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STRUCTURE, FUNCTION, AND DIETARY REGULATION OF Δ6, Δ5, AND Δ9 DESATURASES

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■ **Abstract** Fatty acid desaturases introduce a double bond in a specific position of long-chain fatty acids, and are conserved across kingdoms. Degree of unsaturation of fatty acids affects physical properties of membrane phospholipids and stored triglycerides. In addition, metabolites of polyunsaturated fatty acids are used as signaling molecules in many organisms. Three desaturases, Δ9, Δ6, and Δ5, are present in humans. Delta-9 catalyzes synthesis of monounsaturated fatty acids. Oleic acid, a main product of Δ9 desaturase, is the major fatty acid in mammalian adipose triglycerides, and is also used for phospholipid and cholesteryl ester synthesis. Delta-6 and Δ5 desaturases are required for the synthesis of highly unsaturated fatty acids (HUFAs), which are mainly esterified into phospholipids and contribute to maintaining membrane fluidity. While HUFAs may be required for cold tolerance in plants and fish, the primary role of HUFAs in mammals is cell signaling. Arachidonic acid is required as substrates for eicosanoid synthesis, while docosahexaenoic acid is required in visual and neuronal functions. Desaturases in mammals are regulated at the transcriptional level. Reflecting overlapping functions, three desaturases share a common mechanism of a feedback regulation to maintain products in membrane phospholipids. At the same time, regulation of Δ9 desaturase differs from Δ6 and Δ5 desaturases because its products are incorporated into more diverse lipid groups. Combinations of multiple transcription factors achieve this sophisticated differential regulation.

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INTRODUCTION

Unsaturation of a fatty acid chain is a major determinant of the melting temperature of triglycerides (TGs) as well as the fluidity of biological membranes that are made of a bilayer of phospholipids (PLs). Thus, fatty acid desaturases that introduce a double bond into a long-chain fatty acid are conserved across kingdoms. In addition to this fundamental function of maintaining the physical property of PLs and TGs, another class of unsaturated fatty acids such as arachidonic acid (20:4 n-6) and docosahexaenoic acid (22:6 n-3) is essential for many physiological functions in animals including humans. Three desaturases are known in humans. Stearoyl CoA desaturases (SCDs, also called Δ9 desaturases) catalyze synthesis of monounsaturated fatty acids (MUFAs), whereas Δ6 desaturase (D6D) and Δ5 desaturase (D5D) are required for the synthesis of highly unsaturated fatty acids (HUFAs) (Figure 1). The primary focus of this review is mammalian D6D and D5D. Another mammalian desaturase, SCD, is also discussed in this review to present overlapping as well as distinct roles of these three desaturases. Desaturases in other species are also covered briefly to review the physiological roles of desaturases in a larger context.

SEQUENCE AND STRUCTURE OF DESATURASES

Classifications and Characteristic Features of Desaturases

Because unsaturated fatty acids are essential for maintaining cellular functions, free-living organisms possess fatty acid unsaturation machineries. In many prokaryotes, fatty acid unsaturation is achieved anaerobically by components of the fatty acid synthetic pathway (85). Another mechanism catalyzed by fatty acid desaturases introduces a double bond into fatty acids aerobically. Fatty acid desaturases are nonheme iron-containing enzymes that introduce a double bond between defined carbons of fatty acyl chains. Delta desaturases create a double bond at a fixed position counted from the carboxyl end of fatty acids, whereas omega desaturases act on a specific position counted from the methyl end of a fatty acid. This reaction requires molecular oxygen, NAD(P)H, an electron transport system (ferredoxin-NADPH reductase and ferredoxin, or cytochrome *b*5 reductase and cytochrome b_5), and a terminal desaturase.

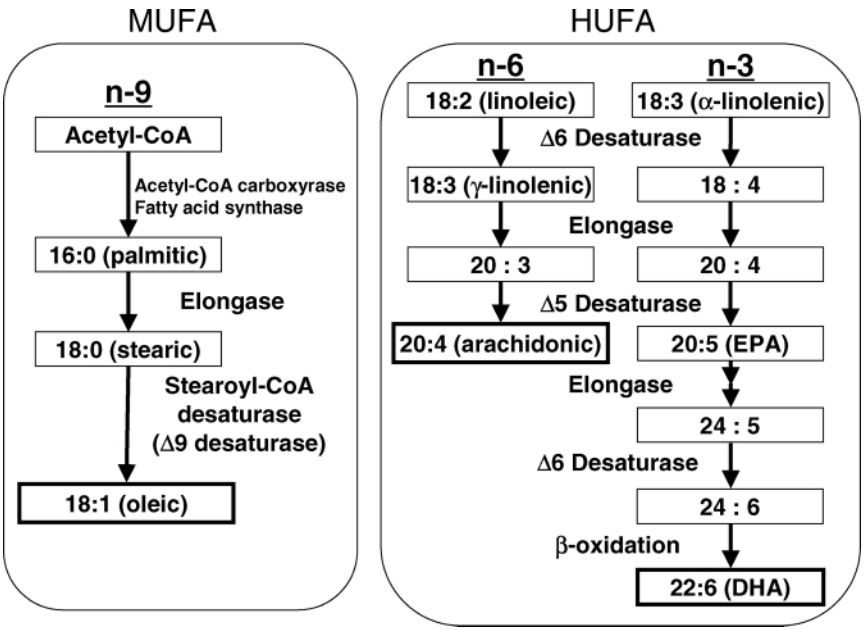

Figure 1 Synthesis of unsaturated fatty acids in mammals. MUFA, monounsaturated fatty acid; HUFA, highly unsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

Desaturases can be classified into two groups: soluble desaturases and membrane-bound desaturases. Acyl-acyl carrier protein (ACP) desaturases are soluble desaturases, which are exclusively localized in the plant plastid. These enzymes require NADPH and oxygen, and are associated with an electron transport sequence comprising ferredoxin-NADPH reductase and ferredoxin (157). Acyl-ACP desaturases contain two atoms of iron and the two D/EXXH motifs of amino acid sequence involved in binding the di-iron complex (28, 157, 163).

Membrane-bound desaturases can be divided into two subgroups. One is the acyl-lipid desaturases. This group of enzymes is localized in the membranes of cyanobacterial thylakoid, plant endoplasmic reticulum (ER), and plastid. Acyl-lipid desaturases use either ferredoxin (in cyanobacteria and plant plastid) or cytochrome b_5 (in plant ER) as an electron donor (177). Ferredoxin, a soluble protein, acts as an electron donor for both acyl-ACP desaturases and acyl-lipid desaturases in plant plastid. Acyl-lipid desaturases in cyanobacteria and plant plastid can desaturate stearic (18:0) and oleic (18:1 n-9) acyl groups in monogalactosyl diacylglycerol (cyanobacteria and plant plastid) and in phosphatidylglycerol (plant plastid), whereas plant ER desaturases mostly use fatty acid in phosphatidylcholine (119, 177).

The other subgroup of membrane-bound desaturases is the acyl-coenzyme A (CoA) desaturases. These desaturases are present in ER membrane and use

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fatty acyl-CoAs as substrates. Like ER-bound acyl-lipid desaturases, acyl-CoA desaturases require cytochrome b_5 as an electron donor (177). Acyl-CoA desaturases are present in animals including insects and nematodes as well as in fungi. All mammalian desaturases that have been identified are acyl-CoA desaturases.

