Steroids 111 (2016) 84–88

Contents lists available at ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

Review

New dimension of glucocorticoids in cancer treatment

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ARTICLE INFO

Article history:
Received 28 December 2015
Received in revised form 22 February 2016
Accepted 23 February 2016
Available online 27 February 2016

Keywords:
Glucocorticoids
Glucocorticoid receptor
Inflammation
microRNA
Tumor
Metastasis

ABSTRACT

Glucocorticoids have been used in clinical oncology for over half a century. The clinical applications of glucocorticoids in oncology are mainly dependent on their pro-apoptotic action to treat lymphoproliferative disorders, and also on alleviating side effects induced by chemotherapy or radiotherapy in non-hematologic cancer types. Researches in the past few years have begun to unveil the profound complexity of glucocorticoids signaling and have contributed remarkably on therapeutic strategies. However, it remains striking and puzzling how glucocorticoids use different mechanisms in different cancer types and different targets to promote or inhibit tumor progression. In this review, we provide an update on glucocorticoids and its receptor, GR-mediated signaling and highlight some of the latest findings on the actions of glucocorticoids signaling during tumor progression and metastasis.

Contents

1. Glucocorticoids and glucocorticoid receptor

Natural glucocorticoids (GCs), named after their role in maintaining glucose homeostasis, are cholesterol-derived hormones secreted by the adrenal glands [1]. The release of GCs into circulation has systemic roles in immune responses, metabolism, cell growth, development, and reproduction. Most, if not all, of these actions are mediated through the glucocorticoid receptor (GR), a member of the nuclear receptor superfamily of transcription factors [2]. There are two isoforms of GR, GR_{α} and GR_{β}, which are generated by alternative splicing of a single gene. GR_{α} is ubiquitously expressed in nearly all cell types, and is responsible for the induction of most GCs-target genes. In contrast, GR_{β} does not bind any GCs evaluated so far, and its function remains unclear.

The GR contains an N-terminal transactivation domain (NTD), a central DNA-binding domain (DBD), a C-terminal ligand-binding domain (LBD), and a flexible hinge region in between the DBD and the LBD [3]. The binding of GCs to GR induces a conformational change in the GR, which releases the receptor from the heat shock proteins (HSPs) complex [4], exposing nuclear localization sequences on the GR, and leading to the nuclear translocation

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http://dx.doi.org/10.1016/j.steroids.2016.02.019
0039-128X/

