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Modulating glucocorticoid receptor actions in physiology and pathology: Insights from coregulators

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ABSTRACT

Glucocorticoids (GCs) are a class of steroid hormones that regulate key physiological processes such as metabolism, immune function, and stress responses. The effects of GCs are mediated by the glucocorticoid receptor (GR), a ligand-dependent transcription factor that activates or represses the expression of hundreds to thousands of genes in a tissue- and physiological state-specific manner. The activity of GR is modulated by numerous coregulator proteins that interact with GR in response to different stimuli assembling into a multitude of DNA-protein complexes and facilitate the integration of these signals, helping GR to communicate with basal transcriptional machinery and chromatin. Here, we provide a brief overview of the physiological and molecular functions of GR, and discuss the roles of GR coregulators in the immune system, key metabolic tissues and the central nervous system. We also present an analysis of the GR interactome in different cells and tissues, which suggests tissue-specific utilization of GR coregulators, despite widespread functions shared by some of them.

Abbreviations: 11β-HSD1, 11β-hydroxysteroid dehydrogenase 1; **AA**, Amino acid; **AAT**, α1-Antitrypsin; **ACTH**, Adrenocorticotropic hormone; **AF-2**, Ligand-dependent activation function-2; **AF1**, Transcriptional activation function-1; **AP-1**, Activator protein 1; **ASH2L**, Absent, small, or homeotic discs 2-Like; **ATPase BRG1**, ATPase Brahma-related gene 1; **C/EBP**, CCAAT/enhancer-binding protein; **C/EBPδ**, CCAAT/enhancer-binding protein delta; **CAK**, Cyclin-dependent kinase-activating kinase; **CARM1**, Coactivator-associated Arg Methyltransferase 1; **CBP**, cAMP response element-binding protein-binding protein; **CCAR1**, Cell division cycle and apoptosis regulator protein 1; **CCAR1**, Cell division Cycle and Apoptosis Regulator 1; **CDK**, Cyclin-dependent kinase; **CeA**, Central nucleus of the amygdala; **CHD**, Chromodomain-helicase-DNA binding; **ChIP-MS**, Chromatin immunoprecipitation coupled to mass spectrometry; **Chip-seq**, Chromatin immunoprecipitation followed by sequencing; **ChIP-SICAP**, Chromatin immunoprecipitation with selective isolation of chromatin-associated proteins; **CNS**, Central nervous system; **CoCoA**, Coiled-coil coactivator; **COMPASS**, Complex of proteins associated with Set1; **CRH**, Corticotropin-releasing hormone; **CRTC2**, CREB regulated transcription coactivator 2; **DAX-1**, Dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1; **DBD**, DNA-binding domain; **Dex**, Dexamethasone; **DMD**, Duchenne muscular dystrophy; **Dpp-4**, Dipeptidyl peptidase 4; **DRIP/TRAP**, DNA Repair/ Transcription-RNA Polymerase II Associated Protein; **ER**, Estrogen receptor; **FKBP52**, Protein FK506-binding protein 52; **FOXO1**, Forkhead box O1; **G6pc**, Glucose-6-phosphatase; **GBS sequences**, GR binding sites; **GCs**, Glucocorticoids; **GLI1**, Glioma-associated oncogene homolog 1; **GLP-1**, Glucagon-like peptide 1; **GR**, GC receptor; **GRE**, GR response elements; **HATs**, Histone acetyltransferases; **HDACs**, Histone deacetylases; **HDMs**, Histone demethylase; **HEK293**, Human embryonic kidney cells; **HES1**, Hairy and enhancer of split 1; **HEXIM1**, Hexamethylene bis-acetamide-inducible protein 1; **Hic-5**, Hydrogen peroxide-inducible clone-5; **HMTs**, Histone methyltransferases; **HNF4**, Hepatocyte nuclear factor 4; **HPA**, Hypothalamic-pituitary-adrenal; **Hsp90**, Heat shock protein 90; **INO80**, Inositol requiring 80; **IRFs**, Interferon (IFN) regulatory factors; **ISWI**, Imitation switch; **Jak/STAT**, Janus kinase/Signal Transducer and Activator of Transcription; **LBD**, Ligand-binding domain; **LPL**, Lipoprotein lipase; **LSP**, Lipopolysaccharide; **MAFbx**, Muscle atrophy F-box protein; **MAPPIT**, Mammalian protein-protein interaction trap; **MASPIT**, Mammalian small molecule-protein interaction trap; **MDMs**, Monocyte-derived primary macrophages; **MeCP2**, Methyl-CpG binding protein-2; **MEFs**, Mouse embryonic fibroblasts; **moDCs**, Human monocyte-derived dendritic cells; **MuRF-1**, Muscle RING finger-1 protein; **NCoA1**, Nuclear receptor coactivator; **NF-κB**, Nuclear factor kappa B; **NR**, Nuclear receptor; **NTD**, N-terminal domain; **p/CAF**, p300/CBP-associated factor; **PEPCK**, Phosphoenolpyruvate carboxykinase 1; **PGC-1α**, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; **Pol II**, RNA Polymerase II; **PPARγ**, Peroxisome proliferator-activated receptor gamma; **PRMT1**, Protein Arg N-methyltransferase 1; **PVN**, Periventricular nucleus; **RIME**, Rapid immunoprecipitation mass spectrometry of endogenous proteins; **RIP140**, Receptor-interacting protein 140; **RORs**, RAR-related orphan receptors; **SETD1A**, SET domain containing 1A; **SETDB2**, SET domain bifurcated 2; **SILAC**, Cells isotopically labeled with amino acids in culture; **SIRT1**, Nutrient-sensing deacetylase sirtuin 1; **SMILE**, Small heterodimer partner-interacting leucine zipper protein; **SRC1**, Steroid receptor coactivator 1; **SREBPs**, Regulatory element binding proteins; **SWI/SNF**, Switch/sucrose-non-fermenting; **TAZ**, Transcriptional coactivator with PDZ-binding motif; **TFs**, Transcription factors; **TG**, Triglyceride; **TLR**, Toll like receptor; **TPR**, Tetratriocopeptode repeat; **TSS**, Transcription start site; **VH**, Ventral hippocampus; **VLDL**, Very low-density lipoprotein; **Wdr5/7**, Wd repeat-containing protein 5/7.

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Contents

1. Introduction

The adrenal cortex produces glucocorticoids (GCs), such as cortisol in humans and corticosterone in rodents. These hormones are released in distinct bursts in response to stress stimuli or rhythmically according to the circadian clock (Astiz et al., 2020; Chung, Son, & Kim, 2011; Salamone et al., 2022; Scheff, Kosmides, Calvano, Lowry, & Androulakis, 2011). GCs help the body cope with the energy demands of stress by suppressing energy-consuming functions like reproduction and inflammation, while promoting energy replenishment through enhanced gluconeogenesis (Sacta, Chinenov, & Rogatsky, 2016). The circadian clock regulates the timing of hormone secretion to optimize physiological processes. However, disruptions to the circadian clock, such as those caused by shift work or jet lag, can disturb the pulsatile GCs rhythm, negatively impacting health and increasing the risk of obesity, insulin resistance, and depression (Astiz & Oster, 2018).

The hypothalamic-pituitary-adrenal (HPA) axis is responsible for regulating circulating levels of GCs, (Fig. 1A). Activation of the HPA axis triggers the release of corticotropin-releasing hormone (CRH) from the hypothalamus, which in turn stimulates the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH). ACTH then stimulates the cortex of the adrenal glands to release GCs (Herman et al., 2016). The body uses a negative feedback mechanism to regulate GC levels in the blood and to prevent overproduction of the hormone, which can lead to glucose intolerance and immune system suppression. When GC levels are high, this mechanism decreases the release of CRH and ACTH, maintaining the body's internal clock and ensuring balanced circulating hormone levels (Gjerstad, Lightman, & Spiga, 2018). In Addison's disease, adrenal insufficiency leads to a decrease in cortisol production, impairing the HPA axis regulation and stimulating a continuous release of CRH and ACTH in an attempt to compensate for the low cortisol levels (Munir, Quintanilla Rodriguez, & Waseem, 2022). On the other hand, endogenous overproduction of cortisol, either as a result of excess ACTH secretion or by autonomous cortisol release from the adrenal cortex, leads to an ultradian pattern of GC secretion and implies a loss in the HPA negative feedback mechanism, defined pathologically as Cushing's syndrome (Oakley et al., 2018; Raff & Carroll, 2015).

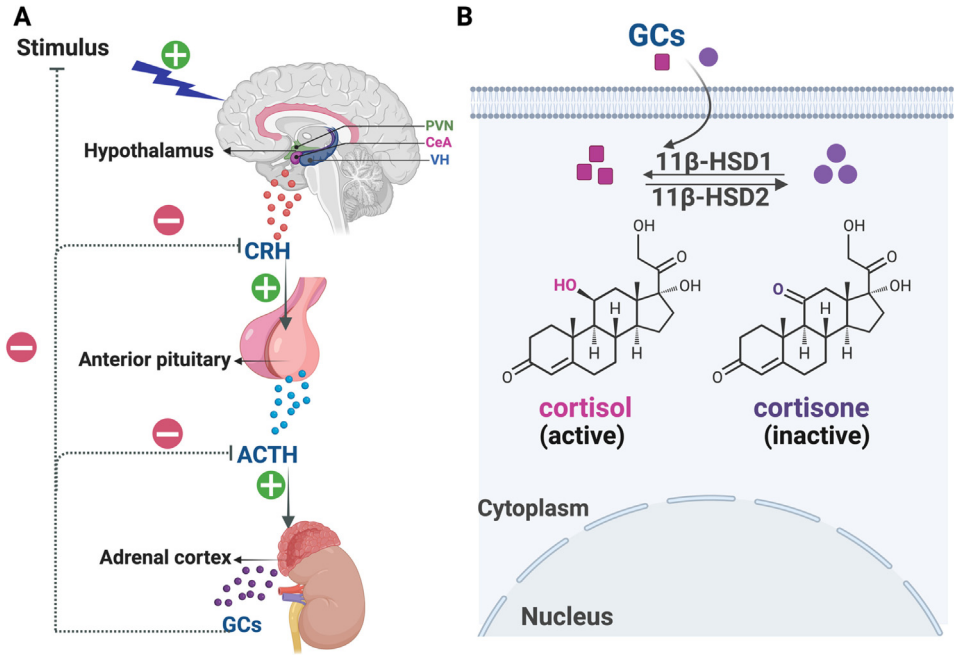

Fig. 1. Regulation of GC levels. (A) Systemic regulation of GC secretion by the hypothalamus-pituitary-adrenal (HPA) axis. In response to circadian Zeitgebers or stress stimuli, the hypothalamus secretes corticosteroid-releasing hormone (CRH), which triggers the anterior pituitary to secrete adrenocorticotropic hormone (ACTH). ACTH then stimulates the adrenal glands to release GCs into the blood stream. Increased levels of GCs trigger a feedback mechanism, suppressing the release of CRH and ACTH. (B) Local regulation of GC levels mediated through opposing activities of two enzymes; the 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) and 11β-HSD2. 11β-HSD1 promotes the formation of the active form of GCs (cortisol), while 11β-HSD2 reduces GC levels by converting them back to the inactive form (cortisone). PVN: periventricular nucleus, CeA: central nucleus of the amygdala, VH: ventral hippocampus.

