# 7 Physiological Convergence and Antagonism Between GR and PPARγ in Inflammation and Metabolism

Marija Dacic, Gayathri Shibu, and Inez Rogatsky

**Abstract**

Nuclear receptors (NRs) are transcription factors that modulate gene expression in a ligand-dependent manner. The ubiquitously expressed glucocorticoid receptor (GR) and peroxisome proliferator-activated receptor gamma (PPARγ) represent steroid (type I) and non-steroid (type II) classes of NRs, respectively. The diverse transcriptional and physiological outcomes of their activation are highly tissue-specific. For example, in subsets of immune cells, such as macrophages, the signaling of GR and PPARγ converges to elicit an anti-inflammatory phenotype; in contrast, in the adipose tissue, their signaling can lead to reciprocal metabolic outcomes. This review explores the cooperative and divergent outcomes of GR and PPARγ functions in different cell types and tissues, including immune cells, adipose tissue and the liver. Understanding the coordinated control of these NR pathways should advance studies in the field and potentially pave the way for developing new therapeutic approaches to exploit the GR:PPARγ crosstalk.

**Keywords**

Glucocorticoid receptor (GR) · Peroxisome proliferator-activated receptor gamma (PPARγ) · Inflammation · Transcription · Immune cells · Metabolic tissues

## 7.1 Introduction

Nuclear receptors (NRs), such as the glucocorticoid receptor (GR) and peroxisome proliferator activated receptor-γ (PPARγ) are a versatile superfamily of structurally conserved transcription factors (TFs) that regulate numerous homeostatic physiological processes, largely in a ligand-modulated manner, thereby adapting gene expression programs to environmental changes.

GR, or NR3C1, named for its role in regulating glucose metabolism, is an archetypal steroid hormone receptor (type I) involved in numerous signaling circuits that maintain metabolic homeostasis. GR is activated by its endogenous gluco-

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corticoid (GC) ligands, whose levels are controlled by the hypothalamic-pituitary-adrenal (HPA) axis. Upon ligand binding, the cytoplasmic GR multiprotein complex, also containing immunophilins and chaperones, undergoes conformational changes and translocates into the nucleus (Reviewed in [1]), where GR binds to specific palindromic DNA sequences called GC-response elements (GRE) or tethers to other DNA-bound TFs, recruits cofactors (coactivators and corepressors) and regulates transcription of associated genes [2, 3].

Peroxisome proliferator activated receptor-γ (PPARγ, also known as NR1C3) is a non-steroid (type II) NR that senses oxidized fatty acids (FA). It is mainly implicated in homeostatic maintenance of lipid metabolism and insulin sensitivity [4, 5]. Similar to the related PPARs and other type II NRs, PPARγ exerts its biological functions by forming heterodimeric complexes with another member of the NR family, retinoic acid receptor α (RXRα). In the absence of a ligand, the PPARγ/RXRα complex binds to specific DNA sequences known as PPAR response elements (PPRE) or direct repeat (DR)1 sequences together with a corepressor complex (reviewed in [6]). Upon ligand binding, the corepressor complex is released, and a coactivator complex is recruited [7].

NRs have been linked to the regulation and maintenance of metabolic homeostasis for decades. Both GR and PPARγ were initially described as regulators of metabolic functions in the liver and adipose tissue, respectively. Since then, a myriad of non-metabolic roles have been described for each receptor, with one of the most renowned functions being the regulation of immune responses and inflammation. Interestingly, despite representing two different families of NRs, GR and PPARγ exhibit a striking functional overlap in the immune system while having disparate roles in healthy liver and divergent ones in lipid metabolism. These overlapping yet distinct outcomes of GR and PPARγ activation stem from differences at multiple levels of regulation, ranging from the ligand-binding events to the engagement of other TFs, co-regulators and components of basal transcriptional machinery and chromatin. In this Chapter, we will discuss the tissue-specific convergence of GR and PPARγ signaling in the immune system and briefly contrast it with some of their antagonistic roles in metabolic tissues. It should be noted that many of these functions have been deduced using NR knock-out (KO) mouse strains and *in vitro* studies with endogenous or synthetic ligands, often at super-physiological concentrations, which remains a limitation to our understanding of NR biology.

## 7.2 GR and PPARγ in Monocytes and Macrophages

During inflammation, both GR and PPARγ play crucial roles in regulating macrophage responses. Indeed, GCs have long been known to exert potent immunosuppressive effects on monocytes and macrophages. Mice lacking GR in macrophages produce more inflammatory cytokines, including IL-1β, IL-6, TNF, and IL-12, and display higher mortality rates during bacterial lipopolysaccharide (LPS)-induced sepsis relative to their wild-type (WT) counterparts [8–11]. Although the role of PPARγ in this context is less understood, it negatively regulates macrophage activation by down-regulating synthesis of TNF, IL-6 and other pro-inflammatory cytokines [12] and decreasing macrophage migration *in vitro* [13]. Myeloid-specific deletion of PPARγ exacerbates inflammation in mouse models of inflammatory bowel disease (IBD) [14]. Consistently, treating mice with pioglitazone, a synthetic PPARγ agonist, reduced systemic inflammatory response during cecal ligation and puncture-induced sepsis [15]. Thus, both receptors down-regulate pro-inflammatory mediators at the nexus of pro-inflammatory responses and effectively curb inflammation *in vivo*.

GR acts on macrophages to dampen inflammation in a variety of ways. One broadly established mechanism of action is direct tethering of liganded GR to effector TFs downstream of Toll-like receptor (TLR) signaling, including NF-κB, AP-1 and interferon regulatory factor 3 (IRF3), and repression of their activity (Fig. 7.1a;

