REVIEW

Peroxisome proliferator-activated receptor-γ: from adipogenesis to carcinogenesis

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ABSTRACT

Peroxisome proliferator-activated receptors (PPARs) are nuclear hormone receptors, initially described as molecular targets for synthetic compounds inducing peroxisome proliferation. PPAR-γ, the best characterized of the PPARs, plays a crucial role in adipogenesis and insulin sensitization. Furthermore, PPAR-γ has been reported to affect cell proliferation/differentiation pathways in various malignancies. We discuss in the present review recent advances in the understanding of the function of PPAR-γ in both cell proliferation and adipocyte differentiation.

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INTRODUCTION

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor family, the largest family of transcription factors (Mangelsdorf et al. 1995). Three distinct members of the PPAR subfamily have been described: α, δ (also called β, NUC-1 or FAAR) and γ, all of them being activated by naturally occurring fatty acids or fatty acid derivatives. PPARs heterodimerize with the retinoid X receptor and regulate transcription of target genes through binding to specific response elements or PPREs, which consist of a direct repeat of the nuclear receptor hexameric DNA core recognition motif spaced by one nucleotide. A number of studies have addressed the important role that PPAR-γ plays in glucose homeostasis and insulin sensitivity. However, in this review we discuss recent data on the function of PPAR-γ in adipogenesis and carcinogenesis.

PPAR-γ AND ADIPOGENESIS

Adipocyte differentiation is a highly regulated process taking place from birth throughout adult life. Adipose tissue is composed of adipocytes, which store energy in the form of triglycerides and release it as free fatty acids (for reviews see Spiegelman & Flier 1996, Fajas et al. 1998). Together with muscle, adipose tissue is the major regulator of energy balance of the body. Excessive accumulation of adipose tissue leads to obesity, whereas its absence is associated with lipodystrophic syndromes. PPAR-γ is highly expressed in the adipose tissue and is required for its development. During adipocyte differentiation, which ensues from PPAR-γ activation, expression of numerous genes specific for fatty acid metabolism is induced. In fact, functional PPREs have been identified in several genes implicated in adipocyte differentiation, most of them involved in lipid storage and control of metabolism. Good examples are aP2 (Tontonoz et al. 1994a), phosphoenolpyruvate carboxykinase (Tontonoz et al. 1995), acylCoA synthetase (Schoonjans et al. 1993, 1995), fatty acid transport protein-1 (Martin et al. 1997, Frohnert et al. 1999), and lipoprotein lipase (Schoonjans et al. 1996), which are all regulated by the PPAR-γ protein. However, the conclusive demonstration of the crucial role that PPAR-γ plays in adipogenesis comes from recent observations in...
PPAR-γ knock-out (KO) mice. PPAR-γ −/− mice are completely devoid of adipose tissue and PPAR-γ +/+ mice are characterized by a decreased adipose tissue mass (Kubota et al. 1999, Miles et al. 2000). Injection of PPAR-γ −/− embryonic mouse cells into wild-type blastocyes produces chimeric mice in which adipose tissue is composed exclusively of PPAR-γ −/− cells, demonstrating that PPAR-γ is necessary to ensure development of this tissue (Rosen et al. 1999). These in vivo results are further supported by in vitro data showing that embryonic stem (ES) cells lacking both copies of PPAR-γ fail to differentiate into adipocytes after appropriate treatment, whereas ES cells expressing PPAR-γ readily differentiate. Moreover, when fibroblastic cell lines (Tontonoz et al. 1994b) or muscle precursor cells (Hu et al. 1995) were infected with retrovirus expressing PPAR-γ, cells differentiated into adipocytes after the appropriate stimuli, supporting an important pro-adipogenic role of PPAR-γ. It seems that this adipogenic property is not unique since a whole range of transcription factors affects adipogenesis when overexpressed (see below).

