PPAR Modulation of Kinase-Linked Receptor Signaling in Physiology and Disease

Kinase-linked receptors and nuclear receptors connect external cues to gene transcription. Among nuclear receptors, peroxisome proliferator-activated receptors (PPARs) are of special interest in relation to widespread human diseases. Mapping out connections between PPARs and kinase-linked receptor signaling is central to better understand physiological and pathophysiological processes and to better define therapeutic strategies. This is the aim of the present review.

A balanced integration of various signaling cues at the cellular level is essential to metazoan development and physiology. There are different kinds of receptors to mediate these stimuli that trigger specific cellular responses, among them kinase-linked receptors and nuclear receptors, which connect external cues to gene transcription.

Kinase-linked receptors are complexes of transmembrane proteins localized at the plasma membrane that have either tyrosine kinase or serine/threonine kinase activities, in the case of receptor tyrosine kinase (RTK) or receptor serine/threonine kinase (RS/TK), respectively. Ligand binding to these receptors triggers the initiation of a phosphorylation cascade that ultimately leads to the recruitment of transcription factors to target gene promoters within the nucleus and activation of transcription. Cytokines (for example IL-1), FGF, and IGF are ligands for RTK, whereas TGF-β activates a RS/TK receptor.

RTKs predominantly signal through the MAPK cascade (60). Briefly, activated RTK coordinates the assembly of a multiprotein complex containing Ras that phosphorylates MAPKKKs such as Raf. In turn, MAPKKs, such as MEK, and then MAPKs, such as ERK, JNK, or p38, are sequentially activated by phosphorylation. At the end of the cascade, activated MAPKs translocate to the nucleus where they phosphorylate transcription factors such c-Jun or c-Fos, which together form the AP-1 complex. Phosphorylation of these transcription factors enhances their ability to induce gene transcription (FIGURE 1).

RS/TK essentially uses Smad signaling (47). A R-Smad (Smad2 or Smad3 for TGF-β signaling) is directly phosphorylated by the RS/TK-activated receptor, which triggers R-Smad/Co-Smad (Smad4) interaction and translocation of this complex to the nucleus where, with the help of other recruited transcription factors and co-activators, the Smad complex initiates gene transcription (FIGURE 1).

Nuclear receptors (NR) are original in the sense that ligand binding and transcriptional functions are associated in the same protein, which concentrates complex transcriptional regulations to a single molecule. Nuclear receptors form homo- or hetero-dimers that recognize a cognate motif on DNA called the response element. Ligand binding to the NR induces conformational changes that modify its protein partners so that a switch from a repressor complex to an activator complex is initiated, which ultimately leads to the recruitment of the transcriptional machinery to the promoters of target genes (FIGURE 1).

The unveiling of multiple cross talks between the kinase-linked receptor and the NR signaling pathways shows that these pathways do not function in parallel but in cooperation. Elucidating these connections is central to better understand developmental and physiological processes. In addition, because both kinase-linked receptors and nuclear receptors are drug targets in humans, it is of the utmost importance to know their functional interactions to better define therapeutic strategies.

Among nuclear receptors, peroxisome proliferator activated receptors (PPARs) are of special interest. Indeed, they are currently drug targets in a wide variety of human diseases, such as dyslipidemia and Type 2 diabetes, and they represent promising targets in various inflammatory processes (fibrosis, atherosclerosis, skin inflammation) as well as in cancer. The PPAR family consists of three isotypes encoded by three distinct genes, PPARα (NR1C1), PPARβ/δ (NR1C2), and PPARγ (NR1C3). At the time they were identified, in the early 1990s (13, 32), no endogenous ligand was known to activate them, but since then a number of lipid derivatives, mostly fatty acids and their derivatives, have been proposed to be endogenous ligands for...
As mentioned above, PPARs have long been considered to be important drug targets by pharmacological companies. As a result, high-affinity synthetic ligands have been developed that are selective for each PPAR isotype and that have proven to be very useful for basic research.

