Fatty acid regulation of gene transcription

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The abbreviations used are: FA, fatty acid; LCFA, long-chain fatty acid; PUFA, polyunsaturated fatty acid; NEFA, non-esterified fatty acid; ALB, albumin; VLDL, very-low-density lipoprotein; LPL, lipoprotein lipase; WAT, white adipose tissue; FAT, fatty acid translocase; FABP, fatty acid binding protein; ACS, acyl-CoA synthetase; SCD1, stearoyl CoA desaturase 1; L-PK, liver-type pyruvate kinase; apo A-1, apolipoprotein A-1; FAS, fatty acid synthase; CAT, chloramphenicol acetyl transferase; PEPCK, cytosolic phosphoenolpyruvate carboxykinase; CPT-1, carnitine palmitoyltransferase; AOX, acyl-CoA oxidase; FARE, fatty acid response element; TF, transcription factor; PPAR, peroxisome proliferator activated receptor; PPRE, peroxisome proliferator response element; DR1, direct repeat 1; RXR, retinoid-X-receptor; PG, prostaglandin; HNF-4, hepatic nuclear factor 4; PL, phospholipids.
Fatty acids (FAs) are highly energetic molecules which play important metabolic roles. They are also integral part of cells as membrane components, thereby influencing fluidity and receptor or channel function. Over the past ten years, it has become evident that FAs can also act as signaling molecules involved in regulating expression of a number of genes. For the major part, these target genes encode proteins having a role in FA transport or metabolism. The corresponding change in the amount of specific proteins is an adaptative process that the cells develop in response to variations in FA concentration in the vicinity of the target tissue. Although interesting progress have been made recently, the mechanism(s) by which FAs modulate gene transcription still remains largely unresolved. The purpose of the present review is to address this important issue.

**Fatty acid structure and metabolism**

A comprehensive description of FA regulation of gene expression requires the notions that 1) FAs include molecules with a common core that are structurally diverse, depending upon chain length and unsaturation degree and 2) FAs are rapidly metabolized in cells.

Long-chain FAs (C16 and above) (LCFAs) can be either saturated or mono- and polyunsaturated (PUFAs) depending upon the introduction of one or more double bonds in the polycarbon chain. The most abundant monounsaturated FA is oleate, in which the chain has 18 carbons and the double bond is between C9 and C10 from the methyl end (C18:1 n-9). The two major classes of PUFAs are n-3 (or ω3) and n-6 (or ω6) depending upon the carbon that bears the first double bond. The precursors of these two classes of FAs cannot be synthesized in humans and must be provided by the diet; they are present in large quantity in fish oil. Interestingly, n-3 and n-6 PUFAs may show opposite properties, probably because they give rise to different eicosanoid (prostaglandins, leukotrienes, thromboxanes) products. For instance, when animal models with a propensity to develop tumors are fed diets containing a
large proportion of n-6 PUFAs, tumor formation is favoured, whereas diets with a similar proportion of n-3 PUFAs are somewhat protective (see reference 1 for a review).

Long-chain FAs are insoluble in water and are carried in plasma either esterified in triacylglycerols arranged in complex structures, the lipoproteins, or in a non-esterified form (NEFAs) loosely bound to to albumin (ALB) (Figure 1). Blood lipoproteins arise from the diet after intestinal absorption and re-esterification (chylomicrons) or they can be produced by the liver (very-low-density lipoproteins; VLDL). In the plasma, lipoproteins are hydrolyzed by the hepatic lipase or by the lipoprotein lipase (LPL) to produce NEFAs locally taken up by the liver or by muscles and adipose tissue. In contrast, circulating NEFAs are produced almost exclusively by white adipose tissue (WAT) as a consequence of lipolysis from the stored triacylglycerols (TAG) during periods of starvation. In lipogenic tissues like liver and WAT, FAs can also be synthetized de novo from glucose and esterified.