In humans, genetic studies have further contributed to determine the role of PPAR-γ in fat metabolism. Several mutations in the PPAR-γ gene have so far been described (Yen et al. 1997, Beamer et al. 1998, Deeb et al. 1998, Ristow et al. 1998, Vigouroux et al. 1998). A rare Pro115 Gln mutation in the NH2-terminal ligand-independent activation domain of PPAR-γ was found in four very obese subjects (Ristow et al. 1998). This mutation, which inhibits the phosphorylation at Ser112, resulted in a permanently active PPAR-γ and led to increased adipocyte differentiation and obesity (Ristow et al. 1998). Phosphorylation at Ser112 was proposed as a mechanism by which growth factors and insulin, through MAP kinase, decrease PPAR-γ activity and adipocyte differentiation (Hu et al. 1996, Adams et al. 1997, Camp & Tafuri 1997). Furthermore, a much more common Pro12 Ala substitution in the PPAR-γ2-specific exon B (Yen et al. 1997, Beamer et al. 1998, Deeb et al. 1998, Vigouroux et al. 1998, Hara et al. 2000), resulting in a less active PPAR-γ form, is associated with a lower body mass index (BMI). These results, together with the observations made on the Pro115 Gln substitution, provide strong evidence for a role of PPAR-γ in the control of adipogenesis in vivo, such that a more active PPAR-γ (Pro115 Gln) results in increased BMI (Ristow et al. 1998), whereas the opposite is seen with a less active PPAR-γ (Pro12 Ala) (Deeb et al. 1998).

Despite the fact that it plays a critical role in adipogenesis, PPAR-γ is not the only factor regulating the complex mechanisms that control adipocyte differentiation. Numerous other positive and negative signaling pathways contribute to this process. During the first phases of adipogenesis, the CCAAT enhancer binding proteins (C/EBP), C/EBP-β and -δ are induced in response to adipogenic hormones such as insulin or glucocorticoids (Wu et al. 1995, 1996, Yeh et al. 1995). Both C/EBPs will induce directly the transcription of PPAR-γ (Clarke et al. 1997). However, other transcription factors might also be in part responsible for triggering PPAR-γ expression early in adipogenesis, since studies in C/EBP-α, -β or -δ KO mice show that PPAR-γ expression and adipocyte differentiation are still occurring, although at a lesser extent. Another protein also induced early during adipocyte differentiation is the basic helix-loop-helix protein ADD-1/SREBP-1 (Tontonoz et al. 1993, Kim & Spiegelman 1996). This transcription factor plays a pivotal role in cholesterol homeostasis and also regulates the expression of several genes in fatty acid metabolism, and hence it is suggested that ADD-1/SREBP-1 might control the generation of PPAR-γ ligands that in their turn enhance the transcriptional activity of PPAR-γ (Fajas et al. 1999). Furthermore, a recent study showed that both ADD-1/SREBP-1 and the related SREBP-2 can induce PPAR-γ transcription through binding to response elements in the PPAR-γ1 and γ3 promoter regions (Fajas et al. 1999). Finally, terminal adipocyte differentiation requires the concerted action of PPAR-γ and C/EBP-α (Tontonoz et al. 1994, Hu et al. 1995, Wu et al. 1999). PPAR-γ controls not only the expression of C/EBP-α, but C/EBP-α, in response, also induces PPAR-γ gene expression, via interaction with C/EBP response elements present in the human (Saladin et al. 1999) and mouse (Zhu et al. 1995, Wu et al. 1999) PPAR-γ promoter. This interdependence or cross-regulation between C/EBPs, PPAR-γ and ADD-1/SREBP-1 is not only required to induce adipocyte differentiation but also to sustain the fully differentiated adipocyte phenotype. Although all the above transcription factors stimulate adipocyte differentiation, evidence in favor of negative regulation of adipogenesis is also accumulating. It has been suggested that PPAR-γ expression and adipogenesis are inhibited by several transcription factors of the GATA family. In particular, constitutive expression of GATA-2 and GATA-3 resulted in a decrease in PPAR-γ expression and a consequent inhibition of adipocyte differentiation (Tong et al. 2000).