The HPA axis plays a crucial role in the systemic regulation of GC levels. However, a local mechanism within tissues also contributes to this balance through opposing activity of two enzymes, the 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) and 11β-HSD2. 11β-HSD1 promotes the formation of the active form of GCs, whereas 11β-HSD2 prevents excessive GC levels by converting them back to the inactive form (Macfarlane, Seibel, & Zhou, 2020), (Fig. 1B).

Since their first clinical application in 1949, GCs have been widely used to treat various inflammatory diseases. They have also been a drug of choice for managing numerous hematological malignancies. However, therapeutic benefits of GCs have been offset by significant side effects, including weight gain, insulin resistance, type 2 diabetes mellitus, osteoporosis and muscle and skin atrophy, which have limited their utility (Benedek, 2011; Li & Cummins, 2022). Given the unsurpassed efficacy and cost-effectiveness of GCs as drugs, there is a great unmet demand for better understanding of GC action so new-generation molecules with improved therapeutic profiles can be developed.

GCs exert their function through their cognate GC receptor (GR), which belongs to the nuclear receptor (NR) superfamily. The human GR is encoded by the NR3C1 gene and the transcript undergoes alternative splicing to generate multiple isoforms, with the two most prevalent being GRα (777 AA) and GRβ (724 AA) (Hollenberg et al., 1985). This review focuses on GRα (referred to as GR), which consists of four functional domains: (Weikum, Knuesel, Ortlund, & Yamamoto, 2017) (Fig. 2A). The N-terminal domain (NTD) is disordered and contains the ligand-independent transcriptional activation function-1 (AF1, tau1), which is critical for maximal transcriptional activation of GR and acts as a docking site for transcription coregulators such as the ATPase Brahma-related gene 1 (ATPase BRG1), the CREB-binding protein (CBP) and its paralog E1A-binding protein p300 (p300), CBP/p300, and also the p300/CBP-associated factor (p/CAF) (Petta et al., 2016; Vettorazzi, Nalbantoglu, Gebhardt, & Tuckermann, 2022; Yoshinaga, Peterson, Herskowitz, & Yamamoto, 1992). The DNA-binding domain (DBD) is highly conserved across the NR family and comprises two zinc finger motifs that enable GR's interaction with

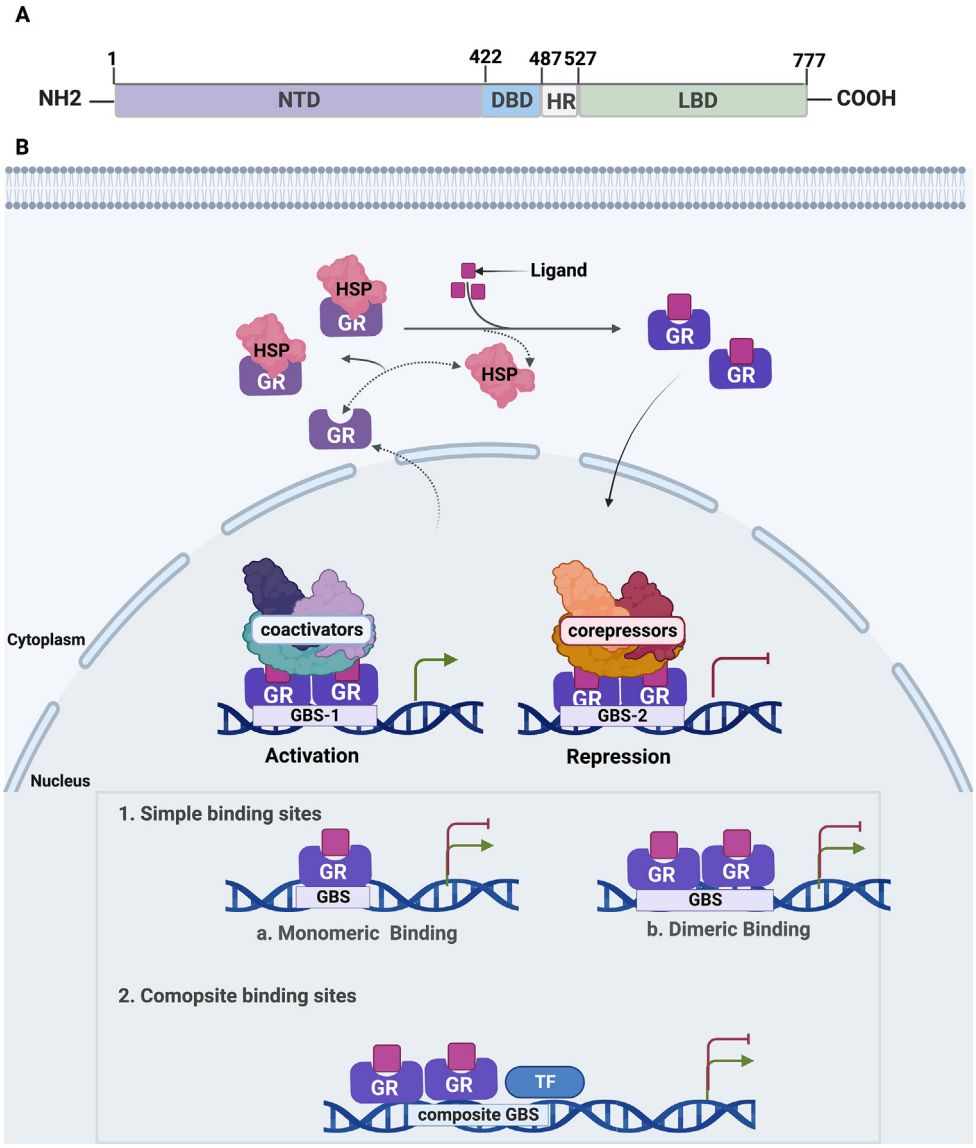

Fig. 2. Structure and mechanism of action of glucocorticoid receptor (GR). (A) Schematic representation of human GRa structural domains, encompassing the N terminal activation domain (NTD), the DNA-binding domain (DBD), the Hinge Region (HR) and the C-terminal Ligand Binding Domain (LBD). (B) GR mechanism of action. In the absence of ligand, GR resides in the cytoplasm in complex with heat shock proteins (HSP). Ligand binding induces conformational changes within the receptor, promoting its nuclear translocation where liganded GR can associate with DNA and activate or repress target genes. Three commonly described types of GR binding sites (GBS) are simple, composite, and tethering, depending on whether GR is the sole DNA-binding protein, binds in conjunction with other transcription factors (TF), or recruited to DNA via another DNA-bound TF, respectively.

DNA at GR binding sites (GBS sequences) and also mediates receptor homodimerization (Weikum, Okafor, D'Agostino, Colucci, & Ortlund, 2017). The moderately conserved ligand-binding domain (LBD) comprises 12 helices and mediates core functions of the receptor, including ligand and chaperone binding, receptor homodimerization, and coregulator recruitment (Schoch et al., 2010). When the LBD ligand binding pocket (LBP) is occupied by steroids, the ligand-dependent activation function-2 (AF-2) is allosterically stabilized and interactions with various coregulators are facilitated. Such coactivators or corepressors often contain a conserved LXXLL motif, where "L" represents Leucin and "X" represents any other amino acid. The p160 family members are a prime example of coregulators interacting with the LBD (Liu, Wang, & Ortlund, 2019; Schoch et al., 2010). The hinge region between the LBD and DBD contributes to GR transcriptional activity and recruits certain coregulators, such as the hexamethylene bis-acetamide-inducible protein 1 (HEXIM1) (Yoshikawa et al., 2008). The transcriptional activation function (tau2) domain spans the junction between the hinge and LBD, and can interact with coregulators, such as hydrogen peroxide-inducible clone-5 (Hic-5, TGFB1I1) (Chodankar, Wu, Schiller, Yamamoto, & Stallcup, 2014).

In the absence of a ligand, GR resides in the cytoplasm, bound to chaperon proteins the heat shock protein 90 (Hsp90) and Hsp70, the co-chaperone protein p23, and tetratriocopeptode repeat (TPR) proteins FK506-binding protein 52 (FKBP52) and FKBP51. Upon ligand binding, GR undergoes conformational changes that result in its translocation into the nucleus. Within the nucleus, the liganded GR may bind to specific GC Response Elements (GRE sequences) within the cis-regulatory region of its target genes, where it can either up- or down-regulate the transcription of hundreds to thousands of genes (Wang, 2005; Weikum, Knuesel, et al., 2017). The hormone-free GR is exported back to the cytoplasm, where it continues to engage in the nuclear-cytoplasmic cycle (Merkulov, Klimova, & Merkulova, 2016) (Fig. 2B).

The most characterized GRE is composed of two pseudo-palindromic hexameric AGAACA repeats, separated by a spacer of three base pairs (He et al., 2021; Luisi et al., 1991). However, GR can also alternatively recognize binding motifs having the inverted sequence repeat, CTCC$(N)_{0-2}$GGAGA, or can bind to canonical half site DNA sequences, the consensus AGAACA (Schiller, Chodankar, Watson, Stallcup, & Yamamoto, 2014).

Chromatin immunoprecipitation followed by sequencing (Chip-seq) has provided strong evidence that the GR 'cistrome', which encompasses all the genomic regions with detectable GR binding, is highly cell type-specific. This specificity correlates with distinct patterns of GR-interacting proteins including pioneering and cooperating transcription factors (TFs) and coregulators, collectively referred to as the GR interactome (Hemmer et al., 2019; Petta et al., 2016; Praestholm, Correia, & Grontved, 2020). Identifying components in the GR interactome across various GR loci can facilitate their selective targeting, enabling a more customized modulation of GR function.

