Role of microRNAs and long non-coding RNAs in glucocorticoid signaling (Review)

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Received August 19, 2022; Accepted October 19, 2022

DOI: 10.3892/ijmm.2022.5203

Abstract. The synthesis and release of glucocorticoids in living organisms are related to their response to unfavorable stressful conditions in order to maintain homeostatic functions and survive. One such hormone in humans is cortisol, which is produced by the hypothalamic-pituitary-adrenal cortex axis and binds with the glucocorticoid receptor (GR) following its secretion. GR controls a number of distinct gene networks. Non-coding RNAs (ncRNAs), such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), regulate the expression and function of GR, having a considerable impact on various biological processes and treatment approaches for numerous disorders. In the present review, the GR pathways and signaling as part of the stress response system are discussed. A detailed report on the role of miRNAs and lncRNAs in glucocorticoid signaling is also presented.

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Abbreviations: ACTH, adrenocorticotropic hormone; AF, activation function; ALL, acute lymphoblastic leukemia; AR, androgen receptor; AVP, arginine-vasopressin; CNS, central nervous system; CRH, corticotropic-releasing hormone; DBD, DNA-binding domain; DUSP1, dual specificity phosphatase 1; FKBPs, FK506-binding proteins; GAS5, growth arrest-specific 5; GC, glucocorticoid; GR, glucocorticoid receptor; GRE, glucocorticoid response element; Hop, Hsp70-Hsp90 organizing protein; HPA, hypothalamic-pituitary-adrenal cortex; HR, hinge region; Hsp, heat shock protein; LBD, ligand-binding domain; lncRNA, long non-coding RNA; LPS, lipopolysaccharide; miRNAs/miRs, microRNAs; MM, multiple myeloma; MR, mineralocorticoid receptor; ncRNA, non-coding RNA; NTD, N-terminal domain; PTGES3/p23, prostaglandin E synthase 3; SRs, steroid receptors

Key words: glucocorticoid signaling, miRNAs, lncRNAs, GR, endogenous glucocorticoids, stress response system

Contents

1. Introduction

All living organisms must cope with a number of adversities during their lifetime and have to maintain a complex dynamic equilibrium called homeostasis (1). The state of threatened (or perceived as such) homeostasis is known as stress and the intrinsic or extrinsic forces that lead to such a state are called stressors (2). Severe or prolonged stress has been associated with several pathological conditions, such as the deregulation of the immune system, cardiovascular disease, neuropsychiatric disorders, metabolic disorders, endocrine disorders, and growth, as well as development impairments (3,4). Thus, in response to stressors, an organism activates multiple complex

and dynamic processes in an effort to restore homeostasis, while the involved processes form the stress response system (5). The stress response system leads to several behavioral and physiological changes, such as increased awareness and enhanced analgesia, as well as an increased respiratory rate and the inhibition of general vegetative functions (6). The stress response system is comprised mainly of two components, the hypothalamic-pituitary-adrenal cortex (HPA) axis and the locus coeruleus/norepinephrine autonomic nervous system (7).

The HPA axis is the neuroendocrine link between stress and an organism's physiological response to such a state (8). A stressor induces a chain of events in the brain that activates the HPA axis. Specifically, neurons whose bodies are located in the paraventricular nucleus of the hypothalamus secrete corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP) into the hypophysial portal system. Then, they target the anterior lobe of the pituitary gland. There, CRH and AVP stimulate proopiomelanocortin cells, which in turn release adrenocorticotropic hormone (ACTH), also known as corticotropin. Finally, ACTH is released into the bloodstream and acts on the cortex of the adrenal glands, thus triggering glucocorticoid (GC) production (cortisol in humans and corticosterone in rats) (9,10). GCs subsequently self-regulate the HPA axis through a negative feedback loop (11). Although elevations in cortisol levels are the physiological response of the body to fear or threat and are beneficial to promoting survival, chronic exposure to stress results in long-term cortisol exposure. This prolonged exposition can lead to a broad range of issues, including the emergence of metabolic syndrome, obesity, cancer, mental health disorders, cardiovascular disease and increased susceptibility to infections (5).

