Role of PPAR γ in Immune Cells

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Abstract. Peroxisome proliferators - activated receptor γ (PPAR γ), which is a type of nuclear receptor, exhibits extensive expression across multiple biological fields. As a transcription factor, it plays a role in regulating gene expression and influencing diverse physiological processes, with a particular emphasis on immune cells. In this article, the biological functions of PPAR γ within macrophages, neutrophils, NK cells, T cells (including CD8+T, Th2, Th9, Th17, and Treg cells), and B cells are investigated.

Keywords: PPARγ, macrophages, neutrophils, NK cells, T cells, B cells, metabolism, differentiation.

1. Introduction

The nuclear receptor γ (PPARγ), which is activated by peroxisome proliferators, serves as a transcription factor that modulates gene expression and has a wide range of physiological effects, such as lipid metabolism, glucose metabolism, energy balance, cell proliferation and differentiation, and inflammatory responses. The PPAR family consists of PPARα, PPARβ/δ, and PPARγ. PPARα is mainly expressed in the liver, heart, kidney, skeletal muscle, myocardium, and brown adipose tissue, and its relationship to plasma cholesterol and triglyceride levels is strong. Meanwhile, PPARβ/δ is found in the gut, brain and adipose tissue and plays a crucial role in glucose and lipid metabolism, promoting wound healing and reducing insulin resistance.

The structural characteristic of PPARγ is essential to fulfilling its function. At the N-terminal of PPARγ protein, a highly active Activation Function 1 (AF-1) is located, which mediates the transcription of PPARγ. This domain is one of several key components of PPARγ, including the DNA binding domain (DBD), hinge region, and ligand binding domain (LBD) at the C-terminal [1]. Various phosphorylation events can regulate AF-1's activity, and the degree of its phosphorylation can modify PPARγ's transcriptional activity [2]. DBD, located at the middle of PPARγ containing two zinc fingers, is responsible for specifically recognizing and binding to PPRE. This process is the basis for PPARγ's ability to regulate downstream gene expression. Hinge region links DBD and LBD and provides PPARγ with certain flexibility, making LBD be able to approach to DNA, and is also involved in interactions with other transcription factors and co-activators [3]. LBD is the most critical part of the domains and its loci is at C-terminal of PPARγ. LBD is responsible for recognizing and binding endogenous or exogenous ligand and also participates in PPARγ's interactions with the interaction of PPARγ with its co-activators or co-repressors, thereby regulating downstream gene expression [3, 4]. LBD is a large pocket containing a variety of ligands with different structures, which explains PPARγ's ability to regulate a wide range of physiological processes [4].

Since its discovery in the early 1990s, as a member of nuclear hormone receptors (NHR), PPARγ has been widely studied due to its crucial role in adipocyte differentiation, maintenance, and function. Forming a heterodimer with retinoid X receptor alpha (RXRα), PPARγ binds to the DNA response element, peroxisome proliferator - activated receptor response element (PPRE), located in its promoter or intron, thereby stimulating the expression of certain genes and participating in the regulation of lipid metabolism, immune cell maturation, and other essential reactions.

The PPARG gene located on human chromosome 3p25.2 encodes PPARγ, a major subtype of PPAR in adipose tissue that is essential in controlling adipocyte differentiation and maturation,

insulin sensitivity, and glucose metabolism. Through different promoter usage and variable splicing, the PPARG gene generates four types of PPARG splicing variants (PPARG1-4), which in turn translate into two protein isoforms, PPARγ1 and PPARγ2. PPARγ1 is translated from PPARG1, PPARG3 and PPARG4 mRNA, while PPARγ2 is translated from PPARG2 mRNA [3].The expression of PPARγ1 is widespread in the liver, colon, heart, skeletal muscle, and a range of immune cells such as monocytes/macrophages, dendritic cells, and T lymphocytes, whereas PPARγ2 is almost exclusively found in adipocytes. In this article, the biological functions of PPARγ in immune cells would be discussed (Figure 1).