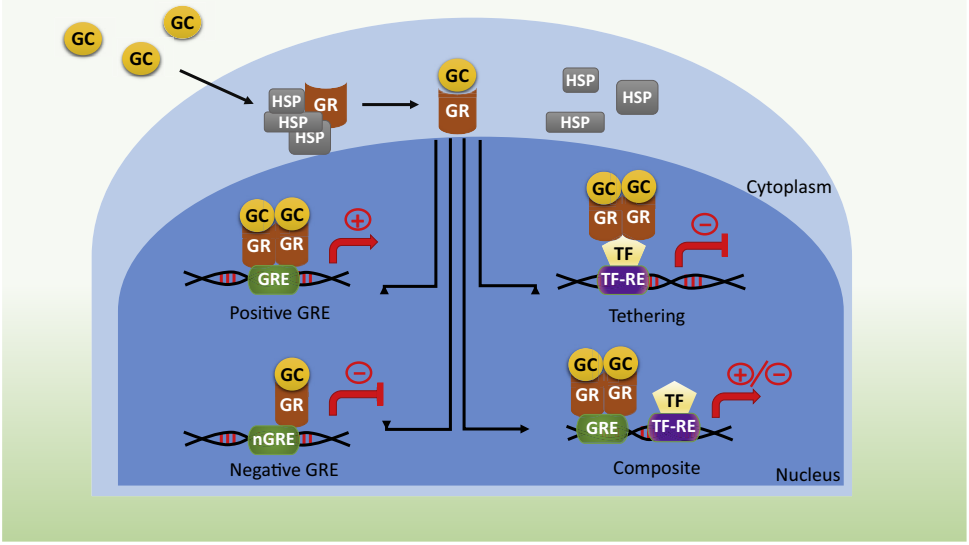

Fig. 1. Schematic representation of the molecular interactions triggered by glucocorticoids (GCs). Once binding to GCs, the cytoplasmic GR undergoes dissociation from accessory proteins, such as heat shock proteins (HSPs), and translocate into nucleus. In the nucleus, GR activates or represses transcription of genes by directly binding to glucocorticoid-response elements (GREs) or negative GREs, or by tethering to other transcription factors (TFs), or as a result of a composite regulation where GR binds to the GREs and interacts with other TFs.

[5]. In the nucleus, GR can activate or repress gene transcription by directly binding to specific glucocorticoid-response elements (GREs) or negative GRE. Alternatively, GR is able to negatively regulate gene expression by interacting functionally with other transcription factors (TFs) through a mechanism known as tethering, without binding directly to DNA. This tethering activity of GR is often considered as the major basis of the immunosuppressive effects of GCs. For some other TFs, GR needs to bind both to a GRE and to the TFs at an adjacent promoter region as a result called composition to affect gene transcription (Fig. 1) [2].

In addition to the classic slow mode of GCs actions mainly via their transcriptional regulation of genes, increasing evidences suggest that GCs can also act rapidly through non-genomic signaling mechanism, which does not require nuclear translocation of GR and GR-mediated transcription. These effects are thought to occur by the membrane-bound of GR or the cytoplasmic GR [6,7]. GR has been shown to interact with and alter the activity of several kinases, including JNK [8], Src [9], ERK1/2 [10,11], phosphatidylinositol 3-kinae (PI3K) [12], and protein kinase C (PKC) [13]. On the other hand, these effects can also be caused by the physiochemical interaction of GCs with the cell membrane, leading to the impaired cation transport through the plasma membrane and increased proton leak of the mitochondria [7], and thus resulting in immunosuppressive effects [14,15]. Although currently the mechanisms of non-genomic GCs signaling are not well understood, these rapid responses may play important roles in the actions of GCs and may provide novel therapeutic targets for GC-related diseases in the future.

2. Inflammation and glucocorticoids

GCs was first recognized in the 1940 s as potent anti-inflammatory agents when Philip Hench successfully treated rheumatoid arthritis with GCs [16], for which he received a Nobel Prize in 1950. Since then, both natural and synthetic GCs have become the most prescribed immune suppression medications worldwide [17]. GCs exert their anti-inflammatory role by acting on nearly all cell types of immune system [18]. Acutely, GCs inhibit vascular permeability that occurs following inflammation and decrease leukocyte recruitment. They evoke immune cells by inducing apoptosis, changing differentiation fate, inhibition of cytokine release, inhibition of migration and other features [19]. The anti-inflammatory and immunosuppressive actions of GCs mainly result from the transrepression regulation of GR through tethering to various DNA-bound TFs, including activating protein-1 (AP-1), nuclear factor (NF)-κB, cAMP response element-binding protein (CREB), interferon regulatory factor 3 (IRF3), nuclear factor of activated T cells (NFAT), signal transducer and activator of transcription (STAT), T-box expressed in T cells (T-Bet), and GATA-3 [20,21]. Genes that are repressed by this tethering mechanism include a vast number of pro-inflammatory molecules, such as interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-12, IL-18, cyclooxygenase (COX)-2, E-selectin, inducible NO synthase (iNOS), interferon (IFN)-γ, tumor necrosis factor (TNF)-α, intercellular adhesion molecule (ICAM), monocyte chemoattractant protein (MCP)-1, and vascular cell adhesion molecule (VCAM) [21]. Additionally, the induction of GRE dependent genes such as DUSP1 also contributes to anti-inflammatory activities of GR [22]. The induction of DUSP-1 by GR reduces pro-inflammatory gene expression by dephosphorylating JNK and p38 MAPK in some cells and in animal models [23,24].

