Proceedings of the Nutrition Society (2002), **61**, 363–369 DOI:10.1079/PNS2002173

A joint meeting of the Nutrition Society with the Nutritional Immunology Group of the British Society for Immunology and the British Inflammation Research Association was held at Harrogate International Centre, Harrogate on 6 December 2001

Mechanisms in nutrient regulation of inflammation

A role for the peroxisome proliferator-activated receptor α in T-cell physiology and ageing immunobiology

Dallas C. Jones[1], Bernadette M. Manning[1] and Raymond A. Daynes[1,2]*
[1]*Department of Pathology, University of Utah School of Medicine, Salt Lake City, Utah 84132, USA*
[2]*Geriatric Research, Education and Clinical Center, Veterans Affairs Medical Center, Salt Lake City, Utah 84112, USA*

Peroxisome proliferator-activated receptor (PPAR) α represents an important member of the nuclear hormone receptor superfamily that can be activated by a variety of natural fatty acids, some of their metabolites and by commonly-used anti-lipidaemic drugs. We recently demonstrated PPARα expression in T lymphocytes, where it controls the initiation of transcription of T-box expressed in T-cells (T-bet) independent of added agonist. T-bet is an activation-inducible transcription factor regulator of interleukin 2 (suppression) and interferon γ (stimulation) synthesis. A suppressed ability to produce interleukin 2 and an enhanced production of interferon γ occurs in activated T-cells from PPARα–/– mice, as well as in T-cells from wild-type aged animals whose lymphocytes express lowered basal levels of PPARα. The dysregulated expression and/or function of cytokines, glucocorticoids or leptin that occurs with advanced age could all be responsible for the reduced expression of PPARα. Dietary supplementation of aged mice with vitamin E, or supplementation with known agonists of PPARα, was associated with elevation of lymphocyte expression of this nuclear hormone receptor, restoration of control over T-bet expression and elimination of the dysregulated production of interleukin 2 and interferon γ following lymphocyte activation. Interleukin 2 and interferon γ play very important roles in the initiation and/or regulation of immune, inflammatory and autoimmune disease states. Thus, the mechanisms that control the timing, magnitude and duration of specific cytokine production by activated T lymphocytes need clarification before appropriate nutritional or therapeutic strategies can be devised to treat disease conditions where cytokine expression and/or activities are deemed to be dysregulated and responsible.

Ageing: PPARα: Immunobiology

Overview of peroxisome proliferator-activated receptors

The peroxisome proliferator-activated receptors (PPAR) are ligand-inducible transcription factors that belong to the nuclear hormone receptor superfamily. To date, three PPAR subtypes have been identified: PPARα, PPARβ/δ and PPARγ (NR1C1, NR2C1 and NR3C1 respectively; Dreyer *et al*. 1992; Chen *et al*. 1993; Lemberger *et al*. 1996). These three PPAR isoforms exhibit a high level of sequence and structural homology, but each isoform displays a divergent pattern of tissue expression and ligand-binding specificity (Kliewer *et al*. 1994; Braissant *et al*. 1996). PPARα was the initially described member of this family, being isolated by Issemann & Green (1990), based on its ability to induce peroxisome proliferation in rodent hepatocytes in response to certain xenobiotic compounds. Since that original observation, it is now known that PPARα is expressed in a number of tissues, including liver, heart, and kidney, whose primary source of energy is derived from fatty acids (Issemann & Green, 1990; Braissant *et al*. 1996). In these tissues PPARα regulates the expression levels of a number of genes involved in fatty acid metabolism, as well as genes involved in lipid homeostasis, cholesterol flux, and control over cellular redox state (Chinetti *et al*. 2000).

Abbreviations: IFN-γ, interferon γ; IL-2, interleukin 2; MAP, mitogen-activated protein; PPAR, peroxisome proliferator-activated receptors; PUFA, polyunsaturated fatty acids; T-bet, T-box expressed in T-cells; WT, wild type.

***Corresponding author:** Dr Raymond A. Daynes, fax + 1 801 581 8946, email daynes.office@path.utah.edu

PPAR positively regulate the expression of genes under their transcriptional control by binding to specific DNA sequences known as peroxisome proliferator response elements as a heterodimeric complex with the 9-*cis*-retinoic acid receptor. In the unliganded state PPARα is thought to be transcriptionally inert, due to its physical association with the nuclear co-repressors N-CoR and SMRT (DiRenzo *et al*. 1997). Following ligand activation, the nuclear co-repressors dissociate from PPARα, thus enabling it to bind nuclear receptor co-activators such as SRC-1 and CBP/p300. These protein complexes restructure the chromatin template through histone acetylation, and allow the basal transcriptional machinery to access the promoter regions driving transcription of target genes under PPAR control (Onate *et al*. 1995; Bannister & Kouzarides, 1996; Kamei *et al*. 1996; Torchia *et al*. 1997).

