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The role of the glucocorticoid receptor in inflammation and immunity☆

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ABSTRACT

Glucocorticoids are potent immunosuppressive agents with complex actions on immune cells evoking the following effects: inducing apoptosis, changing differentiation fate, inhibition of cytokine release, inhibition of migration and other features. Distinct molecular mechanisms of the glucocorticoid receptor (GR) contribute to different anti-inflammatory effects. Recently inflammatory models have been investigated using conditional knockout and function selective mice shedding light on critical cell types and molecular mechanisms of endogenous and therapeutic GC actions. Here we review the multiple effects of GCs on major immune cells, dendritic cells, myeloid cells and B- and T-lymphocytes and give a summary of studies using conditional GR knockout mice.

1. Introduction

Glucocorticoid (GC) or steroid therapy is a common medication throughout westernized medicine to combat allergic and chronic inflammatory diseases, such as asthma, dermatitis, rheumatoid arthritis and even some cancers. Chronic treatment however, evokes severe side effects due to the catabolic actions of glucocorticoids (GCs) in mesenchymal tissues, such as atrophy of the skin, muscle weakness and osteoporosis. Due to its metabolic actions in the liver, in particular gluconeogenesis, GC access leads to insulin resistance and diabetes. Thus, a molecular understanding of cell type specific effects of this pleiotropic hormone is required to develop strategies to overcome side effects by maintaining the therapeutic efficacy of steroids. Here we discuss molecular mechanisms of the glucocorticoid receptor (GR) in different cell types of the immune system. We describe results from studies using conditional GR knockout mice defining the requirement of the GR in selective cell types for therapy.

2. Molecular mechanisms of the glucocorticoid receptor

GCs act primarily via a nuclear receptor namely the glucocorticoid receptor (GR), a member of the nuclear receptor family. In the absence of ligands the GR resides in the cytoplasm in complex with chaperonic molecules composed of heat shock proteins Hsp90, 70, 23 and immunophilins FKBP51, FKBP52, Cyp44 and PP5 [1] (see also Fig. 1). In the cytoplasm the ligand bound GR can interact with signaling pathways such as PI3K, JNK, 14-3-3 proteins and components of the T cell receptor (TCR) signaling complex [2] (Fig. 1), and thereby modulate pro-inflammatory gene expression. Seemingly more important and better characterized are GR actions in the nucleus. Upon ligand binding the chaperonic complex is remodeled, exposing nuclear localization sequences on the GR, which leads to its nuclear translocation. In the nucleus the GR regulates gene expression by two major mechanisms (Fig. 1). The first one involves binding of a dimerized GR to palindromic glucocorticoid response elements (GRE) within the promoter of genes, the subsequent recruitment of co-activators leading to chromatin remodeling and facilitation of transcription. Although GREs were long time considered to be conserved, genome wide analysis of GR binding revealed that base pair variations within the GRE sequence lead to different GR activities [3]. Furthermore it could recently be shown by global ChIP studies that the liganded and – surprisingly – the unliganded GR can bind to highly various DNA themes utilizing different co-activator complexes in a cell type specific manner [4]. Whether the latter always translate to changes of gene expression remain to be proven by further ChIP sequencing approaches.

The second mode of transcriptional regulation is independent of dimerization and DNA binding by tethering of the GR monomer to pro-inflammatory transcription factors, such as AP-1, NF-κB, IRF-3 STAT, CREB, NFAT, T-Bet and GATA-3 (reviewed in [5]). These interactions require the presence of recently identified co-integrators for GR-mediated interference [6,7]. Often this tethering results in the inhibition of pro-inflammatory genes and is supposed to act in the resolution of inflammation by GCs [8]. Lately, synergistic activity of the GR with members of the peroxisome proliferator-activated receptor (PPAR) family namely PPARγ [9] and PPARα [10] had been reported to suppress NF-κB and IRF-3 dependent target genes via tethering mechanisms as well, opening the possibility to increase anti-inflammatory efficacy with GCs when co-treated with PPAR ligands. In the light that PPARγ ligands were newly demon-