Although butyrate, a short-chain (four carbons; C4) FA has been shown in some cases to exert regulation of specific genes besides its well-known effect on chromatin, most of the reported actions of FAs on gene expression have been associated to LCFAs. Clearly, the cell signaling molecule is the free FA (unlinked to ALB) that is transported in and out the cells with the help of a membrane protein, the FA transporter (FAT) for which six potential candidates, the FA translocase (FAT-CD36), the FA transport protein (FATP), the mitochondrial aspartate aminotransferase, caveolin, the adipose differentiation related protein and the FA binding protein (FABP; a cytosolic protein which can bind to membranes) have been cloned and characterized. In the cytoplasm, FAs are taken up by a cell-specific FABP and have alternate destinies (Figure 1). They can be elongated, desaturated, β-oxidized in mitochondria or peroxisomes for energy production, submitted to a peroxidative process or to ω-oxidation in microsomes, exchanged with membrane phospholipids (PL), participate in or interfere with eicosanoid synthesis. It is therefore important to keep in mind that whatever FA
effect is investigated, not only FAs *per se* but also products of FA metabolism or FA-sensitive signal transduction cascade can act as a relay.

**An overview of fatty acid regulation of gene transcription in various organisms**

FA regulation of gene transcription occurs in unicellular and in complex organisms. In *Escherichia coli*, LCFAs are transported and activated in acyl-CoA by FadD, the bacterial acyl-CoA synthetase (ACS). In this simple organism, CoA derivatives, not FAs, bind with high affinity to a transcription factor, the FaDR, preventing its binding to a response element, thereby allowing the gene involved in FA synthesis (*fabA*) to be repressed and those encoding enzymes of FA transport and metabolism (*fadL, fadD, fadE, fabBA, fadH*) to be induced (reviewed in 2).

In yeast it also appears that acyl-CoAs are the active components modulating gene transcription (reviewed in 2). Studies using Saccharomyces cerevisiae have been focused on the regulation of the *OLE1* gene. This gene encodes the Δ−9 desaturase, an integral membrane protein that converts the saturated palmytoyl- (C16:0) and stearoyl- (C18:0) CoAs to the monounsaturated counterparts. As expected from the biological role of the desaturase, *OLE1* gene transcription rate is stimulated in response to exogenous saturated FAs, while exposure to unsaturated FAs sharply reduce transcription (3). The corresponding positive and negative response elements have been located in the *OLE1* upstream promoter region (3). However, the precise mechanisms of activation and of repression remain to be elucidated.

In mammals, the expression of many genes has been shown to be modulated by FAs in a positive or a negative manner. However, only in a few cases has the transcription rate been clearly demonstrated as the main step of control. Post-transcriptional regulation can also occur, as examplified by the PUFA-induced decrease in stability of stearoyl CoA desaturase (SCD1) and glucose transporter 4 (GLUT4) mRNAs in the adipocytes of the 3T3-L1 cell line.
(reviewed in 4). The present review focuses exclusively on the transcriptional aspects of FA control. Studies reporting mRNA variations in response to FAs without the demonstration, by run-on or transfection experiments in differentiated cells, that the rate of transcription is affected are only mentioned when pertinent.

**Negative regulation**

The control of hepatic lipogenic enzymes is currently the best example of negative regulation. Thirty years ago, Allmann & Gibson (5) first observed that feeding mice with linoleate (C18:2 n-6) greatly depressed hepatic lipogenesis and fatty acid synthase (FAS), malic enzyme and glucose-6-phosphate dehydrogenase activities in agreement with what would be expected from the physiology. Surprisingly, however, this effect appeared to be restricted to PUFAs, since neither palmitate (C16:0) nor oleate (C18:1 n-9) was efficient. Following this original observation, several studies showed that a PUFA-rich diet reduced the hepatic mRNA content for FAS, acetyl-CoA carboxylase, L-pyruvate kinase (LPK), ATP citrate-lyase, malic enzyme, SCD1, apolipoprotein A-1 (apo A-1), the S14 protein (reviewed in 4, 6, 7, 8, 9, 10) and more recently, delta-5 and delta-6 desaturases (11, 12).

