EPIGENETICS
2025, VOL. 20, NO. 1, 2468113
https://doi.org/10.1080/15592294.2025.2468113

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

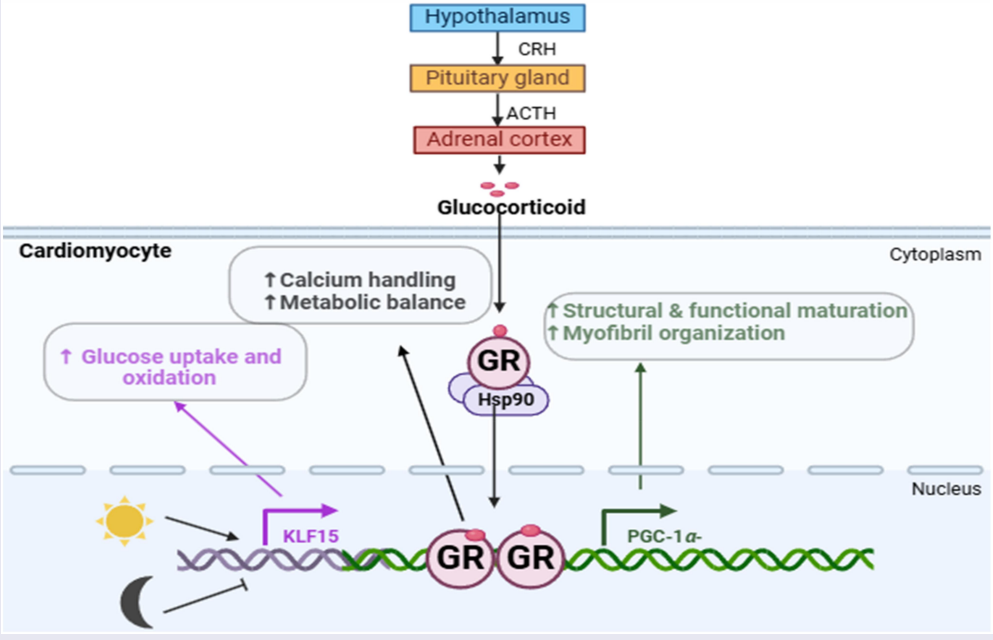
Glucocorticoid receptor epigenetic activity in the heart

Olukunle Akinborewa [a,b] and Mattia Quattrocelli [a,c]

[a]Molecular Cardiovascular Biology, Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [b]Department of Pharmacology, Physiology, and Neurobiology, University of Cincinnati College of Medicine, Cincinnati, OH, USA; [c]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

ABSTRACT

The glucocorticoid receptor (GR) is a critical nuclear receptor that regulates gene expression in diverse tissues, including the heart, where it plays a key role in maintaining cardiovascular health. GR signaling influences essential processes within cardiomyocytes, including hypertrophy, calcium handling, and metabolic balance, all of which are vital for proper cardiac function. Dysregulation of GR activity has been implicated in various cardiovascular diseases (CVDs), highlighting the potential of GR as a therapeutic target. Remarkably, recent insights into GR's epigenetic regulation and its interaction with circadian rhythms reveal opportunities to optimize therapeutic strategies by aligning glucocorticoid administration with circadian timing. In this review, we provide an overview of the glucocorticoid receptor's role in cardiac physiology, detailing its genomic and non-genomic pathways, interactions with epigenetic and circadian regulatory mechanisms, and implications for cardiovascular disease. By dissecting these molecular interactions, this review outlines the potential of epigenetically informed and circadian-timed interventions that could change the current paradigms of CVD treatments in favor of precise and effective therapies.



ARTICLE HISTORY
Received 13 November 2024
Revised 23 January 2025
Accepted 11 February 2025

KEYWORDS
Glucocorticoid receptor; heart; epigenetics; circadian clock

Introduction

Epigenetics explores consequential and sometimes inheritable changes in gene expression that arise from modifications to DNA structure and interaction with proteins, rather than changes in the DNA sequence itself [1–3]. Cardiovascular

CONTACT Mattia Quattrocelli mattia.quattrocelli@gmail.com; mattia.quattrocelli@cchmc.org Molecular Cardiovascular Biology, Heart Institute, Cincinnati Children's Hospital Medical Center, T4.676 Building, 240 Sabin Way, Cincinnati, OH 45229, USA

diseases (CVD) are a leading cause of death worldwide [4,5]. Conditions such as coronary heart disease, hypertension, and heart failure are influenced by a combination of biochemical, environmental, behavioral, and genetic factors, as highlighted by the long-term Framingham Heart Study [6]. The incidence of CVD is rising annually, with an alarming trend towards younger onset ages [7–9]. Recent research emphasizes the significant role of epigenetic modifications in the development and progression of CVD [10–12]. These modifications could serve as important early molecular markers for diagnosing cardiovascular conditions and predicting treatment responses. Given the complexity of CVD pathogenesis and the challenges in treatment, reversibility of epigenetic changes presents new therapeutic opportunities, making epigenetic-based strategies a critical research focus.

In this review, we examine the epigenetic activity of the glucocorticoid receptor (GR) in the heart. GR is a nuclear receptor that mediates the actions of glucocorticoids, which are hormones released in response to circadian rhythms and stress. These hormones are pivotal for homeostasis, metabolism, inflammation, immune responses, cardiovascular function, reproduction, and cognition. Upon glucocorticoid activation, GR functions as a transcription factor, exerting genomic and non-genomic effects. High serum levels of cortisol, a key glucocorticoid, is a known risk factor for heart failure [13], highlighting the impact of GR signaling in cardiomyocytes on disease progression.

GR structure and function

Glucocorticoids are steroid hormones produced by the adrenal glands and are critical for basal and stress-induced homeostasis as end products of the hypothalamic-pituitary-adrenal (HPA) axis [14,15]. They regulate metabolism, inflammation, and immune response [16,17], and serve as immunomodulatory agents in inflammatory, autoimmune, and lymphoproliferative conditions [18–20]. Glucocorticoids exhibit highly potent anti-inflammatory effects in the heart, as well as other major organs in the body such as the liver, brain, skeletal muscles, and adipose tissue [21–24]. They impede the production of inflammatory agents like cytokines and directly repress the transcription of pro-inflammatory genes, while enhancing the expression of anti-inflammatory proteins. Consequentially, they are frequently used to protect the heart from inflammatory injuries in myocarditis treatment [25]. Glucocorticoids are released in response to circadian rhythms and stress through regulation by the HPA axis [26,27], where corticotropin-releasing hormone (CRH) from the hypothalamus signals the anterior pituitary to release adrenocorticotropic hormone (ACTH), which then stimulates glucocorticoid synthesis in the zona fasciculata of the adrenal cortex. Through a negative feedback loop, glucocorticoids inhibit CRH and ACTH production to control their levels and duration in the body [28]. All glucocorticoids are enzymatically derived from cholesterol, and the end-product of this pathway is their inactive forms – cortisone in humans and 11-dehydrocorticosterone in rodents. In the liver, 11β-Hydroxysteroid dehydrogenase enzymes modulate the conversion of these inactive glucocorticoids to their active forms – cortisol and corticosterone, respectively [29]. The cellular effects of these active glucocorticoids are mediated by the glucocorticoid receptor (GR), encoded by the *NR3C1* gene in humans, a member of the nuclear receptor superfamily. The GR is widely expressed in human tissues and functions as a hormone-dependent transcription factor regulating the expression of approximately 3–10% of the human genome, either directly or indirectly [30,31]. The GR has a modular structure comprising several regions: the N-terminal A/B region, or N-terminal domain (NTD) with the first protein-protein interaction domain called AF-1 (activated function 1); the C region, which forms the DNA-binding domain (DBD); the D, or hinge region; and the E region, representing the ligand-binding domain (LBD) with the second interaction domain AF-2 (Figure 1) [30,31]. The human GR locus spans ~ 160 kb on chromosome 5 (5q31.3) and produces two isoforms, GRα and GRβ, via alternative splicing of exon 9 [32–34]. While GRβ works as a negative regulator, GRα - the 'main' GR isoform – is broadly expressed and exerts the glucocorticoid-dependent transcription factor function [33–35].

