REVIEW

Duality of glucocorticoid action in cancer: tumor-suppressor or oncogene?

Isabel Mayayo-Peralta¹, Wilbert Zwart^{1,2*} and Stefan Prekovic^{1*}

¹Division of Oncogenomics, Oncode Institute, the Netherlands Cancer Institute, Amsterdam, the Netherlands

²Laboratory of Chemical Biology and Institute for Complex Molecular Systems, Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, the Netherlands

Correspondence should be addressed to W Zwart or S Prekovic: w.zwart@nki.nl or s.prekovic@nki.nl

*(W Zwart and S Prekovic contributed equally as senior authors)

Abstract

Glucocorticoid receptor (GR) is a key homeostatic regulator involved in governing immune response, neuro-integration, metabolism and lung function. In conjunction with its pivotal role in human biology, GR action is critically linked to the pathology of various disease types, including cancer. While pharmacological activation of GR has been used for the treatment of various liquid cancers, its role in solid cancers is less clearly defined and seems to be cancer-type dependent. This review focuses on the molecular aspects of GR biology, spanning the structural and functional basis of response to glucocorticoids, as well as how this transcription factor operates in cancer, including the implications in disease development, progression and drug resistance.

Key Words

- ▶ glucocorticoid receptor
- ▶ glucocorticoids
- ▶ nuclear receptor
- ▶ cancer
- ▶ transcriptional regulation

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Introduction

The fitness of a given organism is linked to its ability to adapt to various internal and external factors. Through the course of animal evolution, a group of transcription factors with a high affinity for sensing and reacting to various molecules of lipid nature has emerged (Markov & Laudet 2011). While the mode-of-activation of the common ancestor of these proteins, grouped within the nuclear receptor family, is still under debate, strong evidence exists that this protein was a molecular sensor capable of weakly binding to diverse hydrophobic molecules (e.g. steroids and fatty acids). It is proposed that duplications of a single ancestral receptor and divergent molecular evolution led to either loss of ligand binding (group of orphan receptors, reviewed elsewhere Baek & Kim 2014, Mazaira *et al.* 2018) or specialization toward a certain ligand (Markov & Laudet 2011). The evolutionary emergence of the steroid hormone receptor superfamily with the unique ability of sensing cholesterol-based

metabolites came early in the animal lineage (Thornton 2001). These proteins are tightly, intrinsically bound to animal physiology and are causally linked to embryonic development, sex dimorphism, metabolism, salt balance regulation, neuro-integration, and immune system function (Guyton & Hall 2006).

Among the members of this group is the glucocorticoid receptor (GR), specialized toward high-affinity sensing of glucocorticoids (GCs), hormones produced in the adrenal cortex. First evidence illustrating the importance of GCs in physiology came from adrenalectomized animal models. Although capable of surviving, these animals exhibit various metabolic alterations, homeostatic problems and are more likely to die due to mild diseases (e.g. airway infection) (Guyton & Hall 2006). Studies with global and organ-specific GR-knockout models expanded and solidified our understanding of the biology of this important ligand-controlled transcription factor and have been

reviewed by others (Whirledge & DeFranco 2018). Since GR is expressed almost ubiquitously, regulating various aspects of physiology, it is not surprising that alterations of its axis have been found to be causal or associated with numerous disorders, including the ones of the immune system, metabolism, and brain. In addition to that, GR activity or lack thereof has been linked to various aspects of cancer biology; however, its role in cancer seems to be complex and highly context-dependent, as GR has been proposed to be both a tumor suppressor as well as an oncogenic driver.

In this review, we aim to cover the molecular aspects of GR, spanning the structural and functional basis of response to GCs. We discuss how this transcription factor operates in cancer, including implications for disease development, progression and therapy resistance.

The glucocorticoid receptor

In the third quarter of the 20th century, GR was identified as a primary receptor responsible for sensing and reacting to GCs (Munck & Brinck-Johnsen 1968). However, structural insights into the *NR3C1* gene (chromosome 5 (*5q31.3*)) that encodes for GR were only obtained 17 years later when it became the first steroid hormone receptor to be successfully cloned (Hollenberg *et al.* 1985). The *NR3C1* gene contains nine exons that encode for a modular

protein with discrete specialized domains – amino-terminal domain (NTD), DNA-binding domain (DBD), hinge- and ligand-binding domain (LBD) (Giguère *et al.* 1986, Hollenberg & Evans 1988, Hard *et al.* 1990, Bledsoe *et al.* 2002) (Fig. 1). The activity of GR is a direct output of allosteric changes induced by the ligand, different intradomain interactions, partner protein contacts, and the specific sequence of its response elements in the DNA (Gronemeyer & Bourguet 2009, Meijssing *et al.* 2009, Watson *et al.* 2013).