GC signaling is related to the function of non-coding RNAs (ncRNAs) which have been extensively studied for their post-transcriptional involvement in the regulation of gene expression. It has been shown that microRNAs (miRNAs/miRs) can function as direct regulators of GC receptors (GRs) via the hybridization of various miRNAs with the 3'untranslated region (3'UTR) of the GR transcript, interrupting protein synthesis (12). Furthermore, miRNAs are directly or indirectly influenced by GCs, while it has been shown that the expression level of miRNAs is dependent on endogenous GC levels (13). In addition, long ncRNAs (lncRNAs), such as growth arrest-specific 5 (GAS5) (14) and EDN1-AS (15), regulate the expression levels of GRs, interfering with the GC signaling pathways. It is therefore paramount to increase our understanding of how nc-RNAs, mainly via the action of miRNAs and lncRNAs, regulate GR and are regulated by GCs, building an intricate regulatory network to fine-tune the body's response to various stimuli.

2. Glucocorticoid signaling

Endogenous GCs, as the final products of the HPA axis, are the main regulators of the stress response system (16). GCs are steroid hormones and as main regulators of the stress response system, are involved in numerous biological processes, including immune response, metabolism, as well as developmental, cognitive and behavioral functions (17). Endogenous GC secretion displays both ultradian and circadian rhythms. The circadian rhythm refers to physical, mental and behavioral changes that follow a 24-h cycle. Specifically, the circadian peak in GC release occurs in the early morning in diurnal animals and in the early night in nocturnal animals. On the other hand, the ultradian pulses, which are cycles having a duration shorter than a day, but longer than an hour, display a frequency of approximately one or two per hour (18,19), with nocturnal animals exhibiting an increase in amplitude towards the end of the day (20). GCs can bind either the GR or the mineralocorticoid receptor (MR) (21). The MR has a 10-fold higher affinity for naturally occurring GCs than the GR, leading to large receptor occupancy, whereas GR is only activated during circadian peak and stress response (22). Therefore, the actions of GCs are mainly exerted through the GR. GRs are expressed in almost every cell of the body and there are several GR isoforms generated from one gene, due to alternative splicing and various post-translational modifications (14). In particular, GCs function as ligands that bind GR transcripts and enable their action, with the full GRα transcript being the predominant isoform (23,24). It should also be mentioned that due to this wide range of functions GCs display, primarily via their capacity to influence immune response, synthetic GCs, such as dexamethasone and fludrocortisone have been developed and are widely prescribed for the treatment of several diseases, including rheumatic, pulmonary, gastroenterological, and cutaneous diseases (25).

Both GR and MR are members of a structurally-related protein superfamily known as nuclear receptors (NRs) (26). NRs function as transcription factors, regulating gene expression (27). NRs exhibit a characteristic structure, and so does GR. In particular, the GR is encoded by the NR subfamily 3 group C member 1 (*NR3C1*) gene and its functional and structural domains include an N-terminal domain (NTD), a DNA-binding domain (DBD), a hinge region (HR) and a C-terminal ligand-binding domain (LBD) (17). More specifically, the NTD contains an activation function (AF)-1 region that interacts with coregulators (28). Additionally, the highly conserved DNA-binding domain contains two zinc finger motifs and binds specific DNA sequences called GC response elements (GREs) (29). The highly flexible HR contains an amino terminus that is an essential part of the DBD and is involved in receptor dimerization, while the flexibility provided by HR to the GR allows a receptor dimmer to interact with multiple GREs (30). The somewhat conserved C-terminal LBD binds ligands, which in turn lead to conformational changes within the LBD that modulate a second AF region (AF-2) and enable interaction with specific coregulators (28).

In the absence of GCs, GR is located in the cytoplasm, where it is bound to a number of chaperone proteins that render it inactive (29). GR is first bound by heat shock protein (Hsp) 40 kDa (Hsp40), heat shock cognate 71 kDa protein and the Hsp70-Hsp90 organizing protein (Hop), while at later stages, it is bound by Hsp90, FK506-binding proteins (FKBPs) and prostaglandin E synthase 3 (PTGES3/p23) (31). Specifically, following receptor translation, Hsp70 binds the receptor in the cytosol, which leads to the unfolding of the GR and LBD inactivation. This process is accelerated by Hsp40 binding. The Hsp40/Hsp70-GR complex is then recruited to interact with Hsp90 via Hop. Hop, Hsp40 and Hsp70 are then dislodged from the Hsp90-GR complex upon Hsp90 binding,