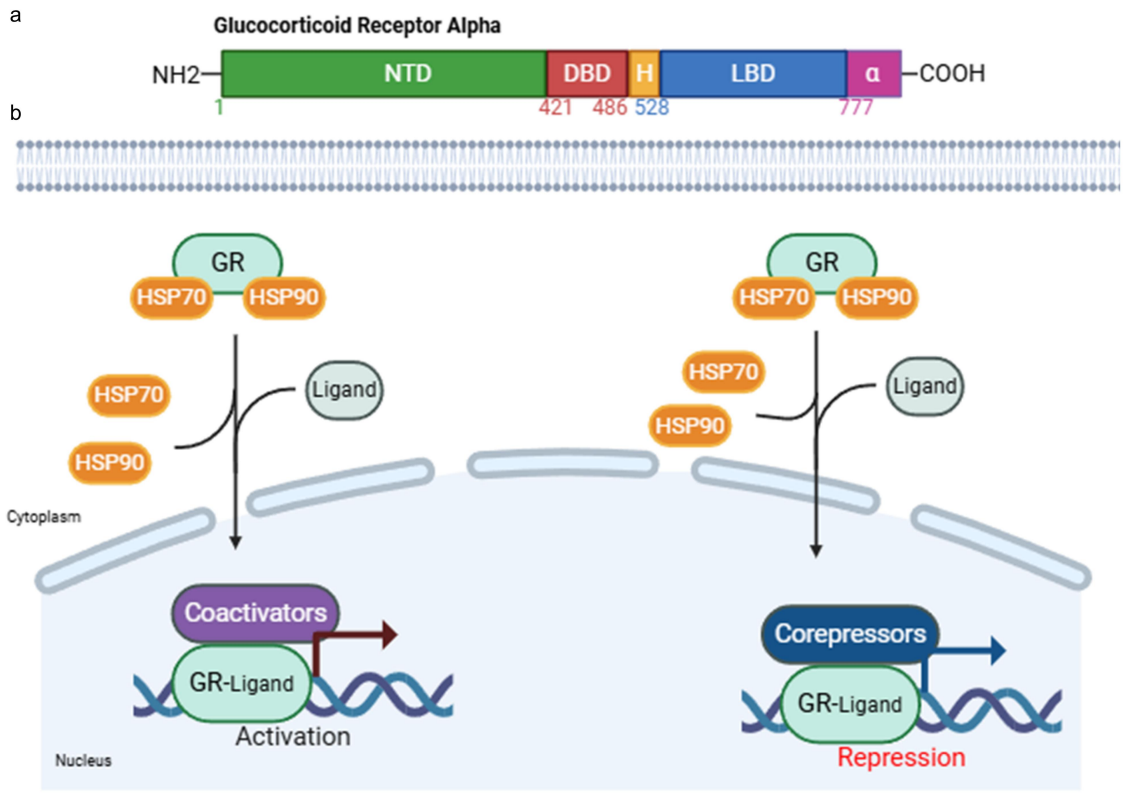


Figure 1. Diagram of GR domains and ligand-induced activity. (A) Linear domain structure of the human GR protein. Domains from left to right: N-terminal domain (NTD), DNA-binding domain (DBD), hinge region (H) and ligand-binding domain (LBD). (B) Mechanism of action of glucocorticoid-driven GR transactivation vs transrepression activity based on context, i.e., interacting co-factors.

Regulation of GR translocation

In the absence of a ligand, GR primarily resides in the cytoplasm as part of a multiprotein complex that includes two heat-shock protein molecules (HSP90 and HSP70) and other proteins (Figure 1) [36–38]. Upon ligand binding, activated glucocorticoid-bound GR dissociates from this complex and translocates into the nucleus [39]. This translocation is facilitated by two nuclear localization signals (NL1 and NL2), with NL1 relying on importin-α for energy-dependent nuclear import. In the cytoplasm, the binding of HSP90 to the ligand-binding domain (LBD) of GR masks NL1 and NL2, keeping the receptor inactive [40]. Once in the nucleus, GR forms a homodimer and binds to specific DNA sequences called Glucocorticoid Response Elements (GREs), which are its canonical binding sites in the DNA [31,39]. This binding allows GR to act as a classic transcription factor by directly interacting with its own recognition site on DNA to enhance gene transcription [40–45]. Notably, GR can also interact with other transcription factors – this interaction allows it to bind to composite elements and regulate gene expression in more complex and tissue-specific ways. After regulating its target genes, GRα either returns to the cytoplasm as part of a protein complex or is degraded in the nucleus via the ubiquitin-proteasome system, which limits its transcriptional activity [46–50].

Regulation of GR cistrome

Chromatin immunoprecipitation followed by genome-wide sequencing (ChIP-seq) has revealed that the GR cistrome is highly specific to each cell type [51,52]. The GR cistrome refers to the complete set of genomic regions regulated by the GR [52–54]. This specificity is linked to unique patterns of GR-associated proteins, such as pioneering and cooperating transcription factors (TFs) and coregulators, collectively termed the GR interactome [55]. Through its cistrome, the GR can activate and repress target genes concurrently. To activate

genes, homodimeric GR recruits coactivator molecules, including steroid receptor coactivators (SRC1–3) and histone acetyltransferases like CBP/p300 [56,57]. In contrast, for gene repression, GR can either tether to transcription factors such as NF-κB, interfering with their ability to activate transcription [58–60], or bind directly to repressive cofactors like NCOR1 and SMRT (also known as NCOR2) [61–63]. Therefore, the GR cistrome can be divided into two groups based on their cell type-specific behavior. The first group consists of genes that are regulated by GR independently of cellular context, such as those involved in maintaining basal cellular processes or circadian rhythms, like *Per1* and *Klf15* [64,65]. The second group includes genes whose expressions vary between tissues in response to glucocorticoid treatment [64]. The cell type-specific nature of the GR cistrome is driven by the unique accessibility and function of lineage-specific enhancers. Understanding how these factors, whether transient or sustained, affect enhancer dynamics, GR binding, and coregulator recruitment will be critical for advancing our knowledge of GR regulation in cardiac tissue.

GR and epigenetic modifiers

Epigenetic mechanisms provide essential control over gene expression and silencing within cells, significantly influencing tissue-specific functions and cell differentiation [66–68]. The three main epigenetic mechanisms include DNA methylation, histone modification, and non-coding RNA (ncRNA)-associated gene silencing [69–71]. Numerous studies have described an interplay between the GR and histone modification, as well as DNA methylation. Histone modifications, such as acetylation, methylation, phosphorylation, and ubiquitylation, adjust DNA-histone interactions, with acetylation generally promoting transcription by loosening chromatin. DNA methylation typically silences genes through the addition of methyl groups to CpG islands in promoter regions, recruiting suppressor proteins and reducing transcription factor interaction [65].

Early life stress is linked to increased methylation of the *NR3C1* gene, which encodes the GR. Raffetti et al. demonstrated that methylation at the exon 1F locus of *NR3C1* is associated with altered morning cortisol levels and may predict substance use in adolescents [72]. Similarly, Cicchetti and Handley found associations between *NR3C1* methylation and adverse conditions in children, such as emotional instability, externalizing behaviors, and depressive symptoms [73].

In adult brain tumor patients, Wiencke et al. identified DNA methylation as a pharmacodynamic marker of dexamethasone (DEX) exposure [74]. DEX is an exogenous glucocorticoid that mediates its effect through the GR. They showed that blood DNA methylation could differentiate DEX-exposed individuals from non-exposed ones. Additionally, neutrophil-specific methylation markers predicted survival outcomes, suggesting a prognostic role for methylation in treatment response. Extending these findings to CVD could provide novel insights into glucocorticoid and GR-based therapies.