The analysis of the predicted amino acid sequences of membrane-bound desaturases indicates that these enzymes contain two long hydrophobic domains that would be capable of spanning the membrane bilayer twice. The comparison of sequences has also revealed the existence of three regions of conserved His-box motifs that contain eight histidine residues: $HX_{3-4}H$, $HX_{2-3}HH$, and $H/QX_{2-3}HH$. These histidine residues are potential ligands of iron atoms and act at the catalytic center of desaturases. Acyl-ACP desaturases are structurally unrelated to membrane-bound desaturases.

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Delta-9 Desaturases

STEAROYL-CoA DESATURASE Monounsaturated fatty acids (MUFAs) are synthesized from saturated fatty acids by Δ9 desaturases (D9Ds). These enzymes introduce the first *cis*-double bond at the 9, 10 position from the carboxyl end of fatty acids. Mammalian D9D, usually referred to as stearoyl-CoA desaturase (SCD), was first purified from rat liver (166). Subsequently, its gene was identified from the amino acid sequence (174, 175). SCD catalyzes the Δ9 desaturation of fatty acyl-CoA with 12 to 19 carbon chains (121). This reaction requires NADH, oxygen, and an electron transport sequence comprising NADH-cytochrome *b*5 reductase, cytochrome b_5, and SCD (22, 166). The sequence analysis indicates that this enzyme contains three regions of conserved His-box motifs. Site-directed mutagenesis study has shown that any of these conserved His residues are essential for the enzyme activity (158).

Four isoforms of stearoyl-CoA desaturases have been identified in mice (SCD-1, -2, -3, and -4), whereas only one SCD that is highly homologous to mouse SCD-1 is known in humans (100, 122). The four SCDs in mice exhibit tissue-specific expression. SCD-1 is expressed constitutively in adipose tissue and is markedly induced in liver in response to feeding with a high-carbohydrate diet (122). SCD-2 is expressed in the brain and harderian gland; SCD-3 is abundant in the harderian gland (122). SCD-4 was recently identified and is expressed exclusively in heart (100). Physiological roles and regulations of these SCD isoforms are unknown.

YEAST OLE1 Yeast *Saccharomyces cerevisiae OLE1* gene encodes the Δ9 fatty acyl-CoA desaturase. Ole1 protein catalyzes the desaturation of palmitic acid (16:0) and 18:0 to produce palmitoleic acid (16:1 n-7) and 18:1 n-9 (167, 168). This enzyme is ER membrane–bound and contains all the structural features of SCD, including two membrane-spanning domains and three His-box motifs. In addition, *OLE1* contains the cytochrome b_5 domain at its carboxyl terminal region (99). Mutation of the cytochrome b_5 domain resulted in the loss of complementation to the unsaturated fatty acid auxotrophy, which indicates that the cytochrome b_5 domain of Ole1 protein plays an essential role in the desaturase reaction (99).

DELTA-9 DESATURASES IN OTHER SPECIES The D9Ds in animals including insects, nematodes, and vertebrates share common features. For example, they are microsomal acyl-CoA desaturases and use NADH, cytochrome b5, and NADH-cytochrome *b*5 reductase. Similar to yeast, a D9D from a fungal strain, *Mortierella alpina* has a putative cytochrome b_5 domain at the C-terminal (151). In cyanobacteria *Anabaena variabilis* and *Synechocystis* sp. PCC 6803, acyl-lipid desaturases catalyze the Δ9 desaturation of 18:0 in the *sn-1* position of glycerolipids (150). In plants, soluble acyl-ACP desaturases catalyze this reaction (157, 177).

Delta-6 and Delta-5 Desaturases

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DELTA-6 DESATURASES D6Ds are membrane-bound desaturases that catalyze the synthesis of polyunsaturated fatty acids (PUFAs). D6D was first cloned from *Synechocystis* using gain-of-function cloning (138). Subsequently, other D6Ds were cloned from *Borage officinalis* (155), *Caenorhabditis elegans* (114), humans (11), mice (11), and rats (1) using a sequence homologous to the *Synechocystis* D6D or other desaturases.

D6D is classified as a front-end desaturase because it introduces a double bond between the pre-existing double bond and the carboxyl (front) end of the fatty acid. Sequence analysis of deduced amino acid has shown that D6Ds contain the amino-terminal cytochrome b_5 domain carrying heme-binding motifs (Figure 2). The *Borage* D6D is an acyl-lipid desaturase that uses linoleate in phosphatidylcholine as a substrate (169), whereas D6Ds in other species are acyl-CoA desaturases. D6Ds also have two membrane-spanning domains and three His-box motifs that are characteristic of membrane-anchored desaturases. However, the first His residue of the third His-box is replaced with glutamine (QXXHH instead of HXXHH). A study using site-directed mutagenesis of borage D6D revealed that this glutamine residue is essential for D6D activity because mutations of glutamine to histidine as well as glutamine to isoleusine abolished the activity (154). Point mutation of the cytochrome b_5 domain revealed that this domain was also essential for the activity of D6Ds (35, 154).

DELTA-5 DESATURASES D5D, another front-end desaturase present in animals, catalyzes HUFA synthesis (Figure 1). After desaturation and elongation by D6D and elongase, respectively, D5Ds introduce another double bond at the Δ5 position of 20-carbon fatty acids 20:3 n-6 and 20:4 n-3 (Figure 1). D5D genes have been cloned from several animals including humans (10), rats (200), and *C. elegans* (186). The human D5D gene encodes 444 amino acids (the same number as the human D6D) and possesses 61% amino acid identity and 75% similarity to the human D6D. The predicted amino acid sequence of D5D contains all of the structural characteristics present in D6Ds (10).

Recently, Hastings et al. cloned and characterized a zebrafish (*Danio retio*) desaturase that is homologous to both D6D and D5D (38). The deduced amino acid sequence of this enzyme shared 64% and 58% identity with human D6D and

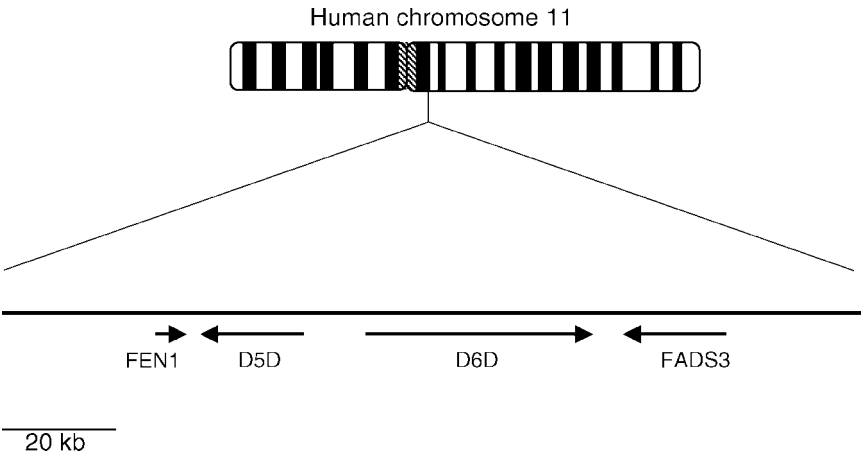

Figure 2 Localization of the human desaturase genes. D5D, Δ5 desaturase; D6D, Δ6 desaturase; FADS3, fatty acid desaturase 3; FEN1, flap-end nuclease 1.