ATP and the subsequent association of FKBPs cochaperones, such as FKBP51 and FKBP52. Hsp90 interaction with GR folds the receptor and leads to a functional LBD. The heterocomplex is stabilized via p23 binding through the N-terminus and middle domains, promoting a conformation with a high affinity for corticosteroids (17,32). The binding of a ligand to the receptor's LBD leads to conformational alterations that change the proteins which comprise the heterocomplex, while also promoting GR dimerization and the subsequent translocation to the nucleus, where it can act as a transcriptional regulator (33,34). GR import is a rapid and active process that relies on GR association with Hsp90, FKBP52 and importin-a. The GR complex is transported into the nucleus by dynein along the cytoskeleton and through the nuclear pore complex (34). Once in the nucleus, the activated GR can either activate or repress gene transcription. As regards the GR signaling pathways, there are three primary ways the receptors interact with molecules and intervene in gene expression. For instance, GR can either bind directly to DNA in specific sequences, or can tether itself to other DNA-bound transcription factors. The third is via direct binding to DNA and interaction with neighboring DNA-bound transcription factors. In particular, transactivation can be achieved directly through GR homodimer binding to a GRE found in gene promoter regions, or indirectly, where GR functions as a monomer and co-operates with other transcription factors to induce transcription (35,36). Transrepression can also be either direct, via GR homodimer or, preferably, monomer binding to a negative GRE, or indirect via GR monomer binding to a pro-inflammatory transcription factor, such as NF-κB (35-37). GR remains bound to DNA for a specific time period which could be influenced by the bound ligand. This influence may be due to differences in ligand-induced conformational changes (38). Following ligand disengagement, GR dissociates from DNA and is either degraded by the proteasome or exported from the nucleus, which is an inactive process, most likely occurring through passive diffusion (34). This system enables the cell to rapidly respond to environmental changes and exercise its effects via the intricate networks established around GR activity.

3. GR pathways

The anti-inflammatory abilities of GCs highlight their critical role in the regulation of the immune system. Specifically, GR inhibits major regulators of pro-inflammatory pathways, such as transcription factors activator protein-1 (AP-1) and the aforementioned NF-κB (39). AP-1 is a protein complex composed of a Jun protein family member dimerized with another Jun protein or with a Fos protein, and enhances the expression of a number of cytokines, such as IL-1 and IL-2. In particular, GR binds the ubiquitously expressed c-Fos/c-Jun dimers via a sequence-specific to c-Fos and inhibits the DNA binding and transactivation abilities of this AP-1 heterocomplex (40). In mammals, the NF-κB protein family of transcription factors includes several proteins, such as p65 and p105/p50, which interact and form distinct homodimers or heterodimers with transcriptional regulation abilities (41). NF-κB binds to specific response elements and regulates the expression of genes encoding proteins, such as pro-inflammatory cytokines, chemokines, receptors and adhesion molecules (42). GR can inhibit NF-κB directly by interacting with the p65 and p50 subunits, or indirectly by inducing the expression of the *TSC22D3* gene, which encodes GC-induced leucine zipper, a protein that binds NF-κB and suppresses its function (39). Under pathological conditions, stress-induced GCs may suppress cell-mediated immunity and may thus lead to viral infection susceptibility and tumor development (43). To illustrate the multifaceted interaction of NR3C1 with other proteins, a gene association network of genes related to the *NR3C1* gene was developed using the Genemania algorithm (44) (Fig. 1). A total of 21 genes were detected in this network, including FKBPs, which interact with, or are influenced by GRα.

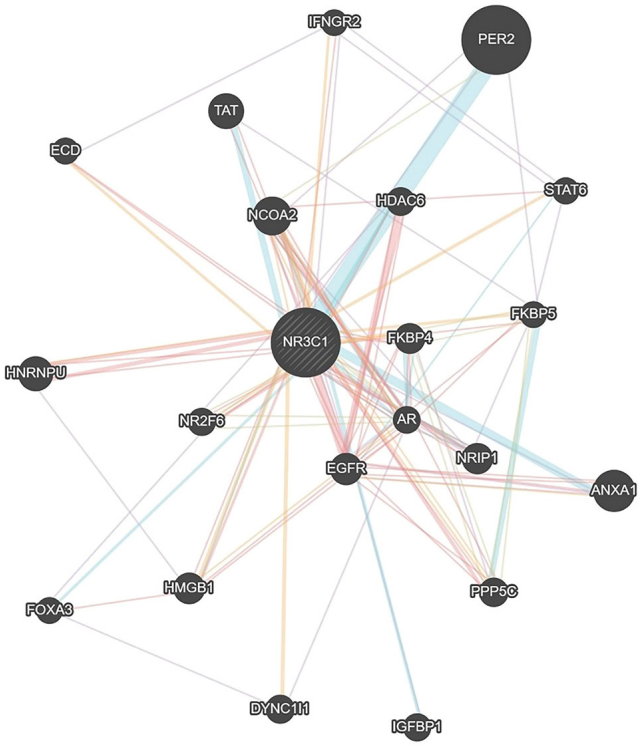

Figure 1. Network of genes related to the NR3C1 gene. Association data include protein interactions (pink lines), pathways (light blue lines), co-expression (purple lines) and protein domain similarity (yellow lines). The network was constructed using the Genemania algorithm with the human network (44). NR3C1, nuclear receptor subfamily 3 group C member 1.