Glucocorticoids are commonly used to treat lymphomas because they can induce lymphocyte apoptosis. However, their effectiveness is often limited due to the development of glucocorticoid resistance. A study by Wu et al identified *Histone-lysine N-methyltransferase 2D (KMT2D)* as a key player in this resistance [75]. *KMT2D* is a histone methyltransferase that regulates gene expression by adding methyl groups to histones [76]. Mutations in *KMT2D* are associated with several cancers and are known to indicate poor prognosis [77]. In their study, they found that knocking out *KMT2D* reduced GR protein levels [75]. Restoring *KMT2D* expression reversed this effect, confirming its role in stabilizing GR levels. They also discovered that KMT2D binds to the GR, and this is amplified in the presence of glucocorticoids. These findings suggest that *KMT2D* mutations may lead to glucocorticoid resistance in cancers by disrupting GR expression and stability.

Ito et al. studied how glucocorticoids regulate IL-1β-induced gene expression and histone modification processes, including histone acetyltransferase (HAT) and histone deacetylase (HDAC) activities [78]. At higher concentrations, DEX increased HAT activity but acetylated lysines K5 and K16 on histone H4, distinct from IL-1β, which targeted K8 and K12. Also, GR recruited HDAC2 to the NF-κB and CREB-binding protein HAT complex, reducing histone acetylation and

suppressing inflammatory gene expression. These findings imply that the GR can modulate histone acetylation by primarily recruiting HDACs and HATs. This mechanism plays a key role in the anti-inflammatory effects of glucocorticoids – suppression of inflammatory gene expression by controlling DNA accessibility to transcription factors.

In the liver, GR modulates histone acetylation to antagonize NRF2 (nuclear factor erythroid 2-related factor 2), a key transcriptional activator of antioxidant genes. This occurs through GR's direct binding to specific DNA sequences called antioxidant response elements (AREs). DEX enhances GR binding to AREs, blocking CBP recruitment and NRF2-dependent histone acetylation [79]. This reduces NRF2-mediated cytoprotection from oxidative stress, linking impaired antioxidant responses to glucocorticoid side effects. Investigating similar epigenetic effects in the heart could provide insights into glucocorticoid impact on cardiovascular health.

Role of cardiomyocyte GR in fetal heart development

Elevated serum cortisol is a known risk factor for cardiac failure [13], emphasizing the role of glucocorticoid signaling in cardiomyocytes and its influence on disease progression. GR plays a critical role in fetal heart development by influencing cardiomyocyte differentiation, metabolism, and calcium signaling, which collectively contribute to cardiac remodeling and function.

Rog-Zielinska et al. investigated the role of GR in heart development and found that glucocorticoids support both structural and functional maturation of fetal cardiomyocytes [80]. They showed that cultured fetal mouse cardiomyocytes have a functional GR that actively responds to glucocorticoid treatment, highlighting GR's role in heart maturation [81]. They further demonstrated that endogenous glucocorticoids, acting via GR, are essential in fetal cardiomyocytes and vascular smooth muscle, where they facilitate myofibril assembly and organization, ultimately enhancing systolic function and cardiac ultrastructural development *in vivo*. Subsequently, they identified PGC-1α, a key regulator of cardiac mitochondrial capacity, among the genes upregulated by glucocorticoid treatment in primary fetal cardiomyocytes, both *in vivo* and *in vitro*. This upregulation also includes genes such as *Myh6* and *Nppa*, reflecting similar gene expression patterns seen in the fetal heart's response to glucocorticoids [81]. In summary, cardiomyocyte GR is required for the development of a structurally and functionally competent fetal heart *in vivo*.

Role of cardiomyocyte GR in adult heart function

GR has high expression levels in the adult heart, where it exerts both genomic and non-genomic effects [82]. DEX-mediated GR activation increases cardiomyocyte size, suggesting GR activation is sufficient to induce hypertrophy, especially in conjunction with growth stimuli [69]. Interestingly, cardiac-specific GR knockout in mice also leads to hypertrophy and heart failure by 3 months of age [83]. Non-genomic GR effects, such as its localization to membranes and mitochondria, may work alongside genomic targets to promote hypertrophy [82].

The Cidlowski group have extensively studied the actions of glucocorticoids in the heart through the GR with transgenic mouse models that specifically target the cardiomyocyte GR. Initially, they demonstrated that glucocorticoids and their associated signaling pathways are crucial for maintaining normal heart function [84,85]. Subsequently, they showed that ablation of cardiomyocyte GR results in sex-specific alterations in cardiac gene expression, eventually leading to heart failure [83]. In male mice, left ventricular systolic dysfunction emerged by 3 months of age, while females took longer to exhibit this phenotype. Supporting these observations, RNA-Seq analysis revealed that GR deletion in male hearts led to more substantial disruptions in the expression of genes involved in heart rate regulation, particularly those controlling calcium handling. Correspondingly, cardiomyocytes isolated from male cardiomyocyte-GR-KO hearts showed abnormal intracellular calcium responses. In contrast, female GR-deficient cardiomyocytes maintained calcium responses comparable to controls, highlighting a sex-specific impact of GR on cardiac function [83]. In another study, they further demonstrated that cardiomyocyte GR

plays a direct and opposing role in regulating heart disease [86]. In addition to its role in preventing failure, GR contributes to maintaining cardiac structural integrity. Glucocorticoids preserve the t-tubular system in ventricular cardiomyocytes by upregulating the autophagic flux [87]. These findings highlight the dual role of GR signaling in promoting hypertrophy while also preventing fibrosis and failure, which show the delicate balance required for optimal cardiac function.

In 2019, Severinova et al. observed a marked increase in cardiomyocyte surface area following 24 hours of DEX treatment, indicating hypertrophy [82]. This aligns with findings by Ren et al., who reported similar hypertrophic changes in H9c2 cells and neonatal cardiomyocytes after 72 hours of Dex exposure [88]. Severinova et al. further identified early GR targets in cardiomyocytes that regulate RNA pol II-dependent transcription and gene expression. These findings complement Rog-Zielinska et al.'s study, which demonstrated similar transcriptional changes in mouse hearts following DEX injection. Among the genes identified in both studies was *Klf9*, which Thakkar et al. recently showed to be crucial for GR-dependent metabolic adaptations in cardiomyocytes [89]. Notably, *Klf9* knockdown was found to inhibit DEX-induced enhancements in glycolytic function and mitochondrial spare respiratory capacity.

In summary, transgenic mouse models engineered to inactivate or overexpress GR in cardiomyocytes have become essential tools for delineating GR's role in the heart. These models reveal that cardiomyocyte GR is crucial both for maturation of the fetal heart and for sustaining normal heart function into adulthood. Table 1 summarizes the actions of GR in the heart. Various findings suggest that cardiac abnormalities observed with glucocorticoid deficiencies or excess may be directly linked to inadequate GR signaling within cardiomyocytes. However, the exact downstream genes in cardiomyocytes and GR's epigenetic mechanisms in heart function remain open research questions.

Circadian control of GR action in the heart

It is well-known that glucocorticoids follow a strong circadian rhythm in their secretion, peaking at the beginning of the feeding phase – early night in rodents and early morning in humans [91–95]. Circadian rhythms are regulated by internal molecular clocks that are influenced by the 24-hour day-night cycle [26,91,96,97]. Light and dark signals are detected by the retina and translated into neuronal activity, which is then transmitted to the brain's suprachiasmatic nucleus (SCN), the central pacemaker of the circadian system [91,98]. The clock gene machinery exists in nearly all body cells, and there is a reciprocal interaction with GR at the transcriptional, translational, and post-translational levels [99]. At the molecular level, the circadian clock operates through a 24-hour feedback loop in which the activators CLOCK (circadian locomotor output cycles kaput) and BMAL1 (brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1) form a heterodimer that stimulates the transcription of their own repressors, CRY1/2 (Cryptochrome 1/2) and PER1/2 (Period 1/2) [100–102]. Remarkably, the relationship between the GR and the circadian rhythm is bidirectional. Glucocorticoids can independently synchronize a wide range of important clock genes, including PER1, CRY1, and BMAL1, by coordinating transcriptional cascades through the GR [103]. Meanwhile, the circadian co-regulators cryptochromes 1 and 2 interact with GR in a ligand-dependent manner, broadly modifying the transcriptional response to glucocorticoids [93]. Research by Oster et al., using circadian microarray profiling of adrenal glands, identified a circadian clock specifically in the outer adrenal cortex. This localized clock drives the rhythmic production of glucocorticoids and mineralocorticoids in the adrenal gland [96]. The interaction between the circadian clock and GR activity has also been established in the immune cells [92] and the liver [104]. Here, we discuss GR-clock interaction in the heart.