The unstructured amino-terminal domain (NTD) of GR contains a constitutively active activation function 1 (AF1), which acts as an interaction hub for co-regulators, chromatin modifiers, and the basal transcription machinery (Vandevyver *et al.* 2014). In addition, this domain is a target of various post-translational modifications that can either repress or enhance receptor action (reviewed by Vandevyver *et al.* 2014). The ability of GR to bind to specific glucocorticoid response elements (GREs) on the DNA is afforded by two highly conserved zinc finger motifs, each containing four cysteine residues that tetrahedrally coordinate zinc ions (Freedman *et al.* 1988, Hard *et al.* 1990, Bledsoe *et al.* 2002, Meijssing *et al.* 2009). The first of the two zinc fingers contain the proximal box (P box), responsible for base-specific contact with the major groove of DNA. The other zinc finger engages in non-specific interactions with DNA via the minor groove and DNA helix backbone (Freedman

Figure 1

Molecular biology of the glucocorticoid receptor. The glucocorticoid receptor protein is translated in the cytoplasm and its folding is facilitated by the heat shock protein complex. In the process of maturation, an exchange of heat shock proteins and binding of FKBP5 occur. The inactive GR complex is now ready to bind the ligand which leads to structural changes, exposure of the nuclear localization sequence, and nuclear translocation. Once in the nucleus, the GR can bind a large number of genomic locations to ultimately regulate a large number of genes across the genome through numerous proposed mechanisms of action. In addition to the action of GR in the nucleus, GCs themselves or dissociation of interacting factors may lead to non-genomic signaling. Furthermore, GR can also regulate cell behavior through affecting mitochondrial transcription or mRNA decay. Data from Protein Data Base (<https://www.rcsb.org/>); IDs 1R4O and 1P93.

et al. 1988, Hard *et al.* 1990). The DNA-binding domain also contains the distal box (D box) with residues imperative for dimerization of the GR (Luisi *et al.* 1991, Watson *et al.* 2013). A flexible linker region, the hinge, is involved in nuclear translocation, transactivation, and structural flexibility of the GR dimer, enabling optimal contact with the GREs. The hinge contains various lysine residues that can be acetylated, leading to changes in GR activity output (Nader *et al.* 2009). For example, GR interaction with GREs is directly diminished by circadian transcription factor-mediated acetylation of the hinge region (Nader *et al.* 2009). After the hinge region, a highly hydrophobic part of the GR forms a ligand-binding pocket lined with both polar and nonpolar residues, containing space for interaction with endogenous or exogenous ligands. Upon ligand binding, various intradomain changes occur, and the activation function 2 (AF2) forms as the scaffold for protein interactions positioned over the ligand-binding pocket (Bledsoe *et al.* 2002).

Versatility of glucocorticoid receptor action

During protein translation and upon release from the ribosome, the GR protein folding will be initiated and facilitated by Hsp70-Hsp40 chaperone complex (Rexin *et al.* 1991, Scherrer *et al.* 1993, Smith & Toft 1993, Morishima *et al.* 2000, Vandevyver *et al.* 2012) (Fig. 1). Subsequently, the Hop protein will enable the exchange of folding chaperones for Hsp90, and finally, recruitment of immunophilins will follow to complete the protein maturation process, increasing the affinity for the ligand (Chen & Smith 1998, Morishima *et al.* 2000). Several kinases, including glycogen synthase kinase 3 (GSK3) and cyclin-dependent kinases, phosphorylate the GR upon ligand binding to alter GR confirmation and its interacting partner repertoire (Riggs *et al.* 2003), ultimately leading to the surface exposure of nuclear localization signal (Vandevyver *et al.* 2012). The GR-Hsp90-FKBP52-p23 complex tethers to dynein, an ATP-dependent motor protein that will move the complex along the microtubule cytoskeleton toward the nucleus. For nuclear translocation to occur, the nuclear localization signal will be recognized by importins which will facilitate GR-complex translocation to the nucleus (Picard & Yamamoto 1987), through a well-described process reviewed elsewhere (Stewart 2007, Kim *et al.* 2017).

Upon ligand-induced translocation to the nucleus, the GR will stochastically and transiently interact with

chromatin until it forms a weak-yet-stable GR-DNA interaction at its binding sites (Groeneweg *et al.* 2014). The sites that can be occupied by GR differ across cell types and are determined by various pioneer factors involved in regulating the accessibility of DNA, such as FOXA1 and GATA3 (So *et al.* 2007). In terms of genomic distribution, the majority of GR binding sites are found at distal enhancers, therefore, chromatin looping is necessary to bring these regulatory elements in close proximity to promoter regions of their target genes (D'Ippolito *et al.* 2018, McDowell *et al.* 2018) (Fig. 1). Once GR occupies its binding sites, it recruits diverse co-regulators, such as NCOA and NCOR proteins, that will enable either transcriptional activation or repression of gene expression across the genome (Xu *et al.* 1999).

