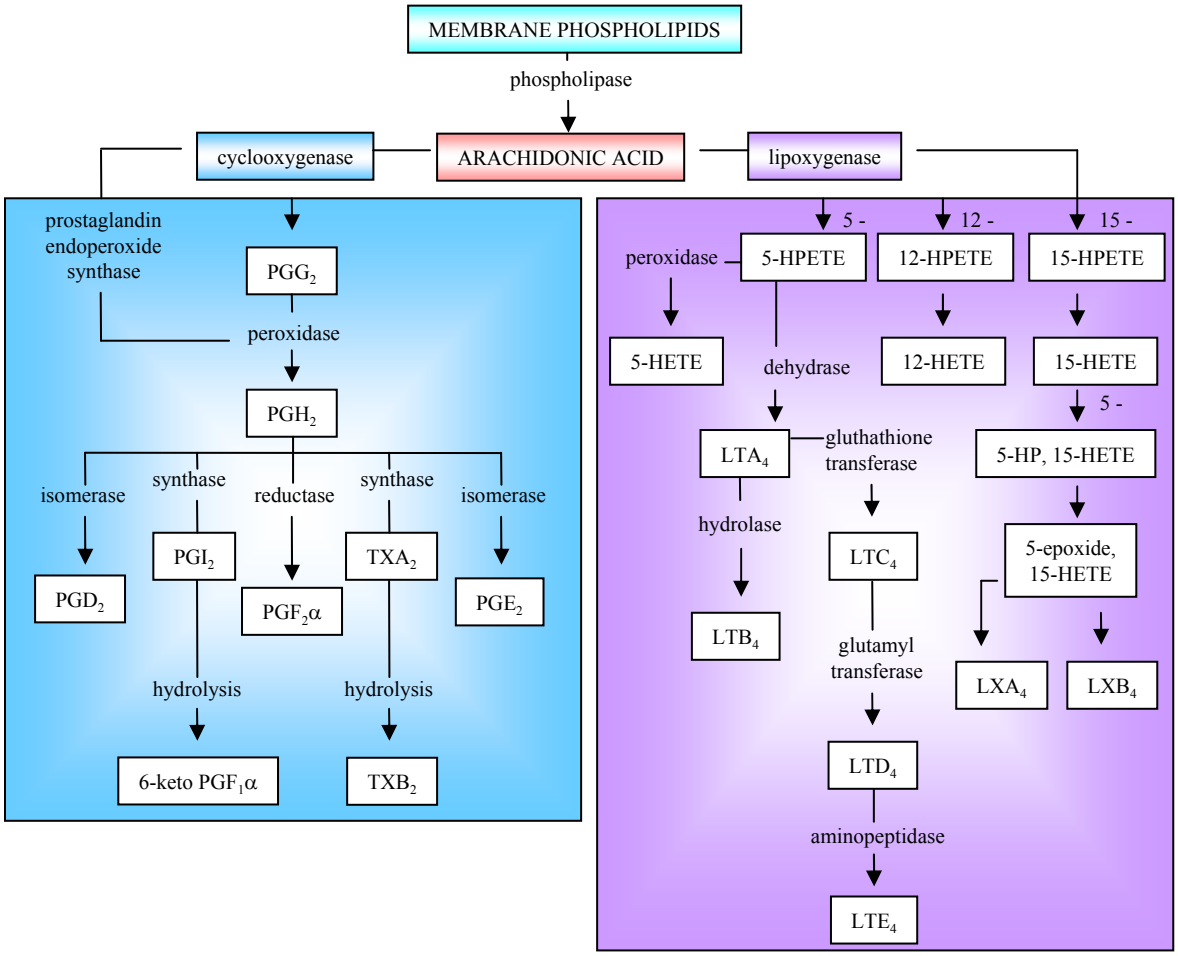

Figure 2-22. Pathways of arachidonate metabolism. Arachidonic acid is transformed into the cyclic endoperoxides by PES. Two single-protein isoenzymes of PES, located within endoplasmic and nuclear membranes, exhibit both cyclooxygenase and peroxidase activities. The cyclooxygenase component of the synthases introduces two molecules of oxygen into arachidonate to yield PGG_2. The peroxidase fraction reduces PGG_2 to PGH_2. Prostaglandin synthases are effectively destroyed by self-catalysis, and therefore, sustained production of prostanoids requires transcription of mRNA and synthesis of new protein. A variety of tissue-specific enzymes compete for the same (unstable) substrate, PGH_2 - dictating the relative amounts of prostaglandins, prostacyclin (PGI_2), or thromboxanes synthesized. Isomerases catabolize PGH_2 into either PGD_2 or PGE_2. A- and B-series prostaglandins are derived from PGE_2 by sequential dehydration and isomerization. Prostaglandin $F_2\alpha$ is generated via reduction of PGH_2. Other (inactive) metabolites of reduction of PGH_2 are 12-L-hydroxy-5, 8, 10-heptadecatrienoic acid and malondialdehyde. Prostacyclin and thromboxane (TX) synthases form PGI_2 and TXA_2. Hydrolysis of PGI_2 and TXA_2 yields inactive by-products (6-keto-$PGF_1\alpha$ and TXB_2) of much greater stability (these are commonly measured in lieu of the precursors). Additional enzymes can interconvert the prostaglandins; for example, PGE_2 can be modified to $PGF_2\alpha$ by the action of PGE_2-9-ketoreductase (the reverse conversion, oxidation of the C-9 hydroxyl group of $PGF_2\alpha$ to a ketone, also can take place).

The second major pathway of arachidonic acid metabolism involves a class of enzymes known as the lipoxygenases; these cytosolic dioxygenases transform arachidonate to hydroperoxides. The site of specificity of attack of the lipoxygenases along the arachidonate molecule is denoted by the number of the product carbon (eg., 5, 12, or 15) at which the hydroperoxy group is attached. The cellular distribution of lipoxygenases is more restricted than that of PES. Leukocytes and mast cells are rich in 5-lipoxygenase. The 12- and 15-lipoxygenase routes are predominant in platelets and respiratory tissues, respectively. Leukotrienes (LTs) originate from the 5-lipoxygenase pathway; they retain, albeit rearranged, the same number of double bonds (4) as arachidonic acid. Arachidonic acid is first metabolized by 5-lipoxygenase to 5-hydroperoxyeicosatetraenoic acid (5-HPETE), which is then either converted by a competing peroxidase to 5-HETE, or dehydrated into an unstable epoxide intermediate, LTA_4 (5-lipoxygenase exhibits dual enzymatic activities, 5-HPETE-forming and LTA4 synthase). Leukotriene A_4 can be hydrolyzed to form a dihydroxy derivative, LTB_4, or is linked with glutathione to create LTC_4. Enzymatic cleavages of g -glutamyl and glycine from LTC_4 yields LTD_4 and LTE_4, respectively. The 6-sulfido peptidoleukotrienes (C, D, and E) are collectively known as the slow-reacting substances of anaphylaxis. Arachidonic acid is transformed into 12-HPETE by 12-lipoxygenase, which is then rapidly reduced to its hydroxy analogue, 12-HETE. Finally, arachidonic acid is metabolized by 15-lipoxygenase into 15-HPETE, which can then be reduced to 15-HETE by peroxidation, or moreover, subjected to the successive action of 5-lipoxygenase to form the tetraene trihydroxy lipoxins (LXs).