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D5D, respectively. This enzyme was able to convert not only linoleic (18:2 n-6) and α-linolenic (18:3 n-3) acids to 18:3 n-6 and 18:4 n-3, but also produced arachidonic (20:4 n-6) and eicosapentaenoic (20:5 n-3) acids when the enzyme was expressed in yeast (38). This result indicates that the zebrafish desaturase possesses both D6D and D5D activities. The existence of Δ5/Δ6 bifunctional desaturase implies that Δ6 and Δ5 desaturases are evolved from common ancestors.

LOCALIZATION OF HUMAN *D5D, D6D,* AND *FADS3* GENES IN HUMAN CHROMOSOME

The computer search of the NCBI database (human genome resources) has shown that *D5D* and *D6D* genes are localized in chromosome 11 (11q12–q13.1) as a cluster (Figure 2). Both *D5D* and *D6D* genes consist of 12 exons and 11 introns spanning the 17.2 kb and 39.1 kb regions, respectively. Interestingly, *D5D* and *D6D* genes are oriented head-to-head, and exon 1 of both genes is separated by the 11 kb region. The proximity of the promoters suggests the possibility that transcription of the *D5D* and *D6D* genes may be coordinately controlled by common regulatory sequences within the 11 kb region. The third putative desaturase gene (fatty acid desaturase 3, *FADS3*) also has 12 exons and 11 introns. *FADS3* is located in the 6.0 kb telomeric side from the *D6D* gene and is oriented in a tail-to-tail manner (Figure 2). *D5D*, *D6D*, and *FADS3* form a cluster within the 100 kb region of human chromosome and have the same exon/intron organization, which suggests that these desaturases have arisen evolutionarily from gene duplication.

The mouse homologues of *D5D*, *D6D*, and *FADS3* are located in mouse chromosome 19 as a cluster. A sequence analysis of a BAC clone (accession no. AC026761) and a mouse genomic database search shows that the orientation and exon/intron organization of these mouse desaturase genes are similar to that of human homologues.

The human *FADS3* gene has an open reading frame of 1338 bp that encodes 445 amino acids, while the mouse *FADS3* gene possesses a 1350 bp open reading frame for 449 amino acids. The predicted amino acid sequence contains all of the conserved structural features of *D6D*. Alignment of the putative amino acid sequence of human *FADS3* with *D5D* and *D6D* demonstrated that *FADS3* had a high degree of identity (52% with *D5D*, 62% with *D6D*) (87). However, the function of this gene product is unknown. A search of the human expressed sequence tag databases revealed that *FADS3* mRNA was expressed in brain, placenta, ovary, B-cell, and skin as well as in fetal brain.

Omega-3 Desaturases

Omega-3 (n-3) desaturases catalyze a reaction that introduces a double bond between three and four carbons from the methyl end of fatty acids. Amino acid sequences of ω3 desaturases contain three conserved His-box motifs and two membrane-spanning domains that are characteristic of membrane-bound desaturases (177). Like other acyl-lipid desaturases, ω3 desaturases also require ferredoxin (plastid) or cytochrome b_5 (plant ER) (177). Vertebrates do not have ω3 desaturases and consequently must obtain n-3 PUFAs from their diet, but a wide range of organisms other than vertebrates can synthesize ω3 PUFA. The *desB* gene of the cyanobacterium *Synechocystis* sp. PCC 6803 encodes an ω3 desaturase (149). This desaturase is localized in plastid and catalyzes the introduction of a double bond into 18:2 n-6 esterified in the *sn-1* position of glycerolipids (149). The higher plant *Arabidopsis thaliana* has three ω3 desaturases: FAD3, FAD7, and FAD8. In ER, FAD3 introduces a double bond in the ω3 position of 18:2 n-6 to produce 18:3 n-3 using phosphatidylcholine as the major substrate (7). FAD7 and FAD8 are localized in chloroplasts and desaturate glycolipid-bound 16:2 n-6 and 18:2 n-6 to 16:3 n-3 and 18:3 n-3, respectively (49, 95). In nematode *C. elegans*, *fat-1* encodes an ω3 desaturase (165). Both plant and nematode ω3-desaturases have preference to the substrates that contain an n-6 double bond (96, 141).

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FUNCTION OF DESATURASES

Physiological Roles of Stearoyl CoA Desaturases

As shown in Figure 1, mammals have all enzymes for the synthesis of MUFAs from acetyl CoA. SCD catalyzes the last step of this synthesis. The main product, oleic acid (18:1 n-9), is ubiquitously present in all tissues. In mammals, adipose TGs mainly consist of long-chain fatty acids with 16 and 18 carbons. Certain amounts of unsaturated fatty acids (18:1 n-9 and 18:2 n-6) are required to maintain physical property at the body temperature of mammals. In humans, 18:1 n-9 is the major species in adipose TGs, comprising nearly half of total fatty acids (135). Therefore, SCD is a vital component for de novo lipogenesis to store excess energy as a TG form. Indeed, disruption of the *SCD-1* gene in mice profoundly affects

energy metabolism and makes the animal resistant to developing obesity (14, 122, 123, 137).

The significant amount of 18:1 n-9 present in PLs in various tissues and serum in mammals (111, 133, 135) contributes to maintenance of biological membrane fluidity. As shown later in this section, yeast has only one desaturase (Ole1, a Δ9 desaturase), which is sufficient to maintain the physical property of membranes in this organism. In contrast to HUFAs, 18:1 n-9 in membrane PLs does not have a role in cell signaling.

SCD is also required for cholesteryl ester (CE) synthesis in liver (101), and is induced by dietary cholesterol (63, 72). Studies suggest that SCD plays a vital role in cholesterol metabolism by providing a substrate for CE synthesis to temporarily store excess cholesterol in liver (63, 72, 101). Another function of SCD was discovered in SCD-1-null mice, which showed defects in lipid synthesis and secretion from skin and eyelid (102). Dietary supplement of 18:1 n-9 did not correct this abnormality, indicating requirement of endogenous synthesis of MUFAs in these tissues. The involvement of SCD in these multiple metabolic pathways requires complex regulation of this gene by various nutrients as discussed in the next section.

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Functions of Δ6 and Δ5 Desaturases

SYNTHESIS OF HUFAs IN MAMMALS HUFAs, such as arachidonic acid (20:4 n-6) and docosahexaenoic acid (22:6 n-3) are required for various physiological functions for mammals including humans. Mammals are unable to synthesize HUFAs from acetyl CoA because neither ω3 desaturase nor Δ12 desaturase is present in mammals. Thus, two PUFAs, 18:2 n-6 and 18:3 n-3, termed essential fatty acids (EFAs), must be supplied from diets. Mammals are able to synthesize HUFAs from these precursor PUFAs (164). Two desaturases, D6D and D5D, are required for the synthesis of HUFAs (Figure 1). Both D6D and D5D are widely expressed in human tissues, with the highest levels in liver (10, 11).

Animal studies showed that the precursors 18:2 n-6 and 18:3 n-3 are readily stored in adipose TGs, which work as a reservoir of EFAs (81, 92). In humans, fatty acid composition in adipose tissue reflects dietary fatty acids (30). In contrast to MUFAs and precursor PUFAs, HUFAs are poor substrates for TG synthesis, and mainly incorporated into PLs (199), contributing to maintenance of membrane fluidity. However, maintaining membrane fluidity is not the main function of HUFAs in mammals. HUFAs are required for many other functions, such as eicosanoid signaling (29), pinocytosis (156), ion channel modulation (57), and regulation of gene expression (12).

