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Fatty Acid–Regulated Transcription Factors in the Liver

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Abstract

Fatty acid regulation of hepatic gene transcription was first reported in the early 1990s. Several transcription factors have been identified as targets of fatty acid regulation. This regulation is achieved by direct fatty acid binding to the transcription factor or by indirect mechanisms where fatty acids regulate signaling pathways controlling the expression of transcription factors or the phosphorylation, ubiquitination, or proteolytic cleavage of the transcription factor. Although dietary fatty acids are well-established regulators of hepatic transcription factors, emerging evidence indicates that endogenously generated fatty acids are equally important in controlling transcription factors in the context of glucose and lipid homeostasis. Our first goal in this review is to provide an up-to-date examination of the molecular and metabolic bases of fatty acid regulation of key transcription factors controlling hepatic metabolism. Our second goal is to link these mechanisms to nonalcoholic fatty liver disease (NAFLD), a growing health concern in the obese population.

Keywords

fatty acids; gene transcription; nuclear receptors; membrane receptors; cell signaling; oxidized fatty acids

INTRODUCTION

A Brief History of Hepatic Fatty Acid–Regulated Transcription Factors

Long-chain ($\geq C_{16}$) fatty acid regulation of hepatic gene transcription was first reported in the early 1990s (10, 54–56, 66). Dietary polyunsaturated fatty acids (PUFAs) suppressed the transcription of genes encoding proteins involved in de novo lipogenesis (DNL), i.e., fatty acid synthase (FASN) and the S14 protein, and glycolysis [L-pyruvate kinase (L-PK)]. In addition, peroxisome proliferator activated receptors (PPARs) were discovered and found to be regulated by fatty acids (34, 47). PPARs are members of the nuclear receptor super-gene family. Together, these early studies established that dietary fatty acids controlled hepatic gene transcription. More than 5,000 papers have appeared in PubMed dealing with fatty acid–regulated gene transcription, and several reviews have been published on the topic (21, 33, 52, 54, 104).

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

Overview of Fatty Acid–Regulated Gene Transcription

Long-chain fatty acids are hydrophobic molecules that affect multiple cellular functions, including membrane composition and fluidity, serving as a source of metabolic energy, functioning as regulatory ligands, and controlling gene expression. Fatty acid effects on hepatic function are diverse, and sorting out these molecular mechanisms is confounded by fatty acid metabolism. Fatty acids regulating hepatic gene transcription are derived from the diet but are also derived from metabolic pathways such as FASN, fatty acid oxidation, and membrane remodeling (Figures 1 and 2). Fatty acids regulate the activity and nuclear abundance of transcription factors through ligand-dependent and ligand-independent mechanisms; they regulate cell-signaling pathways that alter transcription factor function through protein phosphorylation, ubiquitination, or proteolytic cleavage. Some fatty acid–regulated transcription factors, like PPARα, bind directly to DNA, whereas others bind chromatin through protein-protein interaction, e.g., PPARγ-coactivator 1α (PGC1α).

This review focuses on the impact of long-chain ($>C_{16}$) fatty acid regulation of hepatic gene transcription. Our goal is to bring together up-to-date information on how fatty acids control hepatic function through transcriptional mechanisms. Our analysis exposes gaps in our understanding of the molecular details of fatty acid control of several transcription factors. Finally, we examine how fatty acid–regulated transcription factors contribute to the onset and progression of diet-induced nonalcoholic fatty liver disease (NAFLD), a growing health problem in Western societies.

FATTY ACID–REGULATED HEPATIC TRANSCRIPTION FACTORS

Fatty Acid–Regulated Nuclear Receptors

Nonesterified fatty acids (NEFAs) bind to the ligand-binding domain of several nuclear receptors expressed in liver, including PPAR (α, β, γ1, and γ2) (132), HNF4 (α and γ) (29, 129), retinoid X-receptor (RXR) α (69), and liver X receptor (LXR) (α and β) (81). Fatty acids are hydrophobic, and they function like hydrophobic hormones (steroid and thyroid) to control nuclear receptor function. Fatty acid regulation of the PPAR family has been the most extensively studied. PPARs heterodimerize with RXRs and bind *cis*-regulatory elements in promoters of responsive genes (38). All PPAR subtypes bind saturated and unsaturated fatty acids ranging in length from 16 to 20 carbons ($C_{16–20}$), with in vitro binding affinities ranging from K_d = 1 to 10 μM (132). Ligand binding stimulates an exchange of coactivators and corepressors on the chromatin-bound receptors and the recruitment of additional proteins involved in gene transcription, such as ribonucleic acid (RNA) polymerase II (38, 96).

PPARα is the predominant PPAR subtype in rodent liver, and it plays a major role in controlling genes involved in fatty acid elongation, desaturation, oxidation, and transport (52). PPARα, however, is less active in human liver. Studies with PPARα-null mice have established that PPARα is required for PUFA induction of genes encoding enzymes involved in fatty acid oxidation, elongation, and desaturation, but it is not required for PUFA suppression of enzymes involved in other fatty acid–regulated metabolic pathways, such as glycolysis or DNL (94, 126). Although PPARs are sensors of intracellular fatty acids, studies with primary rat hepatocytes suggest that PPARs respond differently to various fatty acids. Challenging cells with oleic acid (OA, 18:1, ω9) or eicosapentaenoic acid (EPA, 20:5, ω3) has different effects on PPARα activation or the induction of PPARα target genes (85). Intracellular NEFAs are considered to be a major intracellular ligand for PPARs, and NEFAs in cells are maintained at very low levels, representing <0.1% of total cellular fatty acids. Challenging cells with a fatty acid that is typically at very low abundance in the liver, such as EPA, promotes a robust response in PPARα target gene expression, e.g.,

cytochrome P450-4A (CYP4A) and cytosolic fatty acyl thioesterase-1. In contrast, challenging cells with fatty acids that are highly abundant in cells, e.g., OA, has little effect on PPARα activation or regulation of its target genes. In addition, some fatty acids may not bind or activate PPARs. Although EPA significantly induces PPARα-regulated target genes in rat primary hepatocytes, α-linolenic acid (ALA; 18:1, ω3), docosapentaenoic acid (DPA; 22:5, ω3), and docosahexaenoic acid (DHA; 22:6, ω3) only modestly induced these same genes. Analysis of hepatocyte fatty acid composition following DPA or DHA treatment shows increases in esterified and nonesterified EPA. EPA arises from the retroconversion of DHA and DPA to EPA (109) (Figure 2). This retroconversion pathway is active in humans and rodents (13, 85, 87, 98). Although cocrystals of PPARβ/δ-EPA have been described, cocrystals of PPARs and fatty acids $\geq C_{22}$ have not been reported (132). PPARs are also regulated by oxidized fatty acids, e.g., eicosanoids (138), and glycerophospholipids, e.g., 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (17).

Although DHA-RXRα interaction in the brain has been described (69), this interaction in liver has not been well studied. Binding of unsaturated fatty acids by LXR (α and β) in cells leads to inhibition of LXR activity (81). LXRα is a key regulator of transcription of multiple genes involved in lipid metabolism and transport (58), including sterol regulatory element–binding protein (SREBP)-1c (95). Some studies support a role of unsaturated fatty acids regulating LXR activity (43, 81), but other short-term (84) and long-term (28) studies fail to show that changes in hepatic unsaturated fatty acid content significantly affect LXR target gene expression, e.g., cytochrome P450-7A (CYP7A), ABCA1, ABCG5, and ABCG8.

Fatty acid binding to HNF4 (α and γ) was documented by X-ray crystallographic analysis of bacterially expressed HNF4 (α and γ) ligand-binding domains (29, 129). HNF4 fatty acid cocrystals reveal several structurally different fatty acids in the putative ligand-binding pocket. Linoleic acid, it appears, is permanently bound to HNF4 (139). Some in vitro studies report that fatty acids are irreversibly bound to HNF4 and fail to exchange with free fatty acids in competitive binding assays (29, 129). Other studies, however, report that linoleic acid binding to HNF4α is reversible (139). In contrast to fatty acid regulation of PPARα, occupancy of HNF4α by linoleic acid does not significantly affect its transcriptional activity. Thus, the role of fatty acid binding to HNF4 remains undefined.