The underlying mechanism by which GR associates with its binding sites can differ and can roughly be segregated into two groups: direct DNA binding or tethering to other DNA-resident transcription factors. The predominant mode of GR action, however, is through direct DNA binding of GR homodimer to its response elements (GRE; *consensus sequence* AGAACAnnnTGTTCT); 15 base-pair long motifs containing two inverted palindromic sequences separated by a 3 base-pair spacer (Luisi *et al.* 1991, Meijssing *et al.* 2009). Two GR monomers bind the opposing palindromic sequences in a head-to-tail fashion interacting through their dimerization surfaces found in proximity to the zinc fingers, forming hydrogen bonds that stabilize GR on DNA (Luisi *et al.* 1991).

In addition to DNA binding of GR as a homodimer, evidence exists that it can also directly bind DNA as a monomer (Schiller *et al.* 2014). This mode-of-action entails GR binding to composite GREs, that is half sites (AGAAC/TGTTCT) in close genomic proximity to binding sites of other transcription factors, with which GR can interact and modulate their influence on target gene expression (Diamond *et al.* 1990, Schiller *et al.* 2014). GR monomers can also bind to negative GREs (nGREs), consisting of inverted repeats and a spacer sequence that varies from 0 to 2 nucleotides (CTCC(N)₀₋₂GGAGA). At these inverted repeats, two GR monomers occupy opposite sides of the DNA, recruiting co-repressors (SMRT/NCOR) and HDACs, and subsequently functioning as transcriptional repressors of nearby genes (Hudson *et al.* 2013). A study has found that under normal cortisol levels in mice, GR is preferentially bound to DNA as a monomer rather than as a dimer (Lim *et al.* 2015). However, upon treatment with a high dose of

GCs, the monomers are removed from their half sites and dimer formation and assembly on classical GREs are observed (Lim *et al.* 2015).

Across the genome, GREs overlap with the DNA recognition sequences of other transcription factors. This results in competition for genome binding between GR and other factors, in which GR can impede the recruitment of other proteins to the DNA, leading to reduced expression of certain genes (Strömstedt *et al.* 1991, Subramaniam *et al.* 1998). Furthermore, evidence exists that in addition to direct DNA interaction, GR can alter transcription by tethering to other DNA-resident transcription factors (e.g. AP1, NF- κ B, STAT) through protein–protein interactions (Biddie *et al.* 2011). By interacting with these factors, GR influences their DNA binding, interaction profile, ultimately affecting their target gene expression programs (Biddie *et al.* 2011, Tan & Wahli 2016).

Alternative modes of GR action

Besides the classic mode of transcriptional control, GR has been suggested to have other modes of action (Fig. 1). In various *in vitro* models, fast, almost instant changes in various signaling cascades, including the PKC, Rho kinase, and PI3K/ATK, in response to GCs have been attributed to non-genomic actions (Panettieri *et al.* 2019). While there is limited evidence that cytosolic GR itself contributes to these (as argued in reviews covering the topic Desmet & De Bosscher 2017, Scheschowitsch *et al.* 2017, Timmermans *et al.* 2019), the non-genomic actions are mostly being attributed to a membrane G-coupled receptor, which has an affinity to endogenous ligands (Orchinik *et al.* 1991) or a membrane-bound GR proposed to be generated through diverse mechanisms including alternative splicing (Vernocchi *et al.* 2013). In addition to that, some features of the non-genomic action (e.g. influence on the MAPK signaling) have been suggested to be mediated by the members of the cytoplasmic GR complex that dissociate upon ligand binding (Samarasinghe *et al.* 2011, Mitre-Aguilar *et al.* 2015).

Another facet of GR non-genomic action is its ability to regulate mitochondrial gene transcription. It has been shown that GR can be translocated to the mitochondria (Scheller *et al.* 2000, Moutsatsou *et al.* 2001) and actively bind GRE-like elements alone or in complex with other proteins in a hepatoma cell line and brain cells of rodent models (Du *et al.* 2009a,b, Psarra & Sekeris 2011), in this way contributing to cellular energy metabolism regulation.

Additionally, it has been proposed that GR has the ability to bind the 5' untranslated region (UTR) of mRNA and regulate its stability. The ability of GR to elicit rapid mRNA degradation is afforded by ligand-induced recruitment of UPF1 in PNRC2-dependent fashion (Cho *et al.* 2015). Furthermore, the HRSP12 endoribonuclease has been reported as crucial for functionality of the active GR complex on mRNA (Park *et al.* 2016). Based on genome-wide analysis of transcripts affected by GR-mediated mRNA-decay, it is implied that these may be involved in various cellular processes, including immune response (Park *et al.* 2016).