ARACHIDONIC ACID SYNTHESIS AND EICOSANOID SIGNALING Arachidonic acid (20:4 n-6) is one of two major HUFAs synthesized by the D6D/D5D pathway (Figure 1). In many tissues and cell types, 20:4 n-6 is esterified to the *sn-2* position of membrane PLs, and is used for the eicosanoid-mediated signaling to

perform specialized cell functions (199). Arachidonic acid esterified in PLs is a storage form and must be hydrolyzed first to be converted to eicosanoids. Upon stimulation or cell injury, free arachidonic acid is released from PLs by phospholipases, and then is enzymatically converted to eicosanoids (29, 153). Eicosanoids work as autocrine/paracrine hormones and mediate a variety of localized reactions, such as inflammation (29), hemostasis (153), and protection of digestive tract epithelium (130, 183). A human case of D6D deficiency showed severe food intolerance and growth retardation. These symptoms were reversed by arachidonic acid supplementation (191), which indicates the essential nature of eicosanoids in the protection of digestive tract mucosa in humans.

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DELTA-6 DESATURASE IN DOCOSAHEXAENOIC ACID SYNTHESIS Docosahexaenoic acid (22:6 n-3) is another important product of the D6D/D5D pathway. The synthesis of 22:6 n-3 shares a pathway with 20:4 n-6 up to the 20:5 n-3 step. D6D is also required for the synthesis of 22:6 n-3 from 20:5 n-3 (Figure 1). The synthetic pathway of 22:6 n-3 from 20:5 n-3 was first proposed by Voss et al. (180) based on the following observations: (*a*) there was no detectable Δ4 desaturase activity in mammals, and (*b*) 24:5 n-3 was desaturated to 24:6 n-3 and then was readily retroconverted to 22:6 n-3 in rat liver. Recent studies suggest that the final desaturation in 22:6 n-3 synthesis may be catalyzed by the same D6D that catalyzes the first step. Fibroblast from a human case of D6D deficiency was unable to desaturate either 18:2 n-6 or 24:5 n-3 (191). Another study showed that rat D6D was able to desaturate both 18:3 n-3 and 24:5 n-3 at the Δ6 position (18). No D6D isozyme specific to 24-carbon fatty acid is known in any species at this time.

Voss et al. also proposed that peroxisome might be the site of β-oxidation for the last step of 22:6 n-3 synthesis (180) because tissue 22:6 n-3 was decreased in peroxisomal disorders (88). This hypothesis is supported by recent studies. The peroxisomal β-oxidation is carried out by three enzymes: acyl CoA oxidase, bifunctional protein, and 3-ketoacyl CoA thiolase. Each of these enzymes has isozymes (139). Studies with human skin fibroblast showed that a deficiency of either straight-chain acyl CoA oxidase or D-bifunctional protein greatly reduced the 22:6 n-3 synthesis, but it did not completely abolish it (23, 170). An in vivo study using straight-chain acyl CoA oxidase-null mice showed the same results as the studies with fibroblasts (51). These studies have demonstrated a critical role of peroxisomal β-oxidation in 22:6 n-3 synthesis, and suggest that straight-chain acyl CoA oxidase and D-bifunctional protein play the major role in the 22:6 n-3 synthesis, but other peroxisomal isozymes can catalyze the reaction in a lesser degree.

Peroxisomes play the major role in the oxidation of very long chain fatty acids (20 or more carbons) (140). Consistent with this function of peroxisome, dietary fish oil rich in 20:5 n-3 and 22:6 n-3 induces peroxisomal oxidation enzymes (2, 116). Therefore, peroxisomes are likely to be involved in both synthesis and oxidation of 22:6 n-3. Although it is currently unknown how synthesis and degradation of 22:6 n-3 are carried out and regulated in the same organelle, it is possible that

22:6 n-3 required for cellular functions is rapidly incorporated into PLs or transported out of peroxisomes, whereas excess 22:6 n-3 remains in peroxisomes and undergoes further degradation.

FUNCTIONS OF 22:6 n-3 Docosahexaenoic acid is abundant in excitable membranes in retina and brain. In particular, 22:6 n-3 is high in PLs in the rod outer segment of retina and in synaptic vesicles and plasma membrane of neurons (152). Docosahexaenoic acid is essential for the function of retina. Studies with primates and rodents showed that a deficiency of n-3 PUFAs causes impairment in visual function (117, 118). In humans, inclusion of 22:6 n-3 in formula accelerated the development of visual functions in preterm infants (40, 126). However, the mechanism of 22:6 n-3 functions in retina is not well understood. Chen et al. suggested that 22:6 n-3 in retina might be involved in shuttling 11-*cis*-retinal to photoreceptors (9), whereas Salem et al. proposed that 22:6 n-3 in PLs increases efficiency of G-protein-mediated signal transduction of rhodopsin (152).

The role of 22:6 n-3 in brain function is less clear. Recent studies reported impairment of spatial task (105) and olfactory-based learning (33) by deprivation of n-3 fat. In humans, patients with dementia including Alzheimer's disease showed low 22:6 n-3 in plasma lipids (15). Also, improvement of neuronal cell survival by n-3 fatty acids suggests that 22:6 n-3 is tied to differentiated functions of neurons (31, 69). The mechanism of 22:6 n-3 in brain functions is unknown. Salem et al. suggested 22:6 n-3 plays a similar role in both retina and brain (152). A recent study has shown an involvement of 20:4 n-6 in neurotransmitter recycling (156), a finding that implies 22:6 n-3 may also have the same function in neurons containing high 22:6 n-3.

OTHER FUNCTIONS OF HUFAs HUFAs are involved in cellular functions in addition to those described above. Classical studies of the essential fatty acid deficiency in rodents demonstrated main symptoms of dry skin, dermatitis, and massive water loss through skin (42, 132). These symptoms were reversed by dietary n-6 or n-3 PUFAs, although 18:3 n-3 is less effective than 18:2 n-6 (42). Subsequent studies have shown that 18:2 n-6 is required in skin ceramides to prevent water loss (50, 172). However, in a human case of D6D defect, severe abnormalities were also reported in skin, hair, and nail, which indicated that desaturation of substrate PUFAs by D6D is required for these functions. Moreover, dietary supplementation of HUFAs did not reverse these symptoms completely (191), highlighting the importance of the endogenous D6D pathway for skin functions. Taken together, these studies suggest that 18:2 n-6 is required not only for ceramide synthesis but also for HUFA synthesis, although the function of HUFAs in skin has yet to be elucidated.

Another potentially important function of HUFAs is prevention of cardiac arrhythmia during reperfusion after ischemia (71). In heart, HUFAs are released from membrane PLs under hypoxia. These nonesterified HUFAs facilitate synchronizing the contraction of cardiac myocytes upon reperfusion by increasing the

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recovery time of ion channels. This effect is more pronounced in n-3 HUFAs (20:5 n-3 and 22:6 n-3) than in 20:4 n-6, and is the likely mechanism by which dietary fish oil could reduce deaths from myocardial infarction. Another study suggests that by slowing the ion channel activity, n-3 HUFAs may also alleviate the symptoms of convulsive seizures, which are characterized by uncontrolled firings of neurons in the central nervous system (181).