Other Fatty Acid–Regulated Transcription Factors

PUFAs suppress the nuclear abundance of several transcription factors involved in carbohydrate and lipid metabolism and inflammation, including SREBP-1, carbohydrate regulatory element-binding protein (ChREBP), max-like factor X (MLX), and nuclear factor κB (NFκB). Fatty acid regulation of these transcription factors, however, may not involve direct fatty acid binding to the protein (41, 50, 52, 91).

SREBP-1—SREBP-1c is a member of a family of transcription factors (SREBP-1a, SREBP-1c, and SREBP-2) that functions as a master regulator of transcriptional networks controlling hepatic and whole-body cholesterol and fatty acid synthesis and transport (41). SREBP-1 controls the expression of genes involved in fatty acid and triglyceride synthesis, and SREBP-2 controls the expression of genes involved in cholesterol synthesis and uptake (41, 42). SREBP-1 and SREBP-2 are structurally similar, but their regulation in the liver by nutrients and hormones is different. This is graphically seen in neonatal rat liver. The combination of high-fat milk diet and low circulating insulin suppresses SREBP1, but not SREBP-2, nuclear content (46). Although there is ample SREBP-2 in hepatic nuclei to drive expression of its target genes, like HMG-CoA reductase, SREBP-1 is virtually absent from hepatic nuclei, and enzymes involved in DNL, e.g., FASNs, are poorly expressed (11, 125).

Two forms of SREBP-1 are expressed in liver, SREBP-1a and -1c. These transcripts originate from the same gene locus but differ in promoter and exon usage (105). SREBP-1c is the predominant hepatic subtype based on messenger RNA (mRNA) abundance. Nutrient control of SREBP nuclear abundance is mediated by transcriptional and posttranscriptional mechanisms. SREBPs are synthesized as precursors (pSREBP, ~125 kd) tethered to the endoplasmic reticulum (ER) (Figure 3). Precursor SREBPs are escorted from the ER to the Golgi by SREBP-cleavage activating protein (SCAP) interacting with the C-terminal regulatory region of SREBP. Once in the Golgi, SREBPs are proteolytically cleaved by site-1 and site-2 proteases. The mature-nuclear form (~65 kd) is released from the ER and is transported to the nucleus by importin-β (76), where SREBP binds sterol regulatory elements in promoters of target genes. Once bound, SREBPs are phosphorylated and interact with coactivators recruited to promoters; these events stimulate gene transcription (9). Phosphorylation of SREBPs also serves as a signal for ubiquitin ligase binding, SREBP ubiquitination, and proteasomal degradation of nuclear SREBP (39, 40, 92).

Mechanisms controlling SREBP-1 and SREBP-2 nuclear abundance play a major role in SREBP-regulated gene transcription. Cholesterol suppresses SREBP-1 and SREBP-2 nuclear abundance by suppressing the proteolytic cleavage step (30, 41). Cholesterol binding to SCAP induces the ER-resident proteins, Insig-1 or Insig-2, to bind SCAP; the Insig-SCAP-SREBP complex is retained in the ER, preventing its movement to the Golgi for cleavage and maturation (1). As such, cholesterol is a feedback inhibitor of cholesterol metabolism by preventing SREBP-2 from accumulating in nuclei and inducing the expression of genes involved in cholesterol synthesis and transport, e.g., HMG-CoA reductase and low-density lipoprotein (LDL) receptor.

Sterols also act at a second level to control SREBP-2 nuclear abundance. When cellular sterol content is low, ubiquitin ligase gp78 binds Insig-1, promoting its ubiquitination and proteasomal degradation. Low ER Insig1 content promotes SREBP proteolytic processing and the accumulation of nuclear SREBP. Increasing cellular sterol levels displace gp78 from Insig-1 and inhibit Insig-1 ubiquitination and proteasomal degradation; this maintains ER Insig1 content and slows SREBP processing to the nuclear form (62).

When compared to SREBP-2, SREBP-1 nuclear abundance is less sensitive to cholesterol control (30) but very sensitive to changes in blood insulin levels. For example, hepatic nuclear abundance of SREBP-1 is low in fasting; ingestion of low-fat/high-carbohydrate diets induces a rise in blood insulin and increases hepatic nuclear SREBP-1 content and the expression of genes involved in DNL, e.g., FASN. Early evidence suggested that the insulin-regulated phosphoinositol-3-kinase-Akt2 pathway played a major role in controlling SREBP-1 nuclear content (48). More recent studies (68) suggest that the mammalian target of rapamycin (mTOR) complex-1 (mTORC1) and complex-2 (mTORC2) are involved in insulin-mediated control of SREBP1 nuclear abundance (36, 86, 88–90, 135, 138).

PUFAs, but not saturated fatty acids (SFAs) or monounsaturated fatty acids (MUFAs), suppress hepatic SREBP-1 nuclear abundance and suppress expression of its hepatic target genes, including those involved in DNL and fatty acid desaturation (FADS) (SCD1, FADS1, FADS2) (130) and elongation (Elovl) (Elovl 5, Elovl 6) (53, 71, 134). Since desaturases and elongase are involved in PUFA synthesis (Figure 2), PUFAs are feedback inhibitors of their own synthesis as well as inhibitors of DNL and MUFA synthesis (52). The mechanism for unsaturated fatty acid control of SREBP-1 nuclear abundance is very complex, affecting the transcription of the SREBP-1c but not the SREBP-1a gene, stability of SREBP-1 mRNA, proteolytic processing of the precursor to the mature (nuclear form), and proteasomal degradation of nuclear SREBP1 (Figure 3).

In cultured cells, unsaturated fatty acids regulate SREBP1 nuclear abundance by controlling the proteolytic processing step by regulating Insig-1 proteasomal degradation through a postubiquitination step (63). Unsaturated fatty acids do not affect Insig1 ubiquitination; they inhibit ubiquitinated Insig-1 extraction from membranes, a valosin-containing protein (VCP)-mediated process. VCP is recruited to Insig-1 by ubiquitin regulatory X (Ubx) d8 (61), an intrinsic membrane-associated protein that functions as an unsaturated fatty acid sensor. Ubxd8 binds p97 and Insig-1; p97 is necessary for Insig-1 to be recognized and degraded by proteasomes. Unsaturated fatty acids block the interaction between Insig-1 and Ubxd8, thus preventing its extraction from the ER (63). As such, ER-associated Insig-1 interacts with SCAP-SREBP-1 and prevents SREBP-1 from processing to the mature nuclear form. The effect of unsaturated fatty acids on SREBP-1 processing is seen in cells depleted of unsaturated fatty acids. In vivo, however, hepatic cells are not deficient in unsaturated fatty acids. In fact, fatty liver is replete with saturated and unsaturated fatty acids, and hepatic nuclear SREBP-1 content remains high (28).

SREBPs are phosphoproteins, and their phosphorylation status controls their capacity to transactivate genes as well as their nuclear abundance (115, 116). SREBP-1 is phosphorylated by cAMP-activated protein kinase A (PKA); phosphorylation of SREBPs within the DNA-binding domain inhibits SREBP binding to sterol regulatory elements (67). Active extra-cellular receptor kinase-1/2 (Erk1/2) phosphorylates SREBP-1a at Ser^{117} (Ser^{117}corresponds to Ser^{92} in SREBP-1c); this event impairs insulin-stimulated regulation of the LDL receptor (LDLR) promoter by SREBP-1a (97). Phosphorylated SREBPs are also ubiquitinated and degraded by the proteasome (39, 40, 92, 115). Glycogen synthase kinase-3β (GSK-3β) phosphorylates SREBPs (92, 115) (SREBP-1a at $TL^{425}TTPPP^{430}SD$, SREBP-1c at $TL^{395}TPPP^{399}SD$, and SREBP-2 at $LM^{434}SPPA^{438}SD$), which promotes binding of the ubiquitin ligase SCF^{Fbw7}. Once ubiquitinated, SREBPs are degraded in the proteasome (92, 115).