In addition to these transcription factors which modulate adipogenesis, several secreted factors are involved in the control of adipogenesis. This is the
case for two cytokines produced by the adipocytes: leptin and tumor necrosis factor-α (TNF-α). Leptin is considered to be an adipocyte-derived signaling factor and is thought to have autocrine, paracrine and endocrine actions mediated by specific cytokine-like receptors. Its pleiotropic action includes control of body weight and energy expenditure (reviewed in Auwerx & Staels 1998). Leptin gene expression is regulated in an opposite fashion by PPAR-γ and C/EBP-α, the first reducing its expression (De Vos et al. 1996, Kalten & Lazar 1996, Zhang et al. 1996), whereas the second induces its expression (He et al. 1995, Miller et al. 1996, Hollenberg et al. 1997). The decrease in circulating leptin levels upon PPAR-γ activation is associated with an increase in food intake, which will provide substrates, subsequently to be stored in the adipocytes. Consistent with this hypothesis, PPAR-γ+/− mice receiving a high-fat diet have a higher circulating leptin level than normal mice (Kubota et al. 1999). Leptin expression is probably less attenuated, due to the weaker expression of PPAR-γ in these PPAR-γ+/− mice.

A similar hypothesis can be formulated in relation to adipose tissue TNF-α production. TNF-α is a potent inhibitor of adipocyte differentiation and exposure of 3T3-L1 adipocytes to TNF-α results in lipid depletion and a complete reversal of adipocyte differentiation (Torti et al. 1985, reviewed in Beutler & Cerami 1988). TNF-α exerts this anti-adipogenic action in part by the down-regulation of the expression of adipogenic factors such as C/EBP-α (Ron et al. 1992, Williams et al. 1992) and PPAR-γ (Hill et al. 1997, Peraldi et al. 1997, Xing et al. 1997). Interestingly, obesity characterized by increased adipose tissue mass is associated with increased TNF-α expression in adipose tissue. Although the exact role of high TNF-α levels in obesity is unclear, it might constitute a regulatory mechanism to limit further increase in adipose tissue mass. This increase in TNF-α levels in obesity also interferes with the insulin signaling pathways (Hotamisligil et al. 1993, 1995) contributing to the insulin resistance characteristic of the obese state (Hotamisligil et al. 1994, 1996). Consistent with the opposing effects of PPAR-γ and TNF-α in adipose tissue, treatment of obese animals with PPAR-γ agonists reduces adipose tissue expression of TNF-α, contributing to weight gain (Hofmann et al. 1994, Okuno et al. 1998). PPAR-γ activation furthermore blocks the inhibitory effects of TNF-α on insulin signaling (Peraldi et al. 1997) as well as the TNF-α-induced glycerol and free fatty acid release (Souza et al. 1998).

Very recently, a family of signaling factors, Wnts, which play a major role in the regulation of cell growth and development, have been implicated in the inhibition of adipocyte differentiation. Ross et al. (2000) demonstrated that forced expression of Wnt-1 in 3T3-F442A cells inhibited the formation of adipose tissue when these cells were grafted into nude mice. Furthermore, 3T3-L1 cells ectopically expressing a dominant negative form of TCF4, a transcriptional mediator of the Wnt pathway, undergo adipogenesis without any hormonal induction (Ross et al. 2000). Repression of PPAR-γ and C/EBP-α expression was suggested as the mechanism by which activation of the Wnt signaling inhibited adipogenesis.

**CELL CYCLE REGULATION DURING ADIPOGENESIS**

Cell proliferation and differentiation are considered to be mutually exclusive events. However, a close relationship has been established between both cell processes during the adipocyte differentiation program. One of the first events occurring during adipogenesis is re-entry into cell cycle of growth-arrested preadipocytes following hormonal induction. After several rounds of clonal expansion, cells arrest proliferation again and undergo terminal adipocyte differentiation. In the first hours of adipocyte differentiation, an increase in the E2F activity has been observed (Richon et al. 1997). E2Fs are transcription factors which regulate the expression of genes involved in DNA synthesis (for reviews see Nevins 1992, Sardet et al. 1997, Helin 1998). Consequently, expression of these genes, such as cyclin D1, c-Myc, or cyclin E, is increased in the early stages of adipogenesis (Reichert & Eick 1999). Interestingly, blocking cell cycle re-entry with a DNA synthesis inhibitor, prevents adipocyte differentiation, suggesting that an active cell cycle machinery is required for the differentiation process (Richon et al. 1997). Similar results were obtained when degradation of p27, a cyclin-dependent kinase inhibitor, was prevented using a protease inhibitor. As a consequence of p27 protein accumulation, cell cycle re-entry was blocked, and thus differentiation of preadipocytes was inhibited ( Patel & Lane 2000).