GR in cancer biology

Activation of GR as a potent therapeutic strategy in hematological cancers

GR action in immune cells

The ability of GCs to suppress the immune system was initially harnessed for the treatment of rheumatoid arthritis (Hench & Kendall 1949). The immune-suppressive action of GCs is underlined by acute inhibition of vascular permeability (Perretti & Ahluwalia 2000), decrease in recruitment of leukocytes (Ince *et al.* 2018), and ultimately direct inhibition of cytokine release (Brattsand & Linden 1996), alterations of differentiation, and block of migration. In terms of the molecular mechanism, trans-repression by monomeric GR was thought to be the main contributor to its immunosuppressive role (Smoak & Cidlowski 2004). The tethering process was proposed to negatively impact the gene expression of various pro-inflammatory molecules including interleukins, TNF- α , interferon- γ , and cell adhesion proteins (Ratman *et al.* 2013, Xavier *et al.* 2016). However, this model has been challenged, illustrating that transactivation may be the main driver of immunosuppression by GR (reviewed in detail by Clark 2007). One example in support of the transactivation model comes from mice lacking a well-characterized direct GR-target gene *DUSP1*, which is regulated by GR homodimer formation on classical GREs. In these models, GCs were unable to inhibit zymosan-induced inflammation (Abraham *et al.* 2006) but still retained the immune-suppressive features in mast cell-dependent anaphylaxis (Maier *et al.* 2007). *TSC22D3* gene, another gene regulated through GR binding to classical GREs, has also been implicated in immune suppression by GR as well as suppression of immunotherapy response by GCs in cancer (Ayroldi & Riccardi 2009, Riccardi 2010, Yang *et al.* 2019). Importantly, a recent in-depth genomic

study using mice with a mutation in GR-DBD that renders the protein unable to recognize DNA but still retain its tethering properties demonstrated that direct GR-DNA binding is essential for both transcriptional activation and repression on a genome-wide level (Escoter-Torres *et al.* 2020).

GR agonists in the treatment of hematologic malignancies

Activation of GR by synthetic GCs (e.g. dexamethasone, prednisone) is effectively being used in the treatment of hematologic malignancies. In various blood cancer types (acute and chronic lymphocytic leukemia, Hodgkin's lymphoma, multiple myeloma, and non-Hodgkin's lymphoma), GCs robustly induce tumor cell death (Kufe *et al.* 2006), through mechanisms further discussed below. However, despite reducing the disease burden, single-agent GCs do not lead to a prolonged delay in remission or complete cancer elimination (Pufall 2015). Consequently, various combination therapies have been developed and refined, drastically improving cure rates in children with leukemia. Today, phase treatment (remission induction, intensification, and maintenance) entails the use of GCs in combination with various other drugs (e.g. vincristine, asparaginase, methotrexate) in specific sequences clinically optimized to effectively eradicate cancer cells (Terwilliger & Abdul-Hay 2017). In adult leukemia patients, however, phase treatment is less effective and cure rates are dismal (Pufall 2015).

Mechanism of GC-induced apoptosis

While details regarding specific components of GR-induced apoptosis in blood cancers are still unknown and appear dependent on cell lineage, activation of the intrinsic apoptotic pathway is required (Smith & Cidlowski 2010). Mechanistically, it has been proposed that GR co-ordinates apoptosis entry threshold by regulating both anti- and pro-apoptotic genes (Ploner *et al.* 2008). Pro-apoptotic family members BIM and BMF are suggested to form a major part of GC response in leukemia cells (Ploner *et al.* 2008). In patient-derived xenograft models of acute lymphoblastic leukemia, GR regulation of *BIM* through a specific GR binding site within its intron has been found essential for GR-induced apoptosis, with the absence of binding correlating with dexamethasone resistance (Jing *et al.* 2015). In addition, downregulation of anti-apoptotic genes, such as *BCL2*, *MCL1* and *BCL2L1*, seems to also be required for entry to apoptosis (Schmidt *et al.* 2006, Jing *et al.* 2015).