Similar to observations reported for other nuclear hormone receptors, PPAR also possess the ability to negatively regulate gene expression through a number of transrepression mechanisms. Anti-inflammatory activities linked to PPAR are largely mediated through an ability of the receptors to physically associate with, and antagonize, the transcriptional activities of many transcription factors, including signal transducers and activators of transcription, activator protein-1, nuclear factor of activated T-cells and nuclear factor kappa B (Gottlicher *et al*. 1992; Miyata *et al*. 1996; Ren *et al*. 1996; Jiang *et al*. 1998; Ricote *et al*. 1998; Staels *et al*. 1998). Similarly, the PPAR have additionally been demonstrated to inhibit the activation of certain protein kinases, thereby affecting downstream transcription factor activities (Desreumaux *et al*. 2001). The PPAR are also known to inhibit expression of certain genes through their ability to sequester important transcriptional co-activators that may be expressed in limited amounts within a cell (Li *et al*. 2000). The ability of the PPAR to mediate positive as well as negative gene regulation allows these nuclear hormone receptors to affect the transcription of a wide range of genes. Consequently, the PPAR are now appreciated to play critical physiological roles as lipid sensors, as regulators of lipid and carbohydrate metabolism, and in the control of many developmental processes.

Natural peroxisome proliferator-activated receptor α ligands: a link to nutrition

When compared with other nuclear hormone receptors, the ligand-binding domains of the PPAR are larger, explaining their capacity to accommodate a broad range of activating ligands (Xu *et al*. 1999). While several ligands, including some fatty acid species, can serve as pan-agonists for all three PPAR isoforms, more recent studies have described the existence of a number of PPARα isoform-specific ligands, including the eicosaniod 8(S)-hydroxyeicosatetraenoate, leukotriene B_4, *n*-3 fatty acids, and *n*-6 fatty acids (Forman *et al*. 1997; Kliewer *et al*. 1997). While a number of these potential ligands are able to activate PPARα *in vitro*, a ligand such as 8(S)-hydroxyeicosatetraenoate is not found at high enough intracellular concentrations *in vivo* to effectively serve as an endogenous ligand for this receptor (Berger & Moller, 2002).

It has been demonstrated through analysis of a number of different assay systems that certain polyunsaturated fatty acids (PUFA) can serve as natural agonists for PPARα. As PUFA can activate PPARα, and a majority of the PPARα-regulated genes are involved in fatty acid metabolism, it is believed that PPARα may be functioning as a 'lipostat', maintaining cellular lipid homeostasis (Djouadi *et al*. 1999). Through this function, PPARα up regulates the expression of genes required for efficient fatty acid utilization in response to increases in cellular lipids.

One well-studied example of the role of PPARα as a 'lipostat' is the cellular response to leptin. Leptin is a cytokine produced by adipocytes in response to excesses in lipid levels. This cytokine signals many peripheral cell types through the leptin receptor and induces an up-regulation of PPARα expression (Ahima & Flier, 2000). PPARα can then be activated by the mobilized fatty acids to up regulate expression of those enzymes and fatty acid transporters necessary for effective mitochondrial fatty acid catabolism and energy generation through the β-oxidation pathway (Wang *et al*. 2001). An inability to effectively regulate the levels of cytosolic lipids can be directly cytotoxic through mechanisms involving the formation of lipid peroxides and ceramide generation (Unger & Zhou, 2001). Such an inability to effectively regulate cytosolic lipid levels would probably occur with cellular depressions in either PPARα expression or in PPARα activities.

Consequences of a generalized depression in peroxisome proliferator-activated receptor α expression

Our laboratory previously reported that expression of the PPARα gene is depressed in cells residing within secondary lymphoid organs isolated from aged donors (Poynter & Daynes, 1998). This reduction in PPARα expression was linked to the constitutive overproduction of certain pro-inflammatory cytokines that had previously been reported to occur in tissues from aged animals, as well as in tissues from mature adult PPARα–/– mice (Spencer *et al*. 1997; Poynter & Daynes, 1998). Further support that depressions in PPARα expression contributed to this pro-inflammatory phenotype came from studies where aged wild-type (WT) and aged PPARα–/– mice were given daily treatments with dehydroepiandrosterone or WY 14 643, two PPARα-specific agonists. Treatment of the WT mice with PPARα agonists restored normal control over the abnormal expression of pro-inflammatory cytokines and the redox-regulated transcription factor nuclear factor kappa B. Aged PPARα–/– mice failed to benefit from agonist treatment, and continued to constitutively express pro-inflammatory cytokines and active nuclear factor kappa B. Interestingly, treatment of aged WT mice with WY 14,643, or with dehydroepiandrosterone, additionally restored normal levels of PPARα within the secondary lymphoid organs of the aged animals (Poynter & Daynes, 1998).