In recent years, researchers have explored GR interactors using diverse methods. Coregulators enriched in the GR interactome have been identified using ChIP coupled to mass spectrometry (ChIP-MS) in mouse tissues, such as the liver, macrophages and mouse embryonic fibroblasts (MEFs) (Escoter-Torres, Greulich, Quagliarini, Wierer, & Uhlenhaut, 2020; Greulich, Wierer, Mechtidou, Gonzalez-Garcia, & Uhlenhaut, 2021b; Hemmer et al., 2019; Quagliarini et al., 2019). The rapid immunoprecipitation mass spectrometry of endogenous proteins (RIME) technique has also been used to identify GR interactors in human lung cancer cell lines including A549, H2122, H1944, H1975 and H460 (Prekovic et al., 2021). The GR interactome in human embryonic kidney cells (HEK293) stably expressing GR was determined using ChIP with selective isolation of chromatin-associated proteins (ChIP-SICAP) combined with MS from cells isotopically labeled with amino acids in culture (SILAC) (Paakinaho et al., 2021). Moreover, the

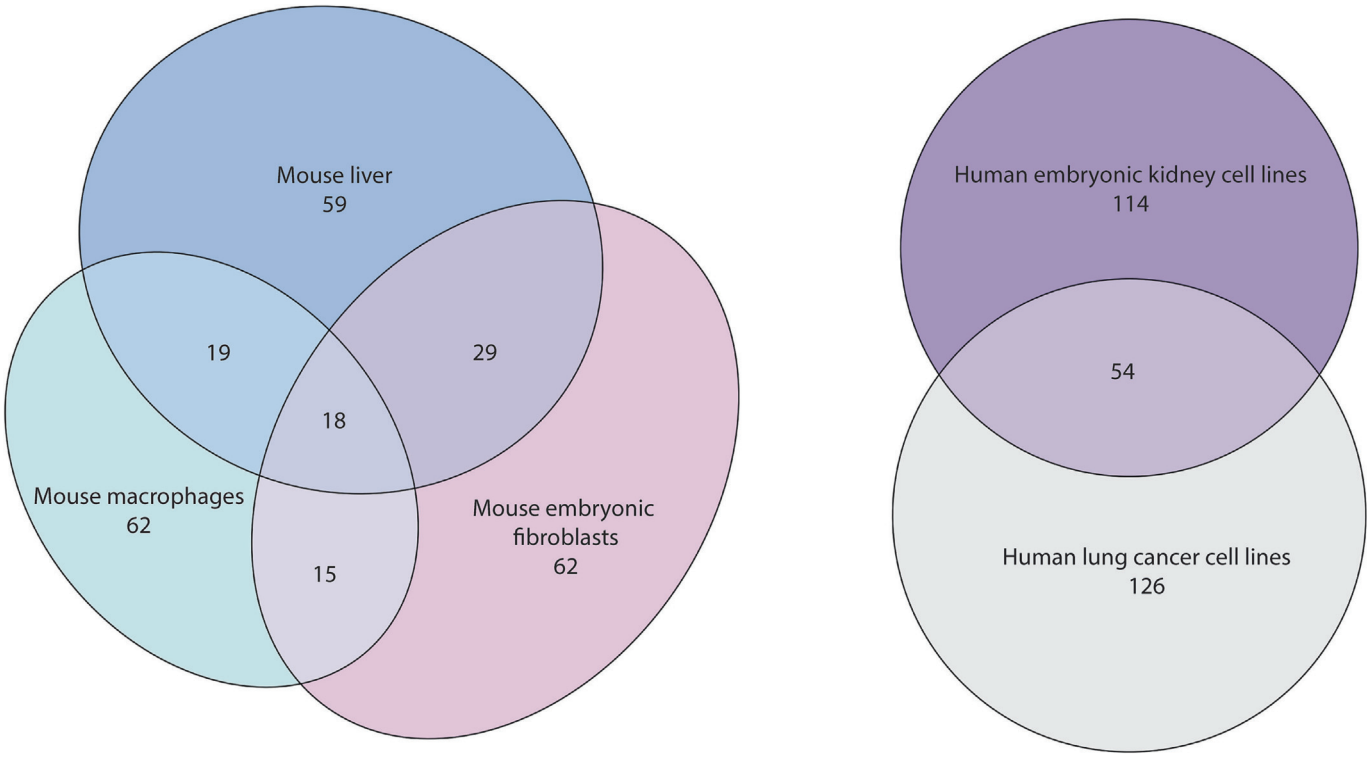

Fig. 3. Coregulators enriched in GR interactome across different tissues and cell types. The left diagram shows the number of shared and unique coregulators identified in mouse livers, macrophages, mouse embryonic fibroblasts (MEFs). The right diagram shows the number of shared and unique coregulators in human lung cancer cell lines (A549, H2122, H1944, H1975 and H460) and human embryonic kidney cells lines (HEK293 and HEK293T). These diagrams provide a visual summary of supplementary table 1, which lists the coregulators compiled from published GR interactomes.

BioID technique, entailing the stable transfection of HEK293T cells with biotin ligase (BirA) fused to the N-terminal region of GR, facilitated the biotinylation of nearby proteins, enabling a comprehensive proteome-wide exploration of the GR interactome (Dendoncker et al., 2019). The mammalian protein-protein interaction trap (MAPPIT) and mammalian small molecule-protein interaction trap (MASPIT) assays utilized cell lysates from HEK293T cells stably transfected with GR as bait to assess interactions between GR and thousands of potential interacting proteins (Lievens et al., 2016).

To provide an overview, we compiled the identified coregulators from these diverse studies, grouped them based on their mode of action, and listed them in Supplementary Table 1. Additionally, we integrated these investigations using two distinct Venn diagrams: one for mouse studies, and the other for human cell line, Fig. 3 both diagrams show that a large fraction of coregulators mediates GR activity in a tissue-specific manner, while some appear to cooperate with GR broadly across different tissues (Stallcup & Poulard, 2020).

Furthermore, ample evidence in the literature suggests that each coregulator is essential for only a subset of GR-regulated genes, making coregulators a potentially viable therapeutic target for precisely tuning GR activity (Bittencourt et al., 2012; Chodankar et al., 2014; Greulich et al., 2021b; Greulich, Wierer, Mechtidou, Gonzalez-Garcia, & Uhlenhaut, 2021a; Rogatsky, Luecke, Leitman, & Yamamoto, 2002; Stallcup & Poulard, 2020; Won Jeong, Chodankar, Purcell, Bittencourt, & Stallcup, 2012; Wu, Ou, Chodankar, Siegmund, & Stallcup, 2014).

This review will briefly introduce the basic molecular biology and physiology of GCs and GR function, with a focus on GR coregulators in the immune system, together with key metabolic tissues, including the liver, muscle, adipose tissue, and the central nervous system. Fig. 4 summarizes the primary functions of GR in these organs.

2. Coregulators of GR

As any TF, GR enlists multiple coregulator proteins that alter the chromatin configuration surrounding its binding site and the transcription start site (TSS) of the target gene, as well as change the composition of the basal transcriptional machinery present at the TSS. These coregulators operate through distinct mechanisms that collaborate to alter the chromatin architecture and create an environment that promotes either the activation or repression of the GR target gene (Lonard & O'Malley, 2012; Millard, Watson, Fairall, & Schwabe, 2013; Rosenfeld, Lunyak, & Glass, 2006) [Fig. 5].

To achieve **chromatin remodeling,** GR recruits **ATP-dependent chromatin remodeling complexes**. Their ATPase domain uses the energy released from ATP hydrolysis to mobilize nucleosomes, which allows TFs to access the underlying DNA (Petty & Pillus, 2013) as well as assists RNA Polymerase II (Pol II) during transcription elongation (Xu et al., 2020). Chromatin remodeling complexes are classified into four subfamilies - **SWI/SNF** (switch/sucrose-non-fermenting), **ISWI** (imitation switch), **CHD** (chromodomain-helicase-DNA binding), and **INO80** (inositol requiring 80), each with specific and shared subunits. In addition, chromatin remodelers can recruit proteins with enzymatic activities such as histone acetylases (**HATs**) or deacetylases (**HDACs**), i.e., NuA4 and NuRD, respectively (Clapier & Cairns, 2009; Clapier, Iwasa, Cairns, & Peterson, 2017)·(Tyagi, Imam, Verma, & Patel, 2016).

Histone modifiers also present important GR coregulators themselves. This family comprises enzymes that add and remove histone modifications as well as proteins that recognize and respond to these modifications. Examples of histone modifiers are HATs, HDACs, histone methyltransferases (**HMT**s) and histone demethylases (**HDMs**) (Bannister & Kouzarides, 2011; Jenuwein & Allis, 2001;