Neurotransmitters are taken up and stored for reuse in very small vesicles via pinocytosis. A study by Schmidt et al. found that endophilin, an essential component in neurotransmitter recycling, is a lysophosphatidic acid acyl transferase (156). Their study suggests that rapid hydrolysis of 20:4 n-6 by phospholipase A2 and reacylation by lysophospholipid acyl transferases change the membrane curvature, and thus play a critical role in pinocytosis in neurons. Docosahexaenoic acid in brain may also serve as a substrate of phospholipases and acyl transferases during pinocytosis because as mentioned previously 22:6 n-3 is highly enriched in the PLs of synaptic vesicles and plasma membrane of neurons (152). It is possible that this postulated function of HUFAs is also used for endocytosis and exocytosis in other tissues such as for insulin secretion in pancreas (53) and for nutrient transport through amniotic fluid during pregnancy (75).

It has long been known that dietary PUFAs suppress lipogenesis in liver (13). In past decades, it became clear that PUFAs and their metabolites exert this effect by regulating gene expression (12, 55). Recent developments further revealed that HUFAs regulate various transcription factors, such as PPAR, liver-X receptor (LXR), HNF4, and SREBP (54). Regulation of desaturase genes by PUFAs is discussed in the next section.

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Desaturase Pathway and Implications for Dietary Requirement of PUFAs

IMPORTANCE OF BALANCED SUPPLY OF n-6 AND n-3 PUFAs Cloning of mammalian *D6D* and *D5D* genes demonstrated that the same enzymes catalyze the synthesis of both n-6 and n-3 HUFAs as shown in Figure 1 (10, 11). Moreover, as discussed in detail in the next section, HUFA synthesis is under strong feedback regulation. This indicates that a balanced supply of dietary n-3 and n-6 fatty acids is important to meet the requirement of both n-3 and n-6 HUFAs. As discussed in the Synthesis of HUFA in Mammals section, both 18:2 n-2 and 18:3 n-3 from diets can be stored in large quantity as adipose TGs (30, 81, 92). However, analyses of fatty acid composition showed very low 18:3 n-3 in adipose TGs in the U.S. population (30, 135), raising concerns that the U.S. dietary supply of 18:3 n-3 may be marginal or deficient. Symptomatic n-3 deficiency has not been identified in humans except for a patient who received lipid emulsion lacking n-3 fatty acid intravenously for a prolonged period (43, 45). Animal studies show that depletion of brain n-3 HUFA is a slow process (117, 118, 152). Therefore, the consequence of marginal n-3 deficiency in humans may take many years to manifest, and could be masked with the loss of brain function by aging.

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POPULATION GROUPS WITH POSSIBLE INSUFFICIENT ENDOGENOUS HUFA SYNTHESIS HUFAs in serum PLs in healthy adults are maintained in a narrow range despite differences in intake of precursor PUFAs (134). Animal studies have shown that tissue 20:4 n-6 stays constant over a wide range of dietary 18:2 n-6 (103, 136). D6D and D5D are fully induced only in EFA-deficient conditions, and are suppressed when adequate precursor PUFAs are supplied from the diet (10, 11), indicating that the capacity of endogenous synthetic pathway is sufficient to meet the requirement of HUFAs in healthy adults.

However, dietary HUFA supplementation may become necessary for certain populations whose endogenous HUFA synthesis is insufficient. Studies indicate that supplementation of n-6 and n-3 HUFAs in preterm infants improves growth and cognitive development (40, 126). Indeed, a search of expressed sequence tag databases reveals the expression of the *D6D* mRNA in human fetus, infant, amnion, uterus, and breast, suggesting maternal contribution of the HUFA supply as well as active HUFA synthesis by fetuses and infants. The elderly is another group that might have insufficient endogenous synthesis of HUFAs. Epidemiological data suggest that consumption of fish oil may be beneficial in preventing dementia (106). As mentioned previously, a chronic marginal deficiency of 18:3 n-3 may be exacerbating the decline of 22:6 n-3 in elderly. Other disease states in which tissue HUFA content and/or synthesis is decreased include diabetes (44, 146), insulin resistance (4), peroxisome disorders (89, 107), and alcoholism (111–113). Although supplementation of dietary HUFA may benefit patients with these diseases, decreased HUFAs are unlikely the central pathology of these disorders.

DIETARY HUFAs AS FUNCTIONAL FOODS Dietary HUFAs also have a property of functional foods because HUFAs exert additional health benefits and therapeutic effects when supplied from diet beyond requirement. When supplied from diets, fish oil rich in 20:5 n-3 and 22:6 n-3 shows a hypotriglyceridemic effect (64) by suppressing secretion of very low-density lipoproteins (25). Dietary n-3 HUFAs also exhibit an anti-inflammatory effect (20) because of a counteracting property of n-3 HUFAs against the formation and actions of 20:4 n-6-derived eicosanoids (67). These studies suggest that combining dietary n-3 HUFAs with a drug therapy may reduce the dose of the drugs required to treat these disorders. However, care must be taken in the use of HUFAs as a functional food because an excessive supplementation of one HUFA (n-3 or n-6) may cause a deficiency in the other. Supplying HUFAs from diets means bypassing the regulation of the endogenous synthetic pathway, and poses potential problems. First, dietary HUFAs markedly change the n-6/n-3 HUFA ratio in PLs because n-6 and n-3 HUFAs compete for the esterification to PLs (189). Second, one group of dietary HUFAs would shut down the synthetic pathway shared by both n-3 and n-6 fatty acids (173), exacerbating the imbalance of n-6/n-3 HUFAs.

Physiological Roles of Desaturases in Other Organisms

UNICELLULAR ORGANISMS Unsaturated fatty acids in PLs increase the membrane fluidity necessary to maintain the proper function of biological membranes. In

particular, desaturation plays an important role in adaptation to a cold temperature in unicellular organisms. In cyanobacteria *Synechocystis* sp. PCC 6803, the growth rate of Fad12 (a Δ12 desaturase) mutant was much lower than the wild type at 22°C but the same at 34°C (182). Also, *desB*, ω3 desaturase in *Synechocystis* sp. PCC 6803, is induced by cold temperature (149). *Escherichia coli* mutants lacking the enzymes in the biosynthesis of unsaturated fatty acid showed auxotrophy for unsaturated fatty acids (16). Ole1, a D9D, is the only desaturase in *S. cerevisiae*, and is required for growth in all temperatures. Mutation of ole1 turns *S. cerevisiae* to auxotroph for oleate (144). *OLE1* mRNA is also increased by cold temperatures, resulting in increased MUFAs in membrane PLs (110).

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PLANTS In higher plants, the cold tolerance is closely correlated with the level of unsaturated fatty acids in phosphatidylglycerol from chloroplast membrane, especially in the *sn-1* position (119). Plants synthesize 18:2 n-6 and 18:3 n-3 from saturated fatty acid 18:0 that are catalyzed by soluble acyl-ACP D9D and membrane-bound Δ12 and ω3 desaturases (119, 177). A *fad2*, *fad6* double mutant of *Arabidopsis thaliana*, deficient with Δ12 desaturase activity, was unable to synthesize PUFAs and showed reduced chlorophyll content and photosynthesis (94). Interestingly, tolerance to high temperature was improved in the transgenic tobacco (knockdown) and *Arabidopsis* mutant, both of which had reduced activity of chloroplast ω3 desaturase (109). The amount of 18:3 n-3 and 16:3 n-3 in chloroplast was lower in these mutants than wild type, whereas 18:2 n-6 and 16:2 n-6 were higher. These results suggest that fatty acid unsaturation determines the temperature range for an optimal chloroplast function in plants.