Insulin induces Akt2 phosphorylation, which in turn leads to the phosphorylation and inhibition of Gsk-3β activity (Gsk3β-S^9) (110, 128) (Figure 3). Thus, part of insulin control of SREBP-1 nuclear abundance likely involves inhibition of its proteasomal degradation. DHA is a very potent suppressor of SREBP-1 nuclear content in rat primary hepatocytes (12). Overexpressed constitutively active Akt does not block DHA-mediated suppression of SREBP-1 nuclear abundance. Although all $C_{20–22}$ ω3 and ω6 PUFAs regulate SREBP-1 at the transcriptional level, as well as SREBP mRNA stability, DHA uniquely regulates SREBP-1 nuclear content by stimulating its proteasomal degradation. The nuclear form of SREBP-1 is more sensitive to DHA regulation than SREBP-1 precursor. Studies in rat primary hepatocytes have found no effect of DHA on insulin-regulated insulin receptor, insulin receptor substrate (IRS1, IRS2) tyrosine phosphorylation, phosphoinositide-dependent kinase-1 (PDK1), or mTor-S^{2448} phosphorylation (12, 134). Moreover, DHA transiently lowers Akt2-S^{473} phosphorylation (12); Akt2-S^{473} is a target of mTORC2 and other kinases, e.g., integrin-linked kinase. DHA, however, does not interfere with insulin-stimulated Gsk3β-S^9 phosphorylation. Instead, DHA induces Erk1/2 phosphorylation. The Erk pathway is a downstream target of hepatic insulin action (118). DHA does not affect the rapid insulin-mediated induction of Erk1/2 phosphorylation in rat primary hepatocytes. DHA induces sustained Erk phosphorylation in the presence of insulin. Inhibitors of MAPK/ERK kinase (MEK), an upstream kinase regulating Erk phosphorylation, have established that MEK activity and/or Erk1/2 phosphorylation are linked to rapid control of SREBP-1 nuclear abundance. Thus, DHA regulates SREBP-1 nuclear abundance through phosphorylation/dephosphorylation and proteasomal mechanisms. The mechanism for DHA regulation of Erk1/2 activity has not been established.

ChREBP and MLX—Pathways and target genes of the ChREBP/MLX heterodimer include hepatic glucose transport (Glut2), glycolysis (L-PK), DNL (ACC, FASN), and MUFA synthesis (SCD1, Elovl6). The ChREBP/MLX heterodimer along with SREBP-1 play nearly equivalent roles in the control of DNL (91). Glucose induces and PUFAs suppress the nuclear abundance of the ChREBP/MLX heterodimer (133). Hepatic glucose metabolism is required for glucose to induce the accumulation of ChREBP in nuclei. Glucose, however, does not regulate MLX nuclear abundance (45, 99, 121, 133). ChREBP is a phosphoprotein, and protein phosphatase-2A (PP2A) is involved in regulating ChREBP phosphorylation status (57). Glucose metabolism through the hexose monophosphate shunt generates xylulose-5 phosphate, a PP2A inhibitor. Phospho-ChREBP migrates to the nucleus where it heterodimerizes with MLX and binds carbohydrate regulatory elements (ChoREs) in promoters of target genes. PUFA suppression of L-PK and other ChREBP target genes involves suppression of both ChREBP and MLX nuclear abundance (26, 133). Although active AMP-kinase (AMPK) inhibits L-PK expression, PUFAs do not increase AMPK activity (133).

NFkB—NFκB is a major transcription factor regulating the expression of genes involved in inflammation (8), including cyclooxygenase (COX)-2, cytokines [e.g., tumor necrosis factor (TNF) α], chemoattractants (e.g., monocyte chemoattractant protein-1), and adhesion molecules [intracellular adhesion molecule-1 (ICAM1) and vascular adhesion molecule-1 (VCAM1)]. Many studies have examined fatty acid effects on NFκB in macrophage and endothelial cells; some studies have assessed fatty acid effects on hepatic NFκB (16, 19, 28, 51). Inflammation in the liver is associated with drug-induced toxicity, viral infections, alcoholic fatty liver disease (AFLD), and NAFLD and involves the resident hepatic macrophage, Kupffer cells, and recruited leukocytes. Paracrine factors generated by these cells will act on other cells, e.g., hepatic parenchymal and stellate cells, to alter hepatic function.

The LDL-receptor knockout ($Ldlr^{-/-}$) mouse has been used extensively to study the onset of diet-induced atherosclerosis. More recently, this mouse model has been used to study diet-induced NAFLD. $Ldlr^{-/-}$ mice fed a high-fat/high-cholesterol (HFHC) diet become obese and develop fatty liver with inflammation (28, 114, 123, 132). In this model of NAFLD, hepatic ω6 PUFA (e.g., 20:4, ω6) content is increased whereas hepatic ω3 PUFA (e.g., DHA) content is decreased. Omega-6 PUFAs are precursors to many proinflammatory oxidized fatty acids, whereas ω3 PUFA are substrates to anti-inflammatory oxidized fatty acids (15, 16). Including $C_{20–22}$ ω3 PUFA (menhaden oil) at 2% energy in the HFHC diet increases hepatic EPA and DHA content and also attenuates expression of several genes linked to inflammation, e.g., *Mcp1* and *CD68*. Dietary lipid effects on the hepatic expression of these genes parallel the nuclear abundance of NFκB (28).

Mechanisms controlling NFκB nuclear abundance involve regulating the interaction between NFκB subunits (p50 and p65) and cytosolic IκB subtypes (α, β, ∈, ζ); IκB sequesters p50 and p65 in the cytosol. Phosphorylation of IκB by IκB-kinase promotes IκB dissociation from p50/p65; IκB is degraded in the proteasome. The NFκB subunits, p50 and p65, move to nuclei and bind regulatory elements in target genes. IκB-kinase activity is regulated by its phosphorylation status; two kinases controlling IκB-kinase phosphorylation status include Akt and transforming growth factor β–activated kinase 1. The NFκB subunits bind promoters as heterodimers of p50/p65, homodimers of p50, and heterodimers of p65 with other transcription factors, like c/EBPα.

Several mechanisms have described ω3 PUFA regulation of NFκB nuclear abundance and the control of inflammation: (*a*) ω3-PUFAs inhibit membrane receptor systems, e.g., Toll-like receptors (TLRs), that activate the NFκB pathway (64); (*b*) activated PPARα negatively

affects NFκB nuclear abundance by inducing IκBα; (*c*) PPARγ binds and sequesters NFκB; and (*d*) ω3-PUFAs selectively suppress p50 versus p65 nuclear abundance (28, 122). Recent studies using the *Ldlr*$^{-/-}$ mouse model of HFHC diet–induced NAFLD established that NFκB-p50 is more vulnerable to ω3 PUFA suppression than is NFκB-p65 (27, 28). Thus, several pathways are involved in fatty acid control of NFκB nuclear abundance and NFκB-regulated gene expression.

REGULATION OF GENE TRANSCRIPTION BY FATTY ACIDS ORIGINATING FROM MEMBRANES

Membrane Structure

Fatty acids are assimilated into membrane lipids. As such, fatty acid structure affects cell signaling by altering membrane fluidity, lipid raft structure, and substrate availability for bioactive lipid synthesis (50). Saturated (16:0) and highly unsaturated fatty acids (DHA) have opposing effects on membrane fluidity, membrane cholesterol content, and lipid raft organization (107, 127). Examples of membrane receptor systems affected by fatty acid composition include TLR2 and TLR4 (44, 64, 65) and Src-family kinases (Fyn, c-Yes) (19, 20, 113). Saturated fatty acids stimulate these signaling pathways, whereas PUFAs antagonize this response. Assimilation of PUFAs into membrane phospholipids disrupts lipid raft structure and interferes with downstream signaling events, like NFκB and its target genes. Although these mechanisms have been described in nonhepatic cells, few studies have specifically examined the impact of fatty acids on hepatic TLR or Src kinases.