It is relatively well understood how PPAR activity can be modulated by kinase-linked receptor signaling (2, 3, 18). However, information about the converse situation, that is how PPARs may control kinase-linked receptor signaling, is more sparse and complicated by the fact that some PPAR ligands have been shown to activate MAPK independently of PPARs (1, 5, 17, 28, 29, 37, 40, 59). A clear overview of the current knowledge on how PPARs regulate RTK-RS/TK should help define new insights into a number of physiological and pathophysiological situations; the aim of the present review is to attempt this overview.

We will first discuss the physiological or pathophysiological contexts in which PPARs control RTK-RS/TK. We will then present a comprehensive report of the molecular mechanisms by which PPARs affect RTK-RS/TK signaling. With this in mind, only data for which a PPAR-dependent effect has been clearly demonstrated by the use of siRNA,
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**REVIEWS**

PHYSIOLOGY • Volume 25 • June 2010 • www.physiologyonline.org

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specific DNA constructs, null-mice, or the use of selective antagonists will be reported.

**Physiological and Pathophysiological Conditions in Which PPARs Modulate Kinase-Linked Receptor Signaling**

Processes and detailed information about the different signaling components that are modulated by PPARs, with mention of the experimental contexts and the control experiments performed to validate PPAR specificity, are given in Table 1.

**Cell Differentiation**

All three PPAR isotypes inhibit TGF-β mRNA synthesis in cultures of rat chondrocytes stimulated by TGF-β and co-treated with PPAR selective agonists. In addition, activated PPARβ/δ as well as activated PPARγ limits TGF-β-induced phosphorylation of SMAD2/3 and ERK1/2 (52). Similarly, activated PPARγ inhibits RANKL-induced differentiation of primary mouse bone marrow cells into osteoclasts by limiting phosphorylation of ERK, JNK, and p38 and by moderately limiting the activity of AP-1 (51). PPARs also affect the kinase-linked receptor pathway in the context of cardiac hypertrophy. Treatment with a PPARα agonist or PPARα overexpression limits cardiomyocyte enlargement induced by endothelin-1 in neonatal rat cultures. This effect was characterized by an inhibition of endothelin-induced phosphorylation of c-Jun, JNK, and AP-1 DNA binding activity (31). Interestingly, similar results were obtained in vivo since PPARα agonists limit cardiac hypertrophy induced by aortic banding in rats (31). Similarly, PPARβ/δ agonists limit angiotensin-induced phosphorylation of ERK in rat embryonic heart-derived cells (41). Collectively, these reports enlighten the action of PPAR activation in downregulating kinase-linked receptor signaling in cell differentiation. However, the opposite effect has also been reported in mouse neural stem cells in which PPARγ activation stimulated EGF synthesis and ERK activation and concomitantly increased cyclin B levels resulting in the promotion of cell growth (64).

**Cell Proliferation and Cancer**

The importance of PPAR in cell proliferation and cancer is well documented (49, 50), and a number of reports have pointed to a modulation of kinase-linked receptor signaling by PPARs in this context. In the skin, PPARβ/δ limits keratinocyte proliferation at the end of the wound healing process by limiting IL-1 signaling in dermal fibroblasts (7). Similarly, PPARβ/δ inhibits TPA-induced keratinocyte proliferation by downregulating kinase activity in mouse skin (34). Activated PPARγ has also been shown to reduce the proliferation of cultured mouse mesangial cells by limiting c-Fos mRNA synthesis (22). However, in the context of psoriasis in human skin, PPARβ/δ enhances keratinocyte proliferation through the induction of heparin-binding EGF-like growth factor (55), and PPARα promotes mouse hepatocyte proliferation after partial hepatectomy by stimulating Ras activity in vivo (67).