3. Glucocorticoids in current cancer therapy

For nearly 70 years, physicians have relied on GCs to treat hematopoietic malignancies of the lymphoid lineage. Synthetic GCs, such as dexamethasone (DEX), are routinely included in all chemotherapy protocols to induce cell apoptosis in malignant lymphoid cancers, such as acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), multiple myeloma (MM), Hodgkin's lymphoma (HL), and non-Hodgkin's lymphoma (NHL) [25]. The GCs-induced apoptosis appears to be a complicated process involving multiple signaling pathways. They include transactivation of apoptosis inducing genes, such as Bim [26], and the negative modulation of survival cytokines via transrepression mechanism through inhibition of AP-1 and NF-κB mediated transcriptions [27] (Fig. 2).

In non-hematologic malignancy, GCs monotherapy or combined therapy with other cytotoxic drugs, such as 5-fluorouracil (5-FU), had shown modest benefit in breast and prostate cancers, but

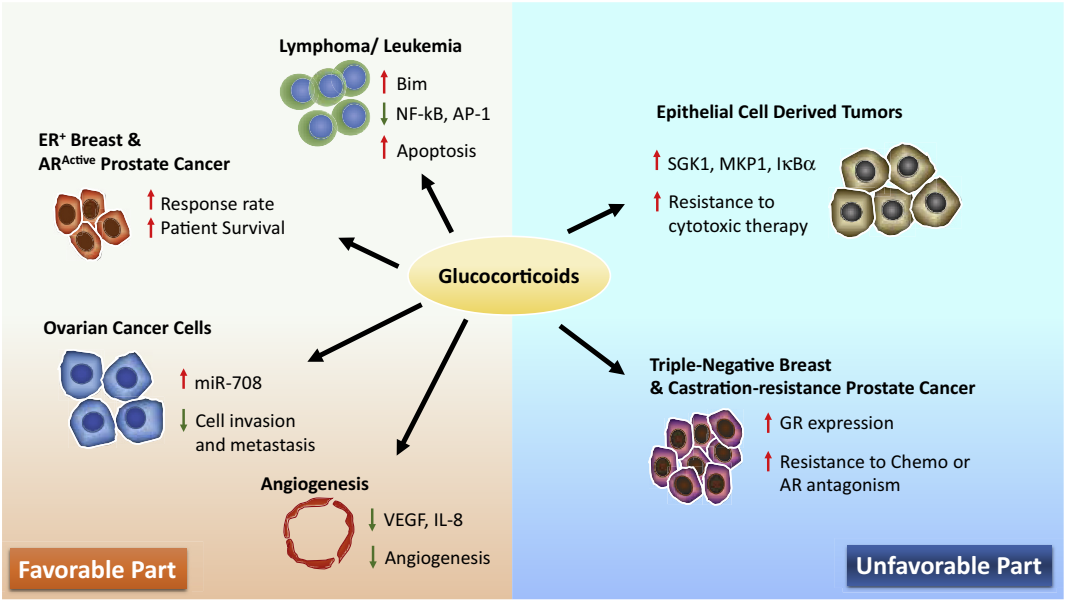

Fig. 2. Current understanding of GCs signaling in tumor progression and metastasis. The response of cancer cells to GCs signaling is controversial. Here is the summary of current findings on the role of GCs in tumor progression and metastasis (left: favorable part of GCs signaling; right: unfavorable part of GCs signaling in tumor inhibition or promotion respectively).

not in other cancer types [28,29]. However, the addition of GCs to other therapy does not change the long-term survival in advanced breast cancer. Little is known about the molecular mechanism underlying the actions of GCs in breast and prostate cancer progression.