Resistance to GC administration

Due to high selection pressure applied by GC therapy, cancers of the lymphoid lineage often become refractory to this type of intervention. Various escape mechanisms have been reported (and extensively reviewed previously Scheijen 2019) including alternative splicing of the *NR3C1* gene (Moalli *et al.* 1993, Rivers *et al.* 1999, Koga *et al.* 2005), inhibition of cell death through altered expression of key apoptotic genes or influence of stromal cells (Bachmann *et al.* 2005, Jiang *et al.* 2011, Ariès *et al.* 2014, Rosenthal & Younes 2017), activation of survival signaling pathways such as PI3K/AKT and NOTCH1 (Real *et al.* 2009, Piovan *et al.* 2013, Revollo *et al.* 2013, Evangelisti *et al.* 2018), direct alteration of GR transcriptional output through reduced SWI/SNF chromatin remodeling complex expression (Pottier *et al.* 2008) or mutations in GR-complex auxiliary factors such as *CREBBP* and *BTG1* (van Galen *et al.* 2010, Mullighan *et al.* 2011, Scheijen *et al.* 2017). Recently, integrative genomic analysis of acute lymphoblastic leukemia samples revealed *CELSR2*, a membrane-bound G-protein-coupled receptor, as a crucial component in GC therapy resistance (Autry *et al.* 2020). Knockdown of *CELSR2* diminished GC response in human leukemia cell lines and revealed that Venetoclax, a potent Bcl-2 inhibitor, synergistically restores sensitivity to GCs in mouse xenograft models (Autry *et al.* 2020).

Dichotomy of GR action in solid cancers

In non-hematological tumors, several studies support the involvement of GR in cancer development, aggressiveness, and therapy response. Studies have linked genetic changes (including copy number loss and single-nucleotide polymorphisms) of the *NR3C1* gene to the development of various solid cancer types, including pituitary adenomas (Huizenga *et al.* 1998), colorectal carcinomas (Wildrick & Boman 1988), gastric cancer (Gu *et al.* 2017), and breast cancer (Curran *et al.* 2001). Furthermore, the influence of GR on tumor biology is supported by carcinogen-induced cancer models in mice, where GCs protected against cancer development (Balansky *et al.* 2010). While in terms of tumorigenesis, most studies point toward a tumor-suppressive role of GR in solid cancers, GR action in solid cancer biology appears cancer-type dependent and influenced by treatment, as will be discussed below.

Breast cancer

GCs have a pivotal role in mammary gland physiology and development (Tronche *et al.* 1998, Wintermantel

et al. 2005). Using mammary gland-specific GR-knockout mouse models, cell proliferation timing during lobuloalveolar development was shown to be dependent on GR (Wintermantel *et al.* 2005). While the GR protein is expressed in almost every cell type of the mammary gland, its expression is decreased during carcinogenesis (Perou *et al.* 2000, Sørli *et al.* 2001, Lien *et al.* 2006, Conde *et al.* 2008, Buxant *et al.* 2010), suggesting a tumor-suppressive role in breast cancer. In line with this, numerous studies using *in vitro* models have linked GR activation by GCs to apoptosis regulation and cell proliferation in estrogen receptor- α (ER α) positive breast cancer. Specifically, it is believed that GCs block the growth of breast cancer through inhibition of growth factor signaling (Osborne *et al.* 1979, Huff *et al.* 1988, Ewing *et al.* 1989, Gutierrez *et al.* 2005, Whyte *et al.* 2009). In addition, GCs also inhibit apoptosis by modulating the expression of apoptotic genes (Schorr & Furth 2000, Mikosz *et al.* 2001, Wu *et al.* 2004) and interfering with p53 function (Moll *et al.* 1992, Sengupta *et al.* 2000). Of particular interest in luminal breast cancer is the interaction of GR and ER α , that are shown to co-occupy the same genomic regions in clinical samples (Severson *et al.* 2018). Cross-talk between these two steroid hormone receptors has been reported to have favorable consequences in terms of prognosis (Abduljabbar *et al.* 2015). This is also supported by *in vitro* studies showing that GCs repress ER α -target genes involved in proliferation (Gong *et al.* 2008, Karmakar *et al.* 2013, West *et al.* 2016, Yang *et al.* 2017). It has been suggested that this negative regulation stems from direct inhibition of ER α enhancer function, accompanied by the loss of co-regulators and recruitment of repressors (Yang *et al.* 2017). The exact features of this negative regulation have previously been reviewed in-depth (Truong & Lange 2018).

While a tumor-suppressive role of GR in ER α -positive breast cancer is well-established, it was found that a specific breast cancer-associated cholesterol metabolite (cholesterol-5,6-epoxides, 6-oxo-cholestan-3 β ,5 α -diol) may shift the role of GR toward oncogenic (Voisin *et al.* 2017). This cholesterol metabolite is able to bind to GR and alter its function, causing GR to regulate a different set of genes than with its physiological ligand (Voisin *et al.* 2017). For example, it was observed that while cortisol-bound GR represses *MMP1* gene expression, 6-oxo-cholestan-3 β ,5 α -diol-bound GR increases its expression, suggesting GR function as an oncogene.