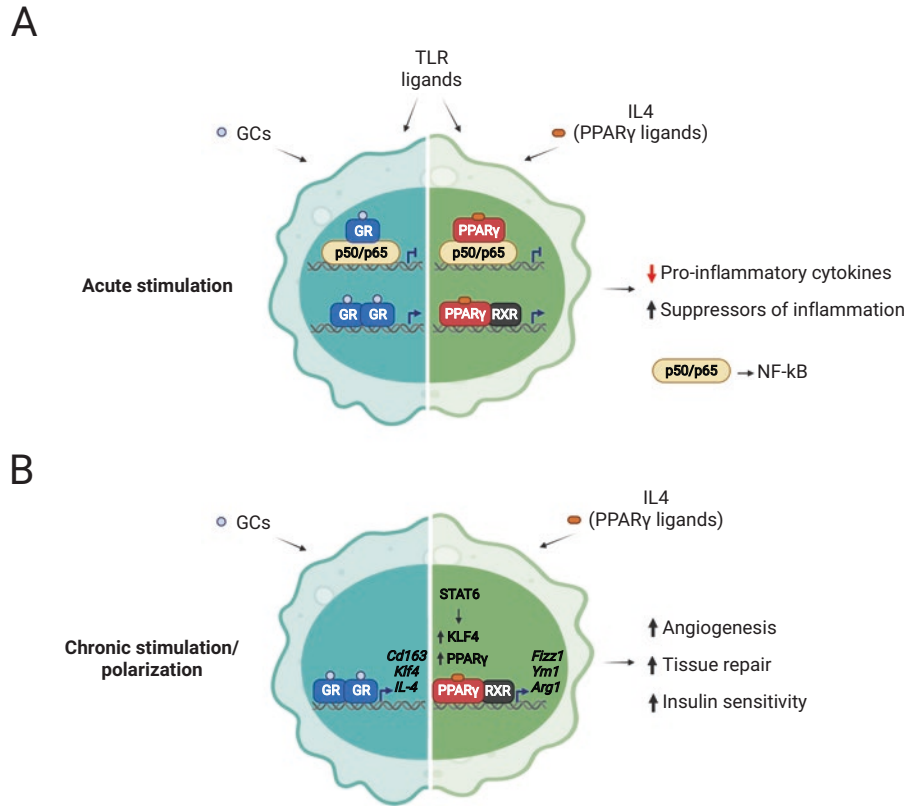


**Fig. 7.1 GR and PPARγ mediate both short-term and long-term anti-inflammatory responses in macrophages.** (**a**) Upon short-term treatment with GCs or PPARγ ligands, and in the presence of inflammatory toll-like receptor (TLR) ligands, GR and PPARγ are recruited to their genomic binding sites and inhibit pro-inflammatory gene transcription (often by binding to the p50/p65 NF-kB heterodimers) and up-regulate suppressors of inflammation. (**b**) Chronic stimulation with GCs or PPARγ ligands up-regulates GR and STAT6 signaling, respectively, and STAT6 in turn increases KLF4 and PPARγ expression. GR and PPARγ promote expression of M2 genes and help establish a stable macrophage sub-type that promotes angiogenesis, tissue repair and increases sensitivity to insulin

reviewed in [16]). Conversely, many genes encoding inhibitors of TLR signaling are activated by GR, such as IL-1 receptor-associated kinase 3 (IRAK3), which negatively regulate mitogen-activated protein kinase 1 (MAPK1) and IL-1 receptor signaling [17]. GILZ is another well-known GR-inducible target that can bind c-Jun and c-Fos components of the AP-1 complex [18] as well as NF-κB [19] and antagonize their actions. GR-activated anti-inflammatory genes also encode proteins that can function at steps further removed from transcriptional modulation. For instance, GR-upregulated ZFP36 facilitates mRNA degradation of several pro-inflammatory genes, most notably *TNF* [20]. Suppressor of cytokine signaling 1 (SOCS1) – encoded by another GC-inducible gene – is an inhibitor of Janus kinase (JAK)–STAT cascade downstream of cytokines binding to their cell surface receptors [21]. GR can also act to suppress inflammation by altering the epigenetic state of chromatin at target promoters through mitogen- and stress-activated protein (MSK1) kinase and GR-interacting protein (GRIP)1 (nuclear receptor coactivator 2, Ncoa2) recruitment, which affects components of basal transcriptional machinery and the rate-limiting steps in RNA polymerase II transcription cycle such as promoter-proximal pausing [22–24]. The opposite arm of regulation includes chromatin

modulators such as BRD9, which attenuates GR-mediated repression of inflammatory genes [25].

Similar to GR, PPARγ represses transcription of pro-inflammatory genes by directly binding NF-kB and AP-1 and interfering with their activities (Fig. 7.1a; [26]). PPARγ directly binds the p65 subunit of NF-kB under basal conditions in human colonic HT29 cells and mouse embryonic fibroblasts (MEFs), and the binding in MEFs increases after stimulation with LPS and TNF [27]. Additionally, PPARγ-deficient macrophages that are unstimulated *in vitro* [28] or sorted from tissues during perinatal development [29] are pro-inflammatory. Contrary to these findings, however, mice lacking PPARγ in the myeloid lineage express less IL-1 than WT after NLRP3 activation *in vivo* and in primary macrophages [30].

In addition to acute actions of each receptor that lead to rapid and dramatic, yet reversible changes in the inflammatory transcriptome, a sustained exposure to pro- or anti-inflammatory signals, including NR ligands, results in a stable change of epigenomic landscape and associated macrophage phenotype, which alters responses to subsequent acute stimuli. Historically, macrophages were thought to have the capacity to be 'polarized' to two distinct phenotypic states. Bacterial products such as LPS and the T helper-1 (Th1) cytokine interferon-γ (IFNγ) bias macrophages toward the inflammatory state termed 'M1'. Conversely, a tissue repair/wound healing phenotype of an 'M2' macrophage was originally described as a polarization state conferred by the Th2 cytokine IL-4 [31]. These macrophages are implicated in the Th2-driven response to parasitic infection or allergies, as well as in homeostatic functions such as wound healing, angiogenesis and insulin-sensitizing metabolic functions (Fig. 7.1b). Signaling downstream of IL-4 involves activation of the TFs STAT6 and KLF4 that cooperatively facilitate the gradual acquisition of the M2 transcriptional state [32]. Depending on the stimuli used *in vitro*, the populations of M2-like macrophages were further classified as M2a (after exposure to IL-4 or IL-13), M2b (immune complexes in combination with IL-1β or LPS) and M2c (IL-10, TGFβ or, importantly, GCs) [33]. This binary M1/M2 view of polarization was later challenged by extensive expression profiling studies that arrived at a spectral model of macrophage activation states whereby every signal or a combination of signals yields a distinct transcriptional make-up [34]. Nonetheless, transcriptomes resulting from stimulation with LPS or IFNγ vs. those produced by IL-4, IL-10 or GCs did cluster at the opposite ends of the spectrum, supporting the idea that M1-like and M2-like phenotypes represent the two extremes of macrophage transcriptional states.