Our laboratory has recently demonstrated using quantitative real-time polymerase chain reaction that the levels of PPARα gene expression are depressed by >50% in a number of tissues isolated from aged animals, including the heart, liver and kidney (Fig. 1(A)). The age-associated

https://doi.org/10.1079/PNS2002173 Published online by Cambridge University Press

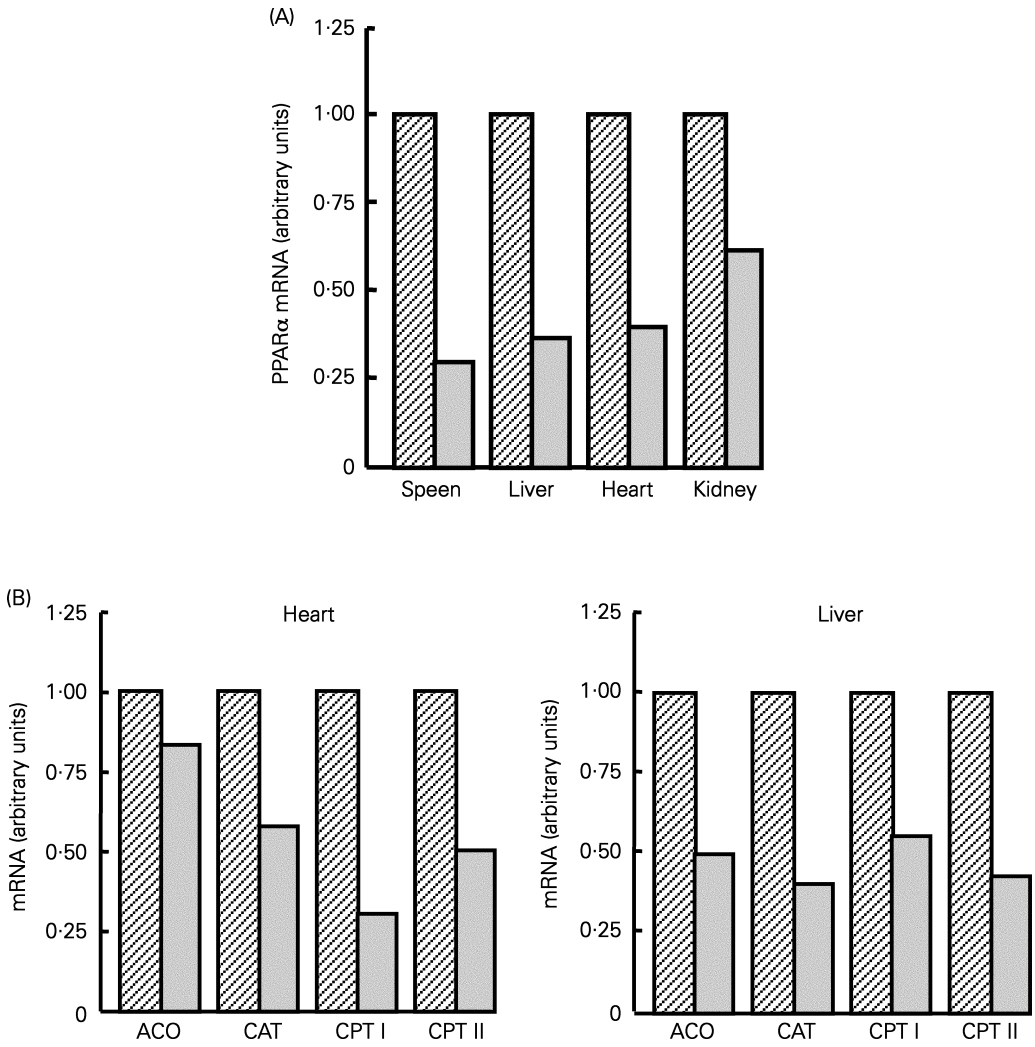

Fig. 1. Transcript levels of (A) peroxisome proliferator-activated receptor (PPAR)α and (B) PPARα-regulated genes are reduced in tissues from aged mice. mRNA was extracted from various tissues of 4-month-old (▨) or 24-month-old (▩) C57BL/6 mice and quantitative real-time reverse transcriptase–polymerase chain reaction was performed. The amount of glyceraldehyde phosphate dehydrogenase transcript in each sample was equalized as a means of standardization. Similar results were obtained in multiple independent experiments. ACO, acyl-CoA oxidase; CAT, catalase; CPT, carnitine palmitoyltransferase.

depression of PPARα expression within these tissues was accompanied by decreases in the expression levels of a number of PPARα-target genes essential for fatty acid metabolism, including carnitine palmitoyltransferases I and II and acyl-CoA oxidase (Fig. 1(B)). A depressed expression of these genes in various tissues is known to correlate with a dysregulation in lipid homeostasis. When frozen sections of affected tissues were harvested and stained to detect the presence of cytosolic lipids with oil red O, tissues from aged mice showed an enhanced presence of cytosolic lipid droplets when compared with comparable tissue sections isolated from mature adult mice (Fig. 2). Watanabe *et al*. (2000) previously reported a similar pathology within the heart tissue of PPARα–/– mice. This group demonstrated that several enzymes essential for normal cardiac fatty acid metabolism are expressed at lower levels within the hearts of PPARα–/– mice. The authors concluded that a reduced ability to effectively metabolize fatty acids was responsible for the development of myocardial damage and fibrosis within the hearts of PPARα–/– mice. We feel that similar effects may be occurring in various tissues with ageing, and that age-associated depressions in PPARα expression may be partially responsible.