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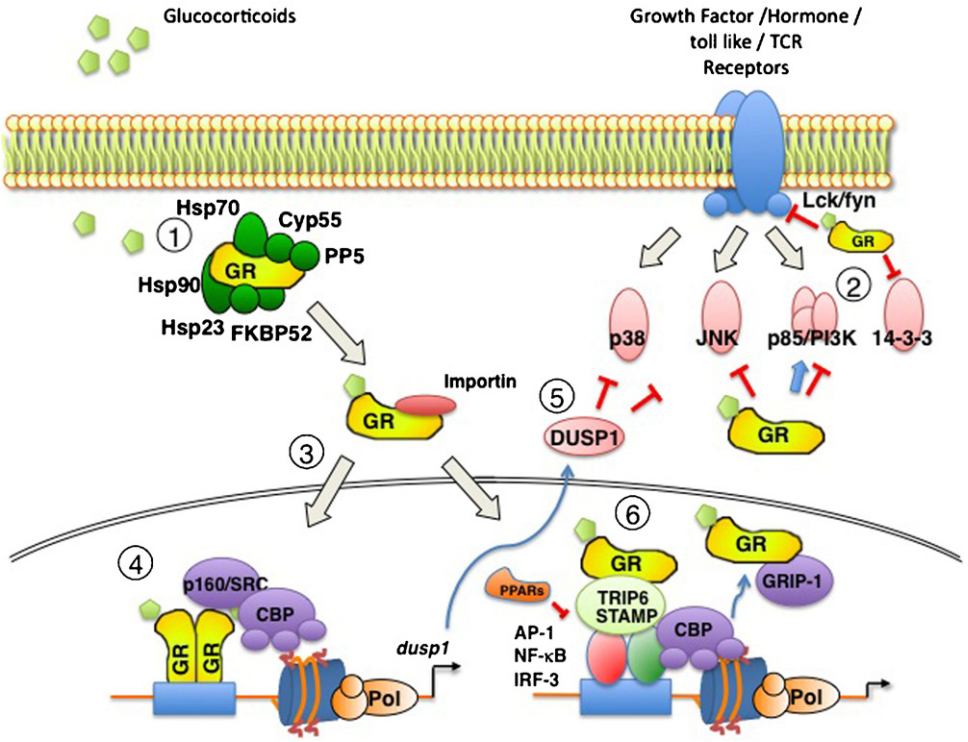

Fig. 1. Molecular mechanisms of GR action. Glucocorticoids act on cells by crossing the cell membrane and binding to the cytoplasmatic glucocorticoid receptor (GR). After ligand binding the chaperonic molecules dissociate from the GR (1). The ligand bound GR exhibit cytoplasmatic activities in particular interfering with signal transducers such as MAP kinases or PI3 kinases, but also with components of the T cell receptor (2). This often results in suppression of these signaling events. The interaction with PI3K can be positive or negative depending on GC concentrations. The hormone bound GR translocates very efficient to the nucleus (3). As a dimer it binds as a bona fide transcription factor to DNA and recruits co-activators such as p160/SRC and CBP leading to chromatin remodeling and facilitated gene transcription (4). Some of the gene products regulated by the GR exert anti-inflammatory activities such as the phosphatase DUSP-1. Enhanced DUSP-1 expression upon GC exposure leads to inhibition of p38 MAPK and JNK (5). The GR monomer also interacts by a tethering mechanism with co-integrators such as TRIP6 and STAMP at sites of pro-inflammatory DNA bound transcription factors (6). Co-activators such as GRIP-1 may be also sequestered from these complexes by the GR. By these mechanisms the activities of AP-1, NF-κB and IRF-3 are modulated or even repressed (6). Recently, the cooperative action of peroxisome proliferator-activated receptors (PPARs) with the GR in suppression of pro-inflammatory transcription factors had been demonstrated.