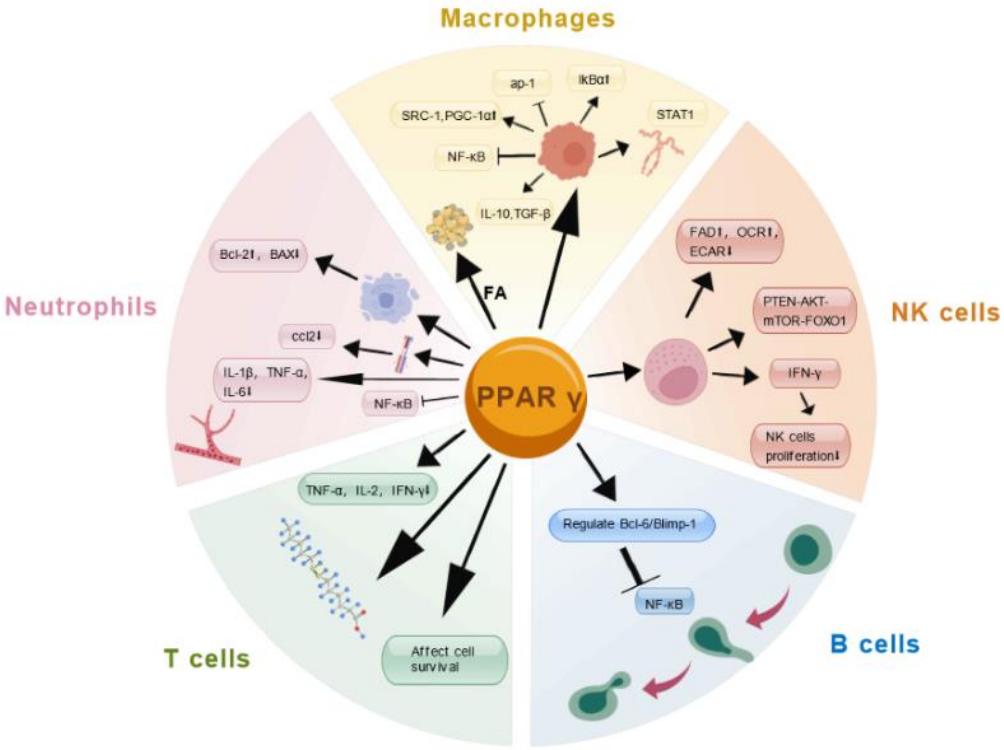


Figure 1. This article elaborates on the subject matter - the role of PPARγ in immune cells - from these aspects indicated on the diagram.

2. PPARγ in macrophages

Macrophages are endowed with a variety of essential roles, such as immune protection, control of inflammation, wound healing, and sustaining tissue equilibrium. PPARγ is an essential transcription factor that governs macrophage functions, especially in aspects such as macrophage polarization, production of inflammatory mediators, regulation of inflammatory pathways, and macrophage metabolism. Macrophages can be classified into two primary types: pro - inflammatory macrophages (M1) and anti - inflammatory macrophages (M2). PPARγ makes positive contribution to fighting inflammatory process mainly by promoting the formation of M2 macrophages [5]. Macrophages of the M2 type foster inflammation abatement and tissue mending through the production of anti-inflammatory cytokines, such as interleukin (IL)-10 and transforming growth factor beta (TGF-β). The conformation of PPARγ is altered upon binding to the ligand, then it binds to coactivators such as steroid receptor coactivator - 1 (SRC - 1) and peroxisome proliferator - activated receptor gamma coactivator 1 - alpha (PGC - 1α), thus intensifying transcriptional activation of PPARγ for downstream anti - inflammatory genes like IL - 10 and TGF - β. These cytokines play a key role in the selective differentiation of macrophages into the M2 type [5]. PPARγ's anti-inflammatory effect is further augmented by its capacity to impede the pro-inflammatory signaling pathway, thus suppressing the expression of a range of pro-inflammatory cytokines, such as TNF-α, IL-6 and IL-1β. This anti-inflammatory action is accomplished by disrupting the activity of essential pro-

inflammatory transcription factors, such as nuclear factor kappa-B (NF-κB). There is evidence that PPARγ inhibits NF-κB's activity in several ways. PPARγ can directly interact with the subunit p65 of NF-κB to block its DNA-binding ability, thereby inhibiting the expression of downstream inflammatory genes. PPARγ can also inhibit the ability of AP-1 to activate pro-inflammatory genes through interaction with AP-1 subunit c-Jun and indirectly reduce the activation of NF-κB signaling pathway. And PPARγ can also inhibit the activation of NF-κB by enhancing the expression or stability of IkBα [6]. PPARγ's binding to STAT1, which inhibits its phosphorylation and dimerization, as well as its binding to DNA, has been demonstrated to reduce the expression of pro-inflammatory cytokines such as IFN-γ and IL-6, in addition to the NF-κB signaling pathway. PPARγ also indirectly affects the inflammatory response by regulating the metabolic pathway of macrophages. Through activating key enzymes in the fatty acid oxidation pathway such as CPT1, PPARγ enhances β-oxidation of fatty acids. This pathway not only provides macrophages with more energy supply, but also helps macrophages maintain stability under metabolic stress. It helps macrophages play a role in anti-inflammatory.