Cyclooxygenases, Lipoxygenases, and CYP-Generated Oxidized Fatty Acids

Membrane fatty acids are excised from phospholipids by cellular phospholipases (e.g., PLA2) and serve as substrates for various enzymes. Although the liver expresses COX1 (constitutive), COX2 (inducible), lipoxygenases (LOX-5, -12, and -15), and cytochrome P450 enzymes (CYP2C and CYP4A), the cellular distribution of these enzymes is not uniform. The liver is composed of many cell types, including hepatic parenchymal cells, sinusoidal cells, Kupffer cells (resident macrophage), stellate cells (involved in vitamin A metabolism and fibrosis), and endothelial cells. COX and LOX enzymes are not expressed in hepatic parenchymal cells but are expressed in other liver cells, possibly Kupffer (resident macrophage), stellate, and endothelial cells. Hepatic parenchymal cells, however, express COX receptors and respond to eicosanoid treatment (70). CYP2C and Cyp4A/F4 are well expressed in hepatic parenchymal cells (4, 5). These enzymes use NEFAs as substrates and generate hydroxyl, epoxy, and hydroxy fatty acids. Some of these fatty acids are established ligands for G-protein receptors and nuclear receptors, e.g., PPARα, β/δ, and γ (136, 137).

Eicosanoids derived from the COX and LOX pathways (124) regulate G-protein receptors that control signaling pathways in response to changes in intracellular second messengers (cAMP and Ca^{+2}). As such, these pathways control transcription factor function by regulating their phosphorylation status. The epoxides generated by the CYP2C family have been reported to control regulatory schemes in cardiomyocytes and kidney (5), but their effects on the liver have not been documented.

Resolvins and protectins are another class of oxidized fatty acids that protect against prolonged inflammation (108). The E-series resolvins (from EPA) and D-series resolvins (from DHA) are formed by the action of COX2 plus aspirin, whereas neuroprotectin-D1 is formed by the action of 5-LOX. Resolvins and neuro-protectins are autocoids that function as stop signals in inflammation (103, 140). Although the liver has the requisite enzymes (COX/LOX) and substrates ($C_{20–22}$ ω3 PUFA) for resolvin and protectin production, there is limited information on their formation or function in liver.

G-Protein-Coupled Fatty Acid Receptors

NEFAs bind G-protein receptors (GPRs), specifically GPR40, GPR41, GPR43, GPR83, GPR119, and GPR120 (14, 78, 79). Like the eicosanoid receptors mentioned above, these membrane receptors control cellular levels of second messengers (cAMP and intracellular Ca^{+2}) and signaling pathways and are expressed in a tissue-specific fashion. These receptors are prominently expressed in nonhepatic cells, like adipocytes, gut enterocytes, and macrophage. We recently examined the hepatic expression of GPR40, GPR41, GPR43, GPR83, GPR119, and GPR120; the expression of these receptors is very low (C_t–value ≥28) when compared to cyclophilin (C_t–value ≥17). This outcome agrees with other reports (24). GPR120, however, is particularly interesting because it binds ω3 PUFA in macrophage and fat cells; binding of ω3 PUFA to GPR120 attenuates NFκB and JNK induction of inflammatory mechanisms (79, 80, 100, 117). The low hepatic expression of these receptors does not exclude a role for fatty acid–regulated GPRs in the control of nonparenchymal hepatic cells. Determining whether GPR120 or other fatty acid–regulated GPRs are involved in fatty acid regulation of hepatic function will require additional study (27).

Oxidative Stress and Isoprostanes

Lipid peroxidation is a hallmark of oxidative stress, and excessive production of lipid peroxides has been implicated in the pathogenesis of human diseases. Free radical–mediated (hydroxy, alkoxyl, peroxyl radicals or perox-ynitrate) lipid peroxidation generates products found in cells, blood, and urine. Formation of these oxidized lipids in membranes likely affects membrane fluidity and the function of membrane-associated signaling pathways. Arachidonic acid (ARA), EPA, and DHA are oxidized to F2-isoprostanes, F3-isoprostanes, and F4-neuroprostanes, respectively, by nonenzymatic processes (73, 74, 101, 102). The impact of diet on hepatic oxidative stress was examined in *Ldlr*$^{-/-}$ mice fed a HFHC diet. This diet promotes fatty liver with many characteristics of nonalcoholic steatohepatitis (NASH), including hepatosteatosis, inflammation, fibrosis, and hepatic oxidative. This diet significantly increases hepatic saturated fatty acid SFA and MUFA content, and it induces oxidative stress as reflected in elevated heme oxygenase-1 (Hmox1) expression. Interestingly, urinary isoprostane levels, a measure of whole-body oxidative stress, are low in these mice. Analysis of plasma and hepatic levels of PUFA indicated that ARA was high and EPA and DHA levels were low when compared to control mice fed a nonpurified (chow) diet. Feeding *Ldlr*$^{-/-}$mice a HFHC diet containing menhaden oil (a source of $C_{20–22}$ ω3 PUFA) increased hepatic content of EPA and DHA and lowered hepatic content of ARA. Hepatic and urinary levels of F2-isoprostanes, F3-isoprostanes, and F4-neuroprostanes were increased in mice receiving the HFHC-menhaden oil diet (28, 101, 102). Increasing tissue $C_{20–22}$ ω3 PUFA content in a setting of elevated oxidative stress, i.e., elevated Hmox1, induced isoprostane formation. Interestingly, elevated urinary F3-isoprostanes and F4-neuroprostanes were inversely correlated with hepatic injury, i.e., hepatic alanine aminotransferase (28).

F2-isoprostanes are biologically active and mimic the effects of eicosanoids; they activate thromboxane and PGF2α receptors and induce vasoconstriction in vascular smooth muscle cells. F3-isoprostanes, in contrast, do not regulate these receptor systems (73, 106). As discussed in a section below, dietary $C_{20–22}$ ω3 PUFAs suppress the expression of multiple inflammatory markers of NASH. Whether the anti-inflammatory effects of dietary $C_{20–22}$ ω3 PUFAs on liver are due, at least in part, to increased production of F3-isoprostanes and F4-neuroprostanes remains to be established.

SOURCES OF FATTY ACIDS AND THEIR CONTROL OF GENE TRANSCRIPTION

Exogenously Supplied Fatty Acids

The impact of dietary fat on hepatic gene expression has been well established (52, 54). High-carbohydrate/low-fat diets induce hepatic lipogenic gene transcription by increasing nuclear abundance of SREBP-1, ChREBP, and MLX. Feeding C57BL/6J mice the high-fat/low-carbohydrate diet (Research Diets Inc., #D12492, 60% calories as fat) suppresses DNL and fatty acid elongation by lowering hepatic nuclear content of SREBP-1 and ChREBP (120, 125). When a high-carbohydrate/low-fat diet (66) also contains $C_{20–22}$ ω3 PUFA at >2% of calories, hepatic content of SREBP-1, ChREBP, and MLX is suppressed, leading to a decline in DNL and an induction of fatty acid oxidation.

Removal of ω3 PUFA, but not ω6 PUFA, from the diet induces hepatosteatosis and insulin resistance in mice (82). As expected, mice fed the ω3 PUFA-deficient diet have depleted levels of hepatic ALA, EPA, and DHA, but not hepatic LA and ARA. A result of lower hepatic ω3 PUFA is lower fatty acid oxidation, a PPARα-regulated mechanism, and increased FASN and triglyceride accumulation, SREBP-1- and ChREBP/MLX-regulated mechanisms. Hepatic lipid metabolism is highly responsive to the type and quantity of dietary PUFA ingested.

