Peroxisome proliferator activated receptors: transcriptional regulators of adipogenesis, lipid metabolism and more...

The recent discovery of lipid-activatable transcription factors that regulate the genes controlling lipid metabolism and adipogenesis has provided insight into the way that organisms sense and respond to lipid levels. Identification of the signaling pathways in which these receptors are involved will help us to understand the control of energy balance and the molecular defects underlying its disorders.

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Free-living cells like bacteria are often exposed to dramatic changes of their environment. They adapt to variations in their surroundings through inducible enzyme systems that respond to environmental signals, which often correspond to nutritional stress. Bacteria and lower eukaryotes invoke such systems to make use of nitrate and phosphate, metabolize sugars and synthesize amino acids and nucleotides. In higher eukaryotes such as vertebrates, most cells of the organism are not exposed to strong environmental fluctuations. Exceptions to this rule include the epidermis, the digestive tract mucosa and the liver, which receives its blood supply directly from the gut via the large portal vein. Hepatocytes are therefore exposed to qualitative and quantitative changes in the supply of nutrients, and sometimes to toxic compounds taken up with food. If the animal ingests a carbohydrate-rich low-fat diet, the presence of glucose activates the transcription of glycolytic and lipogenic genes in the liver. A low-carbohydrate diet, in contrast, induces gluconeogenic enzymes that convert amino acids into glucose, as well as enzymes from the lipolytic pathway which release energy stored as triglycerides [1], while a high-fat diet stimulates genes involved in lipid storage and expenditure [2]. Thus, there must be factors that regulate fuel selection according to the availability of glucose and lipid, and govern their interconversion, transport, storage, mobilization and use.

Obviously, regulation must operate on several metabolic pathways to ensure a healthy energy homeostasis. Obesity is one of the disorders of this balance; it is often associated with type II diabetes, hypertension and atherosclerosis. So far, little is known about the proteins that mediate the nutritional signals for gene control. The recent discovery of the peroxisome proliferator activated receptors (PPARs), a family of lipid-activable transcription factors, thus represents a breakthrough in the molecular understanding of lipid homeostasis [3–6].

PPAR structure, distribution and activation

PPARs are members of the nuclear hormone receptor superfamily and are relatives of the steroid, thyroid and retinoid hormone receptors [7]. All members of this superfamily share a characteristic organization of their structural and functional domains (see Fig. 1a). PPARs are activated by a diverse group of substances called the peroxisome proliferators, which induce massive proliferation of peroxisomes in rodent hepatocytes. The group includes fibrate hypolipidemic drugs such as clofibrate (see Fig. 1b) as well as certain plasticizers and herbicides. The nature of the molecular mechanism by which these various amphipathic carboxylates activate PPARs is still unclear.

PPARs form a distinct subfamily within the superfamily of nuclear hormone receptors, with at least three gene loci in all the species thus far studied. These are α, β and γ in *Xenopus laevis* [4], α, δ and γ in mouse [8] and α, NUC-1 and γ in man [7,9,10]. Evolutionary analyses show that the α and γ loci in different species are homologous, but it is not clear whether the *Xenopus* β gene is the homolog of the mouse δ and human NUC-1 genes [7]. In *Xenopus*, PPARα and β are expressed in oocytes and early embryos, whereas in rodents it is PPARδ that is present at early stages [4,8]. In adults of all species tested, the PPARα gene is highly expressed in tissues with high lipid metabolism (liver, kidney, white and brown adipose tissues) and is transcriptionally regulated by glucocorticoids in liver [3,4,8,11]. PPARβ (*Xenopus*) or δ (rodents) appears to be expressed ubiquitously, albeit at a low level in liver. PPARγ is observed at a high level in white adipose tissue and spleen of rodents [8,12] and in fat bodies of *Xenopus* [4].

Although PPARs were named by virtue of their activation by peroxisome proliferators, the finding that natural fatty acids (such as linoleic acid; see Fig. 1b) activate them as well raises the question of whether fatty acids are the true ligands. If so, this would suggest that nutrient derivatives can act on gene regulation in the same way as steroid or thyroid hormones. So far, it appears that no one fatty acid exclusively activates a given PPAR subtype [5,6,13]. Fatty acids with a chain length of 10 or more carbons activate PPARs from several species, while those