Thus, the anti-inflammatory effects of GC signaling in macrophages range from the acute upregulation of anti-inflammatory and repression of pro-inflammatory genes to more sustained phenotypic changes upon prolonged (beyond 24 h) GC exposure. The latter involves upregulated phagocytosis of apoptotic cells and debris while the production of inflammatory mediators subsides, which together drive the resolution phase of inflammation [35, 36]. GC-polarized macrophages are characterized by high expression of scavenger receptors such as CD163 and type 2 and anti-inflammatory cytokines IL-4 and IL-10 [37].

Similarly, PPARγ is reportedly essential for transitioning to an anti-inflammatory macrophage [38]. Indeed, pharmacological activation of PPARγ increases the expression of *Fizz1, Ym1* and *Arg1*, typical 'M2 genes' in macrophage-like RAW264.7 cells and human peripheral blood mononuclear cells [39]. Conversely, mice with PPARγ-deficient macrophages display impaired wound healing *in vivo* [40]. Thus, PPARγ and GR both drive the M2-like macrophage phenotype with resolving properties, even though the direct gene targets are not fully shared.

Genomic studies revealed that sustained IL-4 signaling leads to the binding of transcription factors: STAT6, and subsequently RXR and PU.1, and to the recruitment of cofactors P300 and RAD21 to a subset of new RXR sites; 60% of them need PPARγ binding to open, and the majority of new RXR sites are PPARγ-dependent irrespective of STAT6 binding (Fig. 7.1b) [41].

IL-4 itself induces the expression of the PPARγ-encoding gene *Pparg,* highlighting the importance of PPARγ for the M2-like phenotype [42]. Notably, these changes are driven by IL-4, not a specific PPARγ ligand, which contrasts with the strict dependence of GR on GCs to drive the M2-like phenotype.

Cofactors provide an additional level of convergence between NR-driven and IL4-induced macrophage polarization. GRIP1/NCoA2 is a member of the p160 family of NR coregulators shared by GR and PPARγ [43]. GRIP1 has further been shown to serve as a coactivator for KLF4, thereby directly contributing to the IL-4:STAT6:KLF4 pathway [44]. Indeed, macrophage-specific GRIP1 deletion in mice shifted their macrophage balance toward the more inflammatory M1-like phenotype *in vitro* and in an obesity-induced model of metabolic inflammation *in vivo* [44]. The role of GRIP1 in facilitating both GR-mediated activation and repression is well established [45, 46]. It is tempting to speculate that GRIP1 may serve as a platform for integrating pathways involved in M2-like macrophage polarization in response to distinct physiological stimuli.

In the context of the human *in vitro* model of atherosclerosis, PPARγ reduces inflammatory cytokine secretion in human umbilical vein endothelial cells exposed to oxidized-low-density lipoproteins (oxLDLs) [47]. In line with these findings, peritoneal macrophages from conditional PPARγ KO mice had more foam cell formation after treatment with oxLDLs *in vitro* [48] suggesting that PPARγ reduces inflammation and pathogenesis of atherosclerosis. The function of PPARγ in atherosclerosis is consistent with *in vitro* effect of PPARγ in macrophages, as well as with GR actions in macrophages *in vivo* in inflammatory settings.

The predominantly immunosuppressive effects of GCs on the immune system contrast observations that, at low doses, GCs can enhance pro-inflammatory signaling [49], in part by upregulating TLR2, TLR4, components of the inflammasome and certain cytokines [50]. On the basis of these studies, it was proposed that low-level GR signaling may sensitize cells to harmful stimuli by promoting the expression of pattern-recognition and cytokine receptors, thus enabling a prompt response to pathogens [9]. These pro-inflammatory effects of GCs mirror the up-regulation of IL-1 expression by PPARγ after inflammasome activation – the pro-inflammatory functions of these TFs are also convergent.

## 7.3 GR and PPARγ in Non-Macrophage Immune Cell Subsets

### 7.3.1 T Cells

It is well established that GCs inhibit $CD4^+$ T cell activity, however, it remains unclear if GCs predominantly affect $CD4^+$ helper T cells, $CD4^+Foxp3^+$ regulatory ($T_{reg}$) cells or both. GCs inhibit T cell activation directly by inhibiting the TFs downstream of TCR signaling: an extensive body of literature has documented a direct repression of NF-kB, AP-1 and nuclear factor of activated T cells (NF-AT) activity by GR via tethering in numerous cell types [51]. GCs were also proposed to inhibit T cell activation through non-genomic effects, by disrupting the TCR-associated GR protein complexes which include the lymphocyte-specific protein tyrosine kinase (LCK) and FYN kinase, ultimately leading to impaired TCR signaling [52]. GCs also affect T cell activation in an indirect manner, by interfering with the function of dendritic cells (DCs; discussed in detail later in the Chapter) in a GILZ-dependent manner and promoting their tolerogenic phenotype, marked by decreased levels of co-stimulatory CD86, CD83 and CD80, decreased secretion of chemokines CCL3, CCL5 and CXCL8 in activated DCs and a subsequent reduction of $CD4^+$ T cell proliferation [53]. Indeed, IFNγ production by $CD4^+$ T lymphocytes was no longer inhibited when DCs were transfected with GILZ siRNA [53]. Thus, GCs reduce the responsiveness of T cells to antigens and regulate the balance between activating and tolerogenic DCs, thereby suppressing effector T ($T_{eff}$)

cell activity through both direct cell-intrinsic and indirect mechanisms.