strated to bind to the GR as partial agonists [11], it is more than worthy to look further into this therapeutic possibility. General it is believed that targeting the tethering mechanism of the GR exclusively by selective GR agonists (SEGRAs) allows to maintain immunosuppressive properties of GR ligands. Side effects dependent on GR DNA binding however would be omitted by these compounds [12]. Indeed cells and mice carrying a mutated GR with a point mutation abrogating the dimerization interface of the GR in the DBD (GR^{dim}) still possess efficient suppression of NF-κB and AP-1 while the induction of GRE dependent gluconeogenetic genes in the liver or transfected mouse mammary tumor virus LTRs is absent [13–15]. Initial studies with GR^{dim} mice also revealed potent anti-inflammatory activities of GCs in irritated skin models, indicating that the tethering mechanism is sufficient for this process [15]. However the extension of analyses of GR^{dim} mice in other inflammatory diseases [16] reveals a requirement of dimerization dependent activity of the GR for anti-inflammation. This is in agreement with the finding, that some of the identified SEGRAs are potent in some inflammatory assays *in vivo* and in part show reduced side effects [17,18], whereas others fail to reduce side effects *in vivo* (reviewed in [19]). In particular, the induction of GRE dependent genes such as DUSP1/MKP-1 can contribute substantially to anti-inflammatory activities of the GR [20]. MKP-1 induced by the liganded GR is a phosphatase, dephosphorylating JNK and MAPK p38, which leads to suppression of pro-inflammatory gene expression and an anti-inflammatory response in some [21,22], but not all animal models [23].

Different GR mechanisms in different cell types might be therefore required for full anti-inflammatory activities of GCs. Below we summarize briefly what has been described for GC effects on selected immune cell types.

3. Cell type specific actions of the GR

3.1. Dendritic cells

Dendritic cells (DCs) are considered as the professional antigen presenting cells, which take up antigen and mature by processing the antigen. Once mature they migrate to draining lymph nodes and potently induce antigen specific T helper cells. Glucocorticoids influence DCs on virtual all levels of their life cycle (Fig. 2). Before they mature after encountering antigen, GCs are potent inducers of DC apoptosis, but not of apoptosis in monocytes, from which they differentiate [24]. Strong activation of DCs by CD40 ligands can counteract this caspase independent apoptosis [25]. GCs stimulate antigen uptake [26,27] and DC activation is potently suppressed by GCs, i.e. by reduction of MHCII, of co-stimulatory molecules, and of cytokine expression [28,29]. Also migration towards the lymph nodes in general is inhibited, as shown by *in vivo* [16,30] and *in vitro* studies presumably due to down regulation of CCR7 expression [31]. However, in an asthma model GC treatment *in vivo* did not affect DC maturation during the sensitization phase [32].

GCs do not simply suppress DC activity they also seem to induce a tolerogenic DC phenotype by suppression of DC activation markers and concomitant up regulation of phagocytic activity and enhanced IL-10 expression [27,33]. Tolerogenic DCs induce T cell anergy, suppression of T cells and generate regulatory T