Peroxisome proliferator-activated receptor α and the immune system

PPARα has been extensively studied in tissues that utilize fatty acids as a primary energy source, such as heart, liver, muscle and kidney (Issemann & Green, 1990; Braissant *et al*. 1996). This receptor isoform has also been found to be expressed in several other tissues and cell types such as chondrocytes, keratinocytes and cells of the immune system

https://doi.org/10.1079/PNS2002173 Published online by Cambridge University Press

(Chinetti *et al*. 1998; Bordji *et al*. 2000; Hanley *et al*. 2000; Padilla *et al*. 2000; Harris & Phipps, 2001). Ligand activation of PPARα or PPARγ in macrophages can effectively inhibit activation-induced inflammatory cytokine production through the active repression of several crucial transcription factors (Chinetti *et al*. 1998). The expression of PPARγ has been described recently in B and T lymphocytes where it has been reported to play a role in cytokine production, cellular proliferation, and susceptibility to apoptosis (Padilla *et al*. 2000; Harris & Phipps, 2001).

We recently established the constitutive expression of PPARα in resting T and B lymphocytes (Jones *et al*. 2002). Interestingly, we demonstrated that the expression of PPARα within T lymphocytes is rapidly down regulated following cellular activation. This finding is in contrast with observations for PPARγ expression in lymphocytes, which appears to increase with T-cell activation (Harris & Phipps, 2001; Jones *et al*. 2002). The dynamic flux that PPARα exhibited within T-cells following activation suggested that this nuclear hormone receptor might be involved in early activation events within T-cells. One of the earliest events to occur in T-cells post activation is the induced synthesis of interleukin 2 (IL-2), an important T-cell growth factor. Interestingly, the amount of IL-2 protein produced by PPARα–/– T-cells post activation is markedly reduced (>75%) when compared with that of WT T-cells. A kinetic analysis of IL-2 mRNA revealed that the transcription of IL-2 in PPARα–/– T-cells is terminated at a much earlier time post activation than the IL-2 transcription in WT T-cells. This finding is in contrast with interferon γ (IFN-γ) gene expression and protein production, which is expressed earlier and is greatly elevated in PPARα–/– T-cells. Thus, dysregulations in the initiation and termination of the transcription of two cytokine genes occurs within T-cells isolated from PPARα–/– animals. We have now determined that the dysregulated production of these two cytokines in T-cells from PPARα–/– donors arises from a kinetically-accelerated post-activation induction of T-box expressed in T-cells (T-bet). This transcription factor has recently been described to induce T-helper 1 cell differentiation through its ability to transactivate the IFN-γ gene, while simultaneously suppressing expression of the IL-2 gene (Szabo *et al*. 2000). T-bet is also required for IFN-γ production by natural killer cells, but is apparently not entirely responsible for controlling IFN-γ production by $CD8^+$ T-cells (Szabo *et al*. 2002).

We (DC Jones and RA Daynes, unpublished results) hypothesized that activation-induced suppression of endogenous PPARα expression in T-cells from WT donors is ultimately responsible for relaxing its controlling influences over the initiation of T-bet transcription and gene expression. This hypothesis was supported by the finding that T-bet expression and IFN-γ production were solidly inhibited in an activated T-cell line which constitutively expressed PPARα following transfection with a cytomegalovirus–PPARα construct. Consequently, the constant presence of PPARα in T-cells was somehow tonically suppressing the initiation of T-bet transcription following activation, and thereby retarding any regulatory influences controlled by this transcription factor.

Since the cellular localization of PPARα within T-cells is exclusively cytoplasmic (Jones *et al*. 2002), we suggested that the ability of PPARα to regulate T-bet transcription was probably not mediated through a DNA-binding-dependent process, but rather through the ability of PPARα to antagonize some signalling pathway essential for T-bet transcription. Previous reports have suggested a prominent role for the p38 mitogen-activated protein (MAP) kinase in both IFN-γ production and T-helper 1 differentiation, processes that are now appreciated to be mediated by T-bet (Rincon *et al*. 1998; Lu *et al*. 2001). We utilized the chemical p38 MAP kinase inhibitor, PD169 316, to determine that p38 MAP kinase activity within T-cells is necessary for T-bet transcription. We also found that the absolute level of phospho-p38 MAP kinase was much higher within activated PPARα–/– T-cells when compared with WT T-cells activated under the same conditions. Furthermore, we determined that constitutive expression of PPARα within a cytomegalovirus–PPARα transfected T-cell line markedly suppressed the levels of phospho-p38 MAP kinase following activation. Together, these findings suggest that the ability of PPARα to regulate T-bet transcription within activated T-cells, and ultimately the protein production, is mediated through the ability of PPARα to regulate the activation of p38 MAP kinase. A hypothetical model, outlining our present ideas concerning the molecular pathways that appear to be controlled by PPARα in WT T-cells is presented in Fig. 3. This model suggests that the ability of PPARα to control the initiation of T-bet transcription is indirect, being mediated through its capacity to somehow suppress the activation of p38 MAP kinase. We are presently investigating the means by which PPARα is able to control p38 MAP kinase activation.