Unexpectedly, a recent study suggested that the $CD4^+$ $T_{eff}$ subset might not be the primary target of therapeutic actions of GCs in T cells. Absence of GR specifically in $Foxp3^+$ $T_{reg}$ cells abrogated therapeutic effects of the GC dexamethasone (Dex) in murine experimental autoimmune encephalomyelitis (EAE) and allergic airway inflammation (AAI) models, suggesting that $T_{regs}$ were necessary for GCs to exert their anti-inflammatory effects [54]. Mechanistically, GR was shown to induce microRNA miR-342-3p expression, leading to inhibition of Rictor, an adaptor protein of the glycolysis-favoring mTORC2 complex; this led to metabolic reprogramming of $T_{regs}$ and induction of oxidative phosphorylation, which ultimately reinforces their suppressive functions [54]. In support of this study, GR-deficient $T_{reg}$ cells were impaired in their ability to suppress T cell-dependent colitis in mice and acquired features typical of Th1 cells [55]. In the house dust mite-induced AAI model, treatment with synthetic GCs reduced $T_{reg}$ recruitment to the lungs [56]. Mice with a T cell-specific GILZ KO had decreased absolute numbers of peripheral $T_{reg}$ cells, an effect reversed by GILZ overexpression [57]. Effects of GR on $T_{reg}$ cells are thus multifaceted, stimulating their activity, metabolism, proliferation and recruitment to inflammatory sites.

Among the $CD4^+$ $T_{eff}$ cell subsets, GCs inhibit Th1 as well as Th17, but up-regulate Th2 cell differentiation [58]. Similarly, in mice overexpressing GILZ in the T cell lineage, $CD4^+$ T cells stimulated with CD3/CD28 antibodies secreted more Th2 and less Th1 cytokines compared to WT, an effect mirrored by up-regulation of Th2-specific TFs GATA-3 and STAT6 and down-regulation of the Th1-specific T-bet [59]. Finally, GILZ in Th17 cells localized to genomic sites in the proximity of Irf4, Batf, Stat3, and RORγt binding sites – TFs that drive Th17 activation and differentiation – suggesting that GC-induced GILZ may act as a transcriptional repressor of Th17-activating TFs [60] and that by upregulating GILZ, GCs shift the balance toward Th2-mediated humoral immunity (Fig. 7.2).

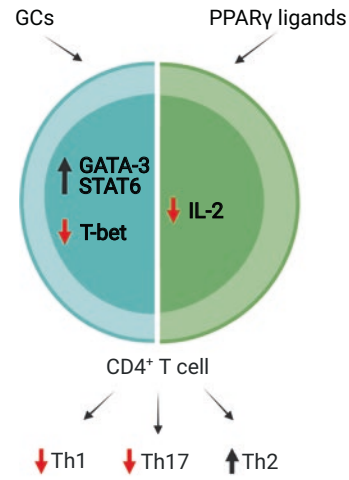


**Fig. 7.2 GCs and PPARγ ligands promote Th2 and inhibit Th1 and Th17 immunity.** Stimulation of $CD4^+$ T cells with GCs increases transcription of TFs GATA-3 and STAT6, and down-regulates T-bet expression, which biases $CD4^+$ T cells toward Th2 immunity and away from Th1 and Th17 responses. Similarly, treatment with PPARγ ligands decreases transcription of IL-2, which favors Th2 responses

Notably, although the predominant view is that GCs primarily affect the $CD4^+$ T cell subset, in some disease contexts, GC-mediated suppression of $CD8^+$ T cells is essential. In a mouse model of acute graft-versus-host disease (aGVHD), for example, lethally irradiated mice receiving a bone marrow transplant with GR-deficient T cells displayed much greater $CD8^+$ T cell infiltration into the jejunum and their $CD8^+$ T cells had augmented cytolytic activity compared to mice with WT T-cell transfer [61]. Thus, GR activity in $CD8^+$ T cells in the context of aGVHD attenuates their inflammatory phenotype, mirroring the effects in $CD4^+$ $T_{eff}$ cells.

During development, pharmacological GCs induce caspase-dependent apoptosis of thymocytes [62–65] with GR deletion rendering GR-KO thymocytes GC-resistant. The mechanism of GC-induced apoptosis was shown to involve the activation of caspase-9 [66–68]. The physiological role of GC-induced thymocyte apoptosis continues to be debated. Although $CD4^+CD8^+$ double-positive thymocytes are particularly sensitive to GC-induced apoptosis, GCs at physiological levels do not appear to regulate

death-by-neglect of these cells [69]. Rather, GCs are needed for optimal TCR repertoire and T cell responses to foreign antigens, thus contributing to negative selection [69]. In other studies, however, absence of GR had no effect on adult thymocyte development, as mice on a mixed background (129sv/C57BL/6) with a whole-body GR deletion had normal numbers of mature $CD4^+CD8^-$ and $CD4^-CD8^+$ cells, suggesting that positive selection was occurring normally [70]. It is yet to be determined if GC-induced thymocyte apoptosis indeed broadly affects T-cell development, or if it is limited to specific mouse models.

In contrast to GR, the overall contribution of PPARγ to the survival of T cells awaits further investigation. Both synthetic and endogenous PPARγ agonists stimulate apoptosis of murine T cells when administered in high doses [71]. Similarly, T cells stimulated with the proliferative agent, lectin phytohaemagglutinin P, undergo apoptosis after treatment with synthetic PPARγ agonists [72]. However, PPARγ-deficient, but not WT $CD4^+$ T cells, showed increased apoptosis after transfer into RAG1 KO mice, suggesting that PPARγ promotes $CD4^+$ T cell survival under conditions of low lymphocyte numbers [73]. Thus, the role of PPARγ in T cell survival remains controversial with net effect relatively poorly defined [74].

With respect to the balance of effector T-cell subsets, the PPARγ function appears similar to that of GR. At pharmacological concentrations, PPARγ ligands inhibit T cell, especially Th1, proliferation and decrease their viability [75], in part, by decreasing the transcription [76, 77] or protein expression [78] of IL-2. In addition, PPARγ ligands downregulate Th1 pro-inflammatory cytokines and augment the production of Th2 cytokines thereby shifting immune responses toward type-2 (Fig. 7.2). *In vivo*, PPARγ was shown to contribute to type-2 responses in T cells and DCs in an AAI model [79]. Specifically, in lung-resident $CD11b^+$ DCs, IL-4 and IL-33 signaling upregulated PPARγ levels, correlating with enhanced DC migration to draining lymph nodes and Th2 priming capacity. *In vitro*, production of IL-12 by DCs after stimulation with CD40 ligand, which normally induces Th1 responses, was inhibited by both endogenous and synthetic PPARγ ligands [80]. Thus, PPARγ mediates DC-T cell interactions in type-2 immunity in the context of *in vivo* Th2 responses, as well as promoting DC phenotypes associated with Th2-immunity *in vitro*.