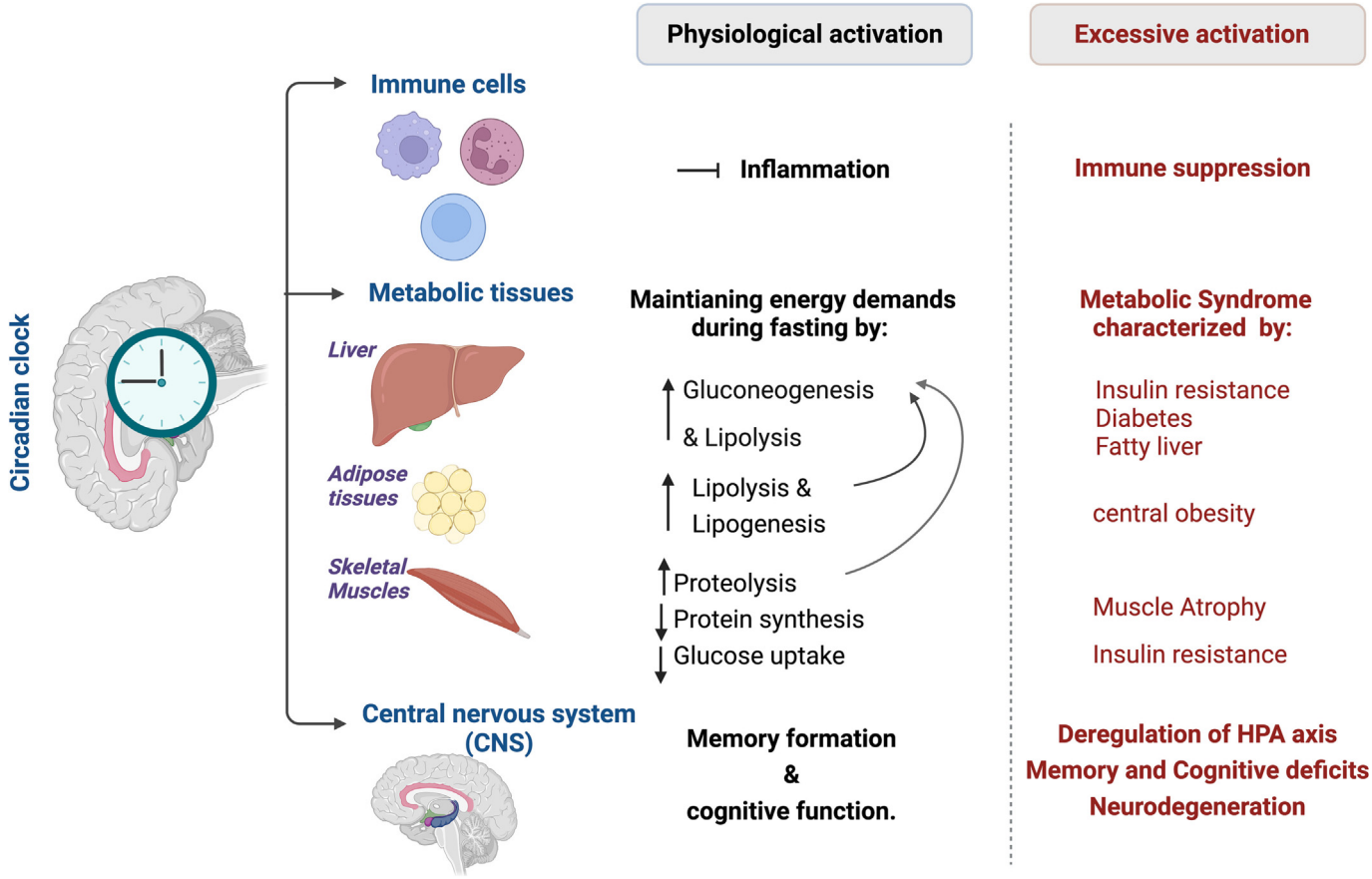

Fig. 4. Overview of the primary functions of GR in various tissues. For each tissue, the primary effects of physiological and excessive GR activation are summarized.

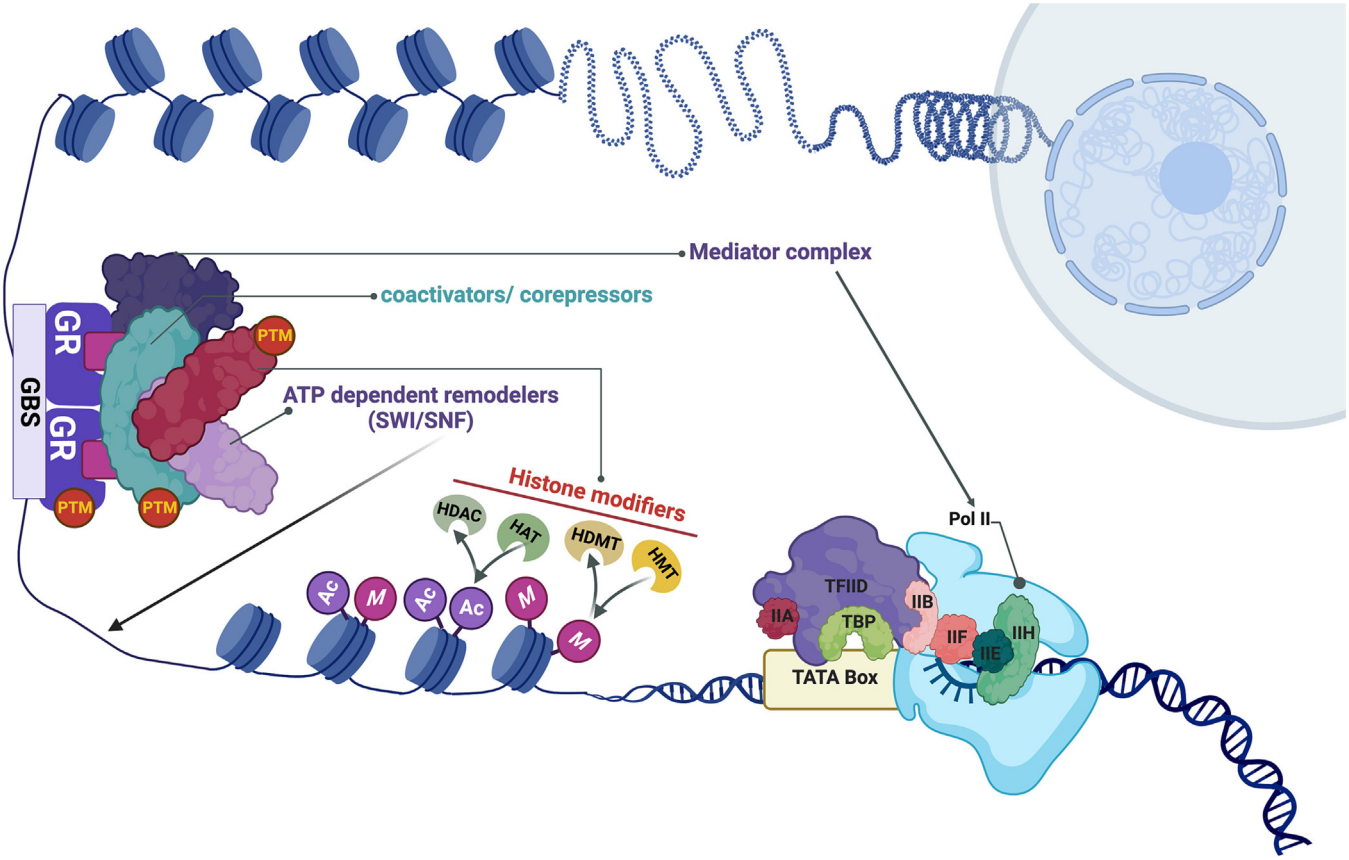

Fig. 5. Coregulator complexes mediating GR transcriptional activity. Upon ligand binding, GR associates with DNA at glucocorticoid receptor binding sites (GBS) and recruits specific coregulator complexes including: **1) ATP-dependent chromatin modifiers** such as the SWI-SNF complex, which use the energy of ATP hydrolysis to shift nucleosomes and to evict histones. **2) Coregulators with enzymatic activities (histone modifiers),** including histone methyltransferases (HMT), histone de-methylases (HDM), histone acetyltransferases (HAT) & histone deacetylases (HDAC), which add or remove post-translational modifications (PTM) such as methyl (M) or acetyl (Ac) groups on histones, GR or other components of the transcription complex. **3) Mediator complex,** which facilitates the recruitment of RNA polymerase II (Pol II) and components of the basal transcriptional machinery to the TATA box; the general TFs (TFIID, IIB, IIH, IIA, IIE), the TATA box binding protein (TBP). 4) **Coactivators or corepressors**, which bind to GR and recruit other coregulators.

Rothbart & Strahl, 2014). The modification induced by these enzymes can either relax or further compact the chromatin, thus enabling transcription activation or repression, respectively (Mustafi et al., 2022). In addition to their effect on chromatin structure, these coregulators can influence gene expression by directly modifying non-histone proteins involved in transcriptional regulation, such as TFs and other coregulators. The posttranslational modifications (PTM) that they add or remove can lead to changes in protein-protein and protein-DNA interactions, protein stability, subcellular localization etc., all of which can impact gene expression (Kim et al., 2016).

The third highly diverse group of coregulators include proteins that lack enzymatic activities, but can bridge GR transcription complexes with components of the basal machinery and mRNA Polymerase II (Pol II) or serve as a scaffold for additional coregulators. Several subunits of the multifunctional **Mediator, the DNA Repair/Transcription-RNA Polymerase II Associated Protein (DRIP/TRAP)- complex,** e.g., MED1/TRAP220 or MED14/TRAP170, have been shown to interact with GR and enable its transcriptional activity (Chen & Roeder, 2007; Hemmer et al., 2019; Hittelman, Burakov, Iniguez-Lluhi, Freedman, & Garabedian, 1999; Jia et al., 2009). The mediator complex manifests in two distinct forms that differ in both composition and function, depending upon its association with a kinase module, the cyclin-dependent kinase (CDK)-activating kinase (CAK). The primary function of both the mediator and the mediator-CAK complex is to facilitate or impede Pol II transcription initiation, and to regulate Pol II elongation (Richter, Nayak, Iwasa, & Taatjes, 2022).

A large number of coregulators were isolated through genetic or biochemical **protein-protein interaction** screens using GR as bait. Among them, the p160 coactivator family, such as such as the steroid receptor coactivator 1 (SRC1, a.k.a nuclear receptor coactivator 1, NCoA1), NCoA2 (a.k.a. SRC2, TIF2, and GRIP1- glucocorticoid receptor interacting Protein 1), and NCoA3 (a.k.a SRC3, CIP, AIB1, ACTR, and TRAM1), all identified through yeast two-hybrid screens with liganded LBDs of various NRs, have become the prototypic coregulators. These proteins may possess intrinsic HAT activity in certain contexts but, importantly, serve as scaffolds that recruit numerous secondary coregulators, including but not limited to HATs CBP/p300 and pCAF; a.k.a KAT2B), HMTs such as Coactivator-associated Arg Methyltransferase 1 (CARM1; also known as PRMT4) and Protein Arg N-methyltransferase 1 (PRMT1), Coiled-coil Coactivator (CoCoA), and Cell division Cycle and Apoptosis Regulator 1 (CCAR1).

Although most coregulators were originally defined as "coactivators" or "corepressors", it is now apparent that the term "coregulator" is more accurate, because many of these proteins can perform both functions for the same TF in the same cell type. For instance, GRIP1, Hic5, and G9a can all act as either coactivators or corepressors, engaging in distinct interactions for different subsets of GR target genes or in response to different physiological stimuli (Chodankar et al., 2014; Purcell, Jeong, Bittencourt, Gerke, & Stallcup, 2011; Rogatsky et al., 2002). In addition, there is much evidence that GR coregulators act in a gene-specific manner (Bittencourt et al., 2012; Chodankar et al., 2014; Greulich et al., 2021a; Greulich et al., 2021b;

Rogatsky et al., 2002; Stallcup & Poulard, 2020; Won Jeong et al., 2012; Wu et al., 2014).