GCs also play a pivotal role in development. *In utero* GC levels influence embryonic development and affect adult physiology and pathophysiology, with a prime example being increased susceptibility to cardiovascular disease (45). In particular, GR in cardiomyocytes may induce the expression of genes, such as peroxisome proliferator-activated receptor γ coactivator 1α, which regulates cardiac mitochondrial capacity and genes encoding other regulators of cardiac metabolism, such as peroxisome proliferator-activated receptor α, Krüppel-like factor 15 and lipin 1 (lpn1). These regulators of cardiac metabolism play critical roles in the transition from the fetal to the neonatal heart (46). Additionally, GR expression in mesenchymal cells has been proven to be necessary for lung maturation. Mesenchymal GR regulates the development, morphological differentiation and remodeling of the lungs in neonates. Mesenchymal and GR-null mice have been shown to exhibit lung cell hyperplasia, suggesting a crucial function

of GC signaling during lung development, via a decrease in proliferation and the thinning of interstitial cells for effective gas exchange (47). Furthermore, GC excess may lead to numerous developmental issues, culminating in congenital disabilities. Specifically, GR can induce the expression of Dickkopf-related protein 1, one of the main inhibitors of the Wnt/β-Catenin pathway which among others, participates in stem cell renewal, cell differentiation and cell proliferation during development (48).

Cardiovascular diseases are directly connected to stress (49). Exposure to a high concentration of GCs, either endogenous or exogenous, is associated with an increased risk of heart failure, ischemic heart disease and hypertension. The cardiovascular and pulmonary system needs to maintain a specific balance of GC levels, while either too high or too low concentrations have adverse effects on the system functions. It has been shown that mouse models with either GR deletion or an altered GR expression in cardiomyocytes exhibit cardiovascular pathologies, irregularly shaped and disorganized myofibrils at embryonic stages, larger hearts, as well as cardiac fibrosis. Males also develop cardiomyocyte hypertrophy, suggesting that the sexually dimorphic actions of GCs can occur in the heart as well (50). Furthermore, research on GR functions in rapid GC-induced hypertension has revealed that following vascular smooth muscle-specific GR deletion, there is a decrease in hypertension in mice (51). The mechanism used by GCs to regulate blood pressure is through the vascular GRs. Additionally, the endothelial GR appears to protect against lipopolysaccharide (LPS)-induced septic shock, via the repression of the release of NF-κB and IL-6, two inflammatory cytokines. On the other hand, the overexpression of GR is associated with atrio-ventricular block and bradycardia, with the first being easily reversed, once the levels of GR are restored (52).

GCs also participate in several metabolic processes. In the liver, GCs can stimulate gluconeogenesis by inducing phosphoenolpyruvate carboxykinase and glucose-6-phosphatase action, while in skeletal muscle and white adipose tissue, they lower glucose uptake and utilization by interfering with the insulin signaling pathway (53,54). In skeletal muscle specifically, GCs decrease insulin receptor substrate 1 transcription, a downstream signaling molecule of the insulin signaling pathway, and increase the transcription of protein tyrosine phosphatase type 1B and p38 mitogen-activated protein kinases (p38 MAPK), which counter insulin action (55). Of note, excessive GC action has been found to be associated with several metabolic diseases, such as type II diabetes and obesity (56).