The role of the retinoblastoma protein (RB) family members, or the pocket proteins pRB, p130, and p107, in adipocyte differentiation seems more complex. The negative role of pocket proteins in cell cycle progression, repressing the expression of the E2F target genes has been demonstrated in several settings. Pocket proteins are inactivated by phosphorylation by the cyclin-dependent kinases, resulting in the activation of the E2F target genes. Consistent with an active cell cycle in the early stages of adipogenesis, pocket proteins have been
found to be hyperphosphorylated following hormo-
nal induction of preadipocytes (Richon et al. 1997).
However, an apparent paradox arises from the
finding that pRB inactivation, by SV40 large T
antigen, inhibits adipogenesis (Higgins et al. 1996).
Moreover, pRB-deficient fibroblasts fail to differenti-
tiate into adipocytes when properly stimulated
(Chen et al. 1996). This apparent paradox was
explained by the participation of RB in the growth
arrest following clonal expansion. This suggests that
RB is involved in two phases of adipocyte differen-
tiation. First, inactivation of RB enables
clonal expansion, whereas growth arrest after this
expansion phase requires active RB, which posi-
tively influences adipocyte differentiation. Interest-
ingly, this function of RB can be compensated by
overexpression of both C/EBP-α and PPAR-γ,
which would mediate the cell cycle arrest after
clonal expansion (Classon et al. 2000). A different
role, independent of the control of cell cycle, has
also been attributed to RB in another aspect of the
regulation of adipogenesis such as the enhancement
of the transactivation capability of C/EBP, via direct
protein–protein interaction (Chen et al. 1996). In
contrast to RB, the other members of the retinoblastoma family, p130 and p107, have been
reported to negatively regulate adipogenesis.
Indeed, fibroblastic cells deficient in both p130 and
p107 differentiate into adipocytes whereas the wild-type cells do not (Classon et al. 2000).
Furthermore, reintroduction of p130 and p107 into
these cells inhibits adipocyte differentiation. These
effects of p107 in adipogenesis have been suggested
to be mediated through down-regulation of PPAR-γ
activity.

Undoubtedly there is a cross-talk between the cell
cycle and the adipocyte differentiation machinery. How the shift in gene expression observed during
the transition between preadipocyte proliferation
and adipocyte differentiation is regulated needs,
however, further investigation.

**ROLE OF PPAR-γ IN THE CONTROL OF CELL CYCLE**

Studies based on tumor cell lines have implicated
PPAR-γ in cell cycle withdrawal. One of the first
pieces of evidence implicating PPAR-γ in the
control of cell cycle came from the observation that
PPAR-γ activation decreased the binding of the
E2F/DP heterodimers to its target genes. This
decrease in E2F/DP activity is in part mediated by
PPAR-γ through the down-regulation of the PP2A
protein phosphatase (Altiok et al. 1997). Inhibition
of E2F/DP activity can also be achieved via
activation of RB. Interestingly, PPAR-γ ligands
were shown to inhibit phosphorylation of RB in
vascular smooth muscle cells (Wakino et al. 2000),
therefore contributing to maintain RB in its active
form. Consequently, the G1/S transition in these
cells was abrogated. Another suggested mechanism
involving PPAR-γ in the mediation of cell cycle
arrest was provided by the study of Morrison &
Farmer (1999), who suggested a role of PPAR-γ in
up-regulating the cyclin-dependent kinase inhibi-
tors p18 and p21 during adipogenesis. PPAR-γ
therefore could control the expression not only of genes
involved in the acquisition of a differentiated
phenotype but also of genes involved in the negative
regulation of cell cycle.