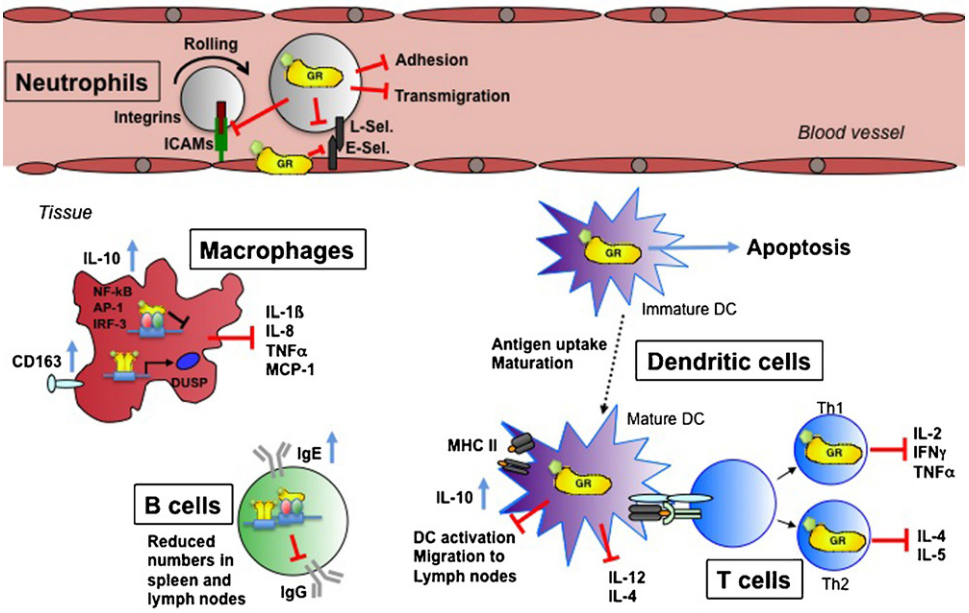

Fig. 2. Multiple effects of the GR on major immune cells. GCs influence neutrophil functions by suppressing rolling, adhesion and transmigration by reducing the expression of adhesion molecules like integrins, selectins (E-Sel., L-Sel.) and intercellular adhesion molecules (ICAMs) in neutrophils and endothelial cells. GCs efficiently suppress classical macrophage activation by induction of IL-10, an immunomodulatory cytokine and by the inhibition of the release of pro-inflammatory cytokines like TNFα, IFNγ or IL-1β. Cytokines are suppressed by mechanisms requiring the dimerized GR (by activating GRE dependent genes like DUSP-1) as well as tethering mechanisms, i.e. interfering with NF-κB, AP-1 and IRF-3. GCs influence dendritic cells (DCs) on all levels of their life cycle. They facilitate antigen uptake of immature DCs but suppress their maturation by reduction of MHCII, co-stimulatory molecules and cytokine expression. Furthermore they potently induce apoptosis of DCs and reduce their migratory capacity. Chronic GC treatment leads to a reduction of splenic and lymph node B cell numbers, reduction of IgG production but enhanced IgE generation. T helper cell differentiation and function is affected by GCs through repression of pro-inflammatory cytokines and by regulation of transcription factors (for details see Fig. 3).

cells. Thereby they protect from autoimmunity or graft versus host response [33]. GCs were found to be among the most potent inducers of tolerogenic DCs [34]. Inducing tolerance reveals therefore a powerful mechanism of anti-inflammatory action of GCs.

3.2. Macrophage

Macrophages derive from monocytes and play a central role in innate immunity and at the initiation of adaptive immunity. Their activation by microbial pattern recognition receptors (e.g. toll-like receptors, TLRs) and their large repertoire to release inflammatory regulators make these cells a prominent relevant target for anti-inflammatory therapy by steroids. Indeed a number of cytokines is efficiently suppressed by GCs by mechanisms requiring both GR dimerization and tethering mechanisms [15,16] (Fig. 2). Extensive expression profiling of murine macrophages revealed mainly tethering mechanisms with p65/NF-κB and IRF-3 for repressed genes [9]. For suppression of IRF-3 activity a sequestering mechanism by competing of GR with IRF-3 and with the co-activator/co-repressor GRIP-1 had been proposed [35]. However, recently an alternative anti-inflammatory phenotype of human monocyte derived macrophages was observed upon exposure to GCs. These immunosuppressive properties are exemplified in a gene expression profile with enhanced phagocytotic activity by up regulation of the scavenger receptor CD163 [36] and induced expression of the immunomodulatory cytokine IL-10. This anti-inflammatory phenotype was also detected in murine cells accompanied with elevated CD163 and Gr-1 expression and down regulation of the CX3CR1 chemokine receptor, a hallmark of inflammatory monocytes [37]. Interestingly, these cells display a high migratory capacity and a similar phenotype like functional myeloid suppressor cells, which share a similar surface expression. How stable this phenotype is *in vivo* under chronic GC treatment remains to be proven and would give some promise for anti-tumorigenic GC therapy. This phenotype could contribute to the anti-inflammatory activity by increasing non-phlogistic phagocytosis of apoptotic neutrophils [38,39].

3.3. Neutrophil granulocytes

Neutrophils or polymorphonuclear leukocytes (PMN) are present in the blood stream and comprise the major infiltrating cell type in acute inflammation. Their attraction by chemokines released by mast cells, endothelial cells and other myeloid cells and their infiltration involves a series of events which are modulated by GCs [40]. Rolling, adhesion, activation, and transmigration through the blood vessel are steps to invade the tissue. GCs suppress adhesion via reducing L-selectin expression in PMNs and E- and P-selectin in endothelial cells. Rolling and firm adhesion is performed by the interaction of the leukocyte integrins β2 (VLA-4) and β2 (LFA-1 and Mac-1) with the endothelial counterparts VCA-1, ICAM-1, ICAM-2 and ICAM-3, which are all reduced in the presence of GCs [40–42] (see Fig. 2). In contrast to the suppression of extravasation of PMNs, GCs increase bone marrow-derived neutrophils in the blood stream. This function is utilized clinically to combat neutropenia usually in combination with G-CSF [43]. However, the molecular mechanism for this phenomenon is not resolved yet. Intriguingly GCs delay granulocyte apoptosis and shift them to a necrosis during acute inflammation which has poorly understood consequences on the resolution of inflammation under GC treatment [38].