In addition to use GCs as therapeutic reagents, GCs are widely accepted as an adjuvant during chemotherapy or radiotherapy for reducing side effects in many cancer types [25,30]. Treatment of GCs increases appetite, decreases weight loss, reduces fatigue, diminishes ureteric obstruction, and prevents vomiting. GCs are also effective in alleviating pain associated with bone metastasis by inhibiting the synthesis and release of prostaglandins [31]. In advanced cancer, GCs are sometimes used in the treatment to reduce side effects for general palliative care [25].

4. The role of glucocorticoid signaling in tumor progression and metastasis in non-hematologic cancer

Whether the action of GCs promotes or inhibits tumor progression is controversial in non-hematologic cancer types. Prior studies have demonstrated that GCs can suppress tumor progression and metastasis [29,32–39], whereas other investigations reported that GCs inhibit chemotherapy-induced cell apoptosis [40–51]. This controversial phenomenon may result from different cancer subtypes, differential GR levels, and the dosage of GCs given. This section will discuss some recent research findings on GCs to provide new insights on the role of GCs signaling in tumor progression and metastasis (summarized in Fig. 2).

4.1. Favorable part of glucocorticoids signaling in cancer treatment

GCs treatments have shown modest benefits on patient survival in endocrine-responsive cancers, including breast and prostate cancer, despite an incomplete understanding of the underlying mechanism [29]. Preclinical data revealed that GR activation may reduce estrogen-induced cell proliferation in ER-positive breast cancer [32], and also attenuate androgen-activated AR gene expression in AR-active prostate cancer [33], suggesting GR may share cooperative nature with the other nuclear hormone receptors-ER and AR to suppress these endocrine-responsive tumor growth.

Cancer metastasis is responsible for most cancer-associated mortality, yet the role of GCs in cancer metastasis had not been well studied. *In vitro* cell model has shown that GCs suppress cell migration/invasion through a number of different mechanisms, such as down-regulation of RhoA [34], MMP2/9 and IL-6 [35], or by induction of E-Cadherin [36]. In term of angiogenesis, studies have shown treatment of GCs suppresses growth of new blood vessels [37] by down-regulation of pro-angiogenic factors, including IL-8 and VEGF [38]. Moreover, recent study provides a novel regulatory mechanism of GCs in suppressing cancer metastasis through one of the metastasis suppressor microRNA (miRNA), miR-708 [39]. Treatment of synthetic GCs induces miR-708 transcription, leading to the inhibition of Rap1B, resulting in the decreased cancer cell migration, adhesion and abdominal metastasis in an orthotopic xenograft mouse model. To date, little is known about the regulation of microRNAs by GCs signaling, which could be important to understand and treat diseases. The identification of miR-708 as a GCs downstream target may help us to further elucidate GCs-mediated gene regulation in tumor progression and metastasis, and may provide additional therapeutic targets to tailor disease treatment accordingly.

4.2. Unfavorable part of glucocorticoids signaling in cancer treatment

Some *in vitro* studies have observed treatment of GCs induces resistance when used together with various cytotoxic anticancer drugs and with radiotherapy in cultured cells or in xenograft mouse model. This phenomenon has been found in many epithelial cancer types, including prostate, kidney, testis, bladder [40], brain [41,42], ovary, breast [43], cervix [44,45], colon, liver [46], lung [47,48], and pancreas cancer [49], raising the concerns of using it in combined treatment regimen. The GCs-mediated resistance to cancer cell death by chemotherapy or radiotherapy was mainly through up-regulation of serine/threonine survival kinase 1 (SGK1), mitogen-activated protein kinase phosphatase (MKP1/DUSP1), and IκBα (negative regulator of NF-κB) [50,51]. However, despite the emerging *in vitro* evidences of cancer cell apoptosis

inhibition by GCs in different cancer models, currently no clinical studies available to support those observations. A retrospective study in ovarian cancer comparing patients who received chemotherapy concurrently with GCs and those without and found no adverse difference on patients outcome [52]. More investigations from retrospective clinical studies and animal model experiments are required before the conclusion can be made.