3. GR coregulators in the immune system

The effects of GR in immune cells have been studied primarily in relation to the key therapeutic properties of GCs: First, their potent anti-inflammatory effects, which propelled GCs to the top of the list of all prescribed medications, and second, their ability to trigger apoptosis in immature and, critically, transformed lymphocytes making GCs indispensable for managing leukemias and lymphomas. GR function in innate immune cells has arguably been studied most extensively in macrophages. Macrophages are a key cell type driving the initiation and resolution of inflammation; they are also a cell type that can be acquired and expanded in sufficient numbers to facilitate large-scale biochemical, genomic, functional and mechanistic interrogation of GR-coregulator complexes.

Macrophages express all three classic p160 coregulators, NCoA1, 2, and 3. Among them, NCoA2/GRIP1/TIF2/SRC2 has emerged as a unique family member whose multifaceted role as a GR coregulator in macrophages places it on the intersection of multiple pathways. The best described function of GR:GRIP1 complexes in macrophages was in the context of activator protein 1 (AP-1)- and nuclear factor kappa B (NF-κB)-occupied sites, whereby GC-dependent recruitment of GR and GRIP1 was associated with direct transcriptional repression of AP1 and NF-κB target genes. Consistently, a conditional loss of GRIP1 in macrophages has led to a broad derepression of the inflammatory transcriptome, which in vivo sensitized mice to inflammation in a number of acute and chronic models (Chinenov et al., 2012; Coppo, Chinenov, Sacta, & Rogatsky, 2016). Given a critical role of RNA Polymerase II (Pol II) pausing for the induction of inflammation-related genes (Adelman et al., 2009; Yu et al., 2020), it is notable that GRIP1 corepressor function was evident at both non-paused genes, activated through signal-dependent Pol II recruitment, and the paused genes at which Pol II pause release was rate-limiting for gene activation (Gupte, Muse, Chinenov, Adelman, & Rogatsky, 2013; Sacta et al., 2018) (Fig. 6). Specifically, ChIP assays in primary bone marrow-derived macrophages (BMDMs) showed that at non-paused genes, GR:GRIP1 co-occupancy with NF-κB precluded the assembly of pre-initiation complexes and Pol II at target promoters; at paused pro-inflammatory genes, on the other hand, GR:GRIP1 promoted the retention of the negative elongation factor and prohibited recruitment of a proxy for Pol II pause-release, Cyclin T1/CDK9 (P-TEFb). The specific mechanisms linking GR and GRIP1 to components of basal transcriptional and pausing machinery remain to be elucidated, however it is notable that GRIP1 was shown to be phosphorylated by P-TEFb, specifically in the context of GRE-associated GR:GRIP1 activation and not tethering repression complexes (Rollins et al., 2017) (Fig. 6). This finding is consistent with an idea that GRIP1 PTMs dictate its recruitment to distinct GR complexes and determine the regulatory outcomes, e.g., activation vs. repression.

Like most coregulators, GRIP1 is not GR- or even NR-specific; rather, it interacts and cooperates with many sequence-specific TFs in different tissues and cell types (Dasgupta, Lonard, & O'Malley, 2014; Scholtes & Giguère, 2022; Zhou, Li, Luo, & Wan, 2022). GRIP1 has been shown to interact with and potentiate the activity of interferon (IFN) regulatory factors (IRFs) 3, 7 and 9 – all involved in the transcription of Ifnb and other type I IFN-stimulated genes (Flammer et al., 2010; Reily, Pantoja, Hu, Chinenov, & Rogatsky, 2006). Interestingly, at least in vitro, binding of GRIP1 to GR vs. IRF proteins was mutually exclusive, whereby GR activation with ligand resulted in GRIP1 loss from the IRF complexes, attenuating gene induction by IFN. Moreover, this effect was reversed by either the administration of the GR antagonist RU486, that disrupts GR:GRIP1 interaction, or GRIP1 overexpression. Although the functional relevance of this competitive coregulator utilization has not been tested in vivo, the results are consistent with a model whereby at homeostasis, GC signaling promotes GRIP1 recruitment to GR activation and repression complexes, the latter providing tonic control over inflammatory gene expression. Conversely, in response to TLR and IFN signaling, GRIP1 redistribution to IRFs would both facilitate a robust IFN response and derepress pro-inflammatory NF-κB targets required for host responses to infection. In this regard, it is interesting to note that while transcription of most inflammatory cytokine genes following TLR signaling and NF-κB activation is repressed by GR, cytokine signaling through the Jak/STAT pathway is typically resistant to GCs. However, type I IFN signals through the STAT1/STAT2/IRF9 heterotrimer, and the presence

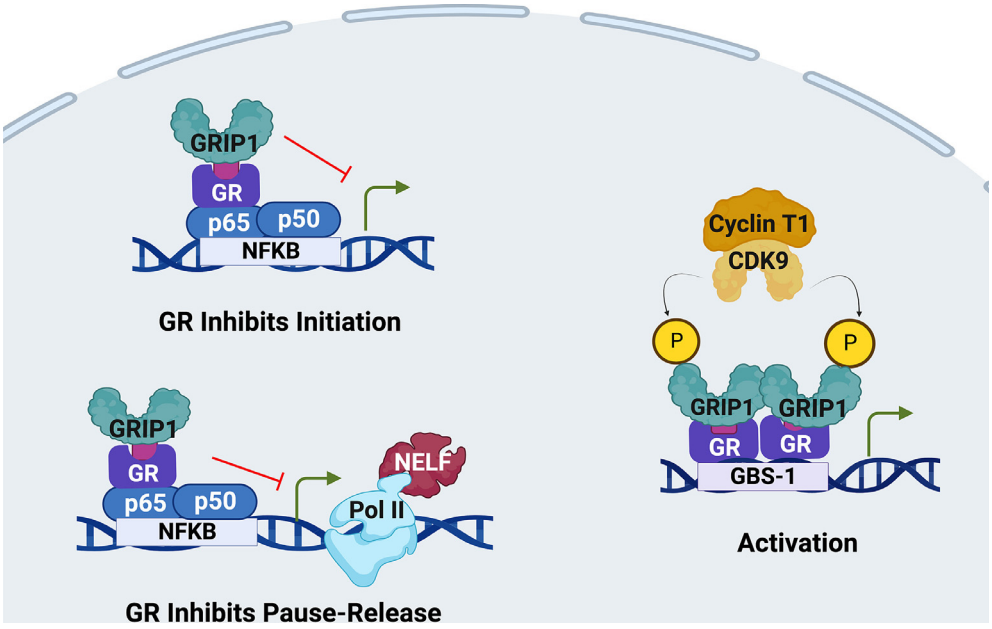

Fig. 6. GR-associated coregulator complexes in macrophages. GR, together with its coregulator GRIP1, represses transcription of pro-inflammatory genes at two distinct steps of the transcription cycle: initiation vs. pause-release. In both cases, GR bound to GRIP1 tethers to the p65/p50 heterodimer at the NFkB response elements. To activate gene transcription, GR and GRIP1 bind to glucocorticoid binding sites (GBS). Cyclin-dependent kinase (CDK)9, complexed with Cyclin T1, phosphorylates GRIP1 specifically at these sites.

of the GRIP1-interacting IRF9 subunit in this complex makes the IFNβ pathway uniquely sensitive to GC inhibition both at the level of transcription and at the level of signaling (Flammer et al., 2010; Reily et al., 2006). Future work is needed to elucidate whether and in what specific contexts GCs can inhibit IFNβ signaling in vivo.

Recently, a serine protease inhibitor, α1-Antitrypsin (AAT), was reported to interact with GR and exert anti-inflammatory effects in human monocytic THP-1 cells and monocyte-derived primary macrophages (MDMs) (Bai et al., 2022). Secreted AAT can be taken up into the cytoplasm, although the receptor responsible for internalization has not been identified. Adding AAT to the culture medium reduced the levels of IL8 secreted into culture supernatant from WT but not GR-deficient MDMs and THP1 cells (Bai et al., 2022). Pre-incubating THP1 cells with AAT and then infecting them with M. tuberculosis or M. intracellular reduced intracellular bacterial burden in WT but not GR-KO THP1 cells (Bai et al., 2022). However, AAT interacted with GR both in the cytoplasm and the nucleus, and additional studies are required to discern whether AAT stabilizes the transcriptional complexes of GR, or induces anti-inflammatory effects via other mechanisms.

Protein interactome studies revealed more novel GR regulators, such as the SET domain Containing 1A /Complex of Proteins Associated with Set1 (SETD1A/COMPASS), which were found to interact with GR in BMDMs and potentiate its anti-inflammatory effects in mouse macrophage-like RAW264.7 cells (Greulich et al., 2021a). GR and the methyltransferase SETD1A co-occupied a subset of sites in the GR cistrome, and SETD1A was necessary for the induction of a specific set of targets, including *Dusp1* and *Tsc22d3/Gilz*, in the presence of lipopolysaccharide (LPS) + dexamethasone (Dex) in the RAW264.7 cells (Greulich et al., 2021a). Another chromatin remodeler, bromodomain containing 9 (BRD9) was shown to be recruited to the same sites as GR, but unlike SETD1A, BRD9 reduced GR occupancy, which correlated with the reversal of GR repressive effects on inflammation mediators Ccl7 and Cxcl1 (Wang et al., 2021).

Despite extensive evidence of the dramatic effects of GCs in other immune cell types (Cannarile et al., 2006; Kim et al., 2020; Li, Munitic, Mittelstadt, Castro, & Ashwell, 2015), specific GR complexes that execute these functions are yet to be discovered. In human monocyte-derived dendritic cells (moDCs), a zinc finger transcription factor DC-specific transcript (DC-SCRIPT), was shown to act as a repressor in protein complexes with GR (Hontelez, Karthaus, Looman, Ansems, & Adema, 2013). Specifically, knocking down DC-SCRIPT with siRNA increased GC-mediated induction of the GR target *Gilz*, which is necessary for DC tolerization, an essential process whereby DCs learn not to activate T-cells in response to body's own ('self')-antigens. DC-SCRIPT is cell type-specific, unlike most that modulate the actions of GR in immune cells. GC-driven differentiation of tolerogenic DCs appears to depend on GR and MAFB binding to methylcytosine dioxygenase TET2, a methylcytosine dioxygenase linked to DC fate determination through demethylation events (Morante-Palacios et al., 2022). TET2 therefore appears to serve as a GR coactivator facilitating DC tolerization, but more mechanistic studies are needed to establish this postulated role. Hopefully, future work will help gain insight into GR-coregulator interactions in other immune cell types.

