Peroxisome proliferator-activated receptors (PPARs) are ligand-dependent transcription factors of the nuclear hormone receptor superfamily, which includes among others the receptors for steroids, retinoids and thyroid hormone. These nuclear receptors are characterized by their ability to bind to specific DNA sequences and regulate gene expression when activated by a ligand. The PPAR subfamily comprises three isoforms designated PPARα, PPARβ and PPARγ. The PPARα subtype is activated by hypolipidemic drugs (fibrates), long-chain fatty acids, arachidonic acid and leukotriene B4, and it is mostly expressed in the liver, intestine, kidney and brown adipose tissue. It increases the production of enzymes involved in the β-oxidation of fatty acids as well as certain apolipoproteins. PPARβ, in contrast, is ubiquitously expressed, and so far no specific role has been described for this isoform. PPARγ is predominantly expressed in adipose tissue, where it is a key factor regulating adipocyte differentiation. It has also recently been shown to be expressed in stimulated monocytes, where it exhibits anti-inflammatory properties. PPARγ binds various natural ligands such as polyunsaturated fatty acids (linoleic acid), 15-deoxy-Δ12,14-prostaglandin J2 (15d-PG J2) and certain non-steroidal anti-inflammatory drugs (NSAIDs) at high concentrations. In addition, the insulin-sensitizing thiazolidinediones, such as troglitazone, have been found to exert most, if not all, of their actions through PPARγ, resulting in increased glucose uptake into muscle and therefore representing a novel therapeutic approach to the treatment of non-insulin-dependent diabetes mellitus (1). Several recent publications have revealed novel actions of PPARs at the molecular and cellular level, and they will be discussed below.

In order to activate transcription, liganded PPARs bind to specific promoter regions of target genes, resulting in the recruitment of the basic transcriptional machinery containing RNA polymerase II, which transcribes the DNA into mRNA. However, the interaction of nuclear receptors with the RNA-synthesizing machinery is indirect and requires other adaptor proteins termed ‘co-activators’. These cofactors can differentially modulate the biological activity of nuclear receptors, e.g. in a tissue-specific manner. An example is the co-activators for the estrogen receptor, which explain at least partially the tissue-specific agonistic and antagonistic action of tamoxifen and raloxifene. As such co-activator proteins might allow tissue-specific pharmacological approaches to nuclear receptor signaling, the identification of novel members of this emerging protein family is of considerable interest. Puigserver et al. (2) have recently reported the cloning of a tissue-specific co-activator for PPARγ (PGC-1) from a brown adipocyte cDNA library using a yeast two-hybrid system for its ability to interact with the ligand-binding domain of PPARγ. No homology was found between PGC-1 and any other known co-activator protein. PGC-1 mRNA is found in brown adipose tissue, heart, kidney and brain, but not in white adipose tissue or muscle. This co-activator has the interesting characteristic of being inducible by exposure to the cold. After mice are exposed to an ambient temperature of 4 °C for 12 h, their PGC-1 mRNA expression in brown adipose tissue is increased 30- to 50-fold. Not normally found in skeletal muscle, PGC-1 expression is induced in this tissue by cold exposure. Functional studies demonstrate that PGC-1 strongly enhances the transcriptional activity of PPARγ and thyroid hormone receptors on the uncoupling protein-1 (UCP-1) gene promoter, a gene that is essential for cold adaptation in rodents. Hence, it is conceivable that PGC-1 is responsible for mediating the well-known increase in UCP-1 during adaptive caloriogenesis. It is of interest that PGC-1 can be induced in skeletal muscle tissue, where the anti-diabetic drug and PPARγ ligand, troglitazone, appears to mediate its insulin-sensitizing action (3). However, it is currently unclear whether PGC-1 enhances the activity of PPARγ on promoters other than UCP-1. If this were the case, strategies aimed at increasing PGC-1 expression in skeletal muscle might result in the enhancement of PPARγ activity in a tissue-specific manner, which would be conceptually preferable to the current approach with troglitazone, by which PPARγ is activated in all target organs, including adipose tissue where the adipogenic capacity of PPARγ ligands is potentially problematic in the long term.