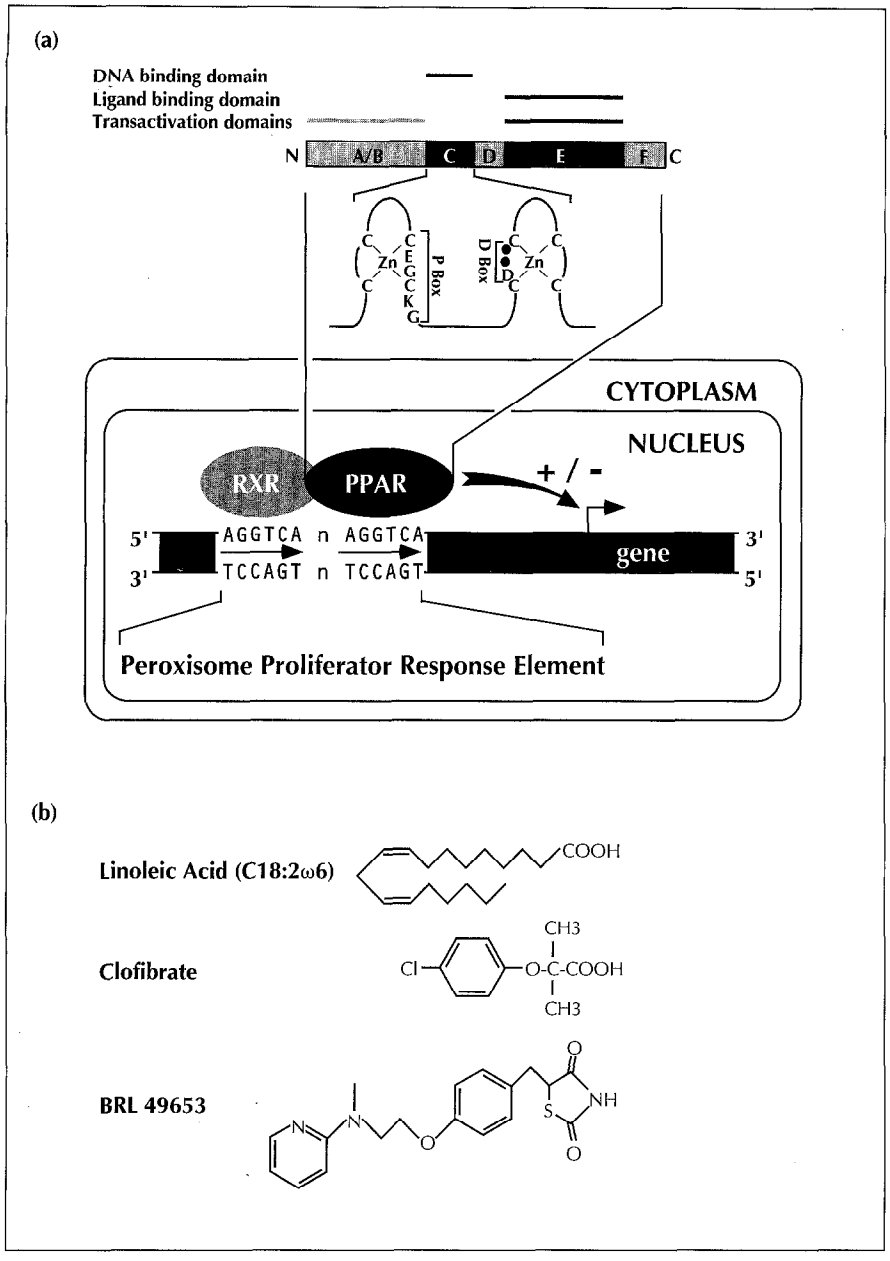

Fig. 1. Peroxisome proliferator activated receptors (PPARs) and PPAR activators. **(a)** PPARs are organized into six structural and functional domains (A–F), like the steroid hormone receptors. The main functions of domains A/B, C and E are indicated. The DNA-binding domain C is characterized by two zinc fingers of the C4 subtype. The P box in the first finger is responsible for specific recognition of the response element and the D box in the second finger, characteristically containing only three amino-acids in PPARs, is involved in dimerization. PPARs regulate transcription of their target genes by heterodimerization with the 9-*cis* retinoic acid receptor, also called the retinoid X receptor (RXR). In the promoter region of target genes, the PPAR/RXR heterodimer binds to a specific peroxisome proliferator response element, which is a direct repeat of the AGGTCA motif with one nucleotide spacing. **(b)** PPAR activators. PPARs are activated by long chain fatty acids (natural fatty acids such as linoleic acid), peroxisome proliferators (including hypolipidemic drugs such as clofibrate), and thiazolidinediones such as BRL 49653 (an antidiabetic agent).

with shorter chains are much less active. With the exception of *Xenopus* PPARα, which has a preference for polyunsaturated fatty acids rather than mono-unsaturated or saturated fatty acids, the position (ω–3 versus ω–6) or number of unsaturated bonds appear to have no major effects. Interestingly, ω–3 fatty acids, like hypolipidemic drugs, lower serum lipid concentrations, suggesting that they may preferentially activate a PPAR subtype that is involved in controlling lipid uptake or breakdown.