In hematological malignancies, GR interactions relevant to its pro-apoptotic effects are likely distinct from those in inflammatory conditions. In T cell Acute lymphoblastic leukemia (T-ALL), GR was shown to bind another NR, Liver Receptor Homolog-1 (LRH-1), leading to mutual inhibition (Michalek et al., 2022). Inhibiting or knocking down LRH-1 made T-ALL cells more susceptible to GC-induced apoptosis, a mechanism which could be harnessed therapeutically. GR also reportedly interacts with the transcription factor glioma-associated oncogene homolog 1 (GLI1) in T-ALL, whereby liganded GR inhibits GLI1, shutting down hedgehog signaling which is often dysregulated in cancer (Bongiovanni et al., 2020). This GR interaction affecting another signaling pathway may represent a potential therapeutic target, as synthetic GCs might be used to control Hedgehog signaling. Interactions of GR with coregulators are also important for B cell acute lymphoblastic leukemia (B-ALL) management: in NALM6 cells, an shRNA screen revealed that depleting histone methyltransferases EHMT1 (GLP) and EHMT2 (G9a) as well as CBX3 (HP1γ), impaired GC-induced apoptosis (Poulard et al., 2019). Furthermore, methylated EHMT1 and EHMT2 were shown to interact with GR, and to require CBX3 to form a fully active coactivator complex (Poulard et al., 2017).

In certain leukemic cells, GR-coregulator interactions were reported to inhibit apoptosis in the absence of the GR ligand. In a human myeloid leukemia cell line, GR was found to bind to Absent, Small, or Homeotic Discs 2-Like (ASH2L), a core subunit of the MLL/SET H3K4 methyltransferase complex (Rocha-Viegas et al., 2020). In a ligand-independent manner, GR along with ASH2L bound to cis-regulatory hormone response elements of the anti-apoptotic gene BCL2L1, which contributed to activation of BCL2L1 and survival of the leukemia cells. Consistent with pro-apoptotic effects of GCs, Dex decreased the binding of GR and ASH2L, reducing BCL2L1 expression and increasing apoptosis (Rocha-Viegas et al., 2020). Whether this or similar mechanism applies to normal cells remains to be investigated. A comprehensive study of GR interactomes in lymphoid malignancies showed that GR most strongly interacts with NCoA1, 2 and 3, as well as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), receptor-interacting protein 140 (RIP140) and dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1 (DAX-1) (Clarisse et al., 2017). Most of these coregulators also modulate GR activity in immune cells under inflammatory conditions, and in numerous other cell types, suggesting a more ubiquitous use of coregulators by GR across tissues.

4. GR coregulators in peripheral metabolic tissues

4.1. Metabolic functions of GR

GR is a master regulator of metabolism, with tightly coordinated functions in multiple organs (liver, skeletal muscle, adipose tissue, pancreas, kidneys), controlling energy utilization during stress, fasting or prolonged starvation (Bose, Hutson, & Harris, 2016). This systemic nature of GC actions may explain why Dex treatment of cultured hepatocytes does not lead to abnormal triglyceride (TG) accumulation, as it does in mouse liver in vivo (Wan et al., 2020).

GR activation promotes gluconeogenesis by directly regulating the expression of key hepatic gluconeogenic genes; phosphoenolpyruvate carboxykinase 1, *PEPCK* (encoding PCK1) and glucose-6-phosphatase, *G6pc* (encoding G6Pase) (Barthel & Schmoll, 2003; Hatting, Tavares, Sharabi, Rines, & Puigserver, 2018; Nader et al., 2010; Sun et al., 2015). In addition, GR activation enhances protein turnover in the muscle, and lipolysis in adipose tissue, providing substrates (amino acids and glycerol, respectively) for hepatic gluconeogenesis (Ahmad et al., 2022; Chen et al., 2021; Peckett, Wright, & Riddell, 2011). Furthermore, GCs reduce glucose utilization in muscle and adipose tissue while enhancing the breakdown of glycogen molecules into their glucose units (Li & Cummins, 2022).

GCs have a dual impact on lipid metabolism in both liver and adipose tissue, where GR activation can promote transcription programs associated with both lipolysis and lipogenesis. Maintaining normal hepatic triglyceride (TG) load requires a balance between lipid uptake and release. Prolonged activation of GR has been shown to impact the balance, resulting in tipping the scale toward lipogenesis and increased hepatic lipid accumulation (Rahimi, Rajpal, & Ismail-Beigi, 2020).

While these physiological GR-driven processes are adaptive, excessive GC exposure can lead to insulin resistance, hyperglycemia, weight gain, and muscle atrophy, as seen in patients with Cushing's syndrome or those receiving prolonged GC treatment. Here, we review studies assessing the function of GR coregulators in key metabolic organs such as the liver, the adipose tissue and the skeletal muscle.

a. **Liver**

GCs orchestrate various energy metabolism pathways in the liver to uphold hepatic homeostasis, reviewed in (Quagliarini, Makris, Friano, & Uhlenhaut, 2023). GCs enhance the transcription of *PEPCK* through a multicomponent cis-regulatory element co-occupied by hepatocyte nuclear factor 4 (HNF4), forkhead box O1, FOXO1, CCAAT/enhancer-binding protein (C/EBP) and other hepatic transcription factors (Imai et al., 1990; Stafford, Waltner-Law, & Granner, 2001; Bergot, Diaz-Guerra, Puzenat, Raymondjean, & Kahn, 1992; Diaz Guerra et al., 1993; Gourdon, Lou, Raymondjean, Vasseur-Cognet, & Kahn, 1999; Opherk et al., 2004; Scott, Mitchell, & Granner, 1996; Stafford et al., 2001). This element provides a surface for recruiting coactivator complexes such as NCOA1 and CBP. The transcription coactivator, CREB regulated transcription coactivator 2 (CRTC2), has been reported to interact directly with the GR LBD and facilitate the binding of both GR and CREB to their respective response elements in the regulatory regions of gluconeogenesis genes, (Hill, Suzuki, Segars, & Kino, 2016). In mouse livers, a targeted knockout of *Crtc2* leads to reduced blood glucose levels, improved glucose tolerance and insulin sensitivity, which is attributed to the accompanying decrease in *PEPCK* and *G6pase* expression (Han, Choi, Kim, Kang, & Koo, 2017). In vivo studies have shown that in the initial stages of fasting, CRTC2 associates with p300, leading to CRTC2 acetylation, thereby activating gluconeogenesis. However, as fasting progresses there is a regulator shift whereby the nutrient-sensing deacetylase sirtuin 1 (SIRT1) becomes more abundant, leading to the deacetylation of CRTC2 and ultimately reducing its activity (Liu et al., 2008).

The peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) can also bind and coactivate HNF4, FOXO1 and GR, thereby enhancing the effect of Dex on *PEPCK1* gene induction (Finck & Kelly, 2006; Handschin & Spiegelman, 2006; Yoon et al., 2001). Moreover, it has been shown that the GR target Kruppel-like factor 9 (Klf9) may serve as a link between PGC1a and GR (Chinenov, Coppo, Gupte, Sacta, & Rogatsky, 2014). Both Dex and fasting induce the expression of Klf9 in the liver, which in turn activates the *PPARGC1A* (PGC1α -encoding) gene and, subsequently, *G6pc*, *PEPCK*, and *Glut2*. Consistently, a liver-specific mutation or deficiency in the *Klf9* gene mitigated the Dex-induced hyperglycemia in mice (Cui et al., 2019).

Small heterodimer partner-interacting leucine zipper protein (SMILE) can suppress gluconeogenesis through multiple mechanisms (Lee et al., 2016): It acts as a repressor for several NRs, including GR and HNF4a, by recruiting HDACs and by competing with coactivators, such as PGC1α and GRIP1, for NR binding (Xie, Nedumaran, & Choi, 2009). Additionally, SMILE can directly bind to CREB/CRTC2 and inhibit their activation of the *PPARGC1A* gene, which ultimately results in reduced expression of *PEPCK* and *G6pc* (Lee et al., 2016; Lee et al., 2018).

Recent studies have identified the transcriptional coactivator with PDZ-binding motif (TAZ) as a novel player in hepatic glucose metabolism, by antagonizing GR-mediated activation of gluconeogenic genes. ChIP-seq data from primary mouse hepatocytes overexpressing TAZ showed a decrease in GR enrichment on the regulatory regions of Pck1 and G6pc. Furthermore, co-immunoprecipitation experiments validated a physical interaction between the ww domain of TAZ and the GR LBD (Xu et al., 2021).

Coregulators can induce epigenetic changes that may persist even after discontinuing treatment with GCs. This phenomenon, known as 'metabolic memory', may be responsible for metasteroid hyperglycemia (Janssen and Lamberts, 2014; Morrow & Mulvihill, 2022). In a recent study, male mice treated with Dex for a short period of time had experienced prolonged hyperglycemia due to a persistent reduction in the concentration of glucagon-like peptide 1 (GLP-1), a hormone that helps lower blood glucose levels. This was accompanied by an increase in the expression of dipeptidyl peptidase 4 (Dpp-4), an enzyme that breaks down GLP. The study detected hyperacetylation of the promoter region of Dpp-4, which might contribute to the metabolic memory phenomenon that leads to metasteroid diabetes. Similarly, in cultured murine endothelial cells, treated with Dex, histone hyperacetylation and increased expression of Dpp-4 were observed. Both of these effects were reversed by treatment with either a HAT inhibitor, or a sirtuin activator (Uto et al., 2021).