3.4. B cells

Despite the long term use of GCs also in B cell dependent pathologies, the actions of GCs on B cells are not intensively investigated. The predominant observations of GC treatment on B cell are basically a reduction of splenic and lymph node B cell numbers at chronic GC treatment, an attenuation of early B cell progenitor proliferation and enhanced IgE, but suppressed IgG production [44,45]

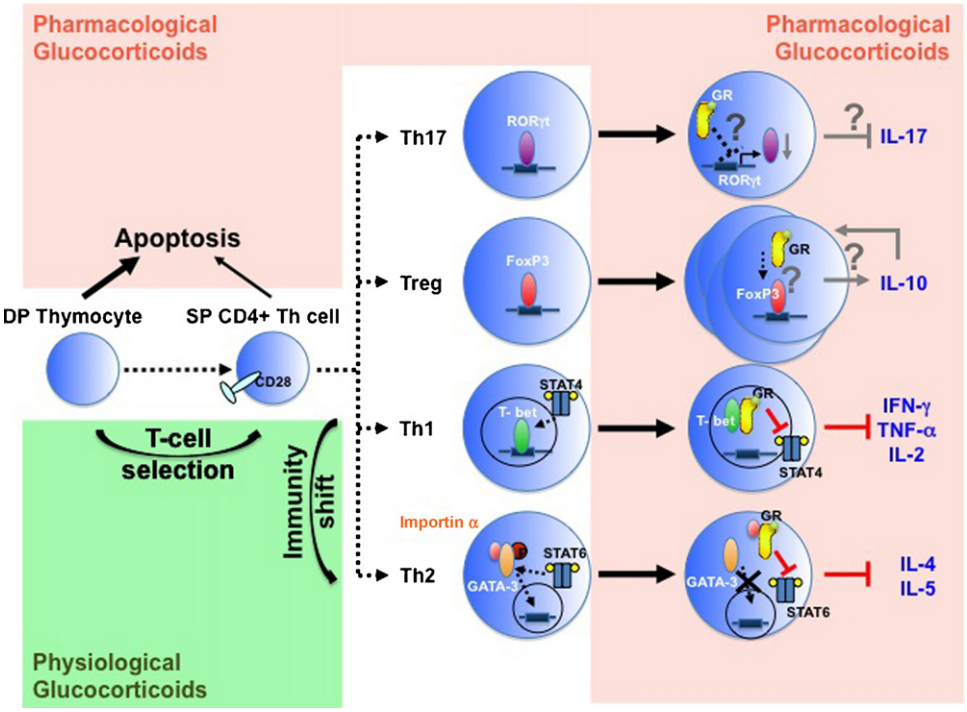

Fig. 3. Complex role of the GR in T cells. GC actions on T helper cells affect thymocyte maturation and Th cell differentiation. DP thymocytes are very sensitive towards GC-induced apoptosis, whereas SPs are less sensitive due to enhanced CD28 expression (left). At physiological doses GCs can cause a shift from Th1 response towards Th2 immunity (left below). Pharmacological doses exert anti-inflammatory effects on the different T helper cell populations by repression of pro-inflammatory cytokines and by regulation of transcription factors (right). RORγt expression is reduced by GCs in Th17 cells by an unknown mechanism. Treg numbers are increased by IL-10 released from tolerogenic myeloid cells. Whether FoxP3 is regulated by GCs is not known. In Th1 cells STAT4 and T-bet activity is inhibited by the activated GR through direct protein–protein interactions. In Th2 cells the GR prevents the nuclear import of GATA-3 and suppresses STAT6 function.

(Fig. 2). Thus GCs could be involved in an enhanced Th2 response. The paucity of animal models with a specific deletion of the GR in B cell lineage prevents a greater insight in GC actions on B cells. Once these animals are generated the relevance of actions of GCs on B cells in complex diseases will be unveiled.