The work by Clarke, Jump and their coworkers provided insight into the mechanism by which FAS and S14 mRNAs are decreased by PUFAs. Blake and Clarke (13) showed that the reduction in hepatic FAS and S14 mRNAs following the administration to rats of a PUFA-rich diet was caused primarily by the inhibition of gene transcription. In that case, n-3 and n-6 PUFAs were both efficient. This effect was shown to be specific since transcription of the cytosolic phosphoenolpyruvate carboxykinase (PEPCK) (a gluconeogenic enzyme) and actin genes were not affected by the treatment. Because of the difficulty in distinguishing *in vivo* nutritional from hormonal effects, primary hepatocytes were then used to ascertain the direct nature of PUFA action (14). Moreover, transfection of hepatocytes with a chimeric gene
containing −4315 to +19 base pairs (bp) relative to the transcriptional start site of the S14 gene linked to the chloramphenicol acetyltransferase (CAT) structural gene demonstrated that the 5′-flanking region of the S14 gene was involved (14). The PUFA response element(s) were located between −220 and −80 bp of the S14 promoter (14). The question whether the actual modulators are PUFAs per se remains open. The observation that prostanoid inhibitors fail to prevent PUFA action suggest that at least prostanoids are not involved (14). Since the effect is restricted to PUFAs and since PUFAs are very sensitive to peroxidation, it is possible that cytotoxic peroxidative products could be the active molecules, a still debated issue (15, 16). This would be consistent with the fact that the effect of PUFA on transcription of genes coding for lipogenic enzymes is restricted to hepatocytes in which peroxidation occurs. However, this tissue-restricted effect of PUFA has been revisited recently and site-specific regulation seems to occur in rat WAT (17). Moreover, in 3T3-L1 adipocytes, arachidonic acid (C20:4, n-6) suppress the expression of genes coding for lipogenic enzymes by a mechanism requiring cyclooxygenase and prostaglandin production (18).

Transcription of at least two other liver-specific genes, SCD1 and apo A-1 is also clearly the target of PUFA negative regulation (19, 20, 21). In the case of the SCD1 gene (and probably also the SCD2 gene), the PUFA response region has been located in the promoter. However the mechanism of repression is not yet resolved (reviewed in 4)

**Positive regulation**

Since the initial observation by Amri et al. (22, 23) that FAs are inducers of the adipocyte lipid binding protein (ALBP; aP2) gene transcription in pre-adipose cells, evidence has accumulated demonstrating that FAs are potent regulators of the adipose differentiation process (adipogenesis). From a physiological viewpoint, it makes sense that FAs induce the expansion of WAT mass when an excess of food is ingested. Here, in contrast to the situation
described above, saturated and unsaturated long-chain FAs (C16 and longer) are equipotent. Therefore, it seems more likely that a mechanism different from that involved in the negative regulation of the liver lipogenic enzymes occurs. The non-metabolisable FA α-bromopalmitate is also a strong inducer, suggesting that the metabolism of FAs is not necessary (24). The stimulation of aP2 gene expression is slow and blocked by cycloheximide, indicating that protein synthesis is required for the induction to occur (22, 23). This result strongly argues against a direct mechanism of FA action on the aP2 gene but rather would suppose that FAs act by altering the synthesis of either a transcription factor or of some other protein with a rapid turnover required for the effect (Figure 2). Indeed, several other marker mRNAs of the adipocyte phenotype (ACS, FAT, LPL, GLUT4, the uncoupling protein 2 etc.) are clearly induced by long-term treatment of preadipocytes with FAs.