Rev-Erb alpha (REV-ERBα), a circadian transcription repressor, directly interacts with the GR in the liver to regulate energy metabolism [104]. GR and REV-ERBα are both nuclear receptors that regulate similar physiological processes, including metabolism and inflammation. Also, REV-ERBα generally influences the protein stability and subcellular localization of the GR [105]. Interestingly,

Table 1. Studies on the GR-mediated effects of glucocorticoids in fetal and adult heart.

Study	Model	Findings
Role of GR in fetal heart maturation [80]	Global inactivation of GR in fetal mice	Decrease in size of fetal hearts. Overall impairment in heart function as shown by a significant rise in the Doppler-derived myocardial performance index (MPI), a measure of combined systolic and diastolic function irrespective of heart rate and size. Diastolic dysfunction in fetal hearts. Absence of normal maturational increase in expression levels of the following genes: ● Alpha myosin heavy chain (Myh6) ● Cardiac ryanodine receptor (Ryr2) ● Sodium calcium exchanger (NCX1) ● Sarcoplasmic reticulum calcium ATPase (SERCA2a) ● Atrial natriuretic peptide (Nppa) ● Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (Ppargc1a)
Role of GR in fetal heart maturation [80]	Tissue-specific inactivation of GR in cardiomyocytes and vascular smooth muscle cells of fetal mice	No change in size of fetal hearts. Overall impairment in heart function as shown by a significant rise in MPI. No impairment of diastolic function in fetal hearts. LV systolic dysfunction in fetal hearts. Impaired calcium handling via dysregulation of SERCA2a and Ryr2. Normal maturational increase in expression levels of *Myh6* and *Nppa*.
Role of GR in fetal heart function [81]	Glucocorticoid treatment in primary fetal cardiomyocytes (*in vivo* and *in vitro)*	Promotion of myofibril assembly and organization via direct GR activity. Enhancement of systolic function via direct GR activity. Upregulation of PGC-1α, a key regulator of cardiac mitochondrial capacity in primary fetal cardiomyocytes.
Role of GR in the adult heart [90]	GR overexpression in cardiomyocytes of adult mice	No major alterations in cardiac function. No cardiac hypertrophy and fibrosis. Bradycardia and atrio-ventricular block.
Role of GR in the adult heart [85]	Cardiomyocyte-specific GR knockout	Premature death from heart failure (median survival age of about 7 months). LV dilation and hypertrophy. LV systolic dysfunction - ↓Ejection Fraction and ↓Fractional Shortening Upregulation of ● Beta-myosin heavy chain (Myh7) ● Skeletal muscle alpha actin (Acta1) ● Smooth muscle alpha actin (Acta2) ● Brain natriuretic peptide (Nppb) Downregulation of ● Ryr2 ● Dystrophin (Dmd) ● Kruppel like factor 15 (Klf15) ● Prostaglandin D2 synthase (Ptgds) ● Lipocalin (Lcn2) ● Tristetraprolin (Zfp36)

REV-ERBα has been shown to be cardioprotective against cardiac hypertrophy, fibrosis, and heart failure [106]. In this study, they revealed that REV-ERBα colocalizes with transcription factors like Myocyte Enhancer Factor 2 (MEF2) and suppresses abnormal gene expression during pathological cardiac remodeling. MEF2 is also a circadian transcription factor, and a molecular interplay of GR and MEF2 has been established in the control of genes important for neuronal plasticity [107]. Hence, it is very possible to implicate the GR as an additional partner in this REV-ERB and MEF2 interaction network in the heart. Thus, a detailed study of the interaction between REV-ERBα and the GR specifically in the heart is required to gain additional insight into the role of GR during pathological cardiac remodeling.

The GR has recently been linked to ventricular arrhythmia (VA), a condition that accounts for 15–20% of deaths worldwide [108]. Sudden cardiac deaths caused by VA show a circadian pattern, with a higher occurrence in the morning. Tikhomirov et al. revealed that mice, like humans, exhibit a morning peak in VA susceptibility [108]. This is driven by circadian rhythms in the expression of key ion channels, including sodium channel protein type 5 subunit alpha (Scn5a) and potassium voltage-gated channel subfamily

H member 2 (Kcnh2), as well as the gap junction protein Connexin 43. They also observed that the biological morning peak in mouse plasma glucocorticoid levels (corticosterone) enhances GR ligand binding and translocation in ventricular cardiomyocytes. More importantly, there is a surge in GR binding to open chromatin profiles of Scn5a and Kcnh2, and consequently increased expression of the ion channels and corresponding ionic currents, I_{Na} and I_{Kr}. Notably, both systemic antagonism of GR and cardiomyocyte-specific GR knockout eradicated the circadian rhythms in the expression of Scn5a, Kcnh2, and Connexin 43. In the same vein, the morning predisposition to VA was abolished in both cases. These findings not only highlight the potential of targeting the circadian regulation of the cardiomyocyte GR in VA therapy, but they also lay a conceptual foundation for similar studies in other CVD associated with the electrical excitability of the heart.

The expression of several Kruppel-like, zinc finger transcription factors (KLFs) have been shown to be directly induced by the GR, particularly KLF15 (Table 1) [109,110]. KLF15 plays a vital role for two main reasons: it is a key regulator of glucose, amino acid, and lipid metabolism in the heart [111–113], and it serves as a central link between the circadian clock and essential rhythmic cardiac function [114]. Importantly, the ablation of KLF15 in cardiomyocytes results in loss of over third of the circadian transcriptome of the heart [114]. Sasse et al. explored the molecular mechanisms of the GR-KLF15 axis, identifying feed-forward circuits as key mediators of this interaction [115].

Furthermore, the therapeutic efficacy of glucocorticoids on heart function appears to be modulated by circadian timing; our lab has shown that dosing prednisone during the light phase offers enhanced cardioprotection in mice compared to dark-phase administration [116]. Specifically, we found that ZT0-dosed chronic prednisone treatment at ZT0 (inactive period) regimen improved mitochondrial abundance and function in the normal myocardium of mice, as compared to the same treatment dosed at ZT12 (active period), and this was paralleled in cardioprotective effects after myocardial infarction based on time-of-intake. We also found that the epigenetic and metabolic effects of ZT0 prednisone were dependent on cardiomyocyte-specific GR and BMAL1, directly implicating the cardiomyocyte-autonomous interplay between glucocorticoid response and clock [116]. This finding highlights the potential for chrono-pharmacology to fine-tune glucocorticoid efficacy in CVD therapy, but further studies are needed to understand cardiomyocyte-specific epigenetic regulation of GR. Identifying more precise targets of glucocorticoid-mediated metabolic remodeling could pave the way for novel CVD therapies. Building on this, our lab recently identified adiponectin receptor 1 (*Adipor1*) and the mitochondrial pyruvate complex (*Mpc1/2*) as key gene targets of the GR-KLF15 axis in cardiomyocytes [117]. *Adipor1*, an adiponectin-activated ceramidase, enhances insulin-sensitive glucose uptake [118], while *Mpc1* and *Mpc2* form the mitochondrial pyruvate carrier crucial for pyruvate oxidation – a cardioprotective pathway [119]. We found that GR's impact on glucose oxidation is influenced by circadian gating, making this axis particularly relevant in metabolic heart disease contexts, such as obesity-related diabetic cardiomyopathy in mice [117]. This new understanding of GR's metabolic targets opens questions about potential new avenues for glucocorticoid-mediated CVD treatment, especially in relation to metabolic disorders like diabetes and obesity.