3. PPARγ in neutrophils

Neutrophils have a significant defensive function within the immune system, especially during the initial phases of inflammation and infection. The influence of PPARγ on neutrophils can be divided into three aspects: anti - inflammatory effect and regulation of cytokines, impact on the migration and chemotactic function of neutrophils, and regulation of the apoptosis and survival of neutrophils. By inhibiting the NF - κB signaling pathway, PPARγ can decrease the release of pro - inflammatory factors like IL - 1β, TNF - α and IL - 6 from neutrophils, thus effectively reducing the intensity and duration of the inflammatory response and preventing tissue damage due to excessive inflammation [7]. PPARγ also indirectly reduces the pro-inflammatory activity of neutrophils by lowering the levels of certain pro-inflammatory factors (while increasing IL-10 levels) to help reduce inflammation and promote damaged tissue repair [8]. PPARγ in neutrophils can not only regulate the expression of inflammatory cytokines, but also affect the migration and chemotactic function of neutrophils. CCL2 is a vital chemokine that can lead neutrophils to the site of inflammation. PPARγ, in order to control the intensity and length of inflammatory reactions and avert tissue harm caused by an excessive immune reaction, lessens the expression of chemokines such as CCL2. Moreover, PPARγ can also regulate the expression of integrin receptors on neutrophils' surfaces through transcriptional regulation and influence their attachment to the extracellular matrix, thus controlling their migration capacity [9]. PPARγ activation can have a marked effect on the expression of lymphocyte function-associated antigen-1 (LFA-1) and complement receptor type 3 (CR3). It influences the rolling, tight adhesion and migration of neutrophils across the vascular endothelium and affects the development of inflammatory response by impacting the ability and efficiency of neutrophils' adhesion and migration. The regulation of PPARγ on integrin's activity may be bidirectional. For example, in acute inflammatory responses, PPARγ contributes to mitigating excessive infiltration of immune cells and tissue damage by reducing integrin's activity. In contrast, in the repair of inflammation, enhancing integrin's activity helps to accelerate inflammation clearance and tissue repair processes. PPARγ is also capable to regulate the survival time of neutrophils by affecting pathways associated with apoptosis, which is critical for limiting inflammatory responses. PPARγ's influence on the expression of anti-apoptotic proteins, like B-cell lymphoma 2 (BCL2), is clear;conversely, it reduces the expression of pro-apoptotic proteins, like Bcl-2-associated X protein (BAX). This helps prolong the survival time of neutrophils and reduce inflammation due to premature cell death. By regulating key molecules in apoptosis signal pathways, such as cysteine-aspartic proteases (Caspase), PPARγ can control the apoptosis process of neutrophils.

4. PPARγ in NK cells

The functions of natural killer cells (NK cells) are varied, primarily encompassing immune surveillance, defense, and regulation of inflammation. The biological function of PPARγ in NK cells is intimately related to the metabolic immune mechanism. According to the research, in transgenic mice with apolipoprotein C - III (Apoc3), a notable decrease in the number of NK cells can be seen and their function is relatively impaired [10]. Specifically, the production of IFN-γ is reduced, the killing ability of the cells is decreased and the degradation of target cells is weakened [10]. And it is found that NK cells of Apoc3 transgenic mice show the characteristics of metabolic reprogramming, specifically manifested as an increase in fatty acid oxidation (FAO), which can be proved by measuring oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) of cells. Among them, NK cells of Apoc3 transgenic mice have lower ECAR (glycolysis decreased) and higher OCR (oxidative phosphorylation increased) than those of wild mice. In further studies, the increased uptake of free fatty acids (FFAs) by NK cells in Apoc3 transgenic mice leads to the activation of PPARγ, which promotes the increase of FAO and leads to changes in the metabolic state of NK cells. This could be confirmed by up-regulation of CPT1α expression.The signaling pathway of the phosphatase and tensin homolog (PTEN) - AKT - mTOR - forkhead box O1 (FOXO1) is significantly impacted by PPARγ activation [11, 12]. It means that increased FFAs promote the activation of PPARγ inside NK cells and the activated PPARγ contributes to the upregulation of PTEN, which inhibits the phosphoinositide 3-kinases (PI3K) /AKT signaling pathway. MTOR, as a key regulator of cell growth and metabolism, is then down-regulated. The decrease in MTOR activity is directly related to the weakening of NK cell function, including IFN-γ production and NK cell proliferation. These results suggest that changes in the signaling pathway induced by PPARγ activation would cause NK cells to undergo metabolic reprogramming, which is embodied in increased fatty acid oxidation, decreased glycolysis and decreased fatty acid synthesis, thereby reducing the biological activity of NK cells.