In the context of tumors or in cancer cell lines, PPARs are, in general, promoters of MAPK signaling. PPARγ stimulates ERK signaling in different cancer cell lines and in vivo cancer models (42, 62, 63, 68). PPARβ/δ also stimulates MAPK signaling through VEGF production in intestinal polyps of APC<sup>−/−</sup> mice (14, 64). However, PPARs can also limit kinase-linked receptor signaling in certain cancer situations. For instance, the use of a dominant negative Pax8:PPARγ fusion construct that
abolishes PPARγ signaling revealed an important role of PPARγ in reducing MAPK signaling in the context of breast cancer in living mice (69). This latter result opens up new treatment modalities for ER-positive breast cancers. Similarly, activated PPARγ limits MAPK signaling in a cell culture model of human lung carcinoma (26), which is the first molecular clue toward explaining the inhibitory effect of fish oils on lung cancer tumor growth by activating PPARγ.

In general, PPARs limit kinase-linked receptor-induced proliferation in physiological conditions but enhance it in pathologies such as psoriasis or cancer (FIGURE 2). However, examples that do not fall in this simplistic scheme are documented.

**Organ Fibrosis**

PPARγ has been the most studied PPAR isotype in fibrosis, and no matter what the experimental context was, it appeared to repress TGF-β-induced fibrosis. This has been consistently observed in a variety of cell culture models, such as human or mouse skin fibroblasts (19, 20, 70), human mesangial cells (43), human aortic smooth muscle cells (16), rat hepatic stellate cells (44), and hepatocytes (23), and also in mouse embryonic fibroblasts (21). On the contrary, PPARβ/δ is expressed in hepatic stellate cells in the liver where it favors fibrosis downstream of p38. However, further investigation is needed to define whether PPARβ/δ controls MAPK signaling in that context (27).

**Vascular Inflammation and Atherosclerosis**

PPARs are expressed in immune cells and in the vasculature. Numerous studies revealed them to be regulators of inflammatory processes (50) and in particular of inflammatory cytokine production. A few reports have documented a PPAR-dependent modulation of kinase-linked receptor signaling in atherosclerosis, a process lying at the interface between inflammation and fibrosis (56). Activation of PPARγ has an anti-inflammatory effect in human endothelial cells partly by blocking ERK phosphorylation induced by TNF-α and IFNγ (46), but it also promotes TGF-β signaling in human vascular smooth muscle cells, which favors apoptosis (58). PPARα activation limits TGF-β-induced vascular smooth muscle cell migration in culture by directly interfering with TGF-β signal transduction (38), which could be of importance in atherosclerosis. Similarly, liganded PPARβ/δ inhibits rat aortic vascular smooth muscle cell activation by controlling TGF-β expression in cell culture and in vivo (35). PPARβ/δ has also been shown to promote extracellular matrix remodeling in human aortic smooth muscle cells through a TGF-β-dependent mechanism (36). This latter finding could be of importance in treatments aimed at limiting atherosclerosis plaque rupture by maintaining their integrity.

PPARs could therefore represent interesting targets to attenuate the risk associated with atherosclerosis since they can limit TGF-β-induced development of atherosclerosis, but they can also probably limit plaque rupture when the disease is already well established.

**Energy Homeostasis and Diabetes**

PPARs are mostly studied for their role in maintaining energy balance. Briefly, PPARγ controls adipocyte differentiation and function and by doing so promotes lipid storage. On the other hand, PPARα and PPARβ/δ favor lipid utilization (through beta-oxidation), with a predominant role in the liver and muscles (10). PPARα and PPARβ/δ are also clearly connected to neoglucogenesis and glycolysis, respectively (33, 39). Below, a few reports are cited that illustrate how PPARs contribute to energy homeostasis through modulation of kinase-linked receptor signaling. FGF21, which activates RTK signaling, has recently emerged as an important player in energy homeostasis (53) and, interestingly, its gene is a direct target of PPARα and PPARγ in liver and adipose tissue, respectively. This has been documented for both mice and humans (8, 30, 66). Similarly, IGFBP, which inhibits the hypoglycaemic effect of IGF, is encoded in a direct PPAR target gene (9).