Interestingly, PPARγ has been recently reported to facilitate group 2 innate lymphoid cell (ILC2)-induced AAI [81]. Loss of PPARγ in hematopoietic cells in mice diminished the function of ILC2 in the lungs, reducing the airway inflammation upon challenge with IL-33 or Papain. The transcriptional target of PPARγ in ILC2s was shown to be the IL-33 receptor ST2, such that overexpressing ST2 rescued the functional defects of PPARγ deficiency. Given that ILC2s and Th2 cells have been shown to collaborate in multiple AAI models [82–84], it appears that PPARγ can enhance both innate and adaptive arms of Th2 immunity.

In non-allergic models of inflammation, PPARγ has been generally shown to exert protective effects. Indeed, in a dextran sodium sulfate (DSS) colitis model, mice lacking PPARγ specifically in T cells exhibited reduced recruitment of $T_{reg}$ cells to mesenteric lymph nodes, decrease in IL-10-producing $CD4^+$ T cells and increase in $CD8^+$ T cells, which together augmented colitis severity [85]. Similarly, in the EAE model of neuroinflammation, T-cell-specific PPARγ KO mice had higher clinical scores and enhanced infiltration of Th17 cells into the CNS [86]. The latter was consistent with *in vitro* data whereby naïve PPARγ KO $CD4^+$ T cells showed enhanced Th17 differentiation, suggesting that PPARγ constrains the Th17 cell lineage commitment [86]. Thus, endogenous PPARγ serves as an important brake on the inflammatory response *in vivo* in different organ systems.

In addition to the transcriptional effects on immune cell-specific genes, as discussed below, PPARγ is a key regulator of lipid metabolism across cell types and, therefore, impacts T cell biology by altering their bioenergetics and metabolic state. For example, the mechanistic target of rapamycin complex 1 (mTORC1)-PPARγ pathway is crucial for the FA uptake program in

activated CD4+ T cells in mice [87]. PPARγ directly binds to promoters of genes associated with FA uptake in CD4+ T cells, leading to their metabolic reprogramming and rapid antigen-induced proliferation *in vivo*. Unlike its effect on genes specific to immune cell functions, the effect of PPARγ on metabolism of CD4+ T cells does not favor their differentiation toward a specific subset, but merely activates them.

### 7.3.2 Dendritic Cells (DCs)

DCs are often viewed as a bridge between the innate and adaptive immune system. Their role is to present pathogen-derived antigens on the cell surface, which get recognized by and activate T cells. Thus, aside from the direct effects of GR or PPARγ on T cells, the two NRs can affect DC activity, thereby potentially producing a less specific effect on T cell immunity.

Mice with a DC-specific KO of GR (GRCD11c-cre) were shown to be highly susceptible to septic shock induced by LPS, as evidenced by augmented production of inflammatory cytokines, a greater susceptibility to hypothermia and higher mortality [11]. Endogenous GCs inhibit LPS-induced inflammation and enhance tolerance by reducing IL-12 production by CD8+ DCs, and consequently, decreasing IFNγ secretion by natural killer cells [11]. The molecular mechanisms underlying GC actions specifically in CD8+ DCs have not been elucidated. However, GCs up-regulate the transcription of GILZ [58] and inhibit NF-kB and AP-1 activities and the MAPK pathway, thereby reducing production of IL-6, IL-12, and TNF [88, 89] in DCs similar to that seen in other cell types (Fig. 7.3). As discussed previously [53], GCs down-regulate co-stimulatory molecules on DCs and decrease their secretion of chemokines in a GILZ-dependent manner, in this way reducing the inflammatory phenotype of DCs (Fig. 7.3).

The prominent functions of PPARγ in DCs have been studied extensively. Over 1000 transcripts, including those of key lipid regulators FABP4 and ABCG2, were modulated by the PPARγ agonist rosiglitazone during GM-CSF- and IL-4-induced DC differentiation from monocytes *in vitro* [90], and PPARγ itself was

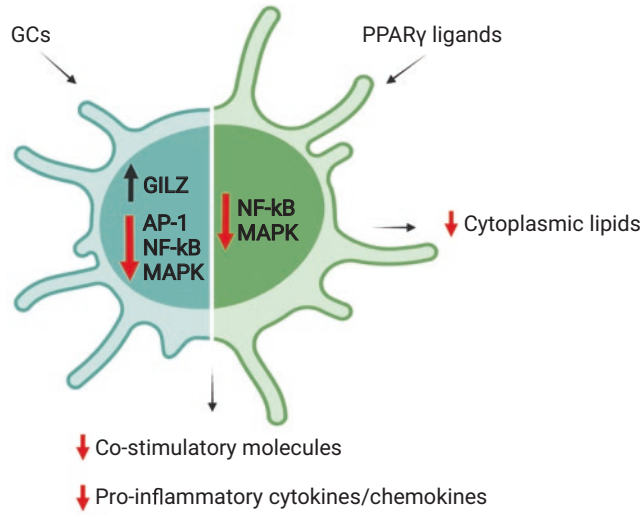


**Fig. 7.3 Effect of GCs and PPARγ on DC activity.** Activation of GR and PPARγ with their respective ligands leads to DC inactivation, manifested as decreased production of co-stimulatory molecules and pro-inflammatory cytokines. Both GR and PPARγ inactivate DCs by down-regulating MAPK and NF-kB pathways, with GR additionally decreasing AP-1 activity. The effects of GR are mediated by GILZ. Unlike GR, PPARγ also affects the lipid metabolism of DCs, decreasing their cytoplasmic lipid content

markedly up-regulated at both the mRNA and protein level [91]. Interestingly, FABP4 expression was elevated when human monocytes were differentiated to DCs in the presence of human serum, rather than specific ligand, suggesting that the endogenous PPARγ ligands were sufficient to drive PPARy-dependent gene transcription. In human monocyte-derived DCs, PPARγ activation inhibited NF-kB and MAPK pathways, down-regulating co-stimulatory molecules and dampening TLR-induced secretion of pro-inflammatory cytokines ([92], Fig. 7.3). Genes linked to lipid metabolism were also up-regulated such that PPARγ-activated DCs had increased capacity to metabolize and re-distribute lipids, resulting in decreased cytoplasmic lipid content (Fig. 7.3). PPARγ hence connects lipid processing in DCs with their immune function. In a mouse model of asthma, knocking out PPARγ in DCs attenuated recruitment of eosinophils to the airways, IL-4 secretion by $CD4^+$ cells and histopathological changes, demonstrating that PPARγ in DCs orchestrates Th2 immunity in the lungs [79]. Given the previously described role of PPARγ agonists in reducing inflammation in asthma, this study demonstrated that endogenous PPARγ in DCs may have the opposite role [93]. The PPARγ-dependent skewing of DCs toward Th2 immunity is concordant with the preference of PPARγ for type-2 responses in both innate and adaptive arms.