Conclusion

The GR plays a multifaceted role in cardiac physiology, affecting gene expression through both genomic and non-genomic pathways and interacting closely with epigenetic and circadian mechanisms. Its regulatory functions in cardiomyocytes are essential not only for fetal heart development but also for adult cardiac maintenance, as GR signaling influences cardiomyocyte hypertrophy, calcium handling, and metabolic homeostasis. Aberrations in GR activity have been linked to CVD, emphasizing the potential of GR as a therapeutic target. The discovery that GR activity is influenced by circadian rhythms, where circadian-specific glucocorticoid administration may enhance therapeutic efficacy, opens exciting new avenues for developing time-targeted treatments.

Further research into the GR's epigenetic landscape and circadian regulation will advance our understanding of heart disease mechanisms and pave the way for innovative, tailored therapeutic strategies for CVD.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by [R01HL166356–01, R03DK130908-01A1, R01AG078174–01] (NIH); Hevolution/AFAR New Investigator Award; and RIP, GAP, CCRF Endowed Scholarship, HI Translational Funds (CCHMC) grants to MQ.

Large language model statement

LLM Microsoft Copilot has been used in generating this text to help with language clarity from non-native English speaker authors.

ORCID

Olukunle Akinborewa http://orcid.org/0000-0002-6735-4802
Mattia Quattrocelli http://orcid.org/0000-0001-7011-1740

References

[1] Al Aboud NM, Tupper C, Genetics JI. Epigenetic Mechanism [Internet]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024[cited 2024 Oct 21]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK532999/

[2] Gibney ER, Nolan CM. Epigenetics and gene expression. Heredity [Internet]. 2010 [cited 2024 Oct 21];105(1):4–13. Available from: https://www.nature.com/articles/hdy201054

[3] Berger SL, Kouzarides T, Shiekhattar R, et al. An operational definition of epigenetics: figure 1. Genes Dev. 2009;23(7):781–783. doi: 10.1101/gad.1787609

[4] Cesare MD, Perel P, Taylor S, et al. The heart of the world. Glob Heart [Internet]. 2024 [cited 2024 Oct 21];19:11. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10809869/

[5] More than half of U.S. Adults don't know heart disease is leading cause of death, despite 100-year reign [Internet]. Am. Heart Assoc. [cited 2024 Oct 21]. Available from: http://newsroom.heart.org/news/more-than-half-of-u-s-adults-dont-know-heart-disease-is-leading-cause-of-death-despite-100-year-reign

[6] Heart Study F. (FHS) | NHLBI, NIH [Internet]. [cited 2024 Oct 21]. Available from: https://www.nhlbi.nih.gov/science/framingham-heart-study-fhs

[7] Andersson C, Vasan RS. Epidemiology of cardiovascular disease in young individuals. Nat Rev Cardiol [Internet] 2018 [cited 2024 Oct 21];15(4):230–240. Available from https://www.nature.com/articles/nrcardio.2017.154

[8] Nawsherwan MS, Bin W, Le Z, et al. Epidemiological trends in cardiovascular disease mortality attributable to modifiable risk factors and its association with sociodemographic transitions across BRICS-Plus countries. Nutrients [Internet]. 2023 [cited 2024 Oct 21];15(17):3757. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10489729/

[9] Almohtasib Y, Fancher AJ, Sawalha K. Emerging trends in atherosclerosis: Time to address atherosclerosis from a younger age. Cureus [Internet]. 2024 [cited 2024 Oct 21];16:e56635. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11032087/

[10] Chapski DJ, Cabaj M, Morselli M, et al. Early adaptive chromatin remodeling events precede pathologic phenotypes and are reinforced in the failing heart. J Mol Cell Cardiol. 2021;160:73–86. doi: 10.1016/j.yjmcc.2021.07.002

[11] Wołowiec Ł, Mędlewska M, Osiak J, et al. MicroRNA and lncRNA as the future of pulmonary arterial hypertension treatment. Int J Mol Sci. 2023;24(11):9735. doi: 10.3390/ijms24119735

[12] Shi Y, Zhang H, Huang S, et al. Epigenetic regulation in cardiovascular disease: mechanisms and advances in clinical trials. Signal Transduct Target Ther [Internet]. 2022 [cited 2024 Oct 21];7(1):1–28. Available from: https://www.nature.com/articles/s41392-022-01055-2

[13] Whitworth JA, Williamson PM, Mangos G, et al. Cardiovascular consequences of cortisol excess. Vasc Health Risk Manag. 2005;1(4):291–299. doi: 10.2147/vhrm.2005.1.4.291

[14] Nicolaides NC, Pavlaki AN, Maria Alexandra MA, et al. Glucocorticoid therapy and adrenal suppression [Internet]. In: Feingold K, Anawalt B, Blackman M, Boyce A, Chrousos G, Corpas E, WW DH, Dhatariya K, Dungan K Hofland J, et al., editors. Endotext. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2024 Oct 21]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK279156/

[15] Smith SM, Vale WW. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues Clin Neurosci [Internet]. 2006 [cited 2024 Oct 21];8(4):383. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3181830/

[16] Munck A, Guyre PM, Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation

to pharmacological actions. Endocr Rev. 1984;5 (1):25–44. doi: 10.1210/edrv-5-1-25

[17] Caratti G, Stifel U, Caratti B, et al. Glucocorticoid activation of anti-inflammatory macrophages protects against insulin resistance. Nat Commun [Internet]. 2023 [cited 2025 Jan 21];14(1):2271. Available from: https://www.nature.com/articles/s41467-023-37831-z

[18] Zhang Y, Du C, Wang W, et al. Glucocorticoids increase adiposity by stimulating Krüppel-like factor 9 expression in macrophages. Nat Commun [Internet]. 2024 [cited 2024 Nov 4];15(1):1190. Available from: https://www.nature.com/articles/s41467-024-45477-8

[19] Elkoshi Z. Autoimmune diseases refractory to corticosteroids and immunosuppressants. Front Immunol. 2024;15:1447337. doi: 10.3389/fimmu.2024.1447337

[20] Prekovic S, Schuurman K, Mayayo-Peralta I, et al. Glucocorticoid receptor triggers a reversible drug-tolerant dormancy state with acquired therapeutic vulnerabilities in lung cancer. Nat Commun [Internet]. 2021 [cited 2025 Jan 21];12(1):4360. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8285479/

[21] Brotman DJ, Girod JP, Garcia MJ, et al. Effects of short-term glucocorticoids on cardiovascular biomarkers. J Clin Endocrinol Metab. 2005;90 (6):3202–3208. doi: 10.1210/jc.2004-2379

[22] Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med. 1995;332(20):1351–1362. doi: 10.1056/NEJM199505183322008

[23] Macfarlane DP, Forbes S, Walker BR. Glucocorticoids and fatty acid metabolism in humans: fuelling fat redistribution in the metabolic syndrome. J Endocrinol. 2008;197(2):189–204. doi: 10.1677/JOE-08-0054

[24] McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev. 2007;87(3):873–904. doi: 10.1152/physrev.00041.2006

[25] Chimenti C, Russo MA, Frustaci A. Immunosuppressive therapy in virus-negative inflammatory cardiomyopathy: 20-year follow-up of the TIMIC trial. Eur Heart J [Internet] 2022 [cited 2025 Jan 20];43(36):3463–3473. Available from doi:10.1093/eurheartj/ehac348

[26] Foster RG. Sleep, circadian rhythms and health. Interface Focus [Internet]. 2020 [cited 2024 Oct 13];10(3):20190098. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7202392/

[27] Kiessling S, Eichele G, Oster H. Circadian clock regulation of glucocorticoid synthesis. Endocr Abstr [Internet]. 2011 [cited 2024 Oct 22];26. Available from: https://www.endocrine-abstracts.org/ea/0026/ea0026s8.2

[28] Gallo-Payet N, Martinez A, Lacroix AE. ACTH action in the adrenal cortex: from molecular biology to pathophysiology. Front Endocrinol. 2017;8:101. doi: 10.3389/fendo.2017.00101

[29] Cooper MS, Stewart PM. 11β-hydroxysteroid dehydrogenase type 1 and its role in the hypothalamus-pituitary-adrenal axis, metabolic syndrome, and inflammation. J Clin Endocrinol Metab [Internet]. 2009 [cited 2025 Jan 18];94(12):4645–4654. Available from doi:10.1210/jc.2009-1412