While most studies on PPARγ have hitherto focused on its role in adipose tissue, it was suspected for some time that this receptor might also play a role in immune regulation. This hypothesis was mostly derived from the observation that (i) the white pulp of the spleen exhibits PPARγ levels similar to those seen in adipose tissue, and (ii) its ligand, 15d-PG J2, can be produced by some immune cells. Two recent papers have now revealed a putative role for PPARγ in inflammation (4, 5). Ricote et al. (4) found that, on stimulating peritoneal macrophages

© 1998 Society of the European Journal of Endocrinology
with thioglycolate, the expression of PPARγ mRNA was increased. When stimulated by interferon-γ (IFNγ), peritoneal macrophages produced increased amounts of inducible nitric oxide synthase (iNOS), nitric oxide and gelatinase B, a matrix metalloproteinase. Peritoneal macrophage activation with IFNγ and co-treatment with either 15d-PG J2 (10 mmol/l) or the thiazolidinedione BRL 49653 (100 mmol/l) resulted in the inhibition of iNOS synthesis and gelatinase B mRNA expression by an unknown mechanism that is dependent on PPARγ. Also looking at cellular models of inflammation, Jiang et al. (5) found that a wide array of PPARγ agonists, such as troglitazone, 15d-PG J2 and high doses of NSAIDs inhibit the production of inflammatory cytokines (such as tumor necrosis factor-α, interleukin-6 and -1) in stimulated monocytes. This is of interest, as NSAIDs at doses well above those needed to inhibit cyclo-oxygenase have been shown to be clinically beneficial in rheumatoid arthritis. This could indicate that NSAIDs may exert additional anti-inflammatory effects through a PPARγ-mediated mechanism. The results of these two papers suggest that PPARγ may modulate the production of inflammatory cytokines by monocytes, as well as the release of mediators of inflammation, such as NO and gelatinase B. Although the signaling pathways remain to be elucidated, PPARγ may indeed play important roles in chronic inflammatory disorders such as rheumatoid arthritis and atherosclerosis as suggested by another series of two recent papers (6, 7).

Atherosclerosis is characterized by the differentiation of monocytes into cholesterol-laden foam cells in the arterial wall, a phenomenon that resembles in certain aspects a chronic inflammatory process. The atherogenic low-density lipoprotein (LDL) particles are normally taken up via hepatic and peripheral LDL receptors, but in atherosclerosis an increased proportion of LDL is oxidized by unknown mechanisms in the subendothelial space, resulting in the preferential binding of oxidized LDL to the scavenger receptors SR-A and CD36 found on macrophages. Scavenger receptors mediate the uptake of acetylated and oxidized LDL, but unlike the bona fide LDL receptor, they do not downregulate as intracellular cholesterol levels rise, thereby providing a mechanism for large amounts of cholesterol to accumulate, e.g. within a prospective foam cell. Tontonoz et al. (6) examined the potential role for PPARs in this process of intracellular lipid accumulation. They showed that PPARγ expression is increased in atherosclerotic lesions, and that 15d-PG J2 in association with the retinoid X receptor ligand LG268 induces monocytes to express the macrophage markers CD11b and CD18. Interestingly the expression of PPARγ itself was increased in macrophages exposed to oxidized LDL, but not by native LDL. Furthermore, stimulation by PPARγ ligands (15d-PG J2 or troglitazone) together with a retinoid increased the binding of oxidized LDL to macrophages by enhancing the expression of the scavenger receptor CD36, thus initiating a vicious circle and potentially promoting the accumulation of intracellular lipids and eventually foam cell formation. In a second paper, the authors then screened various oxidized lipids to determine the nature of the components present in oxidized LDL that interact with PPARγ (7). Two oxidized products of linoleic acid binding directly to PPARγ, 9- and 13-hydroxyoctadecadienoic acid, were found to induce monocyte maturation and expression of the scavenger receptor CD36. That PPARγ agonists might play a major role in the development of atherosclerotic plaques is a potential problem, as thiazolidinediones are an otherwise interesting therapeutic option for patients with non-insulin-dependent diabetes mellitus. However, in the model studied, the conversion of monocytes to foam cells required co-treatment with a retinoid X receptor agonist, and preliminary clinical data show a decrease, rather than an increase, in atherosclerosis among patients taking troglitazone, although this may also reflect the improvement in diabetic control (8). Compatible with this clinical observation are experimental data from Law et al. (9) demonstrating inhibition of vascular smooth muscle proliferation and migration. Hence, any extrapolation from these experimental data with regard to the effects of thiazolidinediones on the vasculature remain highly speculative and it will be of great clinical interest to further define the pathophysiological role and relevance of PPARγ and its ligands in the biology of the atherosclerotic plaque.

References