Endogenously Generated Fatty Acids

The notion that the endogenously generated fatty acids regulate hepatic transcription factors was elegantly established in studies by Chakravarthy et al. (18) using the hepatic-specific FASN-null mouse. FASN activity was required for PPARα signaling. Palmitate (16:0) is a major product of FASN and a known PPARα ligand.

Null mutations in the FADS1, FADS2, and Elovl5 genes have established the requirement for PUFA synthesis as a regulator of multiple physiological processes (31, 75, 77, 111, 112). These enzymes convert dietary LA and ALA to $C_{20–22}$ ω6 and ω3 PUFAs, respectively (Figure 2). In the Elovl5$^{-/-}$ mouse, blood and hepatic ARA and DHA decline and livers become fatty, at least in part, because SREBP-1 nuclear content increases (75). In a mouse model of high-fat (60% calories as fat) diet–induced obesity and glucose intolerance, hepatic expression of Elovl5 is suppressed; other enzymes involved in PUFA synthesis remain unaffected by this diet. These obese mice are hyperglycemic and have fatty livers. Induction of hepatic Elovl5 activity in obese mice using a recombinant adenoviral approach increased the hepatic and plasma content of certain MUFAs (18:1, ω7) and $C_{20–22}$ ω3 and ω6 PUFAs, and it reduced hepatic triglyceride and plasma glucose to normal levels (120). Although the effect of Elovl5 on hepatic triglycerides was linked to the control of fatty acid oxidation, the Elovl5 effect on blood glucose was linked to suppressed expression of enzymes involved in gluconeogenesis, including phosphoenolpyruvate carboxykinase-1 and glucose-6 phosphatase. The forkhead box O1 (FoxO1) transcription factor and its coactivator, PGC1α, are key transcription factors controlling gluconeogenesis. The nuclear abundance of FoxO1 and PGC1α was elevated in livers of obese glucose-intolerant mice but suppressed in livers of obese mice expressing elevated levels of Elovl5. FoxO1 nuclear abundance is regulated by factors controlling its phosphorylation and acetylation status (93). Although phospho-FoxO1 is excluded from nuclei and degraded in the proteasome, acetylated-FoxO1 is retained in nuclei.

Elovl5 exerts an insulinmimetic effect on hepatic FoxO1 nuclear abundance. Elovl5 regulation of FoxO1 requires Akt2; Akt2 phosphorylates FoxO1-S^{256} and other sites. Elovl5 activity regulates Akt2 activity by controlling phosphorylation of Akt2-S^{473} but not Akt2-

T^{308} (a PDK1 site). This specificity is achieved by controlling rictor expression and mTORC2 formation. mTORC2 phosphorylates Akt-S^{473}, which in turn phosphorylates FoxO1-S^{256}; phospho-FoxO1 is excluded from nuclei and degraded in the proteasome (119) (Figure 4). Although Elovl5 elongates both MUFA and PUFA (35, 126) (Figure 2), the effects of Elovl5 on the mTORC2-Akt-FoxO1 pathway were linked to Elovl5 regulation of MUFA synthesis but not PUFA synthesis (Figure 4). Specifically, exogenous 16:1, ω7 and 18:1, ω7, but not 14:1, ω5 or 18:1, ω9, mimicked the effects of elevated Elovl5 activity on rictor, pAkt-S^{473}, and pFoxO1-S^{256} in HepG2 cells (119). Inhibition of fatty acid elongation blocked the 16:1, ω7, but not the 18:1, ω7, effect on rictor, Akt, and FoxO1. As such, 18:1, ω7 is the mediator of Elovl5 regulation of rictor protein expression, Akt and FoxO1 phosphorylation, and gluconeogenic gene expression. These studies uncovered a novel connection between MUFA synthesis and the control of hepatic glucose production by Elovl5, an enzyme typically linked to PUFA synthesis.

HEALTH STATUS AND FATTY ACID CONTROL OF HEPATIC GENE TRANSCRIPTION

Nonalcoholic Fatty Liver Disease

To illustrate how health status affects hepatic fatty acid–regulated transcriptional networks, we present recent findings on the effects of different dietary fatty acids on the onset and progression of NAFLD. NAFLD is a significant health concern in Western societies and is the hepatic manifestation of metabolic syndrome (MetS) (59). MetS risk factors include obesity, elevated plasma triglycerides and LDL cholesterol, reduced high-density lipoprotein cholesterol, high blood pressure, and fasting hyperglycemia (2). NAFLD has increased in parallel with central adiposity, and its prevalence is anticipated to continue to increase (22, 32). NAFLD is now the most common cause of liver disease in developed countries (7) and is defined as excessive lipid accumulation in the liver, i.e., hepatosteatosis (4, 5). NAFLD ranges in severity from simple fatty liver (steatosis) to NASH (3). Simple steatosis is relatively benign until it progresses to NASH, which is characterized by hepatic injury (hepatocyte ballooning and cell death), increased blood levels of hepatic enzymes (alanine aminotransferase), hepatic inflammation, ER stress, oxidative stress, and fibrosis (22, 32, 37, 83). Approximately 30% to 40% of individuals with simple steatosis progress to NASH (72), and NASH can progress to cirrhosis (72), a major risk factor for hepatocellular carcinoma (22). In the two-hit hypothesis for NASH (25), the first hit involves chronic hepatosteatosis as triglyceride and cholesterol (free cholesterol and cholesterol esters). Excessive hepatic lipid sensitizes hepatocytes to the second hit that is manifested by increased inflammation derived from resident (Kupffer cells) and recruited leukocytes/macrophages, induction of oxidative stress, activation of stellate cells, and fibrosis (22, 60). Additional factors contributing to the progression of benign steatosis to NASH and fibrogenesis are the influence of adipokines (e.g., adiponectin, leptin) and gut factors that increase blood levels of bacterial components, like endotoxin (23). The underlying molecular mechanisms for excessive hepatic lipid accumulation and the induction of hepatic inflammation, oxidative stress, and fibrosis, however, remain poorly understood.

Several animal models of NASH have been developed, including feeding rodents high-fat diets or methionine-choline-deficient diets, or using bile duct ligation or carbon tetrachloride injection (intraperitoneal). Ingestion of HFHC diets recapitulates many of the phenotypic features of human NASH, including hepatosteatosis, hepatic damage [plasma alanine aminotransferase (ALT) and aspartate aminotransferase (AST)], hepatic inflammation, fibrosis, and ER and oxidative stress (28, 114, 132). We recently reported on the effects of a HFHC diet (54.4% fat energy, 0.5% cholesterol) on the formation of markers of NASH in *Ldlr*$^{-/-}$ mice (28). After 12 weeks on the HFHC diet, *Ldlr*$^{-/-}$ mice were obese and had

increased levels of stored triglycerides and cholesterol esters (hepatosteatosis), hepatic damage (increased plasma ALT and AST), and increased expression of mRNA markers of inflammation [monocyte chemoattractant protein-1 (*Mcp1*)], fibrosis [collagen (*procol1α1*)], and hepatic oxidative stress (*Hmox1*). Urinary isoprostanes, which reflect whole-body oxidative stress, were low in mice fed the HFHC diet when compared with mice fed a control (chow, nonpurified) diet.

This study also determined if dietary $C_{20–22}$ ω3 PUFA in menhaden oil had the capacity to prevent the onset of NAFLD. As such, dietary $C_{20–22}$ ω3 PUFAs were added to the HFHC diet at 2% total energy (28). This level of $C_{20–22}$ ω3 PUFA is equivalent to the human therapeutic dose of ω3 PUFA used to treat dyslipidemia, i.e., 4 grams per day of Lovaza™ (GlaxoSmithKline) (6). Dietary ω3 PUFA attenuated HFHC diet–induced hepatosteatosis, hepatic damage (plasma ALT and AST), inflammation (*Mcp1*), and fibrosis (*proCol1α1*), but not hepatic oxidative stress (*Hmox1*). Mice fed the HFHC-menhaden oil diet had elevated levels of isoprostanes derived from ω3 and ω6 PUFA, i.e., F2- and F3-isoprostanes and F4-neuroprostanes (28).