**FIGURE 2.** Physiological and pathophysiological outcomes of kinase-linked receptor modulation by PPARs

The modulation of kinase-linked receptor signaling by PPARs is presented in the context of cell proliferation (top) and in the context of inflammation, fibrosis, and atherosclerosis (bottom). Green arrows denote positive regulations, whereas red connectors indicate negative regulations. Numbers in brackets refer to articles commented on in the text (see Refs.).
In the context of Type 2 diabetes, PPARγ ligands have been used for more than 10 years as insulin sensitizers in humans (6). Interestingly, a well-designed study has shown that this sensitization is mediated by JNK inhibition in mice (12). In this same context, PPARβ/δ activation limits ERK signaling in adipocytes and also limits the subsequent pro-inflammatory process that eventually participates in diabetes (54).

The few examples discussed above suggest that combination of PPARs and kinase-linked receptors modulators could be powerful in the context of Type 2 diabetes.

As an overview of this part of the article, we have compiled in FIGURE 2 what we feel is a useful list of physiological and pathophysiological outcomes of kinase-linked receptor modulation by PPARs.

**Molecular Mechanisms by Which PPARs Modulate Kinase-Linked Receptor Signaling**

In this part, we present an integrated review of the different levels at which RTK-RS/TK signaling is regulated by PPARs. Because it is an emerging field, data are fragmented between different experimental contexts. However, we will try to group this heterogeneous information to present a model (FIGURE 3).

**Direct Transcriptional Regulation of Key Players of Kinase-Linked Receptor Signaling**

PPARs regulate the transcription of a number of genes playing a central role in RTK-RS/TK signaling by direct binding to their promoter regions.

A number of ligands that signal through RTK are actually directly regulated by PPARs. The FGF21 promoter is bound by PPARα in fasting conditions as shown by promoter-luciferase and chromatin immunoprecipitation experiments in mice (30), whereas PPARγ is able to directly activate FGF21 transcription in the adipose tissue. In line with this observation, FGF21promoter-luc constructs can be activated by the overexpression of PPARγ and/or its activation by ligands in cell culture (66). Similarly, PPREs were identified in the HGF promoter, which are responsive to PPARγ agonists, as judged by promoter-luciferase assays (43). PPARβ/δ can also promote the production of RTK ligands, for instance, VEGF expression is stimulated by PPARβ/δ in cell lines and in APC−/− intestinal polyps (65), and Hb-EGF is a target of PPARβ/δ in human skin in psoriasis (55). However, there is no evidence that these effects are direct. Interestingly, PPAR can also modulate RTK ligand binding by inducing the production of an RTK signaling inhibitor, as illustrated by its transcriptional control of IGFBPs, which are modulators of IGF signaling. A sophisticated in silico search for PPREs has identified putative motifs in the promoters of human IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-4, IGFBP-5, and IGFBP-6 genes. Moreover, ChIP experiments have shown an association between each of the three PPARs with the transcriptional start sites of IGFBP-1, IGFBP-2, IGFBP-5, and IGFBP-6 (9). Another example along the same lines is that of the inhibition of IL-1 signaling in human skin mediated by PPARβ/δ through the induction of IL-1 receptor antagonist alpha (IL-1Ra). A combination of promoter-luciferase, EMSA, and ChIP assays clearly identified the IL-1Ra gene as a direct positive PPARβ/δ target (7). Finally, RS/TK signaling can also be modulated at the level of ligand production by PPARs since the TGF-β gene has recently been shown to be a direct target of PPARβ/δ. In fact, EMSA assays and ChIP experiments have clearly indicated that PPARβ/δ binds to the TGF-β promoter in a ligand-dependent manner in rat vascular smooth muscle cells (35).