The examples above illustrate that both GR and PPARγ exert primarily anti-inflammatory actions in macrophages, T cells and DCs and bias the immune system toward type 2 responses. Likewise, both NRs can induce thymocyte apoptosis, although PPARγ can favor $CD4^+$ cell survival. Some of the effects of these two receptors on immune cells are conferred via metabolic reprogramming. A well-known GR transcriptional target GILZ is an important effector of downstream responses in DCs, $T_{regs}$ and Th2 subsets. The specific targets of PPARγ in immune cells appear more diverse and cell type-specific.

## 7.4 GR and PPARγ in Adipocytes

The most well-studied cell type-specific role of PPARγ is in adipocytes, where it serves as the master regulator that is necessary and sufficient to induce adipogenic gene expression and lipid accumulation [94]. Adipocyte-specific KO of PPARγ using the aP2-Cre, a target of PPARγ, and resulting in unhindered adipocyte differentiation, allows for assessing the role of PPARγ in the mature cells [95]. PPARγ deletion led to enlargement of white and brown adipocytes and reduction in their numbers. At the systemic level, adipocyte-specific loss of PPARγ resulted in elevated free FA and triglyceride (TG) plasma levels, fatty liver with increased gluconeogenesis, as well as reduced levels of leptin and adipocyte complement-related protein of 30 kDa (ACRP30), known to be secreted exclusively by differentiated adipocytes. Ablation of PPARγ in fat with a more specific Adipoq-Cre, which uses a regulatory region of adiponectin, resulted in severe adipose tissue loss, insulin resistance and other metabolic abnormalities [96].

Multiple TFs and coregulators – coactivators and corepressors – modulate the function of PPARγ in adipocytes [97]. PPARγ and the TF C/EBPα bind to the majority of the genes upregulated during adipogenesis, and both TFs, as well as C/EBPβ, were required for the expression of adipogenesis-inducing genes, suggesting that cooperativity between PPARγ and C/EBP (Fig. 7.4a) is needed for adipogenesis [98]. Coactivators affect PPARγ function in adipocytes by directly binding PPARγ and facilitating the recruitment of additional components of transcriptional machinery or chromatin modifiers, such as thyroid hormone receptor interacting protein 3 (TRIP3) and members of the NCoA/p160 family, e.g., NCoA2/TIF2/GRIP1, NCoA1/SRC-1 and the PPARγ coactivator 1-alpha (PGC-1a). Knock-down of TRIP3 leads to diminished differentiation of adipocytes, so TRIP3 acts as a positive regulator of PPARγ-mediated adipocyte differentiation [99]. NCoA2 promotes

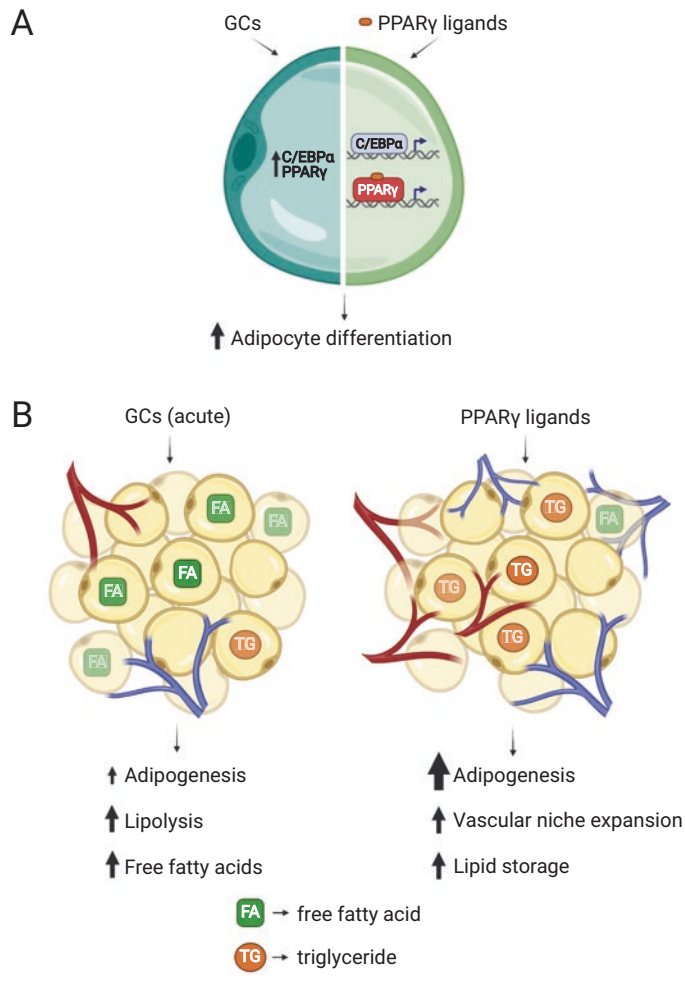


**Fig. 7.4 GCs and PPARγ ligands affect adipose tissue in distinct ways.** (**a**) In adipocytes, GR increases the expression of PPARγ and C/EBPα; PPARγ is the major driver of adipogenesis in cooperation with C/EBPα. (**b**) At the adipose tissue level, GR and PPARγ have disparate functions, with GR up-regulating lipolysis and the levels of free FA in addition to adipogenesis upon acute exposure. PPARγ affects the adipose tissue on multiple levels, by promoting adipogenesis, angiogenesis and lipid storage

PPARγ activity and fat accumulation in white adipose tissue (WAT), whereas NCoA1 enhances energy expenditure and protects from obesity [100]. Mediator complex subunit 14 (MED14) is another direct interactor of PPARγ, which tethers the Mediator complex to PPARγ to activate PPARγ-specific lipogenic genes [101]. In mature 3 T3-L1 adipocytes, the histone acetyltransferase coactivator Tip60 is recruited to PPARγ target genes, and reduction of Tip60 protein levels impedes 3T3-L1 preadipocyte differentiation [102]. These studies indicate that coactivators affect multiple and diverse aspects of the PPARγ function in adipocytes.