The reduction in HFHC diet–induced hepatosteatosis correlated with a reduction in hepatic SREBP-1 nuclear abundance and the expression of its target genes. PPARα target genes, however, were not induced by the HFHC-menhaden oil diet. PPARα function may be impaired by elevated Il-1β (131). Induction of many genes involved in inflammation paralleled the accumulation of NFκB subunits p50 and p65 in hepatic nuclei. Ingestion of the HFHC-menhaden oil diet, however, only suppressed hepatic nuclear abundance of NFκB-p50.

We conducted a follow-up study using the Western diet [43% energy as carbohydrate (27% as sucrose); 41% energy as fat (milk fat and corn oil) plus 0.2% w/w cholesterol] and longer feeding times (16 weeks) to increase the severity of NAFLD in $Ldlr^{-/-}$ mice (27). This study compared the capacity of EPA with that of DHA to attenuate Western diet–induced markers of NASH. DHA was more effective than EPA at suppressing the expression of hepatic markers of inflammation (*Clec4F*, *F4/80*, *Trl4*, *Trl9*, *CD14*, *Myd88*), fibrosis (*sroCol1α1*, *Tgfβ1*), and oxidative stress (NADPH oxidase subunits *Nox2*, *p22phox*, *p40phox*, *p47phox*, *p67phox*). Interestingly, the effects of DHA on NASH markers were achieved without significant reduction in hepatosteatosis. Mice fed the Western diet had higher levels of nuclear NFκB subunits (p50 and p65). DHA, but not EPA, attenuated hepatic nuclear abundance of NFκB-p50 by downregulating NFκB-p50 expression. Neither EPA nor EPA significantly affected hepatic expression of *Hmox1* or Nrf2, a transcription factor controlling the expression of *Hmox1* and other antioxidant response genes. DHA also had little effect on nuclear abundance of Nrf2. In contrast, DHA had a robust suppressive effect on the expression of *Nox2* and its associated components. *Nox2* is a key enzyme involved in generating superoxide (O^-) and has been linked to hepatic fibrosis (49). These outcomes suggest that DHA selectively affects pathways involved in hepatic oxidative stress. In this case, DHA suppression of *Nox2* correlates with the downregulation of stellate cell gene expression involved in fibrosis (*proCol1α1*, *Tgfβ1*).

CONCLUSIONS AND FUTURE DIRECTIONS

Our understanding of fatty acid regulation of hepatic gene transcription has increased considerably over the past 20-plus years. Exogenously supplied and endogenously produced fatty acids alter hepatic gene transcription. These actions of fatty acids change key transcriptional networks controlling hepatic carbohydrate, lipid, and protein metabolism as well as inflammation and oxidative stress. Although some effects of fatty acids are beneficial, e.g., ω3 PUFA attenuation of hepatic inflammation and fibrosis, others are not,

e.g., saturated fatty acid induction of TLR and oxidative and ER stress in NAFLD. Key hepatic targets of fatty acid control include PPAR (α, β/δ, γ), SREBP-1, ChREBP, MLX, NFκB, and FoxO1. Fatty acids use ligand-dependent and -independent mechanisms to control membrane and nuclear receptor function. Several of these molecular targets regulate the phosphorylation status or proteolysis of transcription factors (e.g., SREBP-1, FoxO1) or factors controlling transcription factor function (e.g., IκB, PGC1α). Moreover, fatty acid metabolism plays a critical role in controlling the hepatic fatty acid content. Health status affects hepatic fatty acid metabolism and content. The impact of diet-induced obesity on hepatic Elovl5 activity, an enzyme involved in MUFA and PUFA synthesis, illustrates how a change in MUFA and PUFA synthesis affects the severity of diabetic complications, specifically hyperglycemia and fatty liver.

Despite the progress in defining mechanisms of fatty acid regulation of gene transcription, many unanswered questions remain. Fatty acid regulation of the PPAR family of nuclear receptors represents the best-characterized model, but mechanisms for fatty acid control of other molecular targets, such as SREBP-1, ChREBP, MLX, NFκB, mTORC2, rictor, and Erk1/2, remain poorly defined at the molecular level. Since none of the factors listed above are known to control expression of NADPH oxidase or its subunits, further analysis of ω3 PUFA control of these proteins will likely identify novel fatty acid–regulated mechanisms. Equally unclear is the role that oxidized fatty acids play in hepatic function. Although isoprostanes are generated by nonenzymatic mechanisms, epoxy, hydroxyl, and dihydroxy fatty acids are generated by CYP-mediated pathways. Do oxidized fatty acids generated from ω3 versus ω 6 PUFAs have different effects on hepatic function? Further definition of these pathways will clarify the impact of fatty acids on hepatic function through transcription factor–mediated events.

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Glossary

PUFAs	polyunsaturated fatty acids
DNL	de novo lipogenesis
PPARs	peroxisome proliferator-activated receptors
PGC1α	PPARγ coactivator 1α
NAFLD	nonalcoholic fatty liver disease
RXR	retinoid X-receptor
LXR	liver X receptor
EPA	eicosapentaenoic acid
DHA	docosahexaenoic acid
SREBP	sterol regulatory element–binding protein
ChREBP	carbohydrate regulatory element-binding protein
MLX	max-like factor X
NFκB	nuclear factor κB
mTOR	mammalian target of rapamycin

mTORC	mTOR complex
SFAs	saturated fatty acids
MUFAs	monounsaturated fatty acids
FADS	fatty acid desaturase
Elovl	fatty acid elongase
COX	cyclooxygenase
LOX	lipoxygenase
ARA	arachidonic acid
NASH	nonalcoholic steatohepatitis
FoxO1	forkhead box O1
MetS	metabolic syndrome

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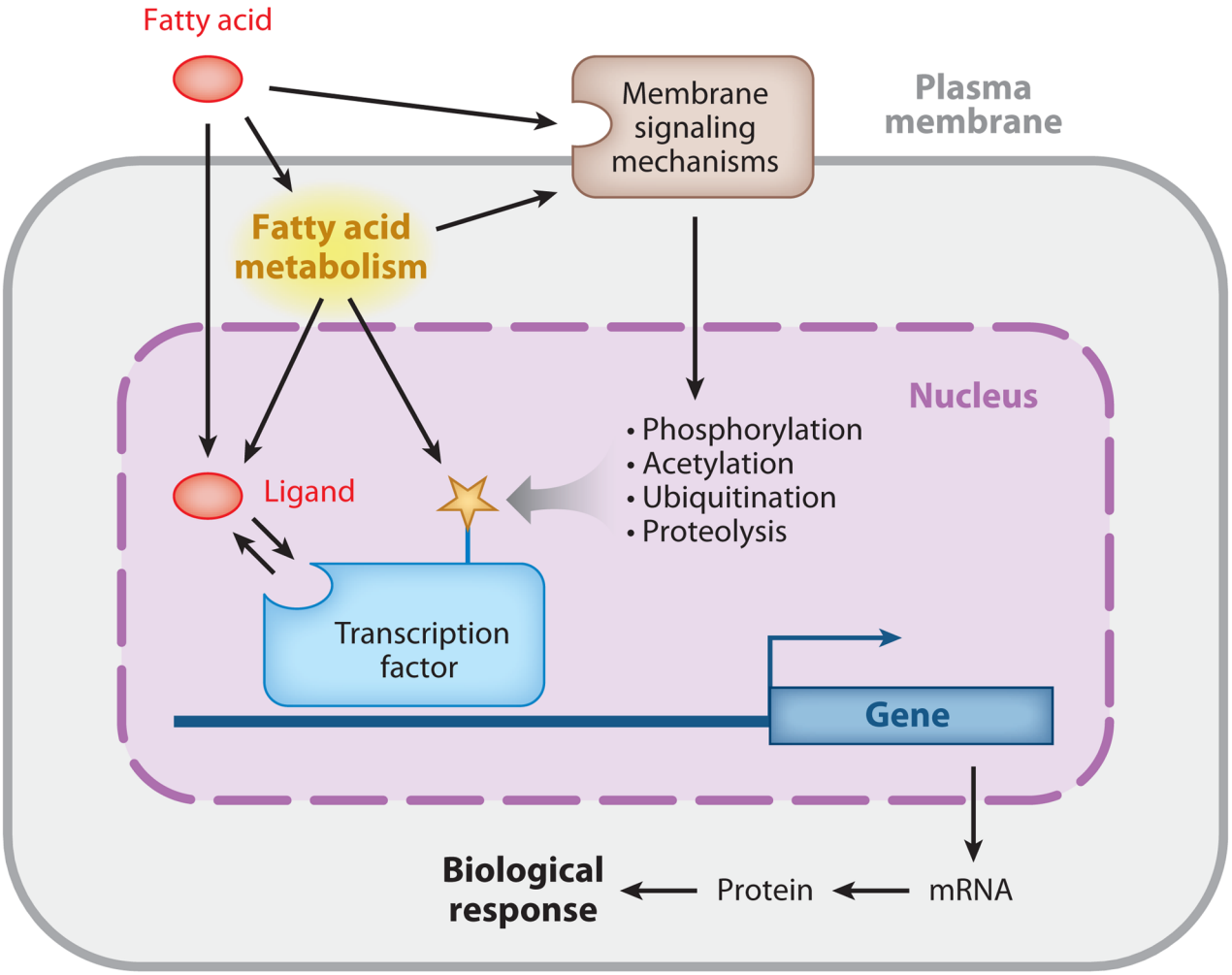

