

PEROXISOME PROLIFERATOR ACTIVATED RECEPTORS

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Abstract

Peroxisome Proliferator- Activated Receptors (PPARs) are members of the nuclear receptor superfamily to which steroid/thyroid/retinoic acid receptors also belong. There have been described three PPAR isotypes, α , δ and γ which have an integrative role in controlling the expression of genes playing key roles in the storage and mobilisation of lipids, in glucose metabolism, in morphogenesis and inflammatory response. The understanding of the molecular bases of the action of these receptors may develop into interesting medical applications in the fields of cardiovascular diseases, obesity, non insulin- dependent diabetes and skin pathologies.

Rezumat

Receptorii activați de către inductorii proliferării peroxizomilor (Peroxisome proliferator- activated receptors-PPARs) fac parte din categoria receptorilor nucleari, la fel ca și receptorii pentru hormonii steroidieni, tiroidieni sau acidul retinoic.

Au fost descrise trei tipuri de PPARs, α , δ , γ , ce au rol integrativ în controlul expresiei genelor țintă cu funcție cheie în stocajul și mobilizarea lipidelor, în metabolismul glucozei, diferențierea celulară și răspunsul inflamator. Înțelegerea bazelor moleculare ale acțiunii acestor receptori face posibilă utilizarea lor în practica medicală, într-o serie de boli, cum ar fi cele cardiovasculare, obezitate, diabet zaharat tip 2, boli de piele.

Key words: Peroxisome Proliferator- Activated Receptors (PPARs), nuclear receptors, glucose metabolism, inflammatory response, obesity.

Introduction

Peroxisome Proliferator- Activated Receptors (PPARs) belong to the nuclear receptors family, which are to be defined as transcription factors activated by ligands (some of the fatty acids and/or their lipids metabolites).

Identified in 1990 as a response to the Peroxisome Proliferation, their role in the control of lipids and lipoproteins metabolism, glucose homeostasis, as well as in the case of cell differentiation, has already been emphasized [1,2,3]. Recently it has been demonstrated that they interfere in the development of tumor process, in the control of inflammatory response, and of the associated disorders [4,5].

Three types of PPARs α , γ and δ (some authors name them β) were described. They are encoded on different types of genes and have different tissue distribution [3,6].

Activated by ligands consolidation PPARs form heterodimers with the help of 9-cis RXR retinoic acid receptors and fix upon the specific response element at the level of target genes promoter. This response elements are generally formed through the direct repetition of hexameric spring (recognition of nuclear receptors, differentiated by nucleotides) [5].

From the structural point of view, as the other nuclear receptors, they have six functional domains. These domains are well preserved for the three types of PPARs, which indicates the origin from an ancestral gene. In humans, PPAR α gene is located on chromosome 22 (22q12) and PPAR γ on chromosome 3 (3p25) [1,3].

Tissue distribution

While PPAR α is often expressed in the tissues where the fatty acids catabolism has an important role (liver, kidneys, heart, muscles), PPAR γ is to be found more often in the adipose tissue, mammary gland [2,7]. PPAR α and γ are equally expressed in the vascular wall cells; they were emphasized in epithelial cells, smooth muscular cells, as well as in monocytes/macrophage [3,5]. There were rediscovered in subendothelium and in the lipid nucleus (atherosclerosis lesions) [8,9,10]. PPAR δ tissue expression is ubiquitous. This receptor is expressed in heart, adipose tissue, brain, intestine, muscles, spleen, lungs, suprarenal gland [3,7,11].

PPARs ligands

Some of the fatty acids are capable to bind and activate PPARs. Linoleic acid is among the numerous activators and may activate the three types of PPARs. It was demonstrated that eicosanoids and in particular prostaglandins (PG) from A, D, J series are PPARs activators. For PPAR δ , PGJ₂, is one of the most efficient ligands. For PPAR α , leucotrine B₄ and B₈ (S) HETTE (8 (s) hydroxyoctadecadienoic acid) were identified with natural ligands [12]. Concerning PPAR δ , numerous fatty polyunsaturated acids can activate them, as PGI₂ is an efficient ligand [7,11].

PPARs expression can be controlled by a high number of factors as inflammatory cytokines, tumor necrosis alpha (TNF- α), interleukin 1 (IL-1), interleukin 6 (IL-6)[13]. These reduce PPARs expression in rat adipocytes. The effect may be inverse after fibrates treatment and different glitazones (oral antidiabetic drugs) [13,14].