In breast cancer cells lacking expression of ER α , GCs take on another role, supporting cancer growth and metastasis, and aggravating clinical aggressiveness (Pan *et al.* 2011, Abduljabbar *et al.* 2015, Chen *et al.*

2015, West *et al.* 2018). Activation of GR in ER α -negative disease supports an epithelial-to-mesenchymal (EMT) gene program, and GR expression levels have been associated with shorter relapse-free survival (Pan *et al.* 2011). Furthermore, a GR activity gene-signature specific for ER-negative breast cancer has recently been developed and associated with relapse despite administration of adjuvant chemotherapy (West *et al.* 2018). In support of these clinical observations, GR activation protects against apoptosis in *in vitro* and xenograft models (Wu *et al.* 2004, Pang *et al.* 2006) and inhibition of its signaling by mifepristone can augment chemotherapy-induced xenograft tumor shrinkage (Skor *et al.* 2013). It is proposed that this effect of GR is mediated through TEAD4, as pharmacological targeting of this transcription factor prevented GC-induced chemo-resistance in breast cancer models (He *et al.* 2019).

As mentioned above, studies have linked GR activation to EMT processes in ER-negative breast cancer. However, proof of functional consequence in terms of cancer metastatic potential was not reported until recently. Using xenograft models of ER-negative breast cancer, Obradović *et al.* (2019) demonstrated that activation of GR increased colonization and reduced survival of animal models. This was attributed to an increase in the expression of kinase ROR1, the ablation of which diminished metastatic outgrowth and prolonged survival of the mouse models used in the study (Obradović *et al.* 2019). These lines of evidence suggest that antagonism of the GR may be a viable strategy for increasing apoptosis chemotherapy efficacy in ER-negative breast cancers, blocking metastatic spread. However, this hypothesis is yet to be tested in a clinical setting.

Prostate cancer

Prostate cancer is one of the most prevalent adult malignancies and the leading causes of cancer-related death in men (Siegel *et al.* 2019). This disease is driven by another steroid hormone receptor – the androgen receptor (AR) (Heinlein & Chang 2004). The biology of primary prostate cancer vastly differs from the advanced, treatment-resistant disease (Prekovic *et al.* 2018a, Linder *et al.* 2018), and as discussed below, the GR function seems to also be altered during the course of disease progression.

In terms of primary prostate cancer, GR expression is lost in the transformation process of healthy epithelial prostate cells to cancer, suggesting that GR may act as a tumor suppressor in this context (Yemelyanov *et al.* 2007). In support of this, the overexpression of GR in anti-androgen sensitive LNCaP cell line model and

GC-treatment caused a robust cell cycle exit, inhibition of proliferation and *in vivo* blockade of angiogenesis and tumor growth (Yano *et al.* 2006, Yemelyanov *et al.* 2007).

In contrast to primary prostate cancer, both GC- and GR-action are altered in advanced anti-androgen resistant disease. Several treatment-selected mutations in the AR cause expansion of ligand repertoire for this receptor (Prekovic *et al.* 2016, 2018b). The AR mutations L702H and T878A increase receptor affinity toward endogenous and synthetic GCs, which can now drive prostate cancer growth by promoting AR signaling (Zhao *et al.* 2000, Krishnan *et al.* 2002, Matias *et al.* 2002). While the mutant ARs can be activated by some of the clinically used GR agonists, they are unable to bind others, therefore, it has been clinically demonstrated that switch from one synthetic GR ligand to another can lead to a sufficient biomarker- and radiological-response (Romero-Laorden *et al.* 2018, Fenioux *et al.* 2019). A genome-wide CRISPR-Cas9 KO screen revealed TLE3 loss to drive anti-androgen resistance in LNCaP prostate cancer cells, by allowing re-expression of GR expression in response to enzalutamide (anti-androgen) treatment (Palit *et al.* 2019). Once expressed, GR can bind to accessible AR sites and completely restore its transcriptional program in case of castration resistance prostate cancer (Arora *et al.* 2013). The latter is afforded by a metabolic adaptation through loss of cortisol catabolizing enzyme 11 β -hydroxysteroid dehydrogenase-2, leading to sustained levels of cortisol in the tumor cell surrounding, maintaining intratumoral GR constitutively active (Li *et al.* 2017). While the preclinical evidence for GR 'take-over' is compelling, the only clinical trial reported to date has shown that addition of mifepristone to enzalutamide after a 12-week enzalutamide lead-in did not delay time to PSA progression (Serritella *et al.* 2020). However, additional clinical testing should be performed to conclusively determine whether GR inhibition may be used to combat anti-androgen resistance in advanced prostate cancer.