Transcription activation by PPARγ is negatively regulated by corepressors such as NCoR/SMRT; these are recruited by PPARγ in the absence of ligand, and dissociate upon ligand binding when they are replaced by coactivators due to a change in PPARγ conformation [103, 104]. In 3T3-L1 cells, knocking down NCoR and SMRT leads to increased expression of adipocyte-specific genes [103]. NCoR deletion in adipocytes was shown to enhance adipogenesis, reduce inflammation and improve insulin sensitivity at the organismal level [105]. Mechanistically, NCoR and SMRT recruit HDAC3 to induce histone deacetylation of PPARγ-bound regulatory regions [106]. However, in adipocytes, NCoR facilitates the recruitment of cyclin dependent kinase (CDK)5, which binds to and phosphorylates PPARγ at S-273 (inhibitory site that reduces recruitment of PGC-1 and GRIP1/NCoA2 and increases interactions with SMRT and NCoR),

leading to impaired regulation of metabolic genes, such as insulin-sensitizing adiponectin [107]. Conversely, ring finger protein 20 (RNF20), which was shown to target NCoR for proteasomal degradation, acts as a positive regulator of PPARγ activity during adipogenesis [108]. A transcriptional cofactor with PDZ-binding motif (TAZ) was shown to act as a PPARγ corepressor [109]. TAZ deletion in adipocytes led to constitutive activity of PPARγ, and improved glucose tolerance and sensitivity to insulin in obese mice [110]. The functions of PPARγ in adipocytes are, thus, modulated by direct repression, which itself may be modulated by secondary cofactors.

In addition to direct gene regulation in adipocytes, PPARγ affects adipose tissue physiology by acting in its resident immune cells. For example, PPARγ modulates $T_{reg}$ accumulation, phenotype and function in the visceral adipose tissue (VAT) [111]. PPARγ cooperates with Foxp3 to upregulate a large number of $T_{reg}$-specific genes in the VAT, as shown by analyzing gene expression of naïve $CD4^+$ T cells retrovirally transduced with *Pparg* and *Foxp3*. Additionally, VAT $T_{reg}$ cells were found to uptake lipids upon stimulation with PPARγ ligand pioglitazone [111]. PPARγ is therefore necessary for the maintenance and accumulation of $T_{reg}$ cells in the VAT, and mediates the insulin-sensitizing activity of pioglitazone. PPARγ activation also promotes anti-inflammatory VAT phenotype by inhibiting resident conventional DC maturation and $T_{eff}$ cell recruitment in both lean and obese mice [112]. In addition, PPARγ directs the establishment and maintenance of the adipose vascular niche. *In vivo*, PPARγ overexpression in the adipose lineage upregulates PDGFRβ and VEGF in adipose progenitor cells, and both of these genes contribute to endothelial cell proliferation and adipose niche expansion [113]. Another important function of PPARγ is promoting the conversion of subcutaneous WAT to brown adipose tissue (BAT) [114]. Nuclear factor I-A (NFIA) assists PPARγ in WAT browning by facilitating the binding of PPARγ to BAT-specific enhancers, as shown in mouse C2C12 myoblasts treated with adipocyte differentiation cocktail that included rosiglitazone [115]. Thus, PPARγ acts as a broad regulator of adipose tissue physiology and metabolism.

GR performs several key functions in adipose tissue, many of which are opposite to those of PPARγ, but there is an overlap with respect to adipogenesis. GCs were shown to promote adipogenesis *in vitro*. Specifically, GR facilitated the up-regulation of C/EBPα and PPARγ mRNA and protein levels in 3T3-L1 cells upon stimulation with Dex and other compounds that promote adipogenesis (Fig. 7.4a, [116]). Consistently, GR KO MEFs failed to up-regulate CEBPα and PPARγ after treatment with a Dex-containing differentiation cocktail [117]. Mechanistically, in response to stimulation of pre-adipocytes with a Dex-containing cocktail, GR binds to transiently acetylated regions to establish a new gene expression program, including upregulation of PPARγ [118]. *In vivo*, however, GCs may facilitate adipogenesis without being absolutely required for it. Indeed, mice with a GR deletion in the BAT (using Myf5-Cre) had normal BAT size and morphology as well as normal expression of adipogenesis marker genes including *Cebpa* and, notably, *Pparg* [119]. Additionally, white and brown GR KO pre-adipocytes undergoing differentiation *in vitro* had reduced levels of adipogenesis markers early on, but eventually reached the levels of the WT [119]. Furthermore, in adrenalectomized (ADX) mice, largely lacking endogenous GCs, injection of MEFs into subcutaneous tissue did result in fat pad formation, although reduced in size compared to those in intact mice [117]. In the same study, injection of both WT MEFs into ADX mice, and GR KO or WT MEFs into WT mice, led to fat pad formation with comparable expression of adipocyte-specific genes, not significantly different from that in inguinal WAT of WT mice. During adipogenesis, therefore, GR and PPARγ may cooperate, thereby accelerating the PPARγ-dependent processes (Fig. 7.4a).

A broadly lipolytic effect of GC exposure in the adipose tissue, opposite to that of PPARγ activation, was reported over 40 years ago (Fig. 7.4b) and confirmed in multiple studies thereafter [120]. Typically, GC-induced lipolysis in the

WAT is associated with an acute hormone exposure due to stress response or fasting [121]. Prolonged or chronic exposure in rats, however, resulted in visceral fat accumulation, adipocyte hyperplasia and reduction in adipocyte size [122]. GR ligands can also enhance lipid storage, but only under specific, often, pathological conditions. For instance, hypercortisolemia during Cushing's syndrome is known to cause an expansion of visceral fat depots due to the synergistic effects of GCs with insulin, whereby GCs upregulate genes involved in lipid deposition [123].

Finally, GR activity in the liver, discussed below, exerts secondary effects on the adipose tissue. Crossing adult STAT5a/b KO mice with Alfp-Cre GR KO generated mice with a combined deletion of GR and STAT5 in hepatocytes [124]. These double KO mice had smaller adipocytes and fat depots, displayed hypercortisolism and aggravated steatosis compared to WT or STAT5 single KO mice.