The profile of cytokine production from activated T-cells isolated from young adult PPARα–/– mice was found to be strikingly similar to that observed from T-cells isolated from aged animals (Engwerda *et al*. 1996). In view of this similarity in cytokine production, we questioned whether there might be a depressed expression of PPARα and an accelerated expression of T-bet within T-cells isolated from aged donors. Using quantitative real-time polymerase chain reaction, we found that PPARα mRNA expression in T-cells from aged mice was three to four times lower than that observed in T-cells isolated from adult mice. T-cells isolated from aged donors also demonstrated a markedly accelerated induction of T-bet that was kinetically similar to what was observed in activated PPARα–/– T-cells.

To further question the role of PPARα in the regulation of T-cell cytokine production, we kinetically analysed T-cells from aged mice placed on diets supplemented with the antioxidant α-tocopherol. Our laboratory had previously demonstrated that providing α-tocopherol supplementation to aged mice increased the PPARα mRNA in splenocytes to levels observed in splenocytes from young donors (Poynter & Daynes, 1998). We had also demonstrated that this therapeutic administration of α-tocopherol normalized the production of cytokines by activated T-cells. When T lymphocytes from aged animals supplemented with α-tocopherol were stimulated *in vitro*, their ability to produce IL-2 was markedly increased compared with that produced by T-cells from unsupplemented aged mice.

https://doi.org/10.1079/PNS2002173 Published online by Cambridge University Press

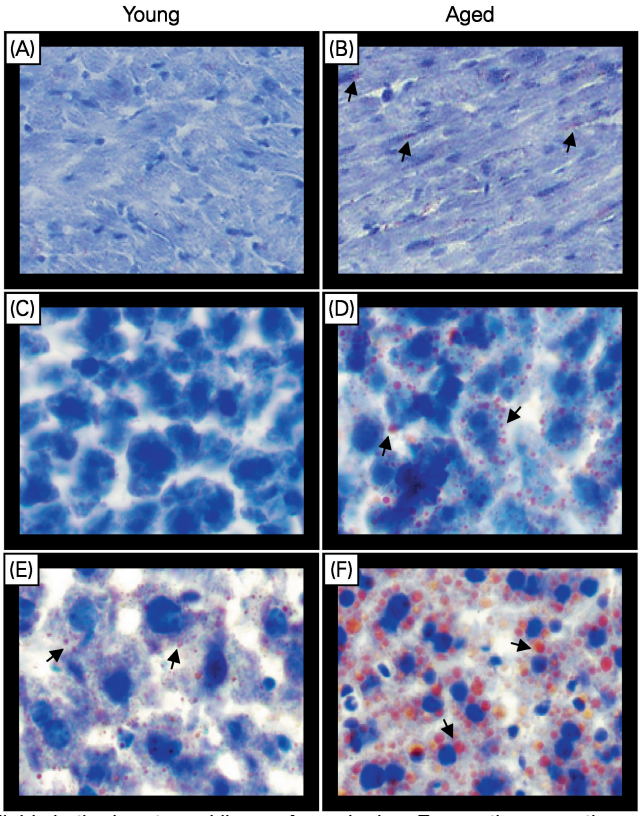

Fig. 2. Accumulation of intracellular lipids in the hearts and livers of aged mice. Frozen tissue sections were prepared from the hearts (A and B) and livers (C–F) of young (A,C and E) or aged (B,D and F) (C57BL/6 × DBA2) F1 mice. Tissues were harvested from mice that were either fed *ad libitum* (A–D) or fasted for 24 h (E and F). All sections were stained with oil red O for analysis of lipid droplets. The presence of red droplets (↑) indicates positive staining for neutral lipids. Photographs are representative of similar results observed in tissue sections prepared from four to six mice per group. Magnification ×400.