Figure 1.
Overview of fatty acid regulation of hepatic gene transcription.

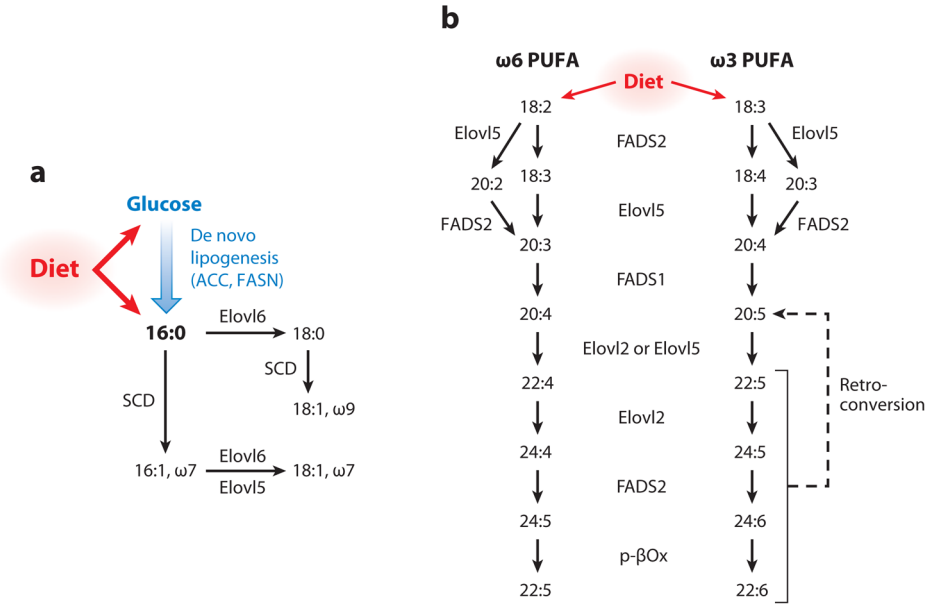

Figure 2.

Pathways for hepatic fatty acid synthesis (FASN). (*a*) The pathway describes the conversion of dietary glucose to palmitate by de novo lipogenesis; the pathway requires acetyl CoA carboxylase (ACC)-1 and fatty acid synthase. Palmitate (16:0) is a product of de novo lipogenesis but is also derived from the diet. Palmitate is subsequently elongated [fatty acid elongase (Elov)l5 and Elovl6] and desaturated [stearoyl CoA desaturase (SCD)] to form $C_{16–18}$ saturated and monounsaturated (ω7 and ω9) fatty acids. (*b*) The essential fatty acids, linoleic acid (18:2, ω6) and α-linolenic acid (18:3, ω3), are derived from the diet. These fatty acids are desaturated [fatty acid desaturases (FADS)1 and FADS2] and elongated (Elovl2 and Elovl5) to form the major $C_{20–22}$ polyunsaturated fatty acids (PUFAs) appearing in cells, i.e., arachidonic acid (ARA; 20:4, ω6) and docosahexaenoic acid (DHA; 22:6, ω3). DHA production requires peroxisomal β-oxidation (p-βOx). C_{22} PUFAs are retroconverted to C_{20} PUFAs by p-βOx.

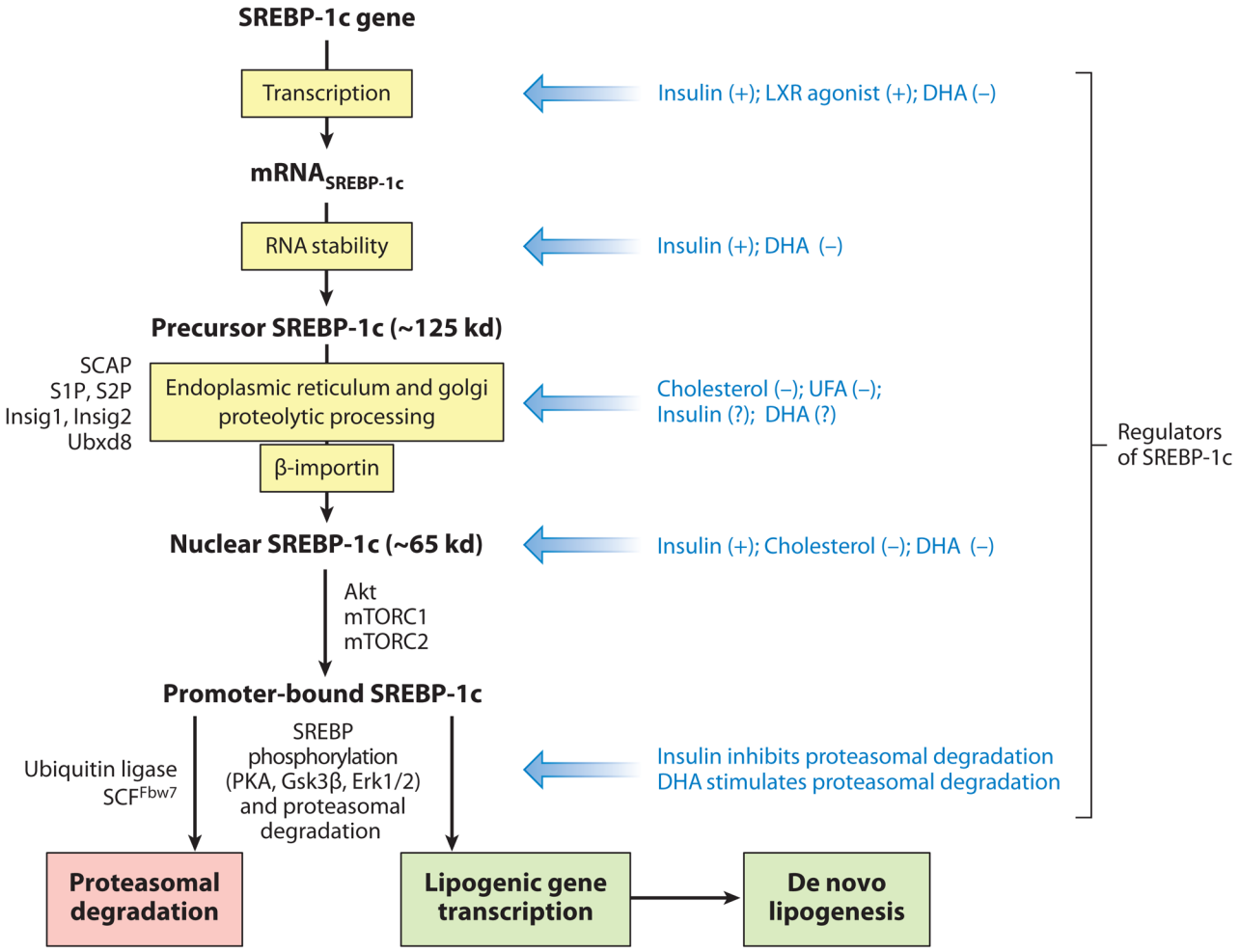

Figure 3.