[30] Daskalakis NP, Yehuda R. Site-specific methylation changes in the glucocorticoid receptor exon 1F promoter in relation to life adversity: systematic review of contributing factors. Front Neurosci. 2014;8:369. doi: 10.3389/fnins.2014.00369

[31] Oakley RH, Cidlowski JA. Cellular processing of the glucocorticoid receptor gene and protein: new mechanisms for generating tissue-specific actions of glucocorticoids. J Biol Chem. 2011;286(5):3177–3184. doi: 10.1074/jbc.R110.179325

[32] Chrousos GP, Kino T. Intracellular glucocorticoid signaling: a formerly simple system turns stochastic. Sci STKE Signal Transduct Knowl Environ; 2005;2005 (304):pe48. doi: 10.1126/stke.3042005pe48

[33] Nicolaides NC, Chrousos G, Kino T. Glucocorticoid Receptor [Internet]. In: Feingold K, Anawalt B, Blackman M, Boyce A, Chrousos G, Corpas E, WW DH, Dhatariya K, Dungan K Hofland J, et al., editors Endotext. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2024 Oct 25]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK279171/

[34] Hollenberg SM, Weinberger C, Ong ES, et al. Primary structure and expression of a functional human glucocorticoid receptor cDNA. Nature. 1985;318 (6047):635–641. doi: 10.1038/318635a0

[35] Bamberger CM, Bamberger AM, de Castro M, et al. Glucocorticoid receptor beta, a potential endogenous inhibitor of glucocorticoid action in humans. J Clin Invest. 1995;95(6):2435–2441. doi: 10.1172/JCI117943

[36] Howard KJ, Holley SJ, Yamamoto KR, et al. Mapping the HSP90 binding region of the glucocorticoid receptor. J Biol Chem. 1990;265(20):11928–11935. doi: 10.1016/S0021-9258(19)38489-3

[37] Charmandari E, Kino T, Souvatzoglou E, et al. Natural glucocorticoid receptor mutants causing generalized glucocorticoid resistance: molecular genotype, genetic transmission, and clinical phenotype. J Clin Endocrinol Metab [Internet]. 2004 [cited 2024 Oct 12];89(4):1939–1949. Available from doi:10.1210/jc.2003-030450

[38] Denis M, Gustafsson JA, Wikström AC. Interaction of the Mr = 90,000 heat shock protein with the steroid-binding domain of the glucocorticoid receptor. J Biol Chem [Internet]. 1988 [cited 2025 Jan 21];263(34):18520–18523. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0021925819813893

[39] Greulich F, Hemmer MC, Rollins DA, et al. There goes the neighborhood: Assembly of transcriptional complexes during the regulation of metabolism and

inflammation by the glucocorticoid receptor. Steroids. 2016;114:7–15. doi: 10.1016/j.steroids.2016.05.003

[40] Kirschke E, Goswami D, Southworth D, et al. Glucocorticoid receptor function regulated by coordinated action of the Hsp90 and Hsp70 chaperone cycles. Cell [Internet]. 2014 [cited 2024 Oct 12];157(7):1685–1697. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4087167/

[41] Præstholm SM, Correia CM, Grøntved L. Multifaceted control of GR signaling and its impact on hepatic transcriptional networks and metabolism. Front Endocrinol [Internet]. 2020 [cited 2024 Oct 12];11:572981. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7578419/

[42] Burd CJ, Archer TK. Chromatin architecture defines the glucocorticoid response. Mol Cell Endocrinol [Internet]. 2013 [cited 2024 Oct 12];380(1–2):25–31. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3762934/

[43] Starick SR, Ibn-Salem J, Jurk M, et al. ChIP-exo signal associated with DNA-binding motifs provides insight into the genomic binding of the glucocorticoid receptor and cooperating transcription factors. Genome Res. 2015;25(6):825–835. doi: 10.1101/gr.185157.114

[44] Voss TC, Schiltz RL, Sung M-H, et al. Dynamic Exchange at regulatory elements during chromatin remodeling underlies assisted loading mechanism. Cell. 2011 [cited 2025 Jan 21];146(4):544–554. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3210475/.

[45] McNally JG, Müller WG, Walker D, et al. The glucocorticoid receptor: rapid exchange with regulatory sites in living cells. Sci [Internet]. 2000 [cited 2025 Jan 21];287(5456):1262–1265. Available from https://www.science.org/doi/10.1126/science.287.5456.1262

[46] Haché RJ, Tse R, Reich T, et al. Nucleocytoplasmic trafficking of steroid-free glucocorticoid receptor. J Biol Chem. 1999;274(3):1432–1439. doi: 10.1074/jbc.274.3.1432

[47] DeFranco DB. Subnuclear trafficking of steroid receptors. Biochem Soc Trans. 1997;25(2):592–597. doi: 10.1042/bst0250592

[48] Petta I, Dejager L, Ballegeer M, et al. The Interactome of the glucocorticoid receptor and its influence on the actions of glucocorticoids in combatting inflammatory and infectious diseases. Microbiol Mol Biol Rev MMBR [Internet] 2016 [cited 2024 Oct 12];80(2):495–522. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4867367/

[49] Kinyamu HK, Chen J, Archer TK. Linking the ubiquitin–proteasome pathway to chromatin remodeling/modification by nuclear receptors. J Mol Endocrinol. 2005;34(2):281–297. doi: 10.1677/jme.1.01680

[50] Kino T, Liou S-H, Charmandari E, et al. Glucocorticoid receptor mutants demonstrate increased motility inside the nucleus of living cells: time of fluorescence recovery after photobleaching (FRAP) is an integrated measure of receptor function. Mol Med Camb Mass. 2004;10(7–12):80–88. doi: 10.2119/2005-00026.Kino

[51] Mundade R, Ozer HG, Wei H, et al. Role of ChIP-seq in the discovery of transcription factor binding sites, differential gene regulation mechanism, epigenetic marks and beyond. Cell Cycle [Internet]. 2014 [cited 2024 Oct 21];13(18):2847. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4614920/

[52] Fadel L, Dacic M, Fonda V, et al. Modulating glucocorticoid receptor actions in physiology and pathology: Insights from coregulators. Pharmacol Ther [Internet]. 2023 [cited 2024 Oct 21];251:108531. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10841922/

[53] Weikum ER, Knuesel MT, Ortlund EA, et al. Glucocorticoid receptor control of transcription: precision and plasticity via allostery. Nat Rev Mol Cell Biol [Internet]. 2017 [cited 2024 Oct 21];18(3):159. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC6257982/

[54] Xavier AM, Anunciato AKO, Rosenstock TR, et al. Gene expression control by glucocorticoid receptors during innate immune responses. Front Endocrinol [Internet]. 2016 [cited 2025 Jan 21];7:31. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4835445/

[55] Hemmer MC, Wierer M, Schachtrup K, et al. E47 modulates hepatic glucocorticoid action. Nat Commun. 2019;10(1):306. doi: 10.1038/s41467-018-08196-5

[56] Li X, Wong J, Tsai SY, et al. Progesterone and glucocorticoid receptors recruit distinct coactivator complexes and promote distinct patterns of local chromatin modification. Mol Cell Biol. 2003;23(11):3763–3773. doi: 10.1128/MCB.23.11.3763-3773.2003

[57] Sheppard KA, Phelps KM, Williams AJ, et al. Nuclear Integration of glucocorticoid receptor and nuclear factor-κB signaling by creb-binding protein and steroid receptor coactivator-1. J Biol Chem. 1998;273(45):29291–29294. doi: 10.1074/jbc.273.45.29291

[58] Scheinman RI, Gualberto A, Jewell CM, et al. Characterization of Mechanisms Involved in Transrepression of nf-κB by activated glucocorticoid receptors. Mol Cell Biol. 1995;15(2):943–953. doi: 10.1128/MCB.15.2.943

[59] Tao Y, Williams-Skipp C, Scheinman RI. Mapping of Glucocorticoid Receptor DNA binding domain surfaces contributing to Transrepression of nf-κB and Induction of Apoptosis. J Biol Chem. 2001;276(4):2329–2332. doi: 10.1074/jbc.C000526200

[60] De Bosscher K, Vanden Berghe W, Vermeulen L, et al. Glucocorticoids repress nf-kappaB-driven genes by disturbing the interaction of p65 with the basal transcription machinery, irrespective of coactivator levels in the cell. Proc Natl Acad Sci USA. 2000;97:3919–3924.