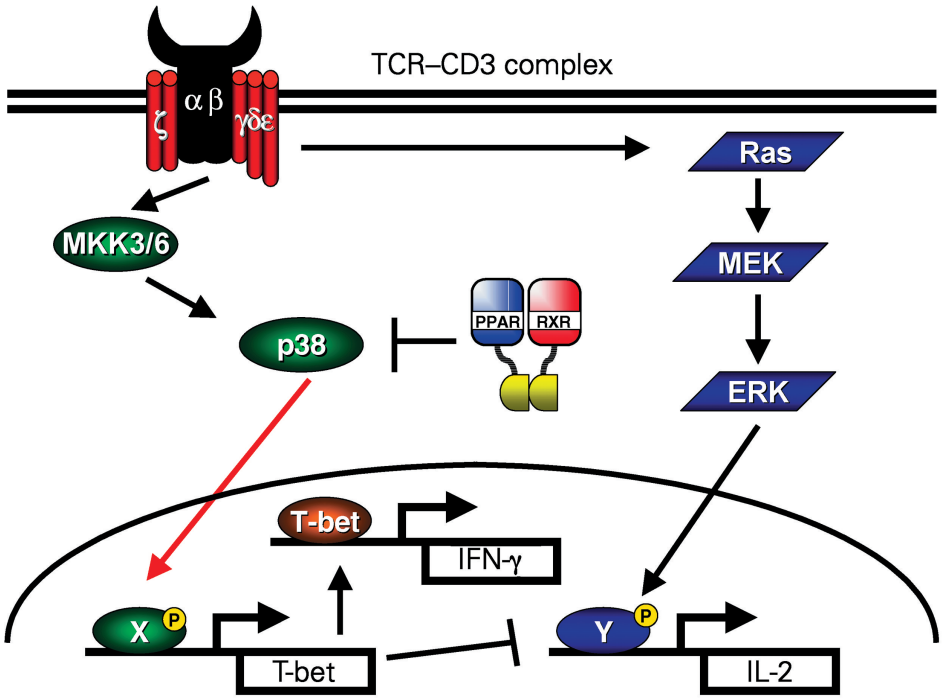

Fig. 3. Model for peroxisome proliferator-activated receptor (PPAR)α-mediated suppression of the transcription of T-box expressed in T-cells (T-bet). The ability of PPARα to alter the kinetic induction of T-bet transcription might arise through this nuclear hormone receptor's ability to transiently suppress the phosphorylation of the p38 mitogen-activated protein kinase following T-cell activation. TCR, T-cell receptor; MKK, MAP kinase kinase; p 38, MAP kinase; X,Y, unknown transcription factors X and Y respectively; IFN-γ, interferon γ; RXR, 9-*cis*-retinoic acid receptor; Ras, monomeric guanine nucleotide protein encoded by the ras proto-oncogene; MEK, MAP kinase kinase; ERK, extracellular signal-regulated kinase; IL-2, interleukin 2.

https://doi.org/10.1079/PNS2002173 Published online by Cambridge University Press

Conversely, the levels of activation-induced IFN-γ were reduced from the normally high levels produced by T-cells from unsupplemented aged animals. The kinetics of T-bet induction in activated T-cells from the supplemented aged animals was found to resemble that of young mice. Together, these observations suggest an expanding role for PPARα in T-cells of the immune system. It will be of great interest and importance to decipher the roles PPARα might play in other cells of the immune system, including B-cells and dendritic cells.

Conclusion

In the short history since their original discovery, it has become quite clear that the PPAR play critical roles in the regulation of energy homeostasis (through their ability to control major aspects of lipid and carbohydrate metabolism). It is also appreciated that dysregulated PPAR activities are involved in a number of pathological states including cancer, inflammation, infertility, demylination and atherosclerosis (Devchand *et al*. 1996; Mueller *et al*. 2000; Berger & Moller, 2002; Takano & Komuro, 2002). Recently, the expression of specific PPAR subtypes have been described in myeloid and lymphoid cell types, creating a possible linkage between PPAR expression and the immune system. PPARγ, known to be expressed in both T and B lymphocytes, is thought to be involved in suppression of cytokine production and proliferation (Padilla *et al*. 2000; Harris & Phipps, 2001). We have recently described that PPARα is also expressed in resting T and B lymphocytes (Jones *et al*. 2002). We now believe that PPARα is playing an unique role in T-cell activation through its ability to regulate the expression of T-bet, ultimately determining the timing, sequence and magnitude of cytokines produced by activated T-cells. Due to the ability of PPARα to carry out these influences within the T-cell, as well as the breadth of metabolic functions PPARα carries out in other cell types, an ability to regulate the expression of PPARα and its activities may represent useful therapeutic strategies to many pathological conditions.

Acknowledgements

This work was supported by National Institutes of Health grants CA25917 and DK55491, a Browning Foundation grant and by DVA Medical Research Funds. D.C.J. was supported by National Institutes of Health DHHS NIDDK Hematology Research Training Grant T32 DK07115.

References

Ahima RS & Flier JS (2000) Leptin. *Annual Review of Physiology* **62**, 413–437.

Bannister AJ & Kouzarides T (1996) The CBP co-activator is a histone acetyltransferase. *Nature* **384**, 641–643.

Berger J & Moller DE (2002) The mechanisms of action of ppars. *Annual Review of Medicine* **53**, 409–435.

Bordji K, Grillasca JP, Gouze JN, Magdalou J, Schohn H, Keller JM, Bianchi A, Dauca M, Netter P & Terlain B (2000) Evidence for the presence of peroxisome proliferator-activated receptor (PPAR) alpha and gamma and retinoid Z receptor in cartilage. PPARgamma activation modulates the effects of interleukin-1beta on rat chondrocytes. *Journal of Biological Chemistry* **275**, 12243–12250.

Braissant O, Foufelle F, Scotto C, Dauca M & Wahli W (1996) Differential expression of peroxisome proliferator-activated receptors (PPARs): tissue distribution of PPAR-alpha,-beta, and -gamma in the adult rat. *Endocrinology* **137**, 354–366.

Chen F, Law SW & O'Malley BW (1993) Identification of two mPPAR related receptors and evidence for the existence of five subfamily members. *Biochemical and Biophysical Research Communications* **196**, 671–677.

Chinetti G, Fruchart JC & Staels B (2000) Peroxisome proliferator-activated receptors (PPARs): nuclear receptors at the crossroads between lipid metabolism and inflammation. *Inflammation Research* **49**, 497–505.