3.5. T cells

In contrast to GC action on B cells a lot of attention has been drawn to T cells. T cells are the main players in the adaptive immune system. The development occurs in the thymus where the cells mature from a double negative (DN: CD4−CD8−) stage via a double positive stage (DP: CD4+CD8+) to the final stage of maturation, the single positive stage (SP: CD4+ or CD8+). At the double positive (DP) stage, positive and negative selection occurs. The positive selection process is mainly determined by a strong T cell receptor (TCR) signaling triggered apoptosis. Negative selection occurs in the virtual absence of TCR signaling also leading to apoptosis. Interestingly, DP T cells are very sensitive towards GC-induced apoptosis (reviewed in [46]) (Fig. 3). GC-induced apoptosis requires the dimerization of the GR [14] and is mediated via the BH3 only pro-apoptotic proteins Puma and Bim [47,48].

In vitro studies showed that TCR signaling can antagonize GC-induced apoptosis and vice versa, GC treatment alleviated TCR triggered apoptosis. Furthermore it was observed that thymic endothelial cells produce GCs locally [49,50]. A 'mutual antagonism' model had therefore been suggested for thymocyte selection [51,52]. Thymocytes expressing TCRs with high avidity for self-peptides/MHC undergo apoptosis due to the strong TCR signal that cannot be overruled by the GR signal. Thymocytes with suboptimal TCR signaling would receive the unopposed GR signal resulting in GC-induced apoptosis. Finally in thymocytes expressing a TCR with a low or moderate TCR avidity for self-peptide, the TCR and GR signal neutralize each other leading to cell survival and differentiation. However, the *in vivo* evidence of endogenous GC action on thymocyte selection is controversial. In studies with mice expressing an antisense GR which reduced endogenous GR expression, the thymus indeed led to a diminished repertoire of TCRs, thereby supporting this model [52,53]. In contrast, mice with T cells entirely lacking GR by targeted gene deletion do not change their TCR repertoire at all [54], although they are resistant to GC-induced apoptosis induced either directly by GC administration or by triggering the HPA axis by systemic inflammation [54,55]. Thus, if and how GC-induced apoptosis plays a role in the selection process in thymus remains to be further explored.

In contrast to the findings in thymocytes, *in vivo* evidence from GR knockout/knockin mice is present for antagonism of TCR mediated cell death in the peripheral T cells by the GR. Using T cell specific deletion of the GR (GR^{LckCre}) and GR^{dim} mice, it could be demonstrated that activation induced cell death (AICD), which reduces the T cell response after infection, is modulated by GCs. This is achieved via suppressing CD95 death protein expression through binding of the dimerized GR to a nGRE binding site [56].

The molecular mechanism of the mutual interference of TCR signaling and GR activity is being to be revealed. Recently, it was shown for peripheral T cells that short-term treatment with GCs cause the disruption of the TCR multi-protein complex and impaired TCR signaling via a non-genomic action of GR [57,58]. In murine and human T cells, GR is part of the multi-protein TCR complex containing the theta TCR chain, ZAP-70 kinase, heat shock protein 90 (HSP90), LCK and FYN kinases [57,58]. GC treatment induced dissociation of this protein complex which results in abrogated LCK/FYN activities and reduced TCR signaling. Interestingly, based on knock down experiments Löwenberg et al. claim a requirement of the unliganded GR for normal TCR signaling [59]. This provocative assumption is challenged by an efficient TCR signal-

ing in T-lymphocytes in the absence of the GR [56,60]. However, a compensatory mechanism in GR knockout mice replacing the GR in the TCR complex cannot be excluded. Thus, a temporal conditional deletion of the GR *in vivo* could finally answer this discrepancy.

Interestingly, mature SP thymocytes and peripheral T cells are less sensitive towards GC-induced apoptosis and display a delayed kinetic of cell death. Reichardt and co-workers propose that in contrast to immature DP thymocytes increased CD28 signaling in SP thymocytes and peripheral T cells counteracts the rapid apoptotic response to GCs [61].