Although it is not yet clear to what extent PPAR subtypes can be specifically activated by different fatty acids, they are distinct with respect to their activation by various synthetic or natural compounds. Pirinixic acid (Wy14,643), an experimental hypolipidemic drug, is a potent activator of mouse PPARα but not of PPARδ and γ [8]. Similarly, the arachidonic acid analog ETYA, so far the most potent activator of *Xenopus* PPARα, does not activate PPARβ and γ [13]. Significant activation of mouse PPARγ is obtained with the leukotriene antagonist LY-171883 and, more interestingly, with an antidiabetic thiazolidinedione (BRL49653; see Fig. 1b), which binds to this subtype with a K_d of 40 nM [14]. For mouse PPARδ, the most potent activator known is linoleic acid [8]. The PPAR subtypes may therefore respond differentially to various physiological activators as well. Together with the varying expression of the receptor subtypes, such differential regulation would allow this receptor family to fulfill a number of distinct functions during development and in adulthood.

Dimerization is essential for the function of most of the members of the hormone receptor superfamily. This holds also for the PPARs; they heterodimerize with the 9-*cis* retinoic acid receptor (RXR), forming a complex that can stimulate gene activity. The dimer of PPAR and RXR binds to a hormone-response element located in the promoter region of target genes. This element comprises a

direct repeat of the AGGTCA motif with a one-nucleotide spacer between the two half-sites (Fig. 1a) [5,15]. The physiological consequences of this convergence between the signaling pathways of fatty acids and retinoids through PPAR/RXR heterodimers remain to be elucidated. It is clear from the involvement of RXR in the action of PPAR that there must be some crosstalk with the receptors for thyroid hormone, all-*trans* retinoic acid and vitamin D, which all also have RXR as a partner. There is, of course, ample evidence that retinoids, thyroid hormones and vitamin D are important in development and cell differentiation. So far, however, there is little evidence for a function of PPARs in cellular differentiation, with the exception of their involvement in adipogenesis [16, 17] and possibly in the formation of the lipid barrier in the epidermis [18].

Role of PPAR in adipogenesis

Adipocytes are of central importance in lipid storage and in the regulation of energy balance. They store energy in the form of triglycerides when food availability is high and release it in the form of free fatty acids under conditions of energy expenditure [19]. The expansion of adipose tissue mass when excess food is ingested requires differentiation of adipocytes from precursor cells. If the signal to differentiate is an elevated level of plasma lipids, a direct signal transduction pathway similar to that used by lipophilic hormones (steroids, thyroid hormones) can be envisaged, in which a lipid-activated transcription factor senses the hyperlipidemic state and triggers adipogenesis. Such a pathway would be similar to the one that controls the release of the sterol regulatory element binding proteins [20]. These transcription factors are

Table 1. Genes regulated by fatty acids (FA) and peroxisome proliferators (PP).

	FA/PP	PPARs	References
Hepatocytes			
1. Extra- and intra-cellular FA transport			
1.1: L-FABP (liver fatty-acid-binding protein)	+	+	[25]
1.2: Apolipoprotein AI	–	–/+[a]	[26]
1.2: Apolopoprotein A II	+	+	[27]
1.2: Lipoprotein lipase	+	+	[28],[b]
1.2: Apolipoprotein C-III	–	n.d.	[29]
1.3: Carnitine–palmitoyl transferase 1	+	n.d.	[30]
1.4: Carnitine-acyl transferase	+	n.d.	[31]
1.5: Carnitine-octanoyl transferase	+	n.d.	[31]
2. Mitochondrial β-oxidation			
Medium chain acyl-CoA dehydrogenase	+	+	[32]
3. Peroxisomal β-oxidation			
Acyl-CoA synthetase	+	+	[33]
Acyl-CoA oxidase	+	+	[4]
Enoyl-CoA hydratase/3-OH-acyl-CoA dehydrogenase	+	+	[34]
3-Ketoacyl-CoA thiolase	+	n.d.	[31]
4. Microsomal ω-oxidation			
P450 4A6 (fatty acid ω-hydroxylase)	+	+	[35]
5. Ketone body synthesis			
HMG-CoA synthase	+	+	[36]
6. Fatty acid synthesis			
Malic enzyme	+	+	[37]
Adipocytes			
1. Extra- and intra-cellular FA transport			
1.1: aP2 (adipocyte lipid-binding protein)	+	+	[12]
1.1: MAL-1 (keratinocyte-lipid binding protein)	+	n.d.	[22]
7. Glyceroneogenesis			
Phosphoenolpyruvate carboxykinase (PEPCK)	+	+	[38]

Some of the genes (bold) are direct targets of PPARs. FA/PP-regulated genes have been studied mainly in hepatocytes (top) and adipocytes (bottom), where they are involved in various lipid metabolic pathways (numbered 1 to 7). Stimulation (+) or repression (–) of gene activity either by FA/PP or by PPARs is indicated. n.d.: direct regulation by PPARs not yet determined.