In addition, PUFAs are used as precursors for the synthesis of oxylipids, which are important signaling molecules for plants. For example, jasmonic acid is synthesized from 18:3 n-3 and participates in various plant physiological functions. A *fad3*, *fad7*, *fad8* triple mutant of *Arabidopsis* that lacked all ω3 desaturases was unable to induce jasmonic acid–mediated defense genes upon microbial infection (145, 179). Pollen development was also impaired in the *fad3, fad7, fad8* triple mutant (93).

ANIMALS In poikilotherms such as fish, unsaturated lipids in membrane are required to adapt to cold temperature. In carp (*Cyprinus carpio*), unsaturation in phospholipid increased at a cold temperatures (178). The D9D activity in carp liver increased without increasing the protein amount shortly after cooling; this was followed by an increase in the amount of transcript from two days after the treatment (176). Eicosanoids are important signaling molecules in fish as well as in mammals. Cyclooxygenese catalyzes the first step of conversion of 20:4 n-6 to prostaglandins (29). Zebrafish have both cyclooxygenase-1 and -2. In zebrafish, thrombocyte aggregation was prevented and bleeding time was prolonged by a cyclooxygenase-1 inhibitor, indomethacin (34). Furthermore, embryo development was impaired by knockdown of the cyclooxygenase-1 gene in zebrafish (34).

A nematode *Caenorhabditis elegans* is capable of synthesizing all necessary PUFAs because *C. elegans* expresses the full range of desaturases such as ω3

desaturase (FAT-1), Δ12 desaturase (FAT-2), D5D (FAT-4), D6D (FAT-3), and D9D (FAT-5, -6, and -7) (97, 114, 131, 165, 187). When *C. elegans* was cultured in a cold temperature, the proportion of PUFAs in PLs increased (172a). These changes in the PLs of *C. elegans* suggest a mechanism of adaptation to a cold temperature. Furthermore, both *fat-2* and *fat-3* mutants showed slow growth rate, sluggish movement, and a reduced brood size (188). The *fat-2* mutant *C. elegans* was deficient in almost all PUFAs and the *fat-3* mutant lacked 20-carbon PUFAs. These results suggest that PUFAs play an important role in the cell growth and neurological development of *C. elegans* (188).

Two D9Ds (Desat1 and Desat2) are the only desaturases identified in the *Drosophila* genome (190). Desat1 introduces the double bond in 16:0, whereas Desat2 prefers myristic acid (14:0) as a substrate. Insects such as the fruit fly *Drosophila* use unsaturated fatty acid to produce cuticular pheromones in addition to the synthesis of membrane PLs (17).

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DIETARY REGULATION OF DESATURASES

Feedback Regulation of Desaturases by Dietary PUFAs in Liver

Mammalian cells require specific amounts of unsaturated fatty acids in PLs for the physical property of membrane and for differentiated cellular functions. In liver, unsaturated fatty acids are also required for synthesis of TGs and CEs. Mammalian desaturases are primarily regulated by induction of the enzyme (11, 120, 173). Promoter activities of desaturases are regulated by multiple transcription factors in liver to meet these various requirements of unsaturated fatty acids. Complex transcriptional regulation by combinations of multiple transcription factors is a mechanism by which higher organisms can achieve diverse functions without increasing the number of genes (77). Thus, regulatory mechanisms of desaturases present fascinating examples of sophisticated transcriptional regulations.

PUFAs are the main dietary component that regulates all three desaturases. Both D6D and D5D are suppressed by dietary PUFAs (10, 11, 129). PUFAs also suppress SCD (41, 124). The suppression of SCD by dietary fat is unique to n-6 and n-3 PUFAs. A product of SCD, 18:1 n-9, is less effective in vivo (41), and has no effect in cells in suppressing SCD expression (3). Two transcription factors, sterol regulatory element binding protein-1c (SREBP-1c) and peroxisome proliferator activated receptor-α (PPARα), play a key role in the regulation of desaturases by PUFAs.

ROLE OF SREBP-1c IN FEEDBACK REGULATION OF DESATURASES BY PUFAs SREBPs are transcription factors of the basic helix loop–helix leucine zipper (bHLHLZ) family, and were initially found as the factors that bind sterol regulatory element (SRE) in the promoter of the *low-density lipoprotein receptor* gene (5). SREBPs have two isoforms, SREBP-1 and SREBP-2, which are transcribed from different genes (48, 196). SREBP-1 has two subforms, SREBP-1a and SREBP-1c, which

are encoded from the same gene by alternative promoter usage (162). SREBP-2 mainly activates the transcription of genes involved with cholesterol synthesis and metabolism, whereas SREBP-1c targets genes for fatty acid synthesis, and SREBP-1a induces both (6, 47). The expression of SREBP-1a is high in dividing cells such as cell lines, whereas SREBP-1c is the major species in many differentiated cells, including hepatocytes (162). SREBPs are synthesized as a larger precursor protein that is anchored to the ER membrane. After proteolytic cleavage, the amino terminal domain migrates to a nucleus and activates target genes (6).

In liver, SREBP-1c activates entire genes of fatty acid synthesis, including all three desaturases (47, 91). SRE has been identified in prompters of many genes, including acetyl CoA synthase (82), acetyl CoA carboxylase (83), fatty acid synthase (84), SCD (171), D6D (115), elongase (104), and S14 (90).

Importantly, SREBP-1c also mediates the PUFA inhibition of D6D (115) and SCD (171, 184) as well as genes involved with fatty acid synthesis, such as fatty acid synthase (193) and S14 (90). PUFAs suppress the target gene transcription by reducing the active form of SREBP-1c (37, 90, 193, 194, 197). More than one mechanism is involved in this process. First, dietary PUFAs reduce nuclear form SREBP-1c in rats (193), and HEK293 cells (37), whereas dietary triolein (18:1 n-9) has no effect (193). Second, PUFAs reduce the stability of *SREBP-1c* mRNA (194). In addition, unsaturated fatty acids inhibit LXR-mediated activation of SREBP-1c by acting as antagonistic ligands in cell lines (127, 197). However, this transcriptional suppression of SREBP-1c by PUFAs is yet to be demonstrated in vivo. The mechanisms by which PUFAs reduce the SREBP-1c processing and the *SREBP-1c* mRNA stability are currently unknown. In *Drosophila* cells, phosphatidylethanolamine suppresses maturation of SREBP (19). In rats, membrane phosphatidylethanolamine was inversely correlated with D6D activity (160). Thus, PUFAs might exert suppression of SREBP-1c processing by changing PL composition in mammals as well.

The target genes of SREBP-1c are not limited to HUFA synthesis; they also include de novo MUFA synthesis, although only PUFAs, not MUFAs, suppress the activity of SREBP-1c. This broader range of targets implies that one physiological function of SREBP-1c is to maintain total unsaturated fatty acids in PLs, and possibly in TGs and CEs as well. Although both substrates and products of the D6D/D5D pathway suppress SREBP-1c processing and mRNA expression, HUFAs are more potent than precursor PUFA, 18:2 n-6 (90, 193). It is currently unknown whether conversion of precursors to HUFAs is required to exert suppression of SREBP-1c.