Non-steroidal anti-inflammatory drugs (AINS) like indometacin and ibuprofen activate PPAR γ and α .

It has been demonstrated that PPAR γ and α may be phosphorylated throughout MAP-kinase. The place of phosphorylation is well conserved for the two types of PPARs [15]. Phosphorylation increases the transcriptional

activity of PPAR α and diminishes that of PPAR γ . A study revealed that insulin can produce the phosphorylation of PPAR γ [16].

PPARs biological functions- Pathological implications

PPAR α

PPAR α plays an important role in the regulation of the lipidic metabolism at the hepatic level [2]. PPAR α interfere in the control of the expression of numerous enzymes which allow the fatty acids oxidative degradation. Activating PPAR α with fibrates will determine the tendency of fatty acids metabolism, rather than oxidization or hepatic reesterification (low level of plasma triglyceride concentration). In humans PPAR α diminishes CIII apoprotein expression which inhibits lipoprotein lipase (LPL) activity, enzyme which catalyses the circulating triglycerides hydrolysis. Also this effect contributes to diminishing the triglycerides level observed during the treatment with fibrates [17]. Liver use of circulating fatty acids is increased by PPAR α activation through a mechanism which sets in action fatty acid transport protein (FATP) induction expression, which facilitates free fatty acids and acyl CoA-synthase transmembranous passage (catalyse their acylation in hepatocytes) [2].

PPAR δ

Biological functions and target genes concerning PPAR δ are less known. Many studies reveal that the nuclear receptor may play an important role in precocious stages of adipose differentiation, allowing the expression of some enzymes involved in the response of fatty acids, before the adipocyte accumulates triglycerides [7,11]. The same authors indicate the fact that PPAR δ activation is important for PPAR γ activation, which is the major actor in the terminal differentiation of the adipocyte. Other studies indicate that PPAR δ may interfere in the regulation by polyunsaturated fatty acids of uncoupled protein (UCP-2) expression into the skeletal muscles of humans [18]. As UCP-2 is involved in the reactive oxygen species (ROS), production control and as PPAR δ and UCP-2 are well expressed by the cells and tissues in which ROS production is important (lung, macrophage, intestine), is possible for PPAR δ be part of the protection mechanisms, for example in the fatty acids oxidation process which generates ROS in great quantities [6,18].

PPAR γ

Studies had clearly proved PPAR γ role in the control of adipocytes differentiation. Mature PPAR gamma adipocytes interfere also in the regulation of genes expression involved in the lipidic metabolism (acyl-Co synthase, LPL, FATP, or adipocyte protein 2 (aP2) fatty acids related

protein). These results show that besides the intervention in adipogenesis, PPAR γ are important in maintaining the lipidic metabolism and the functions of mature adipocyte [7,19,20].

Knowing that thiazolidinedione (TZD) class are in fact PPAR γ ligands and that throughout them transcriptional activity is being stimulated, this led to the idea that PPAR γ is implicated in the mechanism of insulin-resistance [13,14].

The research results (on both humans and animals), clearly demonstrate that molecules derived from TZD family (troglitazone, pioglitazone, rosiglitazone), are capable to correct significant insulin-resistance *in vivo* [21]. There were proposed few hypotheses for explaining the way in which PPAR γ activation with TZD may improve insulin-resistance. These hypotheses do not exclude one another. PPAR γ activation involves adipocytes differentiation and fatty acids storage in adipose tissue (diminishing circulant lipids, which allows the muscle a higher sensitivity to insulin). Gaining weight at animals treated with TZD comes in favour to these hypotheses. Other version would be that PPAR γ activation modifies the expression and adipocyte protein secretion like leptine and TNF- α which may play a role in insulin-resistance [16]. Though there are few human data in favour of this mechanism, it is not excluded for the adipocytes to produce other factors, not yet identified, under the control of PPAR γ .

It is also possible that encoded genes of the proteins involved in insulin action to be target PPAR γ genes and their transcriptional activation through TZD to increase the action of insulin in cells. Due to these hypotheses there are data which demonstrate that PPAR γ activation with rosiglitazone enhances the antilipolitic effect of insulin in the cells. So it is probable that PPAR γ is one of the action mechanism actors of insulin in adipocyte [14,16,22].