GCs influence several central nervous system (CNS) processes. GCs' effect on the CNS is both cell-type and stress-type specific (57). GCs have been shown to regulate stress responses, apoptosis and long-term potentiation (58). These hormones can cross the blood-brain-barrier and alter synaptic physiology, stress responsiveness and behavior (59). Specifically, in the brain, following a GC peak, areas involved in emotional responses and simple behavioral strategies exhibit an enhanced activity, while in the aftermath of stress, areas involved in higher cognitive functions are activated and allow individuals to associate stressful events with a specific context and thus store information for future use (60). Maladaptive behavioral responses to stress have been shown to be associated with mood disorders (61). According to *in vivo* studies, transgenic mice where the GR was deleted in the CNS cells (brain-specific GR knockout), exhibited increased basal corticosterone levels and reduced anxiety. Considering that corticosterone is the rodent analog of human cortisol, the results can be attributed to the loss of central feedback inhibition in the HPA axis stress system. Moreover, mice which did not produce GR in the forebrain exhibited elevated MR expression in the hippocampus. Several variations of GR knockout mice in the hypothalamus resulted in sex specific differences in the HPA axis function, where females exhibited elevated corticosterone levels at the lowest point of the circadian cycle, while males did the same after intense stress. Notably, the depletion of GR in dopamine-receptive neurons resulted in mice with phenotypes of social aversion due to chronic stress (47).

The involvement of stress system dysregulation and more specifically, the dysregulation of the HPA axis in neuropsychiatric disorders is equally unsurprising, given the robust and dynamic nature of stress biology. Affective disorders, including major depressive disorder, bipolar disorder, anxiety and panic disorders, schizophrenia and post-traumatic stress disorder are considered anxiety disorders in which the key neural pathways that regulate the stress response do not function optimally (62). The increased reactivity to threatening stimuli, the reduced ability to finish the stress response, and/or the suboptimal coupling between internal emotional states and the external environment are part of stress system dysregulation. Of these, the latter dysfunction may contribute to mood shifting in an extreme and seemingly random manner in bipolar illness or to 'stick' in a negative manner in major depression. Although both disorders are primarily inherited (63,64), vulnerability to these is directly linked to how the individual responds to the environment (65). Indeed, according to the study by Wray *et al* (66), who examined ~460,000 individuals for the genetics of depression, it appeared that 'all people carry a greater or lesser number of genetic risk factors for major depression', where these are due to the dysregulation of the HPA axis in depression. Major depression is the result of the dysregulation of various genes related to cellular development, cell repair and growth factors. An example of these genes is the fibroblast growth factor (FGF) gene family, which is dysregulated in major depression (67). *FGF2*, which is a member of the FGF family, has been detected to function as an 'endogenous antidepressant'. Its levels in the hippocampus and frontal cortex are low in depression in humans, and they are reduced in rodents as a result of repeated social stress, and have been shown to modulate the HPA axis via GR (68). On the other hand, the levels of *FGF9,* another gene member of the FGF family, are increased in the depressed brain, as this gene functions as a vulnerability factor and is increased by chronic stress in animal models (67), and its selective inhibition in the hippocampus reduces anxiety behavior. Of note, treatment with FGF2 during early life leads to epigenetic changes to GR in the hippocampus, increasing its association with a repressive histone, H3K9Me3 (69), which leads to reduced levels of NR3C1 expression and with a lower number of GRs in the hippocampus (70). In addition to major depression, schizophrenia and bipolar disorder are also associated

Table I. MicroRNAs and glucocorticoid activity.

GR regulators	Brain-related	Cancer-related	Immune/inflammatory-related	Other
miR-124	(90-92)	(99)		(91)
miR-18a	(94)			
miR-137	(96)			
miR-142-3p	(100)	(99)		
miR-101a, -96, -433	(101)			
miR-130b, -181, -636		(103)		
miR-1-3p, -128, -370, -28				(122)
miR-29a				(122,123)
miR-340	(128)			
Regulated by GCs	**Brain-related**	**Cancer-related**	**Immune/inflammatory-related**	**Other**
miR-155		(104)	(105-107)	
miR-511			(108-110)	
miR-98			(112)	
miR-101			(113)	
miR-17-92 cluster		(114-116)		
miR-221/222		(118)		
miR-125b		(120)		

The table presents relations and references (numbers in parentheses) to miRNAs that function as regulators of GR or are regulated by GCs, in brain-related, cancer-related, immune-related or other diseases. GC, glucocorticoid; GR, glucocorticoid receptor.

with the dysregulation of HPA axis activity, under basal conditions and during stress. The decreased mRNA expression of the GR has been observed in both illnesses using multiple post-mortem tissue cohorts and brain regions (71). Moreover, the increased expression of a truncated GR protein isoform has been reproducibly demonstrated in the prefrontal cortex of patients with schizophrenia and bipolar disorder (72,73). Notably, in conjunction with the decreased expression of multiple GR mRNA transcripts and the increased expression of the functional, truncated GRα-D1 protein isoform 35, the altered expression, and the dysregulation of FKBP5, PTGES3 and BAG1 mRNAs have been also detected. Taken together, widespread stress-signaling alterations are detected in both schizophrenia and bipolar disorder (71).