Despite its name being 'glucocorticoid receptor', GR is central to controlling hepatic lipid metabolism. While the mechanisms by which GR regulates lipogenesis and fatty acid utilization, or the coregulators involved, remain to be dissected, the anti-lipogenic factor and transcriptional repressor, hairy and enhancer of split 1 (HES1), was shown to be a direct GR target gene (Herzig et al., 2003). Hes1 is upregulated by CREB but repressed by GCs, whereby GR disassembles the activators CREB and p300, and replaces them with the inhibitory factor IκBα (Lemke & Herzig, 2006). This transcriptional downregulation of Hes1 relieves its inhibitory effect on lipogenesis (Lemke et al., 2008; Revollo et al., 2013). Interestingly, GR was found to recruit the Mediator subunit MED1to repress Hes1 expression. Consistently, microarray data from murine livers revealed increased Hes1 mRNA following Dex treatment in liver-specific MED1 knockouts compared to controls, and these mice were protected from Dex-induced hepatic steatosis (Jia et al., 2009).

Activation of GR, on the other hand, has been shown to decrease lipogenesis by increasing the expression of Insig2a, which in turn inhibits sterol regulatory element binding proteins (SREBPs) (Roqueta-Rivera et al., 2016; Yabe, Brown, & Goldstein, 2002). This process involves a GR coregulator called SET domain bifurcated 2 (SETDB2), which is essential for activating certain GR targets in the liver, including Insig2a. Moreover, the expression of SETDB2 is heightened during fasting or treatment with Dex, suggesting that GR upregulates its own coactivator. Conversely, knocking down SETDB2 results in a blunted GC-mediated suppression of SREBP processing and augmented lipogenesis (Roqueta-Rivera et al., 2016).

b. **Adipose tissue**

The actions of GR in adipose tissue are diverse, affecting adipocyte differentiation, lipolysis, glucose metabolism, and inflammation (Lee, Harris, & Wang, 2018). With increasing focus on the role of GR in adipocytes, our understanding of GR coregulators involved in adipogenesis and energy homeostasis will deepen soon.

During the early stages of adipogenesis, GCs are crucial for upregulating key adipogenic TFs such as CCAAT/enhancer-binding protein delta (C/EBPδ) and peroxisome proliferator-activated receptor gamma (PPARγ) (Farmer, 2006; Ma, Wang, Zhao, & Xu, 2018; MacDougald, Cornelius, Lin, Chen, & Lane, 1994; Pantoja, Huff, & Yamamoto, 2008; Steger et al., 2010; Yeh, Cao, Classon, & McKnight, 1995). GR mainly functions as a recruiter of coactivators to the enhancer regions of these genes, leading to changes in chromatin architecture and transcriptional activity. For instance, recruitment of GR to C/EBPδ enhancers is followed by CBP binding and H3K27 acetylation, which are associated with direct transcriptional activation of C/EBPδ (Park & Ge, 2017).

In addition to GCs, other adipogenic signals such as insulin and cAMP inducers trigger the assembly of GR, p300, C/EBPβ and MED1, followed by histone H3 acetylation at one of the PPARγ enhancers (Steger et al., 2010). Upon removal of these adipogenic signals, GR binding, H3 acetylation, and enhancer activation are all abolished. However, the transcriptional activity of both PPARγ and C/EBPα continues to establish and maintain adipocyte-selective gene expression. Furthermore, the coregulator cell division cycle and apoptosis regulator protein 1 (CCAR1) is also recruited to the Pparg enhancer regions in a GC-dependent manner and is required for its optimal chromatin remodeling (Ou, Chen, Lee, Wang, & Stallcup, 2014). Interestingly, at promoters of estrogen receptor (ER) target genes, CCAR1 binds to the C-terminal AD domain of CoCoA, which in turn binds p300 and other coregulators from the p160 family (Kim et al., 2008). Conceivably, a similar mechanism may operate at the Pparg enhancer regions in response to GCs.

Besides adipocyte maturation and differentiation, GR orchestrates a systemic mechanism to further augment adipogenesis: GCs elevate the level of circulating fatty acids by augmenting lipogenesis, very low-density lipoprotein (VLDL) secretion from the liver, and lipoprotein lipase (LPL) activity (Gathercole et al., 2011; Peckett et al., 2011). This increases the number of adipocytes and the amounts of fatty acids in circulation, which amplifies the potential for fat accumulation in adipose tissue and highlights the complex and multifaceted nature of GR-mediated regulation, with potential implications for metabolic health and disease.

c. Skeletal Muscle

The impact of GR on metabolic regulation in skeletal muscle varies depending on the mode of its activation. At physiological levels of GCs, GR coordinates the expression of genes that downregulate *de novo* protein synthesis in myofibers, while leaving catabolic pathways of proteins unaffected (Rovito et al., 2021). However, excessive exposure to GCs can inhibit protein synthesis and enhance protein degradation, ultimately leading to muscle atrophy, which is a critical side effect of GC treatment (Bruno et al., 2021). In contrast, intermittent doses of GCs have been shown to improve muscle strength in patients with Duchenne muscular dystrophy (DMD) (Beenakker et al., 2005; Waldrop & Flanigan, 2019).

Prolonged activation of GR in skeletal muscle upregulates the expression of Sesn1 and Ddit4, which act as inhibitors of anabolic pathways mediated by mTORC1. At the same time, GR promotes protein degradation by upregulating Foxo (a forkhead box TF) which in turn enhances the expression of atrogenes such as Atrogin-1/MAFbx (muscle atrophy F-box protein) and MuRF-1 (muscle RING finger-1 protein), specialized E3 ubiquitin ligases (Ryu et al., 2022). This disturbs the metabolic balance in skeletal muscle, causing a shift towards protein turnover (Ahmad et al., 2022; Schakman, Kalista, Barbe, Loumaye, & Thissen, 2013). Three GREs were found near the murine Foxo3 gene and Dex-induced Foxo3 transcription was facilitated by p300 (Kuo et al., 2016). Reducing the expression of p300 in C2C12 myotubes by miRNAs reduced the ability of Dex to stimulate Foxo3 gene expression and to elevate Atrogin-1 transcription. Moreover, downregulation of p300 also dramatically reduced the ability of GCs to induce DNA looping within the Foxo3 locus (Kuo et al., 2016). The expression of p300 and its HAT activity are reportedly enhanced in rats following induction of sepsis and Dex treatment (von Knethen & Brune, 2019). The role of p300 in Dex-induced atrophy involves the acetylation of several other TFs apart from Foxo3: the acetylation levels of Foxo1, NF-κB/p65, C/EBPβ and C/EBPδ were increased in L6 myotubes upon Dex treatment and abolished when cells were additively transfected with p300 siRNA (Chamberlain, Gonnella, Alamdari, Aversa, & Hasselgren, 2012; Yang, Menconi, Wei, Petkova, & Hasselgren, 2005). In addition to enhancing the expression levels of p300, thus leading to a hyperacetylated state in muscles, Dex also decreased HDAC expression and activity in septic rats (Alamdari, Smith, Aversa, & Hasselgren, 2010). It has recently been shown that SIRT6 plays a role in GC-induced muscle atrophy; a deficiency in SIRT6 led to an increase in the activation of the PI3K/AKT pathway which in turn protected the muscle against GC-induced wasting (Mishra et al., 2022).

Muscle atrophy during chronic diseases has also been linked to reduced levels of PGC1α, implying a decrease in the activity of CRTC, a positive modulator of PGC1α transcription (Roberts-Wilson et al., 2010). In L6 rat myotube cells treated with Dex, both the mRNA and nuclear protein levels of PGC1α, CRTC1 and CRTC2 were decreased, and the activity of a PGC1α-luciferase reporter was suppressed. Notably, reporter activity could not be restored by overexpressing CRTC1 or CRTC2, implying a direct suppression of PGC1α transcription by GR (Rahnert, Zheng, Hudson, Woodworth-Hobbs, & Price, 2016). It is noteworthy that the oral administration of omega-3 unsaturated fatty acids worsened GC-induced muscle atrophy in Wistar rats by decreasing the protein levels of PGC1α even further (Fappi et al., 2019; Lee et al., 2022).

By differentially regulating the binding of GR to specific target genes, administering GCs once a week rather than daily can improve muscle repair without causing atrophy. Indeed, chronic daily dosing of prednisone, a synthetic GC, promotes atrophy by suppressing the expression of Klf15 in skeletal muscle, while increasing the expression of the Fbxo32 gene, which encodes atrogin-1. Conversely, administering the hormone once a week enhanced the expression of Klf15; with reduced H3K9me3 and increased H3K27ac at the GRE of the Klf15 promoter (Quattrocelli et al., 2017). The efficacy of this intermittent treatment on muscle mitochondrial remodeling is maximal at the rest phase, and dependent on an intact circadian clock and muscle PGC1α.

In mice, intermittent prednisone treatment during the light phase resulted in the co-recruitment of GR and BMAL1 to the *Nampt* and *Ppargc1a* genes, which are involved in mitochondrial biogenesis in quadriceps muscles (Quattrocelli et al., 2022a). NAMPT generates NAD+, which serves as a substrate for sirtuin-mediated deacetylation and activation of PGC1α (Rodgers et al., 2005). Ablation of PGC1α weakened the effect of prednisone on muscle mitochondrial density (Quattrocelli et al., 2022a).

Thus, a prolonged activation of GR blunts the expression of PGC1α, leading to muscle atrophy, whereas transient treatment (mainly at the trough of endogenous GCs) enhances PGC1α expression, which improves nutrient utilization and protects against muscle atrophy.

5. Coregulators of GR in the central nervous system (CNS)

As outlined in the Introduction, GCs are both a product and a fundamental part of the HPA axis, which, as the name implies, is primarily controlled by the central nervous system (CNS; Fig. 1A). Input from both neurotransmitters and GC levels initiate the neuronal axis in the hypothalamus. The periventricular nucleus (PVN) in the hypothalamus is involved in the cessation of CRH production in response to negative feedback from adrenal-produced GCs, whereas parts of the limbic system, the central nucleus of the amygdala (CeA) and ventral hippocampus (VH), initiate CRH production in response to GCs and stress (Whitaker, Farooq, Edwards, & Gilpin, 2016). Thus, GR can both repress the CRH gene in the PVN and activate it in the amygdala (Lachize et al., 2009).

Apart from the HPA axis itself, the release of stress hormones or aberrant GR signaling has been implicated in mood-, stress- and anxiety-related disorders, memory and cognitive deficits, as well as psychiatric and neurodegenerative diseases (Meijer et al., 2023). GR expression and that of its known coregulators varies widely across brain regions and cell subtypes in the CNS (Viho, Buurstede, Berkhout, Mahfouz, & Meijer, 2022). GR is expressed throughout the CNS, with high expression in the cortex, hippocampus, and thalamus (Mahfouz et al., 2016; Meijer et al., 2023). Multiple GR coregulators, including NCoA2/GRIP1/SRC2 and NCoR1, have been shown to be co-expressed with GR in various brain regions (Mahfouz et al., 2016), consistent with the ability of GR to modulate a variety of neuronal processes.