The data discussed above supports the idea that FAs stimulate the general adipogenic process but does not give clues to the mechanism. It is possible that a common response element(s) to a FA-responsive master transcription factor is present in the promoter region of all these genes. One way to decipher the mechanism would be to study in detail the genes when transcription is stimulated by FAs in differentiated adipocytes, at a stage when adipogenesis does not occur. The aP2 and the PEPCK genes meet this criteria (23, 25, 26). PEPCK performs a key glyceroneogenic function in adipocytes during lipolysis, thereby permitting re-esterification of FAs into triglycerides and restraining FA output (27). PEPCK activation also allows esterification of FAs in adipocytes as a consequence of a glucose-free, lipid-rich diet. Therefore, a stimulatory action of FAs on PEPCK is physiologically relevant; in agreement with the physiology, glucose inhibits FA stimulation (25, 26). Using 3T3-F442A adipocytes, it was shown that mono- and poly-unsaturated FAs strongly stimulate PEPCK mRNA, but not saturated FAs. This contrasts to the effect of LCFAs on aP2 (23) or the carnitine palmitoyl-tranferase 1 (CPT-1) and L-FABP in hepatocytes (see below). The effect of FAs is rapid, does not require protein synthesis and acts directly on PEPCK gene
transcription. Induction of PEPCK activity follows (10). Neither inhibitors of prostaglandin or leukotriene synthesis nor antioxidants can prevent FA action (28). Although it was initially believed that oleate also stimulated PEPCK gene expression in hepatoma cells (25), it seems now clear that induction of the PEPCK gene by FAs occurs selectively in adipocytes (10). This behavioural difference of the same gene in two tissues may be related to the difference in the function of PEPCK in WAT (glyceroneogenesis) from that in liver where it is gluconeogenic.

The expression of a number of genes in the liver is under positive FA control in a physiologically relevant manner. These include the acyl-CoA-oxidase (AOX), carnitine palmitoyl transferase 1 (CPT-1), the liver FABP (L-FABP), cytochrome P4504A1, ACS, 3-hydroxy-3-methylglutaryl-CoA synthase, cholesterol 7α-hydroxylase. To date, the effect of FAs on gene transcription has been determined for the AOX (21), CPT-1 (29) and L-FABP (30) genes. CPT-1 and L-FABP gene regulation have been studied in the greatest detail. In both cases, stimulation is restricted to saturated and unsaturated FAs and requires de novo protein synthesis (8, 9, 29, 30). Moreover, at least in the case of CPT-1, recent evidences suggest that inhibitors of FA oxidation and of eicosanoid synthesis do not prevent induction (8, 29, 31).

Interestingly, CPT-1 and L-FABP genes are also induced by FAs in other tissues, L-FABP in the small intestine (9) and CPT-1 in the pancreatic β-cell line INS-1 (32). In both cases, saturated and unsaturated LCFAs have equivalent potencies.

**Is PPAR the FA-responsive transcription factor?**

The main postulated mechanisms of FA regulation of gene transcription are summarized in Figure 2. FAs, FA-CoAs or FA metabolites can : 1) induce a cascade of events leading to a covalent modification of a transcription factor (TF), for instance phosphorylation,
thereby altering its transactivation capacity, 2) directly bind to and activate a TF, 3) modify the mRNA stability or 4) the transcription rate of a TF, hence 5) changing its de novo synthesis. The FA-responsive TF binds to a recognition sequence, the FA response element (FARE) in the promoter-regulatory region of the target gene, either 6) as a monomer or 7) as a homo- or a heterodimer.

Following the cloning in 1990 by Isseman and Green (33) of a new member of the steroid / thyroid receptor superfamily, the so-called peroxisome proliferator activated receptor (PPAR), the hypothesis that it might be the FA-activated receptor arose. This receptor is activated by the hypolipidemic agents fibrates, peroxisome proliferators (PP) and xenobiotics in a transactivation assay in which recipient cells (usually undifferentiated highly proliferative cells selected for their high transfection efficiency) are co-transfected with a PPAR expression vector and a reporter gene placed under the control of a transcription unit which contains a response element recognized and activated by the receptor. Using such an assay, the Gustafsson’s laboratory (34) and the Wahli’s laboratory (35) have first shown that FAs are indeed PPAR activators.