4. miRNAs in glucocorticoid signaling

miRNAs are a class of small ncRNAs ~22 nt in length, which exert their effects by binding to the 3'UTR region of target mRNAs. Compared to other ncRNA classes, they have been the focus of extensive research for the past two decades, due to both their post-transcriptional regulatory capacity, as well as their therapeutic potential (74). To date, >1,900 miRNAs have been discovered in the human genome and more specifically, according to miRbase (release 22.1), there are 1,917 precursors and 2,654 mature miRNAs (GRCh38) (75-81), with regulatory activity spanning across a multitude of biological processes, such as development, metabolism, inflammation, as well as GR protein expression. miRNAs have long been established as dynamic regulators during development, but most importantly during environmental adaptation. As such, their physiological function in the regulation of GR expression is also predominantly in CNS development, as well as the brain's response to both pre- and post-natal challenges (82). Nevertheless, prolonged exposure to environmental stressors can lead to extensive neuronal reprogramming accompanied by altered GC response (83,84). Additionally, due to the extensive use of GCs for cancer treatment (85), accompanied by the central roles of miRNAs in numerous types of cancer (86), investigating the association between miRNAs and GC signaling is pivotal for developing successful therapeutic approaches.

The present review mainly focuses on two aspects of the miRNA regulation of GC signaling. In the first part, focus is placed on miRNAs that have been shown to be direct regulators of GRs, investigating their effects in both brain disorders, as well as in cancer development and treatment. In the second part, miRNAs directly or indirectly influenced by GCs are reviewed (Table I).

miRNAs and GRs. NR3C1, the mRNA transcript of GRα protein, has been shown to harbor a number of conserved miRNA target sites in its 3'UTR (12). Using the well-established miRNA target prediction algorithm TargetScan (release 7.2; March, 2018) (87), 135 conserved putative miRNA 8-mer binding sites (with a <-0.1 context score) were predicted for the human *NR3C1* transcript (Table SI). Extending this search to the gene-network level with the use of the Genemania *NR3C1* network, as shown in Fig. 1, which includes 21 proteins predicted to interact and form a network with GRα and miRDB (88,89), a miRNA target prediction on the 3'UTR region algorithm