5. PPARγ in T cells

The role of PPARγ in T cells is mainly related to its ability to regulate immune response and inflammation. PPARγ influences the differentiation, activation, and function of T cells via various mechanisms, especially in the regulation of inflammation and autoimmune diseases. PPARγ can affect the differentiation, activation and function of T cells in several ways, including reducing the production of pro-inflammatory factors, energy metabolism and cell survival.By directly suppressing the promoter activity of pro-inflammatory cytokines such as TNF-α, IL-2, and IFN-γ, or indirectly influencing other signaling pathways, like NF-κB, PPARγ activation in T cells can be used to decrease their production. PPARγ can regulate the metabolism of fatty acids within T cells and affect their energy sources and use. By regulating the intracellular energy state, PPARγ influences the proliferation and survival of T cells.

5.1. PPARγ in CD8+T cells

The functions of CD8+T cells are mainly pathogen resistance, anti-tumor immunity and local immune response regulation. PPARγ negatively affects the immune clearance of tumor by inhibiting the generation of CD8+T cells and causing an increase in the expression of tumor escape-related cytokines. In immunotherapy for hepatocellular carcinoma (HCC), the interaction between PPARγ and CD8+T cells is the key to the research of immune evasion mechanisms and treatment resistance [13]. In the tumor microenvironment, the expression and activation of PPARγ can affect the immune evasion ability of tumors through multiple mechanisms.The expression of vascular endothelial growth factor (VEGF) can be increased by the activation of PPARγ, thus stimulating the production and activation of certain immunosuppressive cells, such as myeloid-derived suppressor cells (MDSCs), which impede the proliferation and activity of CD8+T cells and lessen its destruction of tumor cells [14]. Studies have revealed that, in cells where PPARγ has been eliminated, the expression

of inflammatory cytokines such as IFN-γ and TNF-α rose, whereas the expression of cytokines linked to tumor escape decreased, such as PD-1 and TIM-3 (TIM-3). Additionally, PPARγ has a direct or indirect effect on CD8+T cell activity by controlling the expression of certain cytokines and receptors. If PPARγ inhibitor GW9662 is used, the function of CD8+T cells could be restored and the immune response to the tumor would be enhanced, which means the interaction between PPARγ and CD8+T cells plays a key role in immune evasion and treatment resistance [13, 14].

5.2. PPARγ in CD4+T cells

The functions of CD4+T cells are diverse, covering immune regulation, anti-infection and response to several inflammatory diseases.Regulating a broad spectrum of activities, such as cell metabolism, proliferation and inflammatory pathway levels, PPARγ has a significant impact on CD4+T cells. PPARγ can regulate the intensity and quality of immune response through affecting the energy balance and lipid metabolism of CD4+T cells. PPARγ has a profound effect on CD4+T cell activation and function by regulating fatty acid metabolic reprogramming. According to some studies, after receiving the co-stimulation signals of T cell receptor (TCR) and CD28, activated CD4+T cells would increase the intake and synthesis of fat, which is crucial for the proliferation, energy uptake and functional driving of T cells. This process involves activation of mTOR signaling pathway and the up-regulation of PPARγ is a key step in mTOR activation. This suggests that PPARγ plays a vital role in regulating energy metabolism and proliferation of T cells. In addition, through preventing T cells from over-activity and reducing the formation of follicular helper T cells (Tfh), PPARγ plays a negative regulatory role in autoimmune responses. T cells lacking PPARγ shows a stronger proliferative response and higher cytokine levels after receiving TCR and CD28 stimulation, revealing the importance of PPARγ in maintaining immune balance. This shows that PPARγ has the ability to regulate the metabolic pathway and signal transduction network in CD4+T cells, thereby exerting its various biological functions in CD4+T cells. Besides, PPARγ also plays a key role in maintaining immune tolerance and limiting the development of autoimmune diseases by inhibiting inflammatory signaling pathways such as NF-κB.