ROLE OF PPARα IN DESATURASE REGULATION PPARα is a transcription factor of the nuclear receptor family. Like other members of the family, PPARα has a hydrophobic ligand-binding pocket and DNA-binding domain. Binding of a ligand causes a conformational change to PPARα, which then forms a heterodimer with retinoid X receptor and activates transcription of target genes by binding peroxisome proliferator response element (PPRE) located in promoter regions of the

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targets (8). Hypolipidemic compounds called peroxisome proliferators such as fibrates and Wy14643 induce fatty acid oxidation enzymes by acting as ligands of PPARα (27), and in rodents, cause peroxisome proliferation in liver (139). Nonesterified long-chain fatty acids are considered endogenous ligands of PPARα because a variety of long-chain fatty acids bind and activate PPARα (27, 65).

Target genes of PPARα include mitochondrial fatty acid oxidative enzymes (36), mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase (147), cytochrome P450 (CYP) 4A (66), straight-chain acyl CoA oxidase, and peroxisomal L-bifunctional protein (86). Induction of fatty acid oxidation and ketogenesis are impaired in PPARα-null mice during starvation, resulting in hypothermia and hypoglycemia, whereas these animals grow normally when food is freely accessible (62, 70, 74). These studies demonstrated that PPARα plays a critical role in the metabolic adaptation to starvation by inducing genes for fatty acid oxidation.

Kawashima et al. first reported that fibrates increase the activity of D6D and SCD in rats (59, 60). Wy14643 strongly induces the *D6D* mRNA in rat liver (39). Nuclear run-on assay showed that transcriptional activation accounts for the induction of *D6D* mRNA by Wy14643 (173). Cell culture studies detected the presence of PPRE in the promoters of *SCD* (98) and *D6D* genes (173). The induction of desaturases by both PPARα and SREBP-1c is paradoxical because except for desaturases, these two transcription factors induce mutually exclusive sets of genes. PPARα in general induces genes of fatty acid oxidation, whereas SREBP-1 induces genes of fatty acid synthesis.

Peroxisome proliferators may induce desaturases in rodents partly by indirect mechanisms. First, administration of peroxisome proliferators is likely to increase the degradation of unsaturated fatty acids by inducing enzymes for fatty acid oxidation in both peroxisomes and mitochondria (139). Second, the requirement of unsaturated fatty acids for membrane PLs would be increased by administration of peroxisome proliferators, which induce proliferation of peroxisomes and enlargement of liver in rodents (60, 139). These changes would increase the demand of unsaturated fatty acids, resulting in induction of desaturases. Indeed, despite a strong induction of HUFA synthesis by peroxisome proliferators, little change was observed in HUFA composition in PLs (39, 60). Moreover, contrary to the rapid induction of PPARα-responsive genes, for fatty acid oxidation, such as *acyl CoA oxidase*, *carnitine palmitoyl transferase-1*, L-*bifunctional protein*, and *CYP4A*, the *D6D* and *D5D* mRNA took longer to reach maximum induction (39). The *SCD-1* gene also showed a delayed induction by clofibrate in mouse liver (98). These results indicate that indirect mechanisms contribute to the strong induction of desaturases by peroxisome proliferators in rodent liver.

In addition to potential indirect mechanisms, recently obtained data indicates that PPARα also directly activates the *D6D* gene and plays a crucial role in the feedback regulation of HUFA synthesis. The *D6D* mRNA was not induced in PPARα-null mice fed EFA-deficient diets, although nuclear SREBP-1c was elevated in both PPARα-null and wild-type mice (79). This demonstrated that SREBP-1c alone is not sufficient, and PPARα also is required to mediate the feedback

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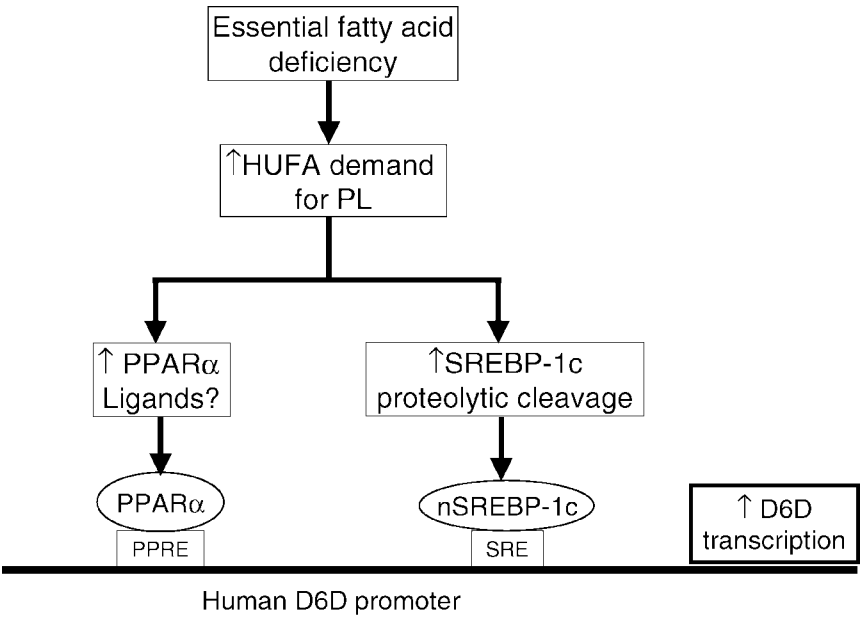

Figure 3 Proposed mechanism of *D6D* gene regulation.

induction of *D6D* when HUFAs are low. Moreover, PPARα-responsive genes such as *acyl CoA oxidase* and *CYP4A* are induced in wild-type mice fed EFA-deficient diets, which suggests endogenous ligands were generated under EFA deficiency (79). As summarized in Figure 3, available data suggest that two mutually antagonistic transcription factors (SREBP-1c and PPARα) act as sensors of HUFA status and together mediate feedback regulation of HUFA synthesis.

Regulation of Desaturases by Other Dietary Components and Hormones

ROLE OF SREBP-1c IN INDUCTION OF DESATURASES BY INSULIN Refeeding a high-carbohydrate diet after fasting rapidly increases SCD protein more than 40-fold in rodent liver, and the induction of *SCD* mRNA parallels its activity (120, 175). Also, both protein and mRNA of SREBP-1c decrease in fasting and increase rapidly in liver upon refeeding (46, 192). Disruption of the *SREBP-1c* gene blunted the induction of lipogenic genes including *SCD* mRNA in mouse liver upon refeeding (80), demonstrating that SREBP-1c at least in part mediates the induction of lipogenic genes. Injection of streptozotocin to rats dramatically decreased *SREBP-1c* mRNA, which was restored by insulin injection (161). Together, these studies suggest that SREBP-1c may mediate insulin effect on lipogenic genes. Consistent with this hypothesis, SREBP-1c binds the insulin response element in the *fatty acid synthase* gene (68, 84, 108). Studies with primary culture of rat hepatocytes showed that

expression of dominant negative SREBP-1c blocked the effect of insulin on transcriptional activation of genes involved in fatty acid synthesis, whereas expression of dominant positive SREBP-1c mimicked the insulin effect (26). The mechanism by which insulin induces *SREBP-1c* is yet to be elucidated.

Conserved SRE sequence GAT/ACAGCAGAG/T is present in the promoters of both *SCD* (3, 171, 198) and *D6D* (115) genes. Also, induction of *SCD* (185) and *D6D* mRNA (146) was diminished in diabetic rats and was restored by insulin administration. However, unlike *SCD*, the *D6D* mRNA was not affected by fasting/refeeding (39, 91). It is currently unknown whether this unresponsiveness is due to the longer half-life of *D6D* mRNA or to other mechanisms.