The situation became more complex with the discovery of other members of the PPAR family. At present, 3 isoforms have been cloned: PPAR α, δ (=β=NUC1=FAAR) and γ, with tissue-specific expression, ligand-specific activation and ability to heterodimerize with retinoid X receptors (RXR) for which 3 isoforms: α, β, γ have also been isolated (reviewed in 36). A PPARγ2 isoform has further been cloned by Spiegelman and coworkers. PPARγ2 is expressed selectively in adipocytes (37). Retrovirus-mediated ectopic expression of PPARγ2 in non-adipose NIH-3T3 cells directs adipocyte differentiation when PPAR activators, like antidiabetic thiazolidinediones or polyunsaturated FAs, are provided (38). This observation suggested that PPARγ2 was the master transcription factor of the adipocyte lineage. However PPARγ2 is not expressed in pre-adipose cells and α-bromopalmitate, an inducer of
differentiation, is an inefficient transactivator of PPARγ. Hence, the hypothesis that FAAR (PPARδ) could play such a role has been proposed and is still a matter of debate (39).

The final evidence that FAs are ligands for the three PPARs came in 1997 (40, 41, 42). Using various methods to estimate binding, some corroborative specificity was shown among FAs, PUFAs being much better ligands than saturated FAs except for PPARα to which palmitate (C16:0) binds with good affinity. Of particular interest also was the observation that specific prostaglandins and leukotrienes are PPAR activators (reviewed in 36). The 15-deoxy-
•12, 14-prostaglandin J2 (15d-PGJ2), an arachidonic acid (C20:4 n-6) metabolite of the PGD2-J2 series, is a very potent and specific PPARγ ligand. The lipoxygenation product of arachidonate, 8(S)-hydroxyeicosatetraenoic acid, is the most potent PPARα activator in a transactivation assay. The leukotriene B4 is a PPARα specific activating ligand. Carbaprostacyclin, a stable analogue of prostacyclin activates PPARα and PPARδ. Therefore, all these molecules could be second messengers for FA transcriptional action. This would imply however that they were produced by the cells in which FAs are directly acting, a debated issue.

Using the above-described transactivation assay, PP response elements (PPREs) have been identified in a number of genes. They consist of imperfect versions of a direct repeat of the AGGTCA consensus sequence separated by one nucleotide (DR1) to which the additional 5’ extended portion AACT appears to be important for polarity and selectivity of recognition (reviewed in 36). Such an element is able to bind PPAR / RXR heterodimers in a gel retardation assay. A degenerate AGGTCA is also the half-site recognition sequence for the 9-cis and all-trans retinoic acids, thyroid hormone, vitamin D subclass of nuclear receptors and for orphan receptors like hepatic nuclear factor 4 (HNF4) and chicken ovalbumin upstream promoter transcription factor (reviewed in 36). A number of genes shown to be FA-responsive respond also to PPAR activators and present a PPRE in their promoter-regulatory region. Hence, it has been assumed that FAs regulate gene transcription via a PPAR / PPRE mediated
process (reviewed in 43). This is the case for instance with AOX, ACS, apo A-1, aP2, CPT-1, L-FABP, SCD1, S14, PEPCK. In this non-exhaustive list can be found positively and negatively FA-regulated genes. However, several recent evidences suggest that alterations of gene transcription by FAs and PPAR activators are often disconnected. Some genes which contain a PPRE, do not respond to FAs. This is the case with, for instance, apo A-II in primary hepatocytes (21) or FAT-CD36 in differentiated adipocytes (our own unpublished results). Moreover, PUFAs repress transcription of the delta-5 and delta-6 desaturases (12, 11) while the same genes are induced by PPAR activators; long chain FAs, not PP, induce CPT-2 in fetal rat hepatocytes (29); fibrate-induced CPT-1 gene expression is impaired by lipoxygenase inhibitors in hepatocytes whereas FA effect is maintained (8); The PEPCK gene promoter-regulatory region contains two DR1-like sequences able to bind a PPAR / RXR heterodimer in a gel shift assay (44) but it is responsive to FAs in adipocytes, not in hepatocytes or hepatoma cells (see above) which however contain large amounts of PPARα. In the S14 gene, the cis-regulatory negative element for the PPARα-specific ligand wy14643 is clearly distinct from that for PUFAs (45).