5.2.1. PPARγ in Th2 cells

T helper 2 cells (Th2) are mainly related to the regulation of immune response and the development of inflammatory diseases. The effects of PPARγ on Th2 cells can be divided into two aspects: the number and the function. First, PPARγ is highly specifically expressed in Th2 cells of mice and humans, but not in other Th cell subpopulations like Th1 or Th17.A study has revealed that PPARγ agonists can lessen the activation of STAT6, a signal transduction and transcriptional activator, thus indirectly decreasing GATA binding protein 3 (GATA3), a transcription factor essential for Th2 cell differentiation. The increased expression of GATA3 is a signifier of Th2 cell differentiation. PPARγ affects inflammatory cytokines produced by Th2 cells and directly controls the production of IL-4, IL-5 and IL-13, which is critical for controlling Th2 cell-mediated inflammatory responses, such as in allergic asthma and other allergic diseases. In addition to that, PPARγ can alter the sensitivity of Th2 cells to IL-33, an important proinflammatory cytokine playing a significant role in inflammatory responses mediated by Th2 cells, thus affecting the effect of Th2 cells in vivo [15]. Moreover, PPARγ can directly control the expression of suppression of tumorigenicity 2 (ST2) on the surface of Th2 cells, which is necessary for Th2 cells to be activated and exert their function through IL-33 signal. This means that PPARγ can affect Th2 cells' ability to respond to IL-33 signal from both the number and sensitivity of receptors and thus affect the intensity and duration of type 2 inflammatory response. PPARγ is also able to indirectly affect the effects of Th2 cells by affecting the ability of CD11b+ dendritic cells (DCs) in the lungs to induce Th2 cells.

5.2.2. PPARγ in Th9 cells

A relatively newly discovered subgroup of T cells, T helper 9 cells (Th9), primarily produces interleukin-9 (IL-9). Th9 cells are particularly associated with promoting inflammation and participating in the development of certain diseases. PPARγ regulates its function by regulating

metabolic level in Th9 cells.Activated cells are stimulated by PPARγ, which activates a series of glycolytic enzymes, such as hexokinase 1 (HK1), glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and lactate dehydrogenase A (LDHA), thereby stimulating the expression of IL-9 rather than IL-13. This process is dependent on the mechanistic target of rapamycin complex 1 (mTORC1), a major regulator of cellular metabolism and effector function in T cells. mTORC1 regulates cell growth and proliferation through the activation of phosphorylated ribosomal protein S6 in Th9 cells and is directly regulated by PPARγ. Beyond that, PPARγ influences the PPARγ-mTORC1-IL-9 pathway and glycolysis to play a key role in activation and proliferation of Th9 cells, which highlights the importance of glucose metabolism in affecting Th9 cells function and links the regulatory role of PPARγ to the metabolic reprogramming of Th9 cells, revealing the direct effects of PPARγ on cytokine expression and cell function by influencing metabolic processes. Other studies show that high glycolytic activity induced by PPARγ can regulate the effector function of Th9 cells, mainly increasing the expression of IL-9 [16]. The glycolysis process activated by PPARγ not only supports the activation and proliferation of Th9 cells, but also regulates their immune function.

5.2.3. PPARγ in Th17 cells

A specialized subset of T cells, T helper 17 cells (Th17), functions primarily by secreting interleukin-17 (IL-17) and other cytokines and has a profound impact on immune function and inflammation. The regulation of PPARγ on Th17 cells is mainly reflected in its ability to inhibit the differentiation and function of Th17 cells. The research of Klotz shows that in multiple sclerosis (MS) models, PPARγ selectively inhibits Th17 cells differentiation.PPARγ, when activated, could impede the expression of RAR-associated orphan receptor gamma T (RORγT), a critical transcription factor that regulates Th17 cell differentiation brought about by TGF-β and IL-6. This suggests that PPARγ inhibits Th17 cells production and alleviates autoimmune diseases of central nervous system by modulating certain transcription factor activity. In addition, PPARγ also has an inhibitory effect on Th17 cells. Park and other experts discovered that PPARγ binds to RORγt by sustaining transcription co-repressors, such as SMRT's silencing mediator and NCOR's nuclear receptor co-repressor, and thereby inhibits RORγt's activity by inducing chromatin compression, thus diminishing IL-17 expression. In addition to affecting the activity of RORγT, PPARγ also influences Th17 cells differentiation through interactions with other transcription factors. For example, the activation of PPARγ can improve the stability of IκBα, and then inhibit the intraconuclear transfer and activity of NF-κB [17]. PPARγ also reduces the activation of NF-κB phosphorylation by inhibiting upstream signaling molecules of NF-κB, such as I kappa B Kinase beta (IKKβ). IKKβ's diminished activity results in NF-κB's activation being inhibited, thereby directly restraining NF-κB's activity, which is a critical factor in proinflammatory processes. Similarly, through this interaction, PPARγ would cause further inhibition of the expression of inflammatory genes associated with Th17 cells function.