Thus, outcomes of GC action upon the adipose tissue are complex, dependent on ligand concentration and duration of exposure, and further modulated by the systemic effects of GCs in other tissues, ultimately leading to adipogenesis and lipid storage, or lipolysis (Fig. 7.4b).

## 7.5 GR and PPARγ in the Liver

GCs were originally named for their ability to promote gluconeogenesis in the liver (Fig. 7.5a). Indeed, liver is a major target organ for GC action and plays a central role in glucose metabolism. In mice, a conditional liver-specific deletion of GR led to hypoglycemic lethality within days of birth [125]. In the clinical setting, excess GC levels during Cushing's syndrome or as a result of GC therapy have been associated with hyperglycemia and central obesity [126].

Two critical rate-limiting enzymes involved in gluconeogenesis, glucose-6-phosphatase and phosphoenolpyruvate carboxykinase, are encoded by the *G6pc* and *Pck1* genes, respectively, both of which are known to be direct GR targets (Fig. 7.5a, [16, 127]). The *Pck1* gene has been studied extensively and has a GRE site upstream of the TSS [128]. Interestingly, later studies pointed to roles of NRs other than GR in *G6pc* and *Pck1* regulation. Specifically, the dominant PPAR in the liver – PPARα, rather than PPARγ – is recruited to both genes and contributes to their transcriptional regulation in addition to GR [129, 130].

Apart from gluconeogenesis, GCs have also been linked to the regulation of FA metabolism in the liver. Patients with Cushing's syndrome often develop dyslipidemia that manifests as high TG and systemic cholesterol levels [131]. Intriguingly, liver-specific KO of GR in mice with hepatic steatosis led to a notable reduction in hepatic TGs and elevated ketone levels in circulation, along with upregulation of genes involved in FA oxidation and TG hydrolysis [132]. Genes mediating lipid storage and transport (e.g., FA transporter *Cd36*) were also significantly downregulated. Thus, liver-specific GR KO ameliorated hepatic steatosis by increasing hydrolysis of TG stores, indicating that under conditions of fatty liver, GR promotes TG storage (Fig. 7.5b).

Analyses of the tissue-specific distribution of PPARs position PPARα as the primary PPAR expressed in the liver; in contrast, PPARγ levels are relatively low. Thus, numerous studies suggested that metabolic effects of PPARγ stem primarily from its action in adipose tissue, with indirect secondary effects on the liver. However, a common phenotype of the adipocyte-specific PPARγ KO, in addition to lipodystrophy, is a substantial increase in hepatic PPARγ along with accumulation of TG in the liver [96]. Interestingly, hepatocyte-specific deletion of *Pparg* alleviated steatosis phenotypes in various animal models [133–135], further indicating that hepatocyte-expressed rather than adipocyte PPARγ was responsible for the fat accrual. Alb-Cre-mediated deletion of PPARγ in the liver markedly diminished the expression of the *Pparg2,* but not *Pparg1* isoform, so PPARγ2 appears to be the major isoform in hepatocytes contributing to fat accumulation [133]. Thus, in the context of liver steatosis, PPARγ can promote TG accumulation similar to GR (Fig. 7.5b).

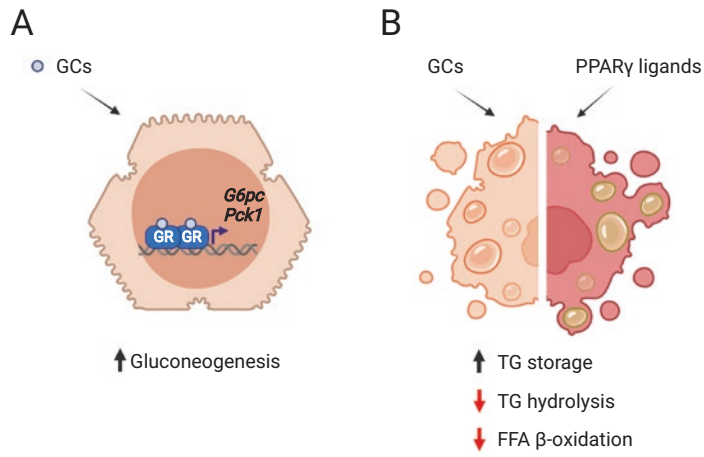


**Fig. 7.5 Effects of GCs and PPARγ ligands in hepatocytes.** (**a**) In healthy hepatocytes GR is the main driver of gluconeogenesis. (**b**) Under conditions of hepatic steatosis, both GR and PPARγ increase TG storage by decreasing TG hydrolysis and FA oxidation

Thus, in healthy liver, GR is a dominant regulator of glucose metabolism which up-regulates *de novo* glucose production, with little to no contribution from PPARγ. Under conditions of liver steatosis, both GR and PPARγ inhibit lipid hydrolysis and FA oxidation, thereby augmenting an increase in liver mass.

## 7.6 Concluding Remarks

GR and PPARγ are highly divergent NRs from steroid and non-steroid families, respectively, both viewed as critical therapeutic targets with a range of actions in the immune system and in metabolic homeostasis. Interestingly, the two NRs share many functions in immune cells at homeostasis and under pathogenic conditions. These TFs are anti-inflammatory during acute and chronic inflammation, and act as drivers of the Th2 response by promoting the M2-like macrophage subtype, biasing T cells towards Th2 and DCs towards tolerogenic state. Apart from a more pronounced role of GR in thymocyte selection, and that of PPARγ in DC development, the functional overlap of GR and PPARγ in immune cells eclipses isolated examples of their distinct roles. In the adipose tissue, however, the differences are striking: PPARγ is essential for adipogenesis and enhances lipid storage in adipocytes, whereas GR is mostly lipolytic upon acute hormone exposure. Finally, in the liver, GR is the uniquely critical regulator of normal glucose metabolism, while the two NRs have overlapping roles in TG metabolism during liver steatosis. Given that these TFs are invaluable therapeutic targets for, among others, autoimmune diseases and type 2 diabetes, novel insights on the consequences of activating both NRs, and understanding the effects their ligands may have at super-physiological doses *in vivo,* could potentially inform the use of combined treatments in clinical settings.

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