These conclusions have been reinforced recently with the analysis of PPARα-deficient mice. In such animals, fish oil administered in vivo or PUFAs added to cultured hepatocytes still repress S14 and FAS gene expression while induction of AOX and CYP4A2 mRNAs is abolished (46). Other studies using these mutant mice demonstrate that PUFA negative regulation of the L-PK gene is independent of PPARα and that the PPARα / RXRα heterodimer does not bind the L-PK promoter (47). Hence, some of the FA effects but certainly not all, can be assigned to PPAR activation.

In search of the FA-responsive transcription factors : other candidates
Several lines of evidence indicate that transcription factors different from the PPARs could mediate FA effect. As mentioned above, other proteins recognize DRI1-like sequences. Among these, the orphan hepatic receptor HNF4 has been shown to bind FA-CoA (48). In transient transfection in recipient (COS-7) cells, oleate and PUFAs inhibit HNF4 transactivation potential on a three C3P copies of the human apolipoprotein CIII gene promoter sequence governing CAT expression. Among saturated FAs, medium- and short-chain have no effect, palmitate is stimulatory and stearate (C18:0) is inhibitory. Whether this observation has any physiological relevance remains an open question. Last but not least, in chick hepatocytes, it has been shown that medium-chain FAs can alter triiodothyronine or estrogen action without interfering with the binding of their respective receptors to their cognate DNA elements (49).

Another route that FA could follow to regulate gene transcription would be to alter the de novo synthesis of a TF as shown in step 5 of Figure 2. Three recent examples suggest this possibility. One is related to the PUFA inhibition of lipogenic genes. Because of the similarities between the negative feedback controls of FA and cholesterol on their respective biosynthetic pathways, Worgall et al., (50) analysed the action that PUFA could exert on genes having sterol regulatory elements (SRE) in their promoter-regulatory regions. In transfected recipient cells they found that oleate and PUFAs reduced expression of SRE-containing genes by decreasing the level of SRE binding protein (SREBP). Saturated FAs were inefficient, a situation reminiscent to what was shown for the PEPCK gene regulation in adipocytes. It was then shown that PUFAs suppress SREBP1 gene expression and nuclear content in liver and in primary hepatocytes but not in 3T3-L1 adipocytes (51, 52). Since SREB1 is a positive effector of the FAS and S14 lipogenic genes, the reduction in SREBP1 quantity accounts for the FA inhibitory effect. This observation is corroborated by results of experiments with transgenic mice either surexpressing SREBP1 (53) or knocked out for this gene (54). Interestingly, the action exerted by PUFAs on SREBP1 is post-transcriptional as
examplified by step 3 in Figure 2, but the mechanism has not been alleviated yet. The second recent report is related to the induction of the immediate-early response genes c-fos and nur-77 in the pancreatic β-cell line INS-1 by palmitate and oleate but not PUFAs (55). In that case, FA affects gene transcription rate as described in step 4 of Figure 2. Moreover, it is shown that this induction is mediated by certain isoforms of protein kinase C (PKC) and requires elevated calcium. This corresponds to step 1 in Figure 2. In the third report, the response of the liver X receptor-α (LXRα) to FAs has been studied (56). Treatment of rat hepatoma cells or primary hepatocytes with unsaturated FAs induces a large increase in LXRα protein, mRNA and gene transcription. Since LXRα is a nuclear receptor thought to be an important regulator of cholesterol, steroid hormone and bile acid catabolic pathways, the observation that it is FA responsive suggests that it plays a role in the cross-talk between FA and cholesterol regulation of lipid metabolism. In the case of SREBP, c-fos, nur-77 and LXRα, FAs modulate the amount of transcription factors potentially acting as regulators of the expression of genes which code for proteins having a metabolic role.