[a]Fibrates down-regulate the transcription of the Apo-AI gene independently of PPARs, whereas PPARs can overcome this down-regulation via a functional PPRE in the Apo-AI promoter.

[b]K. Schoonjans, B. Staels, S. Deeb and J. Auwerx, personal communication.

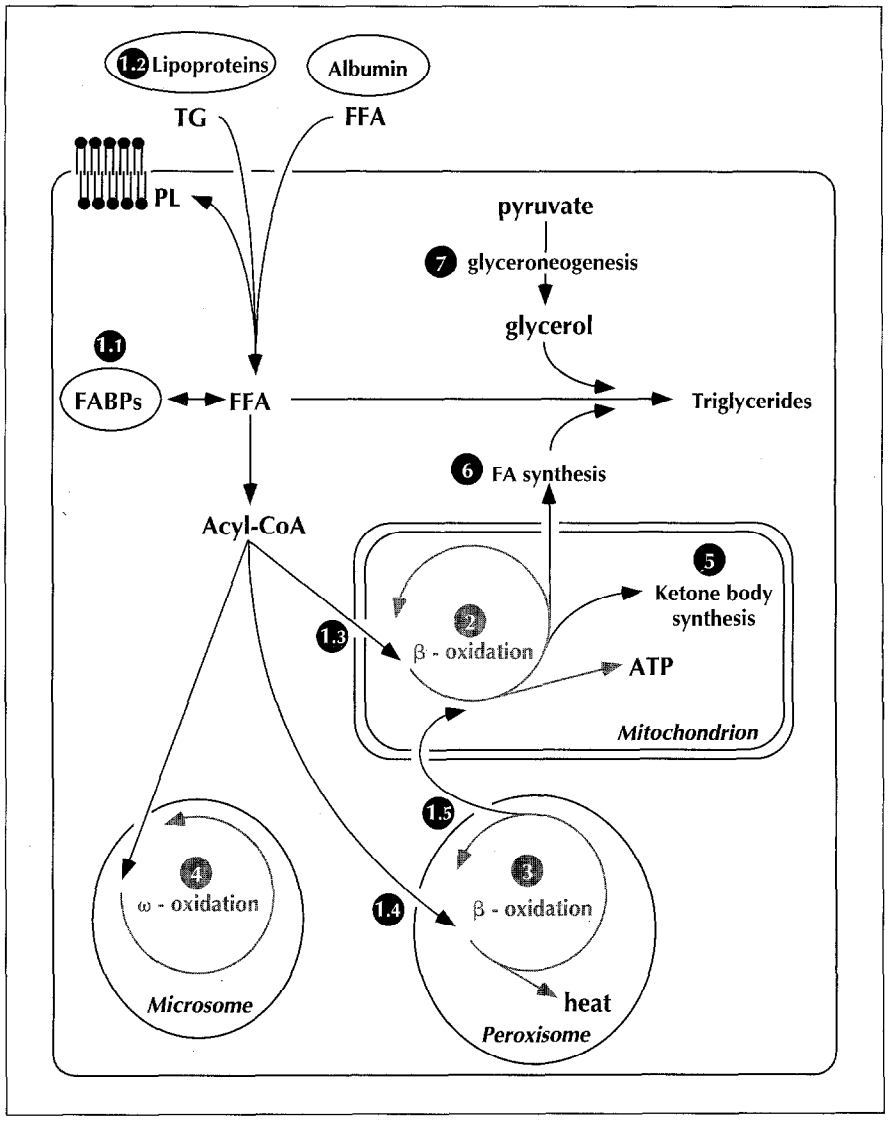

Fig. 2. Main lipid metabolic pathways regulated by PPAR target genes. PPARs are involved in (1) the regulation of fatty acid extra- and intra-cellular transport, (2) mitochondrial β-oxidation, (3) peroxisomal β-oxidation, (4) microsomal ω-oxidation, (5) mitochondrial ketone body synthesis, (6) fatty acid synthesis and (7) glyceroneogenesis. The pathways are numbered as in Table 1. TG, triglycerides; FFA, free fatty acids; PL, phospholipids; FABPs, fatty acid binding proteins.

sensors of sterol levels and are synthesized as membrane-bound precursors. They are proteolytically cleaved and released as active nuclear factors only in the absence of sterols. When sterols overaccumulate in cells as a result of high cholesterol diets, precursor cleavage is abolished and the expression of target genes, such as the gene for the low density lipoprotein receptor, declines.