Chinetti G, Griglio S, Antonucci M, Torra IP, Delerive P, Majd Z, Fruchart JC, Chapman J, Najib J & Staels B (1998) Activation of proliferator-activated receptors alpha and gamma induces apoptosis of human monocyte-derived macrophages. *Journal of Biological Chemistry* **273**, 25573–25580.

Desreumaux P, Dubuquoy L, Nutten S, Peuchmaur M, Englaro W, Schoonjans K, Derijard B, Desvergne B, Wahli W, Chambon P, Leibowitz MD, Colombel JF & Auwerx J (2001) Attenuation of colon inflammation through activators of the retinoid X receptor (RXR)/peroxisome proliferator-activated receptor gamma (PPARgamma) heterodimer. A basis for new therapeutic strategies. *Journal of Experimental Medicine* **193**, 827–838.

Devchand PR, Keller H, Peters JM, Vazquez M, Gonzalez FJ & Wahli W (1996) The PPARalpha-leukotriene B4 pathway to inflammation control. *Nature* **384**, 39–43.

DiRenzo J, Soderstrom M, Kurokawa R, Ogliastro MH, Ricote M, Ingrey S, Horlein A, Rosenfeld MG & Glass CK (1997) Peroxisome proliferator-activated receptors and retinoic acid receptors differentially control the interactions of retinoid X receptor heterodimers with ligands, coactivators, and core-pressors. *Molecular and Cellular Biology* **17**, 2166–2176.

Djouadi F, Weinheimer CJ & Kelly DP (1999) The role of PPAR alpha as a 'lipostat' transcription factor. *Advances in Experimental Medicine and Biology* **466**, 211–220.

Dreyer C, Krey G, Keller H, Givel F, Helftenbein G & Wahli W (1992) Control of the peroxisomal beta-oxidation pathway by a novel family of nuclear hormone receptors. *Cell* **68**, 879–887.

Engwerda CR, Fox BS & Handwerger BS (1996) Cytokine production by T lymphocytes from young and aged mice. *Journal of Immunology* **156**, 3621–3630.

Forman BM, Chen J & Evans RM (1997) Hypolipidemic drugs, polyunsaturated fatty acids, and eicosanoids are ligands for peroxisome proliferator-activated receptors alpha and delta. *Proceedings of the National Academy of Sciences USA* **94**, 4312–4317.

Gottlicher M, Widmark E, Li Q & Gustafsson JA (1992) Fatty acids activate a chimera of the clofibric acid-activated receptor and the glucocorticoid receptor. *Proceedings of the National Academy of Sciences USA* **89**, 4653–4657.

Hanley K, Komuves LG, Ng DC, Schoonjans K, He SS, Lau P, Bikle DD, Williams ML, Elias PM, Auwerx J & Feingold KR (2000) Farnesol stimulates differentiation in epidermal keratinocytes via PPARalpha. *Journal of Biological Chemistry* **275**, 11484–11491.

Harris SG & Phipps RP (2001) The nuclear receptor PPAR gamma is expressed by mouse T lymphocytes and PPAR gamma agonists induce apoptosis. *European Journal of Immunology* **31**, 1098–1105.

Issemann I & Green S (1990) Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. *Nature* **347**, 645–650.

Jiang C, Ting AT & Seed B (1998) PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. *Nature* **391**, 82–86.

Jones DC, Ding X & Daynes RA (2002) Nuclear receptor PPARα is expressed in resting murine lymphocytes: The PPARα in T and B lymphocytes is both transactivation and transrepression competent. *Journal of Biological Chemistry* **277**, 6838–6845.

Kamei Y, Xu L, Heinzel T, Torchia J, Kurokawa R, Gloss B, Lin SC, Heyman RA, Rose DW, Glass CK & Rosenfeld MG (1996) A CBP integrator complex mediates transcriptional activation and AP-1 inhibition by nuclear receptors. *Cell* **85**, 403–414.

Kliewer SA, Forman BM, Blumberg B, Ong ES, Borgmeyer U, Mangelsdorf DJ, Umesono K & Evans RM (1994) Differential expression and activation of a family of murine peroxisome proliferator-activated receptors. *Proceedings of the National Academy of Sciences USA* **91**, 7355–7359.

Kliewer SA, Sundseth SS, Jones SA, Brown PJ, Wisely GB, Koble CS, Devchand P, Wahli W, Willson TM, Lenhard JM & Lehmann JM (1997) Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors alpha and gamma. *Proceedings of the National Academy of Sciences USA* **94**, 4318–4323.

Lemberger T, Desvergne B & Wahli W (1996) Peroxisome proliferator-activated receptors: a nuclear receptor signaling pathway in lipid physiology. *Annual Review of Cell and Developmental Biology* **12**, 335–363.

Li M, Pascual G & Glass CK (2000) Peroxisome proliferator-activated receptor gamma-dependent repression of the inducible nitric oxide synthase gene. *Molecular and Cellular Biology* **20**, 4699–4707.

Lu B, Yu H, Chow C, Li B, Zheng W, Davis RJ & Flavell RA (2001) GADD45gamma mediates the activation of the p38 and JNK MAP kinase pathways and cytokine production in effector TH1 cells. *Immunity* **14**, 583–590.