Nutrient and hormonal regulation of sterol regulatory element–binding protein-1c (SREBP-1c) nuclear abundance. The diagram illustrates the levels of control of SREBP-1c, from gene transcription to degradation of the protein. See text for details on sites of control and regulation of SREBP-1c nuclear abundance. Insulin and liver X receptor (LXR) agonist induce (+) SREBP-1c nuclear abundance, whereas unsaturated fatty acids (UFAs), docosahexaenoic acid (DHA), and cholesterol lower (−) SREBP-1c nuclear abundance. Several enzymes are involved in covalently modifying nuclear SREBP-1, including protein kinase A (PKA), glycogen synthase kinase-3β, extracellular receptor kinase-1 or -2 (Erk1/2), or ubiquitin ligase (SCF^{Fbw7}). Several proteins are also involved in controlling SREBP processing, including insulin-inducible gene (Insig-1 or Insig-2), SREBP coactivating protein (SCAP), site-1 protease (S1P), and site-2 protease (S2P). Abbreviations: GSK-3β, glycogen synthase kinase-3β; mTORC, mammalian target of rapamycin complex; Ubxd8, ubiquitin regulatory X d8; +, induction; -, repression or inhibition; ?, mechanism not defined.

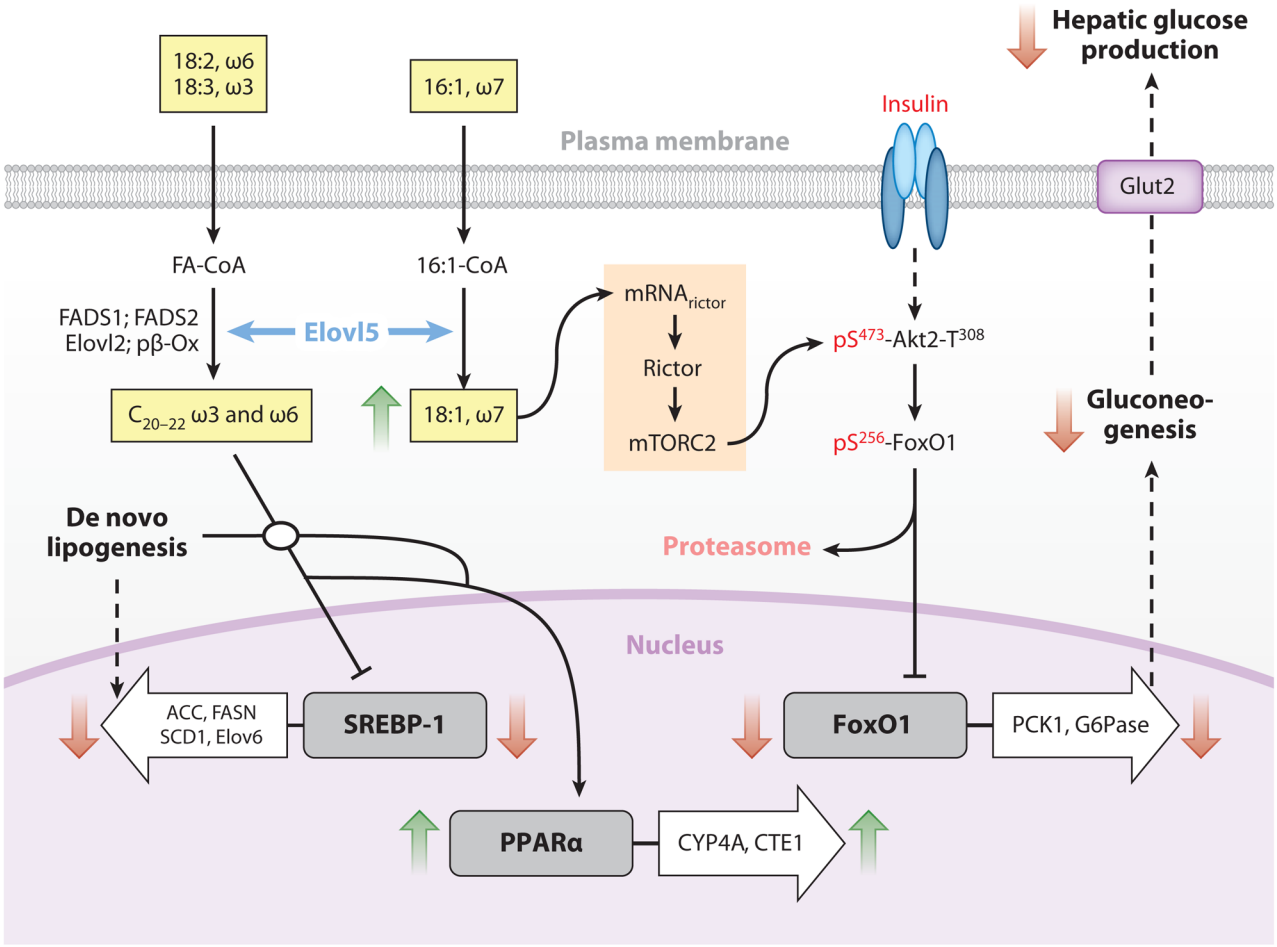

Figure 4.

The role of endogenous fatty acid metabolism in the control of hepatic gene transcription. The generation of fatty acids within hepatic parenchymal cells affects the control of at least three transcription factors, peroxisome proliferator-activated receptor α(PPARα), sterol regulatory element–binding protein 1 (SREBP-1), and forkhead box O1 (FoxO1). The mechanisms include the production of fatty acids by de novo lipogenesis (DNL) and monounsaturated fatty acid (MUFA) (18:1, ω7) and polyunsaturated fatty acid (PUFA) ($C_{20–22}$ ω3 and ω6 PUFA) synthesis. SREBP-1 nuclear abundance is well suppressed by $C_{20–22}$ PUFA, and hepatic conversion of essential fatty acids to $C_{20–22}$ PUFA suppresses SREBP-1 nuclear abundance and DNL. Because this pathway produces both C_{20} and C_{22} PUFAs, PPARα signaling can be affected. C_{20} PUFAs, but not C_{22} PUFAs, are robust activators of PPARα. FoxO1 activity is not affected by exogenous fatty acids or endogenous production of PUFAs. FoxO1 nuclear abundance, however, is regulated by mechanisms that control hepatic conversion of palmitoleic acid (16:1, ω7) to cis-vaccenic acid (18:1, ω7). Increased hepatic production of 18:1, ω7 induces production of rictor, a component of mTORC2. mTORC2 phosphorylates Akt-S^{473}, and active Akt phosphorylates FoxO1-S^{256}. Phospho-FoxO1 is excluded from nuclei and degraded in the proteasome. The outcome is suppressed expression of genes involved in gluconeogenesis (GNG) and hepatic glucose production (HGP). The up (*green*) and down (*red*) block arrows represent induction or repression of the pathway or transcription factor. Abbreviations: CTE1, cytosolic thioesterase-1; CYP4A, cytochrome P450-4A; Elovl, fatty acid elongase; G6Pase, glucose-6

phosphatase; mRNA, messenger ribonucleic acid; Pck1, phosphoenolpyruvate carboxykinase.