The first transcription factor identified as a potential regulator of the adipose differentiation process, C/EBPα, did not meet the requirements for a lipid overload sensor because it does not appear to bind or to be activated by fatty acids [21]. Nevertheless, this basic leucine zipper transcription factor binds to the promoters of several genes expressed in adipocytes, and can induce the adipogenic program in a variety of fibroblastic cells. It is thus thought to be involved in adipogenesis control possibly through a combined action with PPAR [17]. Indeed, PPARγ seems likely to be involved in the regulation of adipose cell number in response to variations in lipid flux. It is highly expressed in fat tissues and it has been recently shown to activate the program of adipocyte gene expression and to stimulate adipose differentiation of cultured fibroblasts in a PPAR-activator-dependent manner [16,17]. Increased levels of fatty acids or fatty acid metabolites may activate PPARγ, in turn stimulating adipogenesis. C/EBPα cooperates with PPARγ to stimulate this differentiation program, suggesting that both transcription factors are required for the development of adipose cells from uncommitted mesodermal precursors [17]. These observations suggest that it may be possible to develop synthetic compounds that would bind to PPARγ and interfere with the regulation of the number of adipose cells in the organism.

Regulation of lipid metabolism

PPAR subtypes are also expressed in a variety of non-adipose tissues, where they are probably also engaged in lipid metabolism. So far, however, the identification of PPAR target genes has concentrated mainly on hepatocytes and adipocytes, because of their importance in systemic lipid metabolism. The target genes identified so far are summarized in Table 1. These control key functions of lipid metabolism, such as transport and cellular uptake of lipids, intracellular balance between free and

bound fatty acids, conversion of fatty acids to their activated CoA form, penetration of fatty acids into membrane-delimited organelles, microsomal ω-oxidation, peroxisomal β-oxidation, mitochondrial β-oxidation and ketogenesis, as well as the production of glycerol for triglyceride synthesis. Indeed, essentially all of the major pathways of lipid metabolism appear to be under the control of one or more PPAR-regulated genes. These pathways are often regulated at several levels, allowing fine-tuning of the whole network response to a stimulus (Fig. 2). Thus, lipids control their own metabolism, mainly by controlling transcription of the genes involved in it.

The homeostasis of lipid levels and that of energy levels are intimately interlinked and are regulated by systems that are sensitive to many stimuli, including those that are environmental (light, temperature), psychological (stress) and physical (activity). The responses to these stimuli by lipid- and energy-regulating systems is coordinated by the brain, mostly through hypothalamic functions. In this article, we have addressed only one aspect of this complex network, namely the control by lipids of their own metabolism. The discovery that fatty acids can activate transcription factors, and can therefore regulate many cellular and physiologic pathways (see Fig. 2), changes our view of lipids from mainly passive to active participants in cell differentiation and metabolic regulation.

PPAR in health and disease: future prospects

Disorders like obesity, hyperlipidemia, atherosclerosis and type II diabetes are often causally linked to each other and associated with the dysfunction of genes implicated in energy homeostasis in a broad sense. Although not all of these will be genes that are directly regulated by PPARs, the interdependence of the systems that regulate the supply of energy and those that regulate lipid metabolism suggests that manipulation of PPAR target genes might have therapeutic benefits. For example, fibrate hypolipidemic drugs and thiazolidinediones, a new class of antidiabetic agents that improve insulin sensitivity in rodent models of non-insulin-dependent diabetes mellitus (NIDDM), appear to act via PPARs [3,4,14,22]. However, the link between the activation of PPARγ by antidiabetics of this class and the reduction of plasma glucose, triglyceride and insulin levels that these compounds induce remains unclear (see [14]). The action of PPARγ may regulate endocrine functions of the adipose tissue, for instance by modulating the production and release of the product of the *ob* gene, which is mutant in obese mice [23], and of TNFα, which affects insulin signaling [24]. The discovery of new PPAR-subtype-specific agonists or antagonists should prove very valuable for a better understanding of the signaling cascade of each subtype, and will help us understand how lipid and energy levels are controlled during normal development and in adulthood. There is no doubt that further investigations on PPARs will provide answers to some of the long-standing questions regarding the contribution of adipogenesis and lipid metabolism to energy balance and the molecular defects underlying its disorders.

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