Differentiated peripheral CD4+ T helper cells are central regulators of the adaptive immune response and participate also in innate immune responses. Upon stimulation with antigen during infection or inflammation, naïve Th cells differentiate into different lineages of Th cells: Th1, Th2, Th17 or Tregs, each of them with distinct functions. Th1 cells that express the lineage specific transcription factor T-bet and activated STAT4 mainly release the pro-inflammatory cytokines IFNγ, IL-2 and TNFα [62]. Their activity facilitates the activation of effector T cells, NK cells and macrophages. Th2 cells express selectively the transcription factors GATA3 and are characterized by the expression of IL-5, IL-4, IL-10 and IL-13 [63]. Th2 cells stimulate mainly B cells to produce antibodies and activate eosinophils and mast cells in allergic responses. IL-17 producing Th17 cells depend on STAT3 mediated induction of the nuclear orphan receptors RORγt and RORα [64–66]. Th17 cells play an important role in autoimmune diseases and in host defense against infection. Regulatory T cells depend in their fate on the transcription factor Foxp3 and counteract Th1 and Th2 cell responses and suppress a variety of pathogenic autoimmune syndromes [67].

GCs inhibit the transcription of many T cell derived cytokines (Fig. 2) and can cause a shift from Th1 to Th2 immunity at physiological doses [68] (Fig. 3). At pharmacological doses GCs are able to reduce the synthesis and release of Th1 cytokines like IL-2 and IFNγ and reduce STAT4 activity [69] and Th2 cytokines like IL-4 and IL-5 [70] (Fig. 3). Furthermore pharmacological doses suppress the activity of Th1 lineage specifying transcription factor T-bet by direct protein–protein interactions. The interaction results in diminished binding of T-bet to DNA. [71]. Also the activity of the Th2 defining transcription factor GATA-3 is suppressed by the GR. This occurs via two mechanisms: first by competition of GATA-3 and the GR for importin and second by preventing phosphorylation of GATA-3 by GC-induced DUSP1/MKP-1 expression. [72]. Furthermore STAT6 activity, involved in Th2 lineage specification is affected by the GR presumably by protein–protein interaction [73].

How GCs act on IL-17 producing T cells has not been extensively studied so far. In RA patients it was found that GC therapy attenuated IL-17 levels [74] and also in asthma patients treated orally with steroids a decrease in IL-17 production could be observed. Animal and *in vitro* studies concerning the role of GCs in Th17 cells are however controversial (Fig. 3). In rat lymphocytes methylprednisolone inhibited antigen-induced IL-17 expression probably due to reduced RORγt expression or diminished IL-6 release by non-T cells [75]. In contrast McKinley and colleagues show that Th17 cell cytokine production is not sensitive to dexamethasone treatment and in a Th17 mediated airway inflammation mouse model glucocorticoids did not attenuate cytokine responses [76].

Whether the modulation of Th17 by GCs is required for the suppression of allergic or autoimmune diseases is not entirely understood and requires specific conditional mouse models, especially to prove eventual functional correlations between the anti-inflammatory features of GCs and Th17 cells.

In contrast to pro-inflammatory acting T cells it was reported that CD4+CD25+ Treg cell populations are enhanced upon dexamethasone treatment *in vitro* and in mice by being more resistant to GC-induced apoptosis [77,78] (Fig. 3). Tregs primed by GCs *in vitro* were indeed capable to reduce EAE (Experimental autoimmune encephalomyelitis) in mice [79]. However, we found that endogenous Tregs in an EAE model are suppressed to a similar extent like other Th subsets in GC therapy of EAE [80].

Overall, to address the specific requirement of GCs in Th subsets in steroid therapy, targeted deletion of the GR in those cell populations is required. Those mice will be generated soon, since respective cre transgenic mouse lines are now available.

4. Critical cells types and mechanisms of the GR for anti-inflammatory GC action

The generation of conditional GR mutant mice in the recent years enabled the finding of critical cell types required for anti-inflammatory GC action. In addition knockin mice such as the GR^{dim} mice allow determining the contribution of dimerization dependent GR action towards steroid therapy in inflammatory diseases.

4.1. Inflammatory skin diseases

A widely used model for irritant and unspecific skin inflammation is phorbol-ester (PMA)-induced edema formation. The skin irritation is characterized by swelling associated with massive and rapid influx of neutrophils and mononuclear cells. GC treatment leads to inhibition of the inflammatory response. In this model for the anti-inflammatory effect the dimerization of the GR is not required. GR^{dim} mice, a total knockin mouse that lack the dimerization function of the GR, show an efficient reduction of the PMA-induced skin irritation [15].