[61] Surjit M, Ganti KP, Mukherji A, et al. Widespread negative response elements mediate direct repression by agonist-liganded glucocorticoid receptor. Cell. 2011;145(2):224–241. doi: 10.1016/j.cell.2011.03.027

[62] Hua G, Paulen L, Chambon P. GR SUMOylation and formation of an SUMO-SMRT/NCoR1-HDAC3 repressing complex is mandatory for gc-induced IR nGRE-mediated transrepression. Proc Natl Acad Sci USA. 2016;113(5):E626–634. doi: 10.1073/pnas.1522821113

[63] Malkoski SP, Dorin RI. Composite glucocorticoid regulation at a functionally defined negative glucocorticoid response element of the human corticotropin-releasing hormone gene. Mol Endocrinol Baltim Md. 1999;13(10):1629–1644. doi: 10.1210/mend.13.10.0351

[64] Uhlenhaut NH, Barish GD, Yu RT, et al. Insights into negative regulation by the glucocorticoid receptor from genome-wide profiling of inflammatory cistromes. Mol Cell [Internet]. 2013 [cited 2025 Jan 21];49(1):158–171. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3640846/

[65] Wiench M, John S, Baek S, et al. DNA methylation status predicts cell type-specific enhancer activity. EMBO J [Internet]. 2011 [cited 2025 Jan 21];30(15):3028–3039. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3160184/

[66] Kornberg RD. Chromatin structure: a repeating unit of histones and DNA. Science. 1974;184(4139):868–871. doi: 10.1126/science.184.4139.868

[67] Xu R, Li C, Liu X, et al. Insights into epigenetic patterns in mammalian early embryos. Protein Cell. 2021;12(1):7–28. doi: 10.1007/s13238-020-00757-z

[68] Zovkic IB. Epigenetics and memory: an expanded role for chromatin dynamics. Curr Opin Neurobiol. 2021;67:58–65. doi: 10.1016/j.conb.2020.08.007

[69] Bure N IV, Kuznetsova MV, Kuznetsova, et al. Histone modifications and non-coding RNAs: Mutual epigenetic regulation and role in pathogenesis. Int J Mol Sci [Internet]. 2022 [cited 2024 Oct 21];23(10):5801. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC9146199/

[70] Loscalzo J, Handy DE. Epigenetic modifications: basic mechanisms and role in cardiovascular disease (2013 Grover Conference series). In: Pulm Circ [Internet]; 2014. Vol. 4. p. 169. Available from cited 2024 Oct 21]. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4070783/

[71] Kaikkonen MU, Lam MT, Glass CK. Non-coding RNAs as regulators of gene expression and epigenetics. Cardiovasc Res [Internet]. 2011 [cited 2024 Oct 21];90(3):430. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3096308/

[72] Raffetti E, Melas PA, Landgren AJ, et al. DNA methylation of the glucocorticoid receptor gene predicts substance use in adolescence: longitudinal data from over 1000 young individuals. Transl Psychiatry [Internet]. 2021 [cited 2025 Jan 19];11(1):1–9. Available from: https://www.nature.com/articles/s41398-021-01601-6

[73] Cicchetti D, Handley ED. Methylation of the glucocorticoid receptor gene, nuclear receptor subfamily 3, group C, member 1 (NR3C1), in maltreated and non-maltreated children: Associations with behavioral undercontrol, emotional lability/negativity, and externalizing and internalizing symptoms. Dev Psychopathol [Internet] 2017 [cited 2025 Jan 19];29(5):1795–1806. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5718163/

[74] Wiencke JK, Molinaro AM, Warrier G, et al. DNA methylation as a pharmacodynamic marker of glucocorticoid response and glioma survival. Nat Commun [Internet]. 2022 [cited 2025 Jan 19];13(1):5505. Available from: https://www.nature.com/articles/s41467-022-33215-x

[75] Wu C-J, Livak F, Ashwell JD. The histone methyltransferase KMT2D maintains cellular glucocorticoid responsiveness by shielding the glucocorticoid receptor from degradation. J Biol Chem [Internet]. 2024 [cited 2025 Jan 21];300. Available from 8):107581. Available from: https://www.jbc.org/article/S0021-9258(24)02082-9/abstract

[76] Froimchuk E, Jang Y, Ge K. Histone H3 lysine 4 methyltransferase KMT2D. Gene [Internet] 2017 [cited 2025 Jan 21];627:337–342. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5546304/

[77] Ardeshir-Larijani F, Bhateja P, Lipka MB, et al. KMT2D mutation is associated with poor prognosis in non–small-cell lung cancer. Clin Lung Cancer. 2018;19(4):e489–501. doi: 10.1016/j.cllc.2018.03.005

[78] Ito K, Barnes PJ, Adcock IM. Glucocorticoid receptor recruitment of histone deacetylase 2 inhibits interleukin-1β-induced histone h4 acetylation on lysines 8 and 12. Mol Cell Biol. 2000;20(18):6891–6903. doi: 10.1128/MCB.20.18.6891-6903.2000

[79] MdM A, Okazaki K, Nguyen LTT, et al. Glucocorticoid receptor signaling represses the antioxidant response by inhibiting histone acetylation mediated by the transcriptional activator NRF2. J Biol Chem [Internet]. 2017 [cited 2025 Jan 19];292(18):7519–7530. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5418050/

[80] Rog-Zielinska EA, Thomson A, Kenyon CJ, et al. Glucocorticoid receptor is required for foetal heart maturation. Hum Mol Genet. 2013;22(16):3269–3282. doi: 10.1093/hmg/ddt182

[81] Rog-Zielinska EA, Craig M-A, Manning JR, et al. Glucocorticoids promote structural and functional maturation of foetal cardiomyocytes: a role for PGC-1α. Cell Death Differ. 2015;22:1106–1116.

[82] Severinova E, Alikunju S, Deng W, et al. Glucocorticoid Receptor-Binding and Transcriptome Signature in Cardiomyocytes. J Am Heart Assoc Cardiovasc Cerebrovasc Dis [Internet]. 2019 [cited

2024 Nov 4];8(6):e011484. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC6475044/

[83] Cruz-Topete D, Oakley RH, Carroll NG, et al. Deletion of the cardiomyocyte glucocorticoid receptor leads to sexually dimorphic changes in cardiac gene expression and progression to heart failure. J Am Heart Assoc Cardiovasc Cerebrovasc Dis [Internet]. 2019 [cited 2024 Oct 27];8:e011012. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC6761632/

[84] Cruz-Topete D, Myers PH, Foley JF, et al. Corticosteroids are essential for maintaining cardiovascular function in male mice. Endocrinology. 2016;157(7):2759–2771. doi: 10.1210/en.2015-1604

[85] Oakley RH, Ren R, Cruz-Topete D, et al. Essential role of stress hormone signaling in cardiomyocytes for the prevention of heart disease. Proc Natl Acad Sci U S A. 2013;110 (42):17035–17040. doi: 10.1073/pnas.1302546110

[86] Oakley RH, Cruz-Topete D, He B, et al. Cardiomyocyte glucocorticoid and mineralocorticoid receptors directly and antagonistically regulate heart disease in mice. Sci Signal [Internet]. 2019 [cited 2024 Oct 27];12(577):eaau9685. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7082727/

[87] Seidel T, Fiegle DJ, Baur TJ, et al. Glucocorticoids preserve the t-tubular system in ventricular cardiomyocytes by upregulation of autophagic flux. Basic Res Cardiol. 2019;114(6):47. doi: 10.1007/s00395-019-0758-6