Ligands of RTK or RS/TK signaling are not the only direct targets of PPARs since c-Fos is also transcriptionally regulated by PPARγ. More precisely, PPARγ inhibits PDGF induction of c-Fos, and this effect is dependent on the concentration of the PPARγ agonist. Although the molecular mechanisms have not been fully elucidated, a direct effect of PPARγ on the c-Fos promoter is possible since activation of ERK downstream of PDGF treatment but upstream of c-Fos induction is not modified by PPARγ ligands (22).

**Modulation of Kinase Activity**

A number of reports have pointed to the modulation of kinase-linked receptor signaling by PPAR at the level of the phosphorylation cascade.

In the rodent liver, PPARα was important for Ras localization at the plasma membrane of the hepatocytes and for its ability to bind to the recombinant Raf domain (67). However, the precise mechanisms remain to be elucidated. In mouse skin stimulated with TPA, PPARβ/δ clearly limited Raf1, ERK1/2, and PKCα kinase activities. These were correlated with a PPARβ/δ-dependent increase in PKCα ubiquitination and subsequent degradation, which was presented as the probable origin of MAPK inhibition. PPARβ/δ could somehow control the free ubiquitin levels in the cytoplasm (34). However, there is no experimental support for this hypothesis, which so far fails to explain how PKCα was selectively affected by major changes in free ubiquitin levels. In 3T3-L1 adipocytes, PPARγ overexpression or PPARγ ligand addition inhibited JNK kinase activity, as well as its binding to GST-Jun (c-Jun is a substrate of JNK). Importantly, this inhibition was blunted if the
PPARγ antagonist or PPARγ siRNA was added to the system (12). Unfortunately, here again the precise mechanisms remain obscure.

**Modulation of Binding to Response Elements**

PPARs can modulate the binding properties of transcription factors downstream of RTK or RS/TK signaling on their cognate response elements. A few reports have mentioned the inhibition of AP-1 binding to a consensus site by PPARγ in EMSA or the reduction of gene expression in promoter-luciferase assays (24, 31, 51). However, the mechanisms are unclear, and PPARγ might regulate AP-1 binding indirectly by regulating JNK or ERK activity at an upstream level, since JNK or ERK phosphorylation are impacted in these situations. It should be noted that PPARγ has also been shown to stimulate binding of the AP-2 transcription factor on the promoter of human ILK when activated by fish oil or selective agonists of this PPAR isotype (26). This effect is not direct and requires p38 activation, as judged from the use of a p38 inhibitor. This situation is of interest because the ILK gene is a well characterized PPAR target, and its promoter region harbors PPREs in the vicinity of the AP-2 sites (11).

**FIGURE 3.** Molecular pathways by which PPARs control kinase-linked receptor signaling

The different mechanisms by which PPARs control kinase-linked receptors are schematized. A number of important players of either RTK or RS/TK signaling are direct targets of PPARs, which can interfere with the MAPK cascade or with transcription factor binding to DNA in the cell nucleus. Green arrows denote positive regulations, whereas red connectors indicate negative regulations. Plain lines are for direct interactions, whereas dashed lines are for indirect ones. Numbers in brackets refer to articles commented on in the text (see Refs.).
This poses a question of how indirect ILK repression via p38 stimulation of AP-2 is favored compared with direct PPARγ induction of ILK transcription via PPRE binding when cells are treated with a PPARγ agonist.

A number of data support a direct role of PPARs in modulating Smad transcriptional complex binding downstream of TGF-β signaling. The idea that PPAR inhibits Smad transcriptional activity by trans-repression mechanisms is supported by reports of PPARγ-mediated inhibition of the p300-Smad2/3 association. In fact, liganded PPARγ inhibited p300 recruitment by phospho-Smad2 or phospho-Smad3 on TGF-β treatment of cultured hepatocytes (23). It should be noted that, under these conditions, the PPARγ ligand affected neither the Smad2/3 protein level nor Smad2/3 phosphorylation. A likely explanation is that activation of PPARγ triggered its association with p300, a known NR co-activator (15), that then became limiting for Smad-mediated transcriptional regulation. A similar situation has been described in neonatal skin fibroblasts where PPARγ agonists inhibited TGF-β-induced stimulation of collagen synthesis. Here also, this inhibition was correlated with inhibition of the formation of the complex between phospho-Smad1/2/3 and p300, which is PPARγ dependent. Moreover, the trans-repression hypothesis was further supported in this case since it was shown that p300 overexpression could rescue collagen synthesis in the presence of a PPARγ agonist (20).