Contact hypersensitivity (CHS), a rodent model for contact dermatitis, is in contrast to the PMA-induced skin irritation, a T cell dependent immune response. In CHS however, binding of the GR to the DNA and an efficient suppression of IL-1β and chemokines, but not of TNFα is required for the anti-inflammatory effect [16]. Using tissue specific GR knockout mice, it turned out that the primary targets of GC therapy in CHS are myeloid cells. $GR^{LysMCre}$ mice, lacking the GR in macrophages and neutrophils, were refractory to GC therapy. In T cells and in keratinocytes GC action is dispensable since GR^{LckCre} mice, lacking the GR in T cells and GR^{K14Cre} mice, lacking the GR in keratinocytes, show perfect anti-inflammatory response to GC treatment [16].

4.2. Experimental autoimmune encephalomyelitis (EAE)

Multiple sclerosis (MS), an autoimmune disease of the central nervous system, is mainly treated with a high-dose GC therapy. A commonly used rodent model of MS is the EAE model. The animals are immunized with myelin oligodendrocyte glycoprotein (MOG), which leads to a chronic fulminant inflammation, demyelinating lesions and subsequent axonal damage. Using different GR deficient mutant mice, we could show that GCs mainly act on peripheral T cells and not on CNS residing T cells or macrophages via induction of apoptosis and suppression of adhesion molecules [80]. The therapeutic effect of GC treatment is accompanied by induction of apoptosis and down-regulation of adhesion molecules in peripheral Th17 and bystander T cells. Furthermore, dexamethasone did block the migration of T cells to the CNS. In contrast to contact allergy, T cells are critical for GC therapy in this autoimmune disease.

4.3. Septic shock

A systemic strong inflammatory response that requires the action of endogenous GCs is septic shock. Sepsis is a complex deregulation of inflammation arising when the host is unable to defeat an infection successfully. Subsequently a fulminant inflammatory response leads to organ damage and finally to death. Septic shock

in rodents can be induced by bolus injection of toll-like receptor 4 (TLR4) agonists, e.g. lipopolysaccharides (LPS). Endogenous GCs are required for survival of septic shock, since adrenalectomized rodents have impaired survival [81]. Patients with severe sepsis often have the additional complication of adrenal insufficiency. Conditional GR knockout mice lacking the GR in myeloid cells exhibit a similar lethality, suggesting that in myeloid cells GR is required to limit endotoxic shock [22]. Here, a defect in GR-mediated inhibition of p38 MAPK by an absence of DUSP-1 expression was shown to be the underlying mechanism. This view is challenged by the fact that GR dimerization deficient macrophages that were activated by LPS and concomitantly treated with dexamethasone exhibit a similar induction of DUSP-1/MKP-1 [21], although GR^{dim} animals display a strong impairment of GC action in septic shock (Kleyman and Tuckermann, unpublished).

Thus, multiple mechanisms lead to a general suppression of cytokine expression and activation of macrophages in septic shock. Open questions are which monocyte subsets might be specifically involved in the protection of septic shock by GCs—and whether an anti-inflammatory phenotype as described for *in vitro* treated monocytes/macrophages [36,37] occur in that process.

4.4. Perspective

So far only a few examples of inflammatory diseases have been analyzed with conditional GR knockout mice, in particular skin inflammation, septic shock and experimental autoimmune encephalomyelitis (EAE). Important common allergic and chronic inflammatory diseases, where GCs are the mainstay of therapy, have not been exploited in mutant animals, yet. For instance, rheumatoid arthritis has been treated with GCs for 60 years, despite the development of new drugs. In this disease numerous cell types, immune cells and also non-hematopoietic mesenchymal cells are important. The specific cell types that respond to GCs to ensure successful therapy remain to be identified. Deletion of the GR in T cells, B cells, dendritic cells and in fibroblasts or osteoblasts in mice will achieve this goal. The identification of such cell types will give the rationale for defining specific steroids that are active only in particular tissues – so-called soft steroids – whose development is just at the beginning [82]. Finally novel GR knockin mice addressing the function of this receptor in the cytoplasm, or specific interference with other signaling pathways will help to clarify molecular mechanisms of steroid therapy *in vivo*.

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