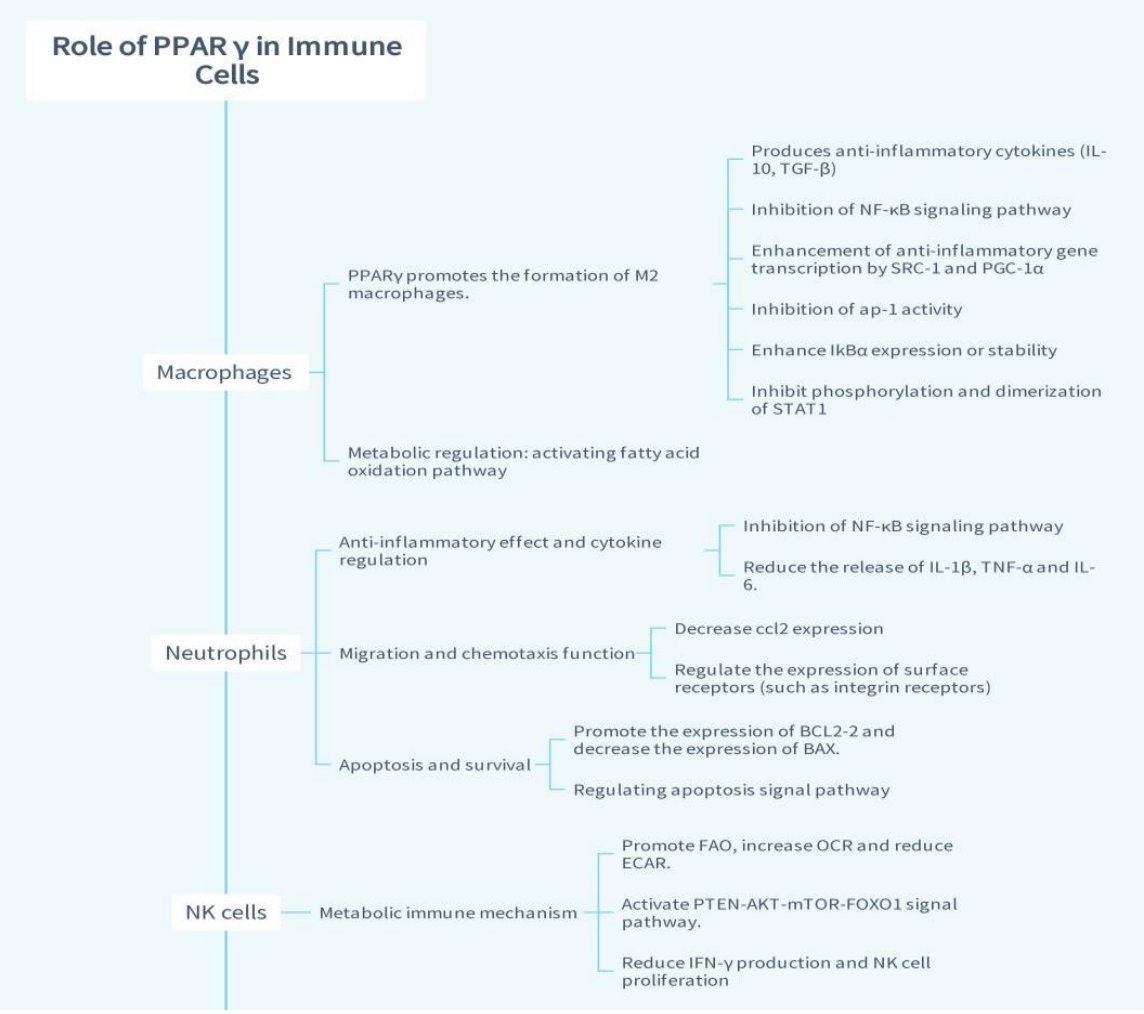
5.2.4. PPARγ in Treg cells

Tregs, employed mainly to sustain immune equilibrium and forestall overabundance of immune reactions, are the regulatory T cells. The functions of PPARγ on Treg cells mainly involve the regulation of transcription and differentiation, energy metabolism and inflammatory signaling pathways. PPARγ affects the transcription of Treg cells by collaborating with Forkhead Box P3 (Foxp3) and enhances the expression of downstream Foxp3 genes that are critical for maintaining immune homeostasis, such as cytotoxic T lymphocyte associated protein 4 (CTLA-4), IL-10 and TGF-β [19]. Through this mechanism, PPARγ helps to keep the regulatory function of Treg cells [6]. Beyond that, PPARγ can enhance CD36 and CPT1, promote fatty acid oxidation process and induce metabolic reprogramming in Treg cells [20]. FAO not only provides Treg cells with necessary energy to maintain their survival and inhibitory function, but also regulates their phenotype and functional status. Some studies indicate that FAO is able to enhance the stability and tolerance of Treg cells against the inflammatory environment [20]. And FAO also participates in the N-glycosylation of transforming growth factor beta receptor II (TβRII) and CD25 on the surface of Treg cells, a process that is crucial for the inhibitory function of Treg cells. In addition, PPARγ accurately regulates the