**Conclusion**

The mechanisms by which FAs control the transcription of specific genes is complex. It seems clear that depending upon the cell-specific context and the target gene, FAs can take very different routes to alter transcription. Although the exact mechanism is still unresolved, rapid progress have been made recently, particularly with the help of mutant mice in which specific transcription factors or nuclear receptors have been either overexpressed or deleted by knockout. In vivo studies using such animal models and analysis of specific cell types derived from these mice would permit the identification of the targeted protein as a FA-responsive regulator. One possibility for which the exact mechanism has been so arduous to decipher may be related to the complexity of chromatin structure added to the difficulty to integrating
selective signals in the rapidly growing network of recently discovered coregulators acting on histone acetylation and altering the transcriptional potency of specific nuclear proteins. Since it is now recognized that plasma FA concentration and quality have profound effects on metabolism, linking nutrition to obesity, diabetes, cardiovascular diseases and cancer, it is of great value to actively elucidate the mechanism by which these molecules alter gene transcription.
FIGURE LEGENDS

Fig. 1. Major pathways of fatty acid production, transport and metabolism
Fatty acids (FA) are released by adipose tissue after lipolysis or by lipoproteins arising either directly from the intestine after a lipid-rich meal or from the liver. FAs circulate in the plasma loosely bound to albumin (ALB) and cross plasma membrane with the help of a FA translocator (FAT). In lipogenic cells like hepatocytes and adipocytes, they can be synthetized from glucose (lipogenesis). Inside the cell they bind to a cell-specific cytosolic fatty acid binding protein (FABP), can be exchanged with FAs of membrane phospholipids (PL). Mainly in liver and adipose tissue they can be activated into fatty acyl-CoA (FA-CoA) and esterified to glycerol-3-phosphate for triacylglycerol synthesis. In many cell types, FAs can be elongated and desaturated by specific enzymes (elongases and desaturases), β-oxidized in mitochondria or peroxisomes, ω-oxidized in microsomes, peroxidized or participate in eicosanoid (prostaglandins, leukotrienes, thromboxanes) synthesis.

Fig. 2. Postulated mechanisms for fatty acid control of gene transcription
The fatty acid (FA) per se, FA-CoA or FA metabolite modulate (±) transcription of a responsive gene, encoding a protein involved in FA transport or metabolism, through various non-mutually selective potential mechanisms. [1] A signal transduction cascade is initiated to induce a covalent modification of a transcription factor (TF), therefore modifying its transcriptional potency. [2] The FA itself or its derivative acts as a ligand for a TF which now can bind DNA at a FA response element (FARE) and activate or repress transcription. [3], [4], [5] FA action can be indirect. In that case, alteration in either TF mRNA stability [3] or gene transcription [4] results in variations of TF de novo synthesis [5] with an impact on the transcription rate of genes encoding proteins involved in FA transport or metabolism. On
binding to the cognate response element, TF acts either as a monomer [6], a homodimer or a heterodimer with TF*, a different TF [7].
REFERENCES


Figure 1
Figure 2

Signal transduction cascade

1. FA, FA-CoA, FA metabolite
2. TF
3. AAA, TF mRNA
4. TF gene
5. TF synthesis
6. FARE
7. Protein involved in FA transport or metabolism

FA-responsive gene

Ligand binding

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TF mRNA
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