NCoA1/SRC1 is the most well-studied p160 family member in the brain. However, all three are expressed throughout the brain and spinal cord, with some differences in regional distribution (Sun & Xu, 2020). The p160 family members may perform compensatory functions as SRC1 deletion led to upregulation of NCoA2/GRIP1/SRC2 (Meng et al., 2022). In multiple tests for anxious behavior, coordination of motor function, and pain response, there were differences between individual p160s as well as unique sex differences between them (Stashi, Wang, Mani, York, & O'Malley, 2013). For example, in the elevated plus maze test for anxiety, SRC1-/- male and SRC2-/- female mice exhibited less anxiety compared to both control mice and those of the opposite sex, whereas female SRC3-/- mice displayed an increase in anxiety. Each SRC/p160 family member displayed individual behavioral function based on localization within brain regions, with some overlap. Thus, both sexual dimorphism and the potential compensatory contribution of the p160 family members have to be considered when evaluating

loss of function phenotypes. Interestingly, GR agonist treatment of adrenalectomized mice increased SRC1 and decreased GR expression; the levels of other GR interactors, STAT3 and HDAC1, were decreased in female mice only (Heck, Thompson, Uht, & Handa, 2020), suggesting that not only adrenal-produced but also exogenous GCs can modulate expression of GR as well as specific coregulators and they do so in sex-specific manner.

Mice completely lacking SRC1 lose their responsiveness to Dex treatment both in the PVN and CeA (Lachize et al., 2009). Importantly, however, SRC1 encodes two splice variants, SRC1a and SRC1e, which differ in their C-terminal domain (van der Laan, Lachize, Vreugdenhil, de Kloet, & Meijer, 2008). SRC1a contains an additional LXXLL motif and a repression domain, whereas SRC1e possesses an exon with a stop codon upstream of the repression domain, which makes it possible to study the splice variants by exon skipping with antisense oligonucleotides (Zalachoras et al., 2016). Reportedly, the two isoforms are expressed at different levels across brain regions: SRC1a is highly expressed in the PVN, whereas SRC1e is highly expressed in the CeA, a region involved in the stress/fear response. Moreover, the two variants appear to play distinct roles in the HPA axis regulation, with SRC1a being critical for GR-mediated repression of the HPA axis. In the pituitary cell line At-20, GR-mediated repression of CRH production was increased with SRC1a overexpression and decreased with overexpression of SRC1e (van der Laan et al., 2008). In response to stressors and excitatory signaling, liganded GR activates CRH transcription in the CeA to ensure cortisol production. Loss of SRC1e ablated the upregulation of CRH in CeA in response to Dex treatment, thereby interrupting the fear/anxiety response to stimuli in a gene-specific manner (Zalachoras et al., 2016). Consistently, among rats exposed to an odor of a predator, those with increased avoidant behavior had decreased expression of SRC1 in the PVN and increased expression in the VH (Whitaker et al., 2016). The importance of SRC1 at the GREs in the CRH regulatory region has been demonstrated in humans, rodents, and tree shrews for both activating and repressing transcription. In fact, the tree shrew CRH promoter contains an additional active GRE (that may be not functional in the homologous human locus) making it much more responsive to GR agonist treatment. The GR transcription complex at this site has been demonstrated to include SRC1, CRSP150 (SP1-related coregulator subunit), and Trap220 (Fang et al., 2016).

Among the known GR coregulators, ATP-dependent chromatin remodelers have also been studied as modulators of GR function in the CNS. GR-mediated repression of the pituitary POMC gene is a part of the negative feedback loop of the HPA axis. In this context, BRG1, the catalytic component of the SWI/SNF complex, recruits GR, NGFI-B, and HDAC2 to the POMC promoter and helps stabilize the repression complex (Bilodeau et al., 2006). Abnormalities in BRG1 expression or subcellular localization were found in samples of corticotroph adenomas from Cushing's Disease patients and correlated with disruption of HPA feedback and GC resistance (Bilodeau et al., 2006). Histone modifiers in addition to HDAC2 and DNA methyltransferases were found to act as coregulators of GR target genes in the CNS, and the HPA axis specifically. In a rat neuronal cell line, GR was shown to interact with HDAC1 and methyl-CpG binding protein-2 (MeCP2) to form a repressive complex at the CRH promoter (Sharma, Bhave, Gregg, & Uht, 2013). Thus, GR relies on combinatorial CNS region- and gene-specific functions of panels of transcriptional coregulators to elicit precise responses of the HPA axis to changing physiological and environmental settings.

GR is a phosphoprotein with numerous sites targeted by a plethora of kinases (Ismaili & Garabedian, 2004). Interestingly, two sites, S267 and S134, identified specifically in the CNS, are targets for the BDNF-Trkb kinase pathway (Arango-Lievano et al., 2019; Lambert et al., 2013), and the pattern of phosphorylation changes in aging-related contexts including Alzheimer's disease (Dromard et al., 2022). Importantly, phosphorylation at those neurotropic sites is also reportedly required for neuronal plasticity in learning (Arango-Lievano et al., 2019). Phosphorylation of GR has long been known to dictate differential coregulator recruitment and, thus, context-specific activation or repression of GR target genes (Garabedian, Harris, & Jeanneteau, 2017; Ismaili & Garabedian, 2004). Conceivably, sites of CNS-specific phosphorylation create a unique landscape of coregulator utilization, providing an additional tissue-specific layer of regulation of GC function.

The GR-encoding NR3C1 gene gives rise to multiple variants through alternative promoter and transcription initiation site usage (Ke et al., 2015). Interestingly, one GR variant is highly expressed in the hippocampus and is reportedly upregulated in male rats with intrauterine growth restriction, a disorder with high risk for neurodevelopmental delays (Ke et al., 2015). These neurodevelopmental deficits may be impacted by alterations in the HPA axis negative feedback loop. The existence of GR transcriptional isoforms is likely another variable shaping regional differences in coregulator recruitment across the CNS.

6. GR and the circadian system

As mentioned above, most physiological processes in the cardiovascular, endocrine, metabolic and immune systems are modulated by rhythmic oscillations of internal circadian clocks (Richards & Gumz, 2013). The clock is organized hierarchically, with the master clock in the suprachiasmatic nucleus of the hypothalamus modulating the peripheral clocks found throughout the body (Takahashi, 2017). The core clock is regulated by three overlapping feedback loops: the central loop involves BMAL1:CLOCK which induce PER1-3 and CRY1-2, which downregulate their own expression via negative feedback (Curtis, Bellet, Sassone-Corsi, & O'Neill, 2014). As part of the second loop, RAR-related orphan receptors (RORs) upregulate BMAL1 and REV-ERBs repress it (Curtis et al., 2014).

GR operates within core clock machinery, as part of the GR:CLOCK:BMAL1 complex, binding to the promoter and repressing the expression of *Nr1d1/Rev-erbα* (Murayama et al., 2019). REV-ERBα in turn represses Bmal1, so the interaction of GR with the core clock proteins comprises an important regulatory loop. Interestingly, NCoA2/GRIP1/SRC2 has been identified as a coregulator of the BMAL1:CLOCK complex, acting as a coactivator needed for proper rhythmicity of the central clock and liver clock gene expression (Stashi et al., 2014). Although GR and GRIP1 have not been reported in a complex with BMAL1:CLOCK together, there is sufficient evidence to speculate that GR and GRIP1 cooperate in regulating the core clock genes.

Cryptochromes 1 and 2 were reported to act as GR corepressors, interacting with the liganded receptor in MEFs and showing overlapping binding patters by ChIP-seq in mouse livers harvested around the clock (Lamia et al., 2011). They inhibited the GR-regulated core clock gene Per1, as well as Pck1 in the liver (Lamia et al., 2011). The systemic effects of GR on circadian system and metabolism are both regulated by the cryptochromes, which themselves bridge the two systems in response to metabolic cues.

The tight connection between the circadian and metabolic system has been well-described, wherein core clock TFs directly modulate liver metabolic enzymes, as well as the liver clock (Reinke & Asher, 2016). For example, deletion of REV-ERBs in the liver derepresses clock genes and leads to hepatic steatosis (Bugge et al., 2012). In the liver, genes repressed by feeding appear to be co-regulated by GR and FOXO1. Postprandially, GR and FOXO1 co-occupancy at enhancers of feeding-repressed genes, such as Pck1 and Angptl4, was reduced (Kalvisa et al., 2018). In the future, it will be informative to dissect the causal links between GR and FOXO1 occupancy and the regulation of these genes.

The possibility of exploiting the effects of GR on diurnal rhythms has been tested in mice in vivo by targeting GR coregulators to improve oxidation of nutrients in dystrophic muscle. As described above, administration of prednisone to mice only in the light phase enhanced the interaction of GR with BMAL1, specifically at the regulatory regions of genes controlling muscle NAD+ production and mitochondrial

biogenesis (Quattrocelli et al., 2022b). In a different pathophysiological setting, during high-fat diet-induced obesity in mice, co-occupancy of STAT5 and GR at enhancers of metabolic genes doubled in livers at the beginning of the dark cycle, and the increased binding of GR was STAT5-dependent (Quagliarini et al., 2019). The gained sites at metabolic enhancers were associated with GR-dependent downregulation of lipid metabolism and triglyceride levels in the liver during the dark cycle. The translational relevance of targeting the GR:STAT5 or the CRY/BMAL1 interactions awaits further investigation. approaches.

7. Conclusion

GR coregulators play a crucial role in regulating receptor function in various cell types and systems. Our analysis of GR interactome data along with the extensive body of literature reviewed here, indicate that many of these proteins modulate GR activity in a tissue-specific manner, whereas others have more widespread effects across different tissues. Undoubtedly, this diversity enables GR to adapt to complex and changing environments with remarkable precision, however, it also poses significant challenges for developing drugs that target GR function. Therefore, a better understanding of the specific roles of GR coregulators remains key to improving existing and generating novel therapeutic modalities.

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Declaration of Competing Interest

The authors (Lina Fadel, Marija Dacic, Vlera Fonda, Baila A. Sokolsky, Fabiana Quagliarini, Inez Rogatsky, N. Henriette Uhlenhaut) have no competing interests to declare.

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Appendix A. Supplementary data

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