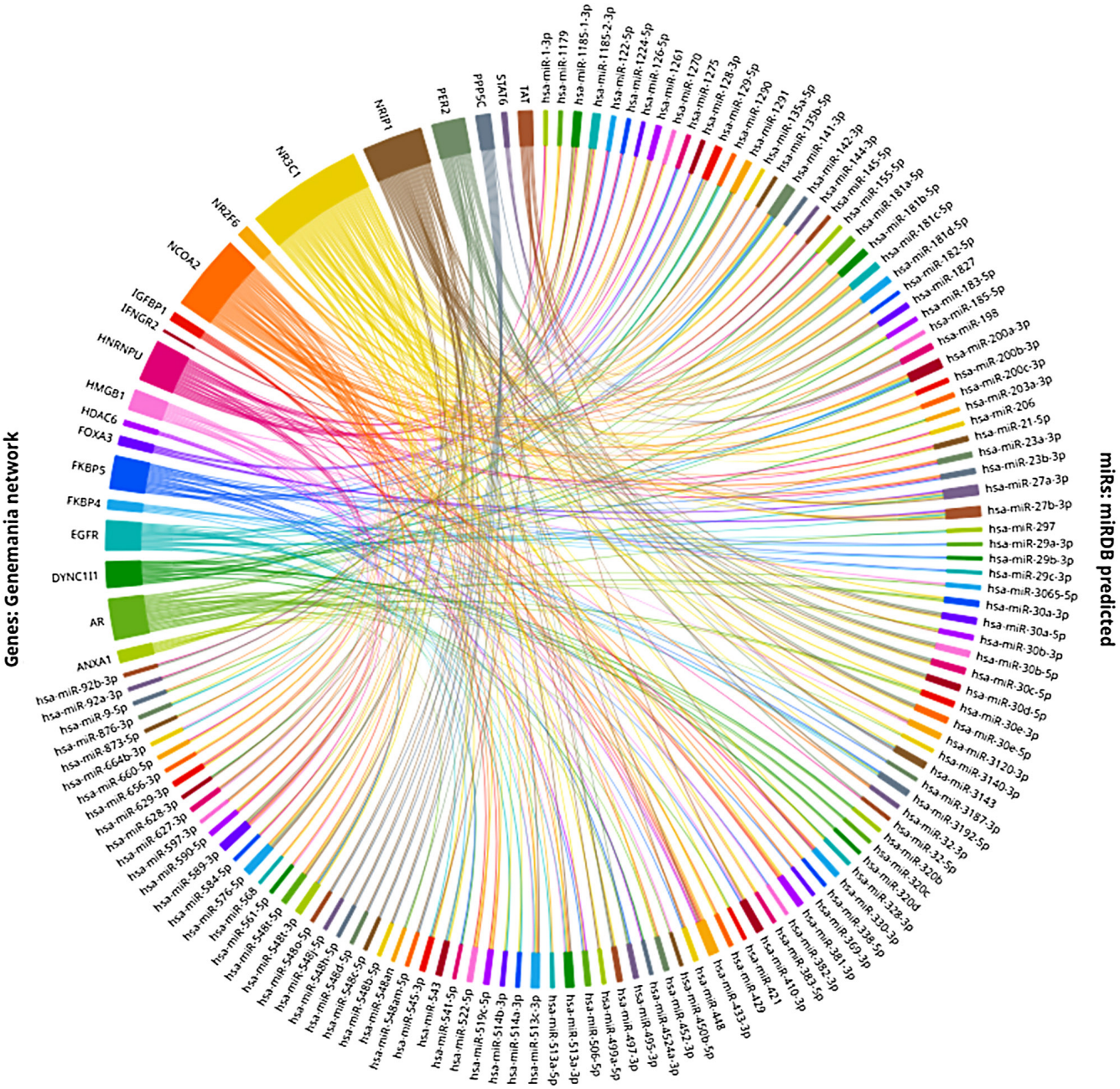

Figure 2. Circular diagram exhibiting the extended regulatory potential of microRNAs on the GRα network. A total of 120 microRNAs were predicted to target more than one transcript of the human NR3C1 network (constructed with Genemania). microRNA root thickness corresponds to the target prediction score, as generated by the miRDB algorithm. The diagram was built using R version 4.0.3 with the chorddiag (164) package. NR3C1, nuclear receptor subfamily 3 group C member 1; GR, glucocorticoid receptor.

which allows for the concurrent investigation of multiple genes. Thus, this made it possible to identify 120 miRNAs predicted to regulate more than one of the proteins of the Genemania network, via targeting their respective mRNA 3'UTRs (Fig. 2). This simple analysis serves to show the extensive regulatory effects multiple miRNAs can have on different levels of the GC network, as well as the great fine-tuning potential they can apply on GRα levels. Thus far, a number of these miRNAs have already been shown to interact with GRα and thus exert their regulatory effects.

First and foremost is miR-124, a miRNA induced by GC treatment, which has been the subject of extensive studies in relation to GR expression. Using *in vitro* experiments in Jurkat T-cells and T-cells from healthy volunteers and patients with sepsis, miR-124 was previously shown to decrease the expression of GRα by direct binding of the 3'UTR of the *NR3C1* transcript (90). This direct binding was also further validated in experiments using 293/293T cells (91). Notably, miR-124 levels have been found to be increased in patients with major depressive disorder (92,93), while depression-like behaviors in mice were able to be effectively treated by miR-124 antagomir administration, effectively blocking the inhibitory activity of miR-124 and establishing it as both a biomarker and an interesting therapeutic target for depression treatment (91). miR-124a, which is exclusively expressed in the brain and is the most abundant miRNA in the vertebrate central nervous

system, was shown to regulate GR expression by direct binding of the GR mRNA in P19 cells, a well-established neuronal differentiation cell line (94). A similar inhibitory activity was also observed for miR-18, although the binding potential for the GR transcript was not observed *in vitro* (94). Nevertheless, additional studies have implicated miR-18a as a direct post-transcriptional regulator of GR. Direct binding was observed in cultured neuronal cells, while miR-18a overexpression was concomitant with suppressed GR protein levels in a model of stress-susceptible rats, further establishing the direct GR regulation potential of the miR-18 family (95). miR-137, a miRNA identified as a potential regulator in schizophrenia, as well as other brain disorders, has been implicated in neuronal plasticity through GR-dependent signaling, while in silico target prediction algorithms identified *NR3C1* transcript as its putative target in both humans and mice (96). In a model of depression, following chronic unpredictable mild stress, miR-382-5p levels were found to be elevated with the concomitant suppression of GR levels in the hippocampus of rats. si-miR-382-5p treatment restored GR levels, as well as its downstream target levels of BDNF and p-TrkB62 (97).