balance between Treg and Th17 by regulating the activity of several STAT proteins. In Treg cells, STAT5 is activated due to IL-2 and promotes the expression of Foxp3, while STAT3 responds to proinflammatory cytokine signalings like IL-6 and promotes the expression of RORγT in Th17 cells. Besides, PPARγ can reduce the differentiation and activity of Th17 cells by inhibiting the production and signal transduction of IL-6 and IL-23, while promoting the differentiation and expansion of Treg cells. In this mechanism, PPARγ has a profound impact on the balance between Treg and Th17 cells, maintaining immune system homeostasis by enhancing the inhibitory capacity of Treg cells and limiting the pro-inflammatory effects of Th17 cells.

6. PPARγ in B cells

B cells have a critical role in both innate and adaptive immune responses and transform into effector antibody - secreting plasma cells and memory B cells to guarantee an effective response in adaptive immunity. It has been shown that the expression of PPARγ in B cells is crucial for an optimal humoral immune response. PPARγ is involved in several important processes of B cell, such as differentiation and antibody production. It has been proved that the lack of PPARγ in B cells leads to a decrease in the expression of Bcl-6 and Blimp-1, which are vital for the development of GC B cells and plasma cells. PPARγ affects Bcl-6 and Blimp-1 in direct and indirect ways. There are multiple PPAR response elements in 3'-untranslated regions of Bcl-6 and Blimp-1. Through this mechanism, PPARγ would directly regulate Bcl-6 and Blimp-1. In addition, PPARγ down-regulates Bcl-6 by inhibiting NF-κB translocation to the nucleus. Therefore, PPARγ can also regulate Bcl-6 indirectly (Figure 2).