The anti-proliferative effects of PPAR-γ go
further than participation in the cell cycle arrest
during the adipocyte differentiation process.
PPAR-γ expression is not restricted to adipose
tissue, being expressed in several other cell types.
Furthermore, it has been reported that PPAR-γ
expression is increased in several epithelial cancer
cells. Whereas the physiological function of PPAR-γ
in normal epithelial cells is largely unknown,
PPAR-γ activation was reported to inhibit the
proliferation of malignant cells from different
lineages such as liposarcoma (Tontonoz et al. 1997),
breast adenocarcinoma (Elstner et al. 1998, Mueller
et al. 1998), prostate carcinoma (Kuboto et al.
1998), colorectal carcinoma (Brockman et al. 1998,
Sarraf et al. 1998, Kitamura et al. 1999), non-small
lung carcinoma (Chang & Szabo 2000), pancreatic
carcinoma (Motonura et al. 2000), bladder cancer cells (Guan et al. 1999), and gastric
carcinoma cells (Sato et al. 2000). In adipocytes,
macrophages, breast, prostate and non-small cell
lung cancer cells, thiazolidinediones are reported to
induce apoptosis (Chinetti et al. 1998, Elstner et al.
1998, Kuboto et al. 1998, Mueller et al. 1998,
Okuno et al. 1998, Chang & Szabo 2000). These
observations suggest that induction of differentia-
tion by activation of PPAR-γ may represent a
promising novel therapeutic approach for cancer as
already demonstrated for liposarcoma (Demetri
et al. 1999) and in xenograft models of prostate
(Kuboto et al. 1998) and colon cancer (Sarraf et al.
1998). Going along with this hypothesis is the
observation that somatic mutations in the PPAR-γ
gene are present in certain colon cancers (Sarraf
et al. 1999). The medical relevance of this last
observation is at present unclear, until more
biopsies have been analyzed. In addition, treatment
of patients with advanced prostate cancer with the
PPAR-γ agonist troglitazone, resulted in a high-
incidence stabilization of prostate-specific antigen
levels (Mueller et al. 2000), an effect mediated at
least in part by the inhibition of the androgen receptor activation (Hisatake et al. 2000). Other evidence for the involvement of PPAR-\(\gamma\) in tumorigenic processes comes from the identification in a subset of thyroid follicular carcinomas of a chromosomal translocation resulting in a fusion protein PAX8-PPAR-\(\gamma\) (Kroll et al. 2000). This fusion protein behaves as a PPAR-\(\gamma\) dominant negative, which abrogates the effects of ligand activation of the wild-type PPAR-\(\gamma\) protein.

In sharp contrast with this, however, are the studies showing that activation of PPAR-\(\gamma\) promotes the development of colon tumors in C57BL/6J-APC\(^{Min/+}\) mice (APC is the tumor suppressor protein in adenomatous polyposis coli) (Lefebvre et al. 1998, Saez et al. 1998), a clinically relevant model for both human familial adenomatous polyposis and sporadic colon cancer (Groden et al. 1991, Nishisho et al. 1991, Miyoshi et al. 1992, Su et al. 1992, Powell et al. 1993). Even if the exact role of PPAR-\(\gamma\) in the development of colorectal cancer is not yet elucidated, several observations support the idea that this receptor is involved in these pathologies. First, PPAR-\(\gamma\) is highly expressed in the colon (Considine et al. 1996, Mansen et al. 1996, Lefebvre et al. 1998). Secondly, the development of colorectal cancer is influenced by prostaglandins (Kinzler & Vogelstein 1996), which are potential ligands of PPAR-\(\gamma\). Indeed, in mice with mutations in the cyclooxygenase (COX)-2 gene or in animals and humans treated with COX inhibitors, decreased production of prostaglandins prevents or attenuates colon cancer development (Thun et al. 1991, Jacoby et al. 1996, Oshima et al. 1996). Finally, there is a strong correlation between the intake of fatty acids from animal origin (potential activators of PPAR-\(\gamma\)) and colon cancer (Giovanucci & Willet 1994, Wasan et al. 1997). Activation of PPAR-\(\gamma\) by two different synthetic agonists increased the frequency and size of colon tumors in C57BL/6J-APC\(^{Min/+}\) mice (Lefebvre et al. 1998, Saez et al. 1998). Tumor frequency was only increased in the colon (by 425\% for rosiglitazone-treated and by 183\% for troglitazone-treated animals), whereas the frequency did not change in the small intestine, coinciding with the colon-restricted expression of PPAR-\(\gamma\). A similar increase in the frequency of colon tumors was observed previously when these mice were fed with a diet high in saturated fats (Wasan et al. 1997), suggesting that PPAR-\(\gamma\) could be involved in establishing the link between a high-fat diet and colon cancer (Giovanucci & Willet 1994). Treatment with PPAR-\(\gamma\) agonists furthermore increased \(\beta\)-catenin levels both in the colon of C57BL/6J-APC\(^{Min/+}\) mice and in HT-29 colon carcinoma cells (Lefebvre et al. 1998). These observations seem at odds with the above antiproliferative properties associated with PPAR-\(\gamma\) activation. It is, however, most likely that the differences are mainly due to the differences in model systems used. In fact, the C57BL/6J-APC\(^{Min/+}\) mouse studies are an adequate model to study the effects of PPAR-\(\gamma\) on the spontaneous development of colon cancers, whereas the xenograft model is better suited to study the anti-proliferative capacity of PPAR-\(\gamma\) activation in cancerous cells. Hence, the action of PPAR-\(\gamma\) on cell cycle, proliferation, differentiation and apoptosis seems to depend on the cell type and/or the mutational events that predisposes tissues to cancer development.