Miyata KS, McCaw SE, Patel HV, Rachubinski RA & Capone JP (1996) The orphan nuclear hormone receptor LXR alpha interacts with the peroxisome proliferator-activated receptor and inhibits peroxisome proliferator signaling. *Journal of Biological Chemistry* **271**, 9189–9192.

Mueller E, Smith M, Sarraf P, Kroll T, Aiyer A, Kaufman DS, Oh W, Demetri G, Figg WD, Zhou XP, Eng C, Spiegelman BM & Kantoff PW (2000) Effects of ligand activation of peroxisome proliferator-activated receptor gamma in human prostate cancer. *Proceedings of the National Academy of Sciences USA* **97**, 10990–10995.

Onate SA, Tsai SY, Tsai MJ & O'Malley BW (1995) Sequence and characterization of a coactivator for the steroid hormone receptor superfamily. *Science* **270**, 1354–1357.

Padilla J, Kaur K, Cao HJ, Smith TJ & Phipps RP (2000) Peroxisome proliferator activator receptor-gamma agonists and 15-deoxy-delta(12,14)(12,14)-PGJ(2) induce apoptosis in normal and malignant B-lineage cells. *Journal of Immunology* **165**, 6941–6948.

Poynter ME & Daynes RA (1998) Peroxisome proliferator-activated receptor alpha activation modulates cellular redox status, represses nuclear factor-kappa B signaling, and reduces inflammatory cytokine production in aging. *Journal of Biological Chemistry* **273**, 32833–32841.

Ren B, Thelen A & Jump DB (1996) Peroxisome proliferator-activated receptor alpha inhibits hepatic S14 gene transcription. Evidence against the peroxisome proliferator-activated receptor alpha as the mediator of polyunsaturated fatty acid regulation of s14 gene transcription. *Journal of Biological Chemistry* **271**, 17167–17173.

Ricote M, Li AC, Wilson TM, Kelly CJ & Glass CK (1998) The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. *Nature* **391**, 79–82.

Rincon M, Enslen H, Raingeaud J, Recht M, Zapton T, Su MS, Penix LA, Davis RJ & Flavell RA (1998) Interferon-gamma expression by Th1 effector T cells mediated by the p38 MAP kinase signaling pathway. *EMBO Journal* **17**, 2817–2829.

Spencer NFL, Poynter ME, Im S-Y & Daynes RA (1997) Constitutive activation of NF-κB in an animal model of aging. *International Immunology* **9**, 1581–1588.

Staels B, Koenig W, Habib A, Merval R, Lebret M, Torra IP, Delerive P, Fadel A, Chinetti G, Fruchart JC, Najib J, Maclouf J & Tedgui A (1998) Activation of human aortic smooth-muscle cells is inhibited by PPARalpha but not by PPARgamma activators. *Nature* **393**, 790–793.

Szabo SJ, Kim ST, Costa GL, Zhang X, Fathman CG & Glimcher LH (2000) A novel transcription factor, T-bet, directs Th1 lineage commitment. *Cell* **100**, 655–669.

Szabo SJ, Sullivan BM, Stemmann C, Satoskar AR, Sleckman BP & Glimcher LH (2002) Distinct effects of T-bet in TH1 lineage commitment and IFN-gamma production in CD4 and CD8 T cells. *Science* **295**, 338–342.

Takano H & Komuro I (2002) Roles of peroxisome proliferator-activated receptor gamma in cardiovascular disease. *Journal of Diabetes and Its Complications* **16**, 108–114.

Torchia J, Rose DW, Inostroza J, Kamei Y, Westin S, Glass CK & Rosenfeld MG (1997) The transcriptional co-activator p/CIP binds CBP and mediates nuclear-receptor function. *Nature* **387**, 677–684.

Unger RH & Zhou YT (2001) Lipotoxicity of beta-cells in obesity and in other causes of fatty acid spillover. *Diabetes* **50** Suppl. 1, S118–S121.

Wang ZW, Pan WT, Lee Y, Kakuma T, Zhou YT & Unger RH (2001) The role of leptin resistance in the lipid abnormalities of aging. *FASEB Journal* **15**, 108–114.

Watanabe K, Fujii H, Takahashi T, Kodama M, Aizawa Y, Ohta Y, Ono T, Hasegawa G, Naito M, Nakajima T, Kamijo Y, Gonzalez FJ & Aoyama T (2000) Constitutive regulation of cardiac fatty acid metabolism through peroxisome proliferator-activated receptor alpha assocaited with age-dependent cardiac toxicity. *Journal of Biological Chemistry* **275**, 22293–22299.

Xu HE, Lambert MH, Montana VG, Parks DJ, Blanchard SG, Brown PJ, Sternbach DD, Lehmann JM, Wisely GB, Willson TM, Kliewer SA & Milburn MV (1999) Molecular recognition of fatty acids by peroxisome proliferator-activated receptors. *Molecular Cell* **3**, 397–403.

https://doi.org/10.1079/PNS2002173 Published online by Cambridge University Press