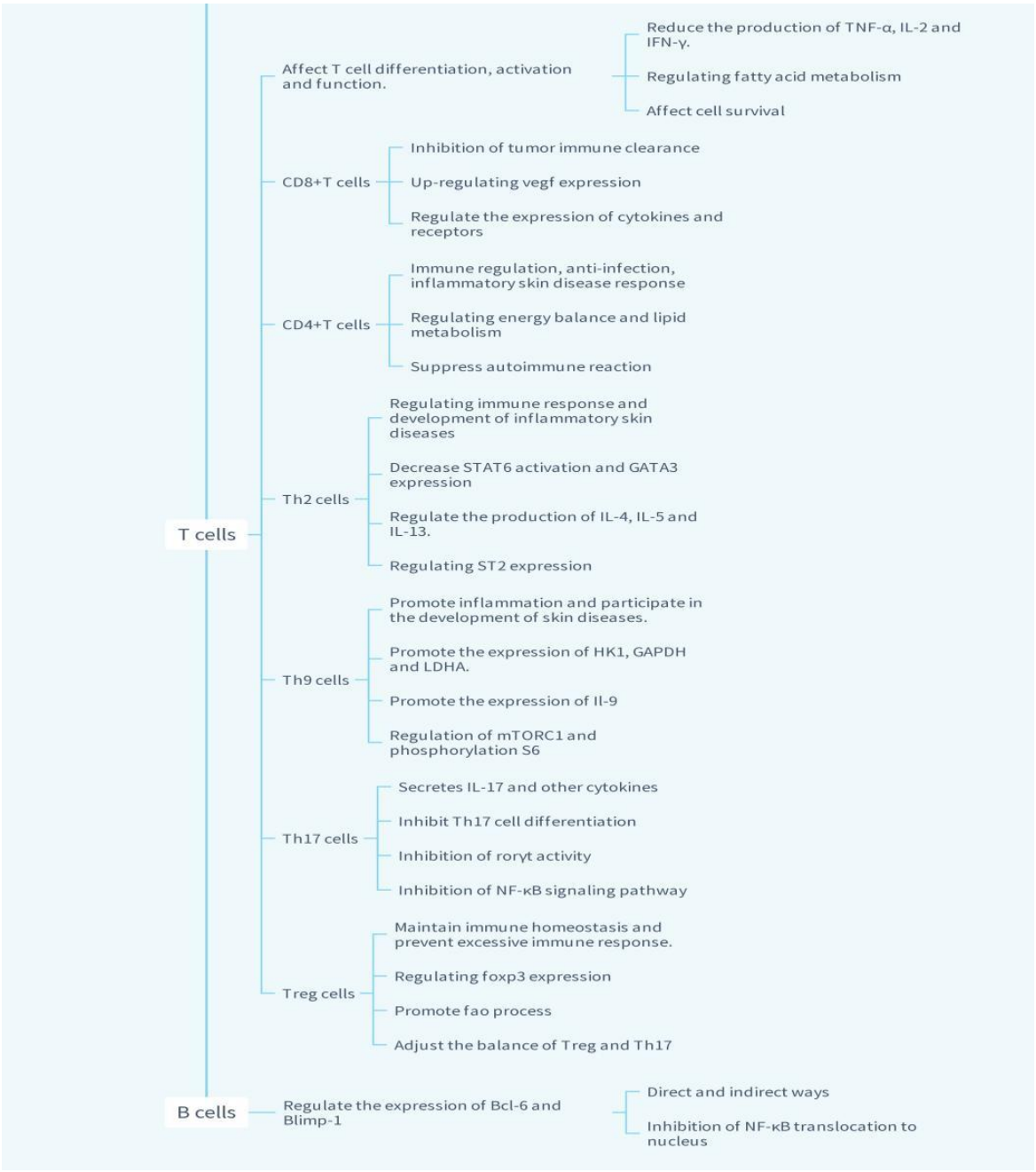


Figure 2. This mind map summarizes the role of PPARγ in immune cells, including macrophages, neutrophils, NK cells, T cells and B cells.

7. Conclusion

PPARγ, in the form of heterodimer with RXRα, binds to the DNA response element PPRE located in the target gene promoter or intragenic region to activate the expression of specific genes and participate in some essential reactions, such as regulating lipid metabolism, immune cell maturation and function. PPARγ plays a wide range of roles in organisms, ranging from the regulation of cellular energy balance to the key processes involved in apoptosis. PPARγ's role in macrophages is to augment the expression of IL-10 and TGF-β, impede NF-κB, and foster the differentiation of macrophages into the anti-inflammatory M2 type, which is capable of anti-inflammatory action through its binding to SRC-1 and PGC-1α coactivators. In neutrophils, PPARγ can affect the chemotactic process of neutrophils by regulating the expression of inflammatory factors, integrins and chemokines. PPARγ can also control the apoptosis process of neutrophils by regulating

apoptosis-related proteins BCL2 and BAX and reduce the damage caused by excessive activation of neutrophils. In NK cells, PPARγ promotes the metabolic reprogramming process of NK cells and reduces their biological activity through the regulation of the PTEN-AKT-mTOR-FOXO1 signaling pathway, the increase of the FAO process and changes in several metabolic pathways. PPARγ's activation and up-regulation of VEGF expression in CD8+T cells encourages the production of MDSCs, thereby augmenting PD-1 and TIM-3 expression and thus advancing the immune escape process. In CD4+T cells, PPARγ activates the mTOR pathway and regulates the metabolic processes of CD4+T cells, while PPARγ limits the development of autoimmunity by inhibiting the activation of the inflammatory signaling pathway of NF-κB and restraining the excessive proliferation of CD4+T cells. In Th2 cells, PPARγ can reduce the activation of STAT6 and consequently reduce the expression of key transcription factor GATA3. PPARγ can also regulate Th2 cell-mediated inflammatory response by modulating the expression of IL-4, IL-5 and IL-13. At the same time, PPARγ can also regulate the sensitivity of Th2 cells by regulating ST2 and then modulate the intensity and duration of type 2 inflammation. In Th9 cells, PPARγ activates mTORC1 and phosphorylates ribosomal protein S6, thereby affecting several key enzymes in the glycolytic pathway, such as HK1 and GAPDH. This promotes the expression of IL-9 and the activation and proliferation of Th9 cells. In Th17 cells, PPARγ can inhibit the differentiation of CD4+T cells into Th17 cells and promote the contraction of RORγT chromatin to inhibit the activity of RORγT by maintaining the binding of inhibitory transcription factor SMRT and NCOR to RORγT. Moreover, PPARγ also inhibits Th17 cell proliferation and function through the IKKB-NF-κB pathway. PPARγ, in Treg cells, has the ability to regulate their function by augmenting Foxp3 expression. Additionally, it can influence the FAO process of Treg cells by augmenting CD36 and CPT1, thus stabilizing the immune system. In B cells, PPARγ regulates Bcl-6 and Blimp-1 directly and indirectly by inhibiting NF-κB.

Consequently, delving deeply into PPARγ's biological purpose and its involvement in a variety of illnesses is of great importance for the formation of novel therapeutic approaches. In the future, research should focus on exploring the interaction of PPARγ with other cell signaling pathways and how to optimize disease treatment by regulating PPARγ activity.By conducting rigorous investigations into PPARγ's functions, we can gain a deeper understanding of its part in cell biology and pathobiology, thereby furnishing both theoretical foundations and practical advice for the treatment of associated illnesses.

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