Interestingly, a recent study also showed the involvement of another isoform of PPAR, PPAR-\(\delta\), in the development of colorectal cancer (He et al. 1999). PPAR-\(\delta\) like PPAR-\(\gamma\) is expressed in the colon and can be activated by fatty acids. He et al. (1999) showed that PPAR-\(\delta\) is a target gene for the \(\beta\)-catenin/Tcf-4 transcription complex, which is formed when the tumor suppressor protein APC is mutated (Kinzler & Vogelstein 1996). These investigators propose that PPAR-\(\delta\) can mediate the pro-tumorigenic effects of fatty acids on colon cancer formation. Non-steroidal anti-inflammatory drugs, which perturb the production of endogenous PPAR ligands, were suggested to inhibit PPAR-\(\delta\) activity. At present it is unclear how these observations on PPAR-\(\delta\) articulate with the above discussed involvement of PPAR-\(\gamma\) in cell proliferation and colon cancer. One hypothesis that definitely merits further exploration relates to an eventual role of PPAR-\(\delta\) in the control of PPAR-\(\gamma\) gene expression. Indeed, PPAR-\(\gamma\) expression is in part controlled by a PPRE in its own promoter (Saladin et al. 1999). Therefore it is possible that part of the pro-tumorigenic effects of PPAR-\(\delta\) are mediated by PPAR-\(\gamma\).

All these in vivo and in vitro data related to the effects of PPAR-\(\gamma\) on cell cycle, apoptosis and carcinogenesis definitely warrant follow-up. Careful monitoring of type 2 diabetes patients chronically treated with PPAR-\(\gamma\) agonists is indicated. In addition, these data dictate the need for additional laboratory studies to address the role of PPAR-\(\gamma\) in tumorigenesis. Finally, it will be of interest to evaluate a potential role of cofactors in these phenomena and to determine if mutations or modulation in expression of coactivators or corepressors, affecting their function, could be involved in PPAR-\(\gamma\)-dependent tumor formation. A possible precedent for such a role of cofactors was highlighted in estrogen receptor-dependent breast cancers in which cofactors such as the coactivator
amplified in breast cancer-1, a member of the steroid receptor coactivator-1 family (Anzick et al. 1997), or nuclear corepressor were mutated or down-regulated (Lavinsky et al. 1998, Takimoto et al. 1999).

CONCLUSIONS

Differentiation of preadipocytes into adipocytes is part of a metabolic response to nutritional and hormonal signaling. This differentiation process requires a cascade of changes in gene expression. Both in vivo and in vitro data have substantiated the important role of PPAR-γ in mediating such changes during terminal adipocyte differentiation. Despite a large body of knowledge about the role of PPAR-γ in this differentiation process, a lot needs to be learned. For instance, little is known about the molecular mechanisms preceding PPAR-γ expression and activation. The identification of transcription factors triggering the expression of PPAR-γ and the onset of differentiation are of utmost importance. Furthermore, we expect that studies in genetically modified animals and of factors interacting with PPAR-γ will be helpful for a better understanding of PPAR’s function. We also predict that characterization of new PPAR-γ modulators and ligands might address some of the scientific problems in the PPAR-γ field. Although a wide variety of fatty acids have been reported to be capable of activating PPAR-γ in vitro, it is at present unknown which fatty acids are activating PPAR-γ in vivo. One important remaining question is whether in tissues where PPAR-γ is expressed, adequate levels of natural ligands are present. Finally, the observation that PPAR-γ expression is elevated in several human malignancies merits further investigation to elucidate the role of PPAR-γ in such proliferative disorders.

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