Pancreatic cancer

Human cortisol plays a critical role in pancreas development and function, contributing to the regulation of glucose homeostasis and nutrient metabolism. Both development and function of α - (Dumortier *et al.* 2011) and β -cells (Fine *et al.* 2018) of the pancreas are affected by GCs. Specifically, GR exerts its influence on glucagon secretion and insulin regulation of glycemia (reviewed by Rafacho *et al.* 2014). While the role of GC in the pathology of the pancreas is well-established and clinically exploited, it is still unclear to which extent

GCs contribute to pancreatic cancer biology. Currently, experimental evidence hints toward a tumor-suppressive action of GR in pancreatic cancer (Norman *et al.* 1994). This is also suggested by clinical data, as intraoperative dexamethasone administration may lead to improved survival in human pancreatic cancer patients (Call *et al.* 2015, Sandini *et al.* 2018). Specifically, using the multivariable Cox proportional hazard survival model, it was shown that patients who received intraoperative dexamethasone survived longer than patients not receiving this treatment (Call *et al.* 2015). Another study demonstrated that intraoperative dexamethasone slightly decreases infection complications and is independently associated with stage, pathologic characteristics and adjuvant therapy with improved overall survival in patients with pancreatic adenocarcinoma (Sandini *et al.* 2018). In line with this, GC-treatment blocks proliferation (Norman *et al.* 1994), invasiveness (Hirata *et al.* 1996) and leads to a reduction in IL-8 secretion (Egberts *et al.* 2008) in various pancreatic cancer cell line models. Furthermore, GCs diminished local recurrent tumor volume and the number of metastatic lesions in xenograft models (Egberts *et al.* 2008). The latter observation is further supported by a recent study showing that GCs inhibit the growth of patient-derived pancreatic cancer xenograft models through suppression of NF- κ B, EMT, IL-6, and VEGF (Yao *et al.* 2020).

Non-small cell lung cancer

It is well established that GR is a crucial component in lung development, physiology, and disease, including cancer (extensively reviewed by Taylor *et al.* 2016). In context of non-small cell lung cancer, GR is a tumor suppressor as its gene expression strongly correlates with favorable overall and progression-free survival (Lu *et al.* 2006). In support of this, various *in vitro* and xenograft models have shown that GR activation in non-small lung cancer causes growth arrest (Taylor *et al.* 2016), but the direct mechanistic underpinnings thereof still remain elusive. The most compelling evidence for a tumor-suppressive role of GR in animal studies comes from cigar smoke-induced lung cancers, in which GC administration delayed cancer development and diminished cancer growth (Balansky *et al.* 2010). Despite promising preclinical results, the effect of GC monotherapy has not been established in the clinical setting (reviewed by Keith 2008), and the only clinical trial addressing the effect of GC-monotherapy on lung cancer was performed in the 1960s in patients with advanced lung cancer which showed no survival

benefit. In support of the protective effect of GCs on lung cancer development, is an observational epidemiological study on chronic obstructive pulmonary disease, which reported that inhaled GC use is associated with lower lung cancer incidence (Parimon *et al.* 2007). Moreover, clinical trials have shown that in patients with lung lesions, GCs decrease the number of nodules detected by CT (van den Berg *et al.* 2008). Furthermore, pre-existing non-solid or partially solid nodules with a high chance of becoming cancerous, diminished in size following GC treatment (Veronesi *et al.* 2011).

Ovarian cancer

The interplay of cortisol and estradiol (E2) has been shown to be imperative for follicular development and ovulation (Breen *et al.* 2005). Specifically, cortisol has a direct effect on the ovary by affecting oocyte maturation, granulosa cell differentiation, steroidogenesis, and lipid metabolism (Breen *et al.* 2005, González *et al.* 2010, Simerman *et al.* 2015).

In ovarian cancer, high *NR3C1* mRNA expression levels have been associated with aggressive clinical features (histologic subtype, higher grade, and advanced stage) and correlated with poor prognosis (Veneris *et al.* 2017), independently of *BRCA* mutation status (Veneris *et al.* 2019), suggesting that in this cancer type GR may act as a disease driver. It was observed that GC administration to ovarian cancer patients is followed by a rapid transcriptional response and upregulation of two anti-apoptotic GR-target genes, *SGK1* and *DUSP1*, suggesting that GCs may decrease chemotherapy effectiveness in ovarian cancer (Melhem *et al.* 2009). In agreement with clinical data, various *in vitro* and xenograft studies have found that GR specifically diminishes sensitivity to chemotherapy-induced cell death. In ovarian cancer cell lines, GC-treatment induces the expression of a caspase inhibitor *clAP2*, which was essential for GR modulation of apoptosis sensitivity (Runnebaum & Brüning 2005). Furthermore, in xenograft models, antagonistic targeting of GR restored sensitivity to chemotherapy-induced cell death by suppressing its survival signaling (Stringer-Reasor *et al.* 2015).