On the other hand, recent studies have pointed to an interesting observation on the effects of GR activity, which is dependent on concomitant ER and AR activity. In early stage ER negative breast cancer, high tumor GR expression correlates with poor prognosis [53]. GR activation suppresses chemotherapy-induced apoptosis in triple negative breast cancer xenograft tumors [54], and treatment with GR antagonist can reverse these effects [55]. Similar to the case in breast cancer, the effects of GR activity in prostate cancer are also dependent on AR activation status. Clinical evidence and animal model both indicate high expression of GR and GR-downstream genes, including SGK1, in AR antagonist enzalutamide resistant prostate tumors [56]. In fact, GR shares structural similarity with AR, and they recognize nearly identical consensus DNA binding motif, and thus regulate a subset of overlapping genes [33,57], suggesting the possibility that GR signaling can replace AR function in the presence of AR antagonist. In castration resistant prostate cancer model, treatment of GR antagonist restored its sensitivity to AR antagonism [56,58]. Although much remains to be understood about using GR as therapeutic agents in breast and prostate cancer, recent studies suggest whether GR activity promotes or inhibits tumor progression is dependent on the expression and activity of ER or AR.

5. Glucocorticoids-regulated microRNAs in cell biology and diseases

GR is known as ligand-activated transcription factor that regulates many gene transcriptions, however, currently it remains unclear about the regulation of GR by miRNA(s) or conversely, regulation of miRNAs by GR-mediated signaling. Understanding these regulations might be critical when treating diseases with GCs. Several microRNAs were found to be up-regulated upon GCs treatment, including miR-223, miR-15b, miR-16 [59], miR-23a [60], and miR-708 [39], while some were down-regulated in the appearance of GCs, such as miR-17∼92 [61], miR-145 [62], and miR-132 [63]. The expression of GR was also found to be regulated by miRNA wherein miR-18 and 124a suppress GR expression in brain [64]. Those miRNAs regulated by GCs target different genes including Rap1B in ovarian cancer [39], Bim in lymphoma [61], and brain-derived neurotrophic factor (BDNF) in brain [63]. Since both GR and miRNAs can regulate gene expressions, their interaction within different cell types can be very complicated. Changes in these interactions can have profound impact on the cells and ultimately affect the outcome of the disease. More investigations should be performed to further elucidate those signaling networks.

6. Conclusions

GCs are the first line of defense to treat inflammation and chronic inflammatory diseases, and are commonly used in cancer patients for a variety of different purposes. However, how GCs function in the tumor progression is a question remain unanswered. This review is aimed to highlight the most recent findings in the molecular mechanism of GCs and its receptor, GR, in inflammation and in cancer research. We have discussed the complexity and controversial observations when treating GCs in non-hematologic cancer types. GCs treatment might favor the growth of malignant solid tumors in certain cancer types, meanwhile, it might play a suppressive role in tumor progression and metastasis in other cancers. Simple cellular experimental models may not suffice to accurately predict the therapeutic outcome. Different cancer types, differential GR levels, the dosage of GCs given, and even the activity of other hormone nuclear receptors, such as AR or ER, have to be taken into account to understand comprehensively of GCs-mediated actions. The dosage of GCs given varies widely for different proposes: for treating lymphocytic malignancy, virtually all patients given synthetic GCs 50–100 mg daily [28]; for relieving chemotherapy-induced nausea and vomiting, the dose of synthetic GCs varies from 8 to 20 mg [28]; for induction of genes or microRNAs in mouse xenograft model, the human equivalent dose of synthetic GCs used can be as low as 0.1–0.3 mg [39]. Future studies are needed to elucidate the optimal timing, duration, dosage, as well as the choice of appropriate GCs among different cancer subtypes to develop customized strategy to meet each individual need.

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