[88] Ren R, Oakley RH, Cruz-Topete D, et al. Dual role for glucocorticoids in cardiomyocyte hypertrophy and apoptosis. Endocrinol [Internet]. 2012 [cited 2024 Oct 31];153(11):5346. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3473206/

[89] Thakkar C, Alikunju S, Niranjan N, et al. Klf9 plays a critical role in GR –dependent metabolic adaptations in cardiomyocytes. Cell Signal. 2023;111:110886. doi: 10.1016/j.cellsig.2023.110886

[90] Sainte-Marie Y, Nguyen Dinh Cat A, Perrier R, et al. Conditional glucocorticoid receptor expression in the heart induces atrio-ventricular block. FASEB J Off Publ Fed Am Soc Exp Biol. 2007;21(12):3133–3141. doi: 10.1096/fj.07-8357com

[91] Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. Nat Rev Immunol. 2017;17 (4):233–247. doi: 10.1038/nri.2017.1

[92] Venneri MA, Hasenmajer V, Fiore D, et al. Circadian rhythm of glucocorticoid administration entrains clock genes in immune cells: A DREAM trial ancillary study. J Clin Endocrinol Metab. 2018;103(8):2998–3009. doi: 10.1210/jc.2018-00346

[93] Lamia KA, Papp SJ, Yu RT, et al. Cryptochromes mediate rhythmic repression of the glucocorticoid receptor. Nature. 2011;480(7378):552–556. doi: 10.1038/nature10700

[94] Kino T, Chrousos GP. Acetylation-mediated epigenetic regulation of glucocorticoid receptor activity: Circadian Rhythm-associated alterations of glucocorticoid actions in target tissues. Mol Cell Endocrinol [Internet]. 2011 [cited 2024 Oct 13];336(1–2):23–30. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3057275/

[95] So A-L, Bernal TU, Pillsbury ML, et al. Glucocorticoid regulation of the circadian clock modulates glucose homeostasis. Proc Natl Acad Sci U S A [Internet] 2009 [cited 2024 Oct 13];106(41):17582–17587. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2757402/

[96] Oster H, Damerow S, Kiessling S, et al. The circadian rhythm of glucocorticoids is regulated by a gating mechanism residing in the adrenal cortical clock. Cell Metab. 2006;4:163–173.

[97] Shimba A, Ikuta K. Glucocorticoids regulate circadian rhythm of innate and adaptive immunity. Front Immunol [Internet]. 2020 [cited 2024 Oct 13];11:2143. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7533542/

[98] Li Y, Androulakis IP. Light entrainment of the SCN circadian clock and implications for personalized alterations of corticosterone rhythms in shift work and jet lag. Sci Rep [Internet]. 2021 [cited 2025 Jan 21];11(1):17929. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8429702/

[99] Nader N, Chrousos GP, Kino T. Interactions of the circadian CLOCK system and the HPA axis. Trends Endocrinol Metab TEM. 2010;21(5):277–286. doi: 10.1016/j.tem.2009.12.011

[100] Quagliarini F, Mir AA, Balazs K, et al. Cistromic Reprogramming of the diurnal glucocorticoid hormone response by high-fat diet. Mol Cell [Internet]. 2019 [cited 2024 Oct 13];76(4):531–545.e5. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7928064/

[101] Guan D, Lazar MA. Interconnections between circadian clocks and metabolism. J Clin Invest. [cited 2024 Oct 13];131(15):e148278. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8321578/

[102] Fagiani F, Di Marino D, Romagnoli A, et al. Molecular regulations of circadian rhythm and implications for physiology and diseases. Signal Transduct Target Ther [Internet]. 2022 [cited 2024 Oct 13];7(1):41. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8825842/

[103] Reddy AB, Maywood ES, Karp NA, et al. Glucocorticoid signaling synchronizes the liver circadian transcriptome. Hepatol Baltim Md. 2007;45 (6):1478–1488. doi: 10.1002/hep.21571

[104] Caratti G, Iqbal M, Hunter L, et al. Reverba couples the circadian clock to hepatic glucocorticoid action. J Clin Invest. [cited 2025 Jan 20];128:4454–4471. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6160001/

[105] Okabe T, Chavan R, Fonseca Costa SS, et al. REV-ERBα influences the stability and nuclear localization of the glucocorticoid receptor. J Cell Sci [Internet].

2016 [cited 2025 Jan 20];129(21):4143–4154. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5117207/

[106] Zhang L, Zhang R, Tien C-L, et al. REV-ERBα ameliorates heart failure through transcription repression. JCI Insight. [cited 2025 Jan 20];2(17):e95177. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5621902/

[107] Harrington AJ, Bridges CM, Berto S, et al. MEF2C hypofunction in neuronal and neuroimmune populations produces MEF2C Haploinsufficiency syndrome–like behaviors in mice. Biol Psychiatry [Internet]. 2020 [cited 2025 Jan 20];88(6):488–499. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7483399/

[108] Tikhomirov R, Oakley RH, Anderson C, et al. Cardiac GR mediates the diurnal rhythm in ventricular arrhythmia susceptibility. Circ Res [Internet]. 2024 [cited 2025 Jan 21];134(10):1306–1326. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11081863/

[109] Reddy TE, Pauli F, Sprouse RO, et al. Genomic determination of the glucocorticoid response reveals unexpected mechanisms of gene regulation. Genome Res [Internet]. 2009 [cited 2024 Oct 31];19(12):2163. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC2792167/

[110] Bagamasbad P, Ziera T, Borden SA, et al. Molecular basis for glucocorticoid induction of the krüppel-like factor 9 gene in hippocampal neurons. Endocrinol [Internet]. 2012 [cited 2024 Oct 31];153(11):5334. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3473204/

[111] Prosdocimo DA, Anand P, Liao X, et al. Kruppel-like Factor 15 is a critical regulator of cardiac lipid metabolism. J Biol Chem [Internet]. 2014 [cited 2024 Oct 31];289(9):5914. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3937660/

[112] Gray S, Feinberg MW, Hull S, et al. The Kru¨ppel-like Factor KLF15 Regulates the Insulin-sensitive Glucose Transporter GLUT4. J Biol Chem. 2002;277(37):34322–34328. doi: 10.1074/jbc.M201304200

[113] Gray S, Wang B, Orihuela Y, et al. Regulation of Gluconeogenesis by Krüppel-like Factor 15. Cell Metab [Internet]. 2007 [cited 2024 Oct 31];5(4):305. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC1892530/

[114] Zhang L, Prosdocimo DA, Bai X, et al. KLF15 establishes the landscape of diurnal expression in the heart. Cell Rep. 2015;13(11):2368–2375. doi: 10.1016/j.celrep.2015.11.038

[115] Sasse SK, Mailloux CM, Barczak AJ, et al. The Glucocorticoid Receptor and KLF15 regulate gene expression dynamics and integrate signals through feed-forward Circuitry. Mol Cell Biol [Internet]. 2013 [cited 2024 Oct 31];33(11):2104. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3648070/

[116] Wintzinger M, Panta M, Miz K, et al. Impact of circadian time of dosing on cardiomyocyte-autonomous effects of glucocorticoids. Mol Metab. 2022;62:101528. doi: 10.1016/j.molmet.2022.101528

[117] Durumutla HB, Prabakaran AD, Soussi FEA, et al. Glucocorticoid chronopharmacology promotes glucose metabolism in heart through a cardiomyocyte-autonomous transactivation program. JCI Insight [Internet]. 2024 [cited 2025 Jan 21];9. Available from 22). Available from: https://insight.jci.org/articles/view/182599

[118] Holland WL, Xia JY, Johnson JA, et al. Inducible overexpression of adiponectin receptors highlight the roles of adiponectin-induced ceramidase signaling in lipid and glucose homeostasis. Mol Metab [Internet]. 2017 [cited 2024 Oct 31];6(3):267. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC5323887/

[119] Bricker DK, Taylor EB, Schell JC, et al. A mitochondrial pyruvate carrier required for pyruvate uptake in yeast, drosophila, and humans. Sci [Internet]. 2012 [cited 2024 Oct 31];337(6090):96. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3690818/