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INDUCTION OF LIPOGENIC GENES BY CARBOHYDRATES AND THE ROLE OF ChREBP

Storing excess dietary carbohydrates as TGs is another important function of de novo lipogenesis. High glucose adds to the effects of insulin on the induction of glycolytic and lipogenic genes in liver. The carbohydrate response element (ChoRE) that mediates this glucose effect had long been identified in *liver-type pyruvate kinase* and *S-14* genes, although identity of the transcription factor that binds the element was elusive (61, 159). ChoRE consists of tandem E-box (CACGTG)-like sequences separated by five nucleotides. Although the E-box-like sequence suggested that a transcription factor of the bHLHLZ family bound ChoRE, known factors such as upstream stimulating factor did not bind the sequence (61). Recently, the transcription factor that mediates the glucose effect by binding ChoRE has been purified with affinity chromatography and named as carbohydrate response element-binding protein (ChREBP) (195). As predicted, ChREBP is a transcription factor of the bHLHLZ family (195). Under a high glucose condition, ChREBP is dephosphorylated and translocated to nucleus, resulting in the activation of target genes (58). Protein phosphatase 2A, which is activated by xylulose-5-phosphate (an intermediate of the pentose phosphate cycle), is capable of dephosphorylating ChREBP (56).

ChREBP is specifically expressed in liver (195) and adipose (76, 78), two major sites of TG synthesis, whereas SREBP-1c is widely expressed, including in tissues that lack a significant capacity of TG synthesis (162). Moreover, ChREBP was markedly induced when 3T3 preadipocytes differentiated into adipocytes (78), whereas SREBP-1c was not expressed in either 3T3 preadipocytes or adipocytes (162). These studies suggest that ChREBP, not SREBP-1c, plays the major role in the induction of lipogenic genes for storage of excess energy.

In addition to the *liver-type pyruvate kinase* gene, ChoRE has been identified in promoters of *fatty acid synthase* (148), *acetyl CoA carboxylase* (125), and *S14* (159). The presence of ChoRE in *fatty acid synthase* and *acetyl CoA carboxylase* is consistent with the report that these genes are still partially induced in the SREBP-1c-null mice upon refeeding (80). It is likely that ChREBP also regulates *SCD* because (*a*) oleic acid is the major constituent of TGs, and (*b*) disruption of SREBP-1c only partially reduced the induction of *SCD* mRNA upon refeeding (80). Fructose is more potent than glucose in inducing lipogenic mRNA such as

SCD (185) and *fatty acid synthase* (24). It has yet to be elucidated whether ChREBP mediates this fructose effect.

CHOLESTEROL SCD is also required for CE synthesis in liver (101). Dietary cholesterol induces SCD, whereas it depresses D6D and D5D (72, 73). LXR is the likely mediator of cholesterol effect on *SCD*. LXRs are transcription factors of the nuclear receptor family. Two isoforms have been identified: LXRα is the most abundant in liver; LXRβ is expressed ubiquitously (143). LXRs form heterodimers with retinoid X receptor and bind a direct repeat-4 element (LXR response element, LXRE) in target genes (21). Cholesterol metabolites, oxysterols, are its natural ligands and activate LXRs. LXRs activate a group of genes involved in reverse cholesterol transport (21, 143). In liver, activated LXRα induces the messages of *CYP7A* and *ATP-binding cassette transporters G5* and *G8* (143). Because CYP7A is an enzyme that catalyzes the rate-limiting step of bile acid synthesis, and ATP-binding cassette transporters G5 and G8 are cholesterol transporters, an overall effect of LXRα activation in liver is an increase in the bile acid synthesis and the secretion of cholesterol and bile acid to bile. When the LXRα gene is disrupted, the mouse becomes intolerant to dietary cholesterol and accumulates cholesterol in liver, underscoring the physiological function of LXRα (128). In addition, synthetic LXR agonists induce *SREBP-1c*, and LXRE is identified in the mouse *SREBP-1c* promoter (142). Thus, LXR agonists induce the lipogenic genes targeted by SREBP-1c, and increase production of very low-density lipoprotein in liver (32). A physiological role of this SREBP-1c induction by LXRα in liver may be providing fatty acids for the synthesis of PLs, which are also an essential component of bile.

Recently, LXRE was identified in the rat *fatty acid synthase* promoter (52). Also, dietary cholesterol was found to induce the *SCD-1* mRNA in an SREBP-1c-independent manner (63). These observations are consistent with a study of SREBP-1c-null mice in which an LXR agonist failed to induce *glucose-6-phosphate dehydrogenase* and *malic enzyme*, whereas residual induction was observed in *acetyl CoA carboxylase*, *fatty acid synthase*, and *SCD-1* by the LXR agonist (80). Therefore, like in the *fatty acid synthase* gene, the *acetyl CoA carboxylase* and *SCD-1* promoters may also have LXRE, and LXR may induce these genes both directly and indirectly via LXRE and SRE, respectively. Because CEs act as a reservoir when cholesterol is in excess, provision of fatty acids for CE synthesis may be the role for the SREBP-1c-independent induction of these three lipogenic genes by LXR. This explanation fits well with the finding that D6D and D5D were not induced by dietary cholesterol (72).

CONCLUSIONS

Recent cloning of desaturases in many species revealed the conservation of this group of enzymes across kingdoms, and indicated the essentiality of desaturases for free-living organisms. A common function of desaturases for organisms is

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maintaining the physical property of membrane PLs and stored TGs. In addition, many animals and higher plants use PUFAs and metabolites for other functions, cell signaling in particular. Although eicosanoid functions are well characterized, mechanisms of many other functions of PUFAs are yet to be elucidated. Three mammalian desaturases share an overlapping function of maintaining unsaturated fatty acids in PLs. SCD is also required for TG and CE synthesis in liver, whereas D6D and D5D have a role in HUFA synthesis for a variety of cellular functions. Reflecting their functions, the regulation of three desaturases demonstrates shared as well as distinct mechanisms. Recent progress in elucidating regulatory mechanisms of desaturases presents exciting examples of the sophisticated control of mammalian gene transcription that is achieved by a combination of multiple transcription factors such as SREBP-1c, PPARα, ChREBP, and LXR.

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ABBREVIATIONS

16:0, palmitic acid; 16:1 n-7, palmitoleic acid; 18:0, stearic acid; 18:1 n-9, oleic acid; 18:2 n-6, linoleic acid; 18:3 n-3, α-linolenic acid; 20:4 n-6, arachidonic acid; 22:6 n-3, docosahexaenoic acid; ACP, acyl carrier protein; bHLHLZ, basic helix-loop-helix leucine zipper; CE, cholesteryl ester; ChREBP, carbohydrate response element-binding protein; ChoRE, carbohydrate response element; CYP, cytochrome P450; D5D, Δ5 desaturase; D6D, Δ6 desaturase; D9D, Δ9 desaturase; EFA, essential fatty acid; ER, endoplasmic reticulum; HUFA, highly unsaturated fatty acid; LXR, liver X receptor; LXRE, LXR response element; MUFA, monounsaturated fatty acid; PL, phospholipid; PPARα, peroxisome proliferator activated receptor-α; PPRE, peroxisome proliferator response element; PUFA, polyunsaturated fatty acid; SCD, stearoyl CoA desaturase; SRE, sterol regulatory element; SREBP, SRE binding protein; TG, triglyceride.

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