While GR activation may be deleterious in terms of chemotherapy response, evidence suggests that its signaling may be beneficial in suppressing the metastatic progression of ovarian cancer. Specifically, activation of GR leads to an increase in miR-708 expression, which targets *Rap1B*, necessary for integrin-mediated focal adhesion

(Lin *et al.* 2015). This in turn leads to impaired abdominal metastasis formation in an orthotopic xenograft mouse model (Lin *et al.* 2017). Jointly, these studies illustrate that GR may act in opposing fashions in ovarian cancer, diminishing metastatic progression while at the same time reducing response to chemotherapies.

Endometrial cancer

In healthy endometrial tissue, GR has an antagonistic role in relation to $ER\alpha$, opposing the growth-induction caused by $ER\alpha$ activation (Vahrenkamp *et al.* 2018). Clinical data imply that the function of GR is altered in endometrial cancer, specifically it has been reported that expression of GR in primary endometrial cancer is linked to disease aggressiveness and dismal prognosis (Tangen *et al.* 2017). This observation is supported by experimental data, showing that GCs do not oppose E2-induced proliferation in a cell line model of endometrial cancer (Vahrenkamp *et al.* 2018). In-depth molecular analysis of transcriptomes and DNA-binding landscapes of endometrial cancer models revealed that $ER\alpha$ and GR co-operate to promote disease progression (Vahrenkamp *et al.* 2018). Mechanistically it is proposed that $ER\alpha$ may assist GR chromatin loading altering the genomic actions of GR and generating a unique transcriptome under dual activation. Of importance is the E2 and GC-induced downregulation of various cell adhesion genes which may contribute to an increase in the metastatic potential of endometrial cancers (Vahrenkamp *et al.* 2018).

Other solid cancer types

In addition to the cancer types discussed above, GR status or its activity have been associated with various biological features in other solid cancer types. Due to the lack of follow-up studies and mechanistic insights into the function of GR, we do not discuss these in further detail in this review. Nonetheless, high GR expression levels have been shown to correlate with favorable outcome in bladder cancer (Zheng *et al.* 2012, Ishiguro *et al.* 2014) and impairment of the GR-STAT5 axis in the liver has been reported to promote spontaneous hepatic tumorigenesis (Mueller *et al.* 2011). In contrast, high GR activity has been associated with an increase in proliferation in both metastatic colon cancer (Tian *et al.* 2019) and glioma (Langeveld *et al.* 1992). Further extensive research would be required to elucidate the biological impact of GR signaling, along with the clinical implications thereof, in these and other tumor types.

Figure 2

Impact of GCs on various cancer types. The signaling related to glucocorticoid receptor activation may result in either tumor suppression or may facilitate tumor progression depending on the cancer type or disease setting.

Conclusions

While general features of GR response are well known and characterized, the biological consequences of its signaling across different cancers remain only superficially explored. In this review, we discuss the biological role of GR in various cancer types. Specifically, how GR can act either as a tumor suppressor, blocking growth and metastatic spread or as an oncogene, contributing to tumor progression depending on cancer type or disease setting (Fig. 2). It is still unknown what causes this duality of GR action in cancer and which underlying molecular players contribute to this. Furthermore, the oncogenic features GR activation may elicit seem to differ between cancer types, as is the case of ER α -negative breast cancer and ovarian cancer. We speculate that changes in co-regulator repertoire, genetic mutations in GR gene itself, cross-talk with other steroid hormone receptors, activation by non-standard ligands, changes in chromatin accessibility, or activation of receptor kinase pathways may alter GR mode-of action pushing it toward tumor promotion in specific cancer types. Further genomic studies, in combination with functional screens, should be performed to better understand the difference between tumor suppressive and oncogenic GR signaling. Understanding these mechanisms may lead to the development of treatment strategies that rely on reverting GR to a tumor suppressor. It is tempting to suggest that cancer cells undergoing this GR-induced growth arrest may become reliant on other signaling pathways, which could potentially be targeted in a synergistic fashion.

Various synthetic GCs are used in clinical treatments of cancer, mostly to alleviate side effects without considering their effect on the tumor cells. Taking various studies into account on how GR activation in

tumors can diminish chemo-response and increase metastatic potential, the impact of GC therapy should be reevaluated. While combating cancer therapy-related side effects are a necessity, patients may benefit from an altered strategy regarding GC treatment. It could also be interesting to design novel selective GR modulators (Meijer *et al.* 2018) that especially diminish the cancer therapy-related side-effects without having a negative impact on cancer progression. Moreover, long-term usage of GCs to treat certain diseases can result in reduced sensitivity or resistance to GCs, as well as hypersensitivity to GCs. Whether these differences in GC-response in the general population influence tumor development and progression, as well as cancer therapy response, remain to be further explored.

In conclusion, future research should shed light on these features of GC-response and could potentially lead to exciting discoveries that may be therapeutically exploited.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement

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