Recently it has been postulated the PPAR γ role in the inflammatory process and atherosclerosis [9]. PPAR γ expression has been emphasized in spleen, human monocytes and backbone precursor cells. PPAR γ expression is notably increased in rat activated macrophages and the treatment with TZD inhibits the production induced by activating markers. In human activated monocytes, PPAR γ agonists inhibit the pro-inflammatory cytokines production: TNF- α , IL-1, IL-6 [5,23]. These effects may interfere in atherosclerosis, at the level of atheroma where the activated macrophage products (MMP-9 gelatinase, IL-1, TNF alpha) play an important role [8,23].

Other studies suggest that PPAR γ may interfere in apoptosis and that this function could be used against the proliferation of different tumor cells which strongly express PPAR γ (colon, prostate) [4,24].

Atherosclerosis is a long process which implies the recruitment and activation of different types of cells, in particular monocytes/macrophages, endothelial cells, smooth muscular cells, intima T lymphocytes involving a local inflammatory response. Clinical studies demonstrated that fibrates slow the progression of atherosclerotic lesions in humans and animals, which suggest the implication of PPARs in atherosclerosis [7,25]. Troglitazone inhibits the proliferation of smooth muscular cells, and diminishes the thickening of intima and media tunic of human carotid. Recent studies revealed that PPARs are expressed at the level of atherosclerotic lesions, in macrophage, smooth muscular cells, foamy cells [6,8,26].

In the vascular wall, PPARs interfere with chemotaxis and cell adhesion of monocytes, T lymphocytes, eosinocytes. In the human endothelial cells, TZD inhibits monocyte chemotactic protein-1 (MCP-1) transcription, a protein which plays a major role in the initiation of atherosclerotic inflammatory process [27, 28]. On the other hand PPAR α agonists inhibit vascular cell adhesion molecule-1 (VCAM-1) expression, an adhesion molecule involved in leukocytes recruitment implicated in atherosclerosis process. In the endothelial cells, PPAR α and γ ligands, repress endothelin-1 expression, a vasoconstrictor peptide capable to induce the proliferation of smooth muscular cells. PPARs seem to be also implicated in creating foamy cells. [26,27].

An unbalance between pro and antithrombotic factors may involve acute coronary disorders. The inhibitor of plasminogen activator (PAI-1) factor has anti-fibrinolytic and pro-thrombotic proprieties. Different studies suggest a regulation of PAI-1 through PPARs ligands (though their role represents a polemic) [27].

Clinical studies demonstrated that fenofibrate diminishes IL-6 plasmatic concentration, fibrinogen, reactive C protein (PCR) in patients presenting a moderate hyperlipemia [17,25]. In subjects with IIb hyperlipoproteinemia, the fibrates reduce TNF-alpha and interferon- γ plasmatic concentration. These data are in favour of an antiinflammatory activity of PPAR agonists in humans [29].

Contrary to what it has been written about smooth muscle cells, fatty acids and AINS derivatives, as well as the synthetic alpha PPAR ligands, Wy 14643, induce COX-2(cyclooxygenase-2) transcription into the epithelial cells of mammary glands and colon [24,30].

The regulation of COX-2 activity throughout PPAR γ agonists has been studied in respect of colon cancer models. PPAR γ activation does not modify COX-2 expression either in mice adenoma or human circular lines in colon cancer. If PPAR γ ligands may debase the colon epithelial cells function

in independent COX-2 manner then agonists PPAR α induce COX-2 transcription in epithelial cells [30, 31]. In patients suffering from Crohn disease, who present a hypertrophy of mesenteric adipose tissue, PPAR α and TNF- α levels of expression in adipocyte are high. This overexpression could be responsible for the hypertrophy and inflammatory reaction noted for these patients [32]. It has been demonstrated that PPAR γ agonists inhibit the endothelial inflammatory response in the animal models suffering from strip. In the circular lines of colon cancer, PG-J2 and rosiglitazone inhibit IL-8 expression induced by IL-1 beta [21]. These results are still uncertain since recent data indicate the fact that PG-J2 effect would be independent of PPAR γ .

PPAR δ expression was found high in human colorectal cancer and an AINS, sulindac was found to inhibit the carcinogenesis in human cells by inhibiting these receptors [3,4].

Conclusions

The evaluation of PPARs functions started 15 years ago and continues in the present. At the beginning it was stated their key role in the regulation of lipidic metabolism. Afterwards there was demonstrated their implication in lipidic metabolism, as mediators of the inflammation, atherosclerosis, dygestive inflammatory diseases. These observations suggest that some of the pharmacologic and nutritional compounds could activate immune cells throughout PPARs.

If we refer only at using TZD in diabetes mellitus we may consider this as a promising therapeutic alternative.

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