PPARα and PPARγ have also been shown to inhibit the binding of activated Smads on their response elements in rat vascular smooth muscle cells and human liver cancer cells, respectively (25, 38). In vascular smooth muscle cells, it was shown that PPARα ligands inhibit the binding of the transcription factor complex SP1/Smad4 on a TGF-β response element of the β3-integrin gene. It was further shown that liganded PPARα binds to a complex containing Smad4 (no direct binding could be proven). It is thus possible that the trans-repression mechanism may occur not only at the level of co-activator sharing by NR and TGF-β signaling but also at the level of specific components of RS/TK signaling, such as Smads.

It is important to mention that the PPAR-mediated modulation of Smad binding onto a RE not always results in an inhibition. An interesting case of cooperative promotion of transcription between PPARs and Smad3 was reported for the collagen3A1 (col3a1) gene (36). This gene was found to harbor both a functional Smad response element and a functional peroxisome proliferator response element, as observed in EMSA and ChIP experiments. Co-binding of Smad3 and PPARβ/δ was needed for optimum transcription of col3a1 on TGF-β treatment of vascular smooth muscle cells. There is also an extensive temporal overlap in TGF-β1 and PPARβ/δ functions during wound healing, which suggests a cross talk between these two signaling pathways that fine-tunes wound closure. During the healing process, the ability of TGF-β1 to inhibit inflammation-mediated induction of PARβ/δ is Smad3 dependent and involves an inhibitory effect on AP-1 activity and DNA binding at the PPARβ/δ gene. Reciprocally, PPARβ/δ limits Smad3 activity indirectly via the ILK-Akt axis (61).

**Concluding Remarks**

Even though there is still a limited amount of data on the control of kinase-linked receptors by PPARs, one can already appreciate their relevance in physiology and diseases. PPARs modulate RTK-RS/TK signaling in a large spectrum of cell types and physiological contexts, from bone development to vascular cell inflammation, from liver fibrosis to lung cancer, and Type 2 diabetes. However, efforts should be made to accumulate more in vivo data, since most of what we have reported here was obtained in cell culture models.

In general, it has been found that PPARs repress kinase-linked receptor signaling, except in cancer where they promote it, although counter examples do exist (FIGURE 2).

On the molecular side, the PPAR control over kinase-linked receptor signaling can occur on different levels (FIGURE 3); PPARs can modulate ligand or antagonist production and they can affect the transduction pathway by interfering with the phosphorylation cascade or with transcription factor binding on DNA.

The recent finding that some RTK can be shuttled to the nucleus where they could behave as transcription factors (4, 45) could be seen as yet another hint of an unsuspected kind of cross talks between nuclear receptors and RTKs. It is likely that future work will unveil exciting novel mechanisms of the combined action of PPARs and kinase-linked receptors. This should pave the way to a better understanding of the cross talks between PPARs and the MAPK pathway and PPAR and TGF-β signaling. Therapeutic strategies should certainly benefit from this knowledge, and one can already envisage the use of combinatorial approaches with PPAR and RTK-RS/TK agonists or inhibitors. For instance, a combination of PPARγ agonist and TGF-β inhibitor might be very powerful for limiting fibrosis.

We thank Nathalie Constantin for help in collecting the material to prepare this review. We thank Alexandra Montagner for comments on the manuscript.

Work performed in the authors’ laboratory was supported by the Swiss National Science Foundation (through...
individual research grants and the National Center of Competence in Research Program Frontiers in Genetics, the State of Vaud, and the Bonizzi-Theler-Stiftung.

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