A number of miRNAs that regulate GR expression have been implicated in various types of cancer. In the case of miR-124, it has also been shown that it can exert indirect regulatory effects on the GC response and sensitivity. The upregulation of GRα expression, accompanied by increased cAMP levels and the decreased expression of phosphodiesterase 4B, has been observed under stable miR-124 expression, in diffuse large B-cells lymphoma cell lines (98). Additionally, in patients with acute lymphoblastic leukemia (ALL), miR-124 levels have been shown to be increased, while this miRNA contributes to GC resistance, decreased apoptosis and decreased GR expression (99). Another miRNA that has been shown to be able to directly bind the *NR3C1* transcript and regulate its expression in various instances is miR-142-3p. This miRNA, which is upregulated in patients with leukemia, has been shown to be able to regulate GC response in T-leukemic cells by directly binding with the 3'UTR of the GRα mRNA (100). miR-142-3p was also identified in the study by Riester *et al* (101), where following ACTH stimulation, miR-101a, miR-142-3p, miR-96 and miR-433 were identified as putative direct regulators of GRα. Following modification of the 3'UTR of the *NR3C1* transcript in an *in vitro* experiment, it was shown that these four miRNAs could directly bind the 3'UTR and inhibit GRα expression by up to 40% (101). By investigating GC sensitivity in multiple myeloma cell lines, Tessel *et al* (102) identified miR-130b, miR-181a and miR-636 as miRNAs with direct binding potential to the 3'UTR of the *NR3C1* transcript, while also exhibiting differential expression between GC-sensitive and resistant cell lines. miR-130b overexpression *in vitro* caused decreased GR expression, concomitant with GC resistance, and decreased GC-induced apoptotic effects. Due to the common usage of GCs as a treatment for various forms of cancer, including leukemia and multiple myeloma, miRNA expression patterns can be used to identify GC responsiveness and resistance development (12,103).

GC regulation of miRNAs. Several miRNAs are involved in the mechanisms of the immune and inflammatory response, which are modulated and regulated by GCs. One of the first oncogenic miRNAs with elevated levels in several types of cancer (104), is miR-155. Increased levels of miR-155 have been reported in fibroblasts and macrophages in rheumatoid arthritis, where this miRNA appears to contribute to increased expression of chemokines and pro-inflammatory cytokines (105,106). It was previously demonstrated that the administration of GC dexamethasone to primary macrophages and macrophage cell lines, spleen and liver cells of LPS-injected mice, inhibited the expression of miR-155, suggesting that a decrease in miR-155 expression is an anti-inflammatory result of GCs (107,108).

miR-511 is a miRNA produced by the fifth intron of mRNA encoding the C-type mannose receptor CD206. More specifically, miR-511-5p contributes to impaired sensitivity to LPS and reduced expression of the classically activated (M1) macrophage marker IL-12, targeting the Toll-like receptor 4 and IL-12p40 subunit (109). In addition, miR-511-5p targets the p55 TNF receptor mRNA, thus providing TNF resistance, in cases where there is increased expression of this miRNA due to high levels of endogenous GCs (110). In conclusion, changes in the expression level of miR-511 are dependent on levels of endogenous GCs and have an impact on the differentiation and activation of myeloid cells, as a byproduct of altered *MRC1* gene expression (111).

A member of the let-7 miRNA family miR-98 is another GC-induced miRNA that reduces the expression of the p75 TNF receptor in T-lymphocytes by targeting *Tnfrsf1b* mRNA. Moreover, this miRNA is considered to target 3'UTR of IL-13, which plays a pathogenic role in asthma. In this way, miR-98 may contribute to the therapeutic effects of GCs on asthma (112). miR-101 is involved in inflammatory responses in myeloid and other cells and targets the 3'UTR of dual specificity phosphatase 1 (DUSP1) to regulate the activation of p38 MAPK in macrophages. Numerous studies have demonstrated that GCs in combination with pro-inflammatory stimuli, enhance DUSP1 expression, leading to the inactivation of p38 MAPK. In the study by Zhu *et al* (113), it was shown that GCs inhibit the expression of miR-101, thus leading to prolonged expression of DUSP1, which in turn led to reduced activation of p38 MARK and consequently to a decreased expression of p38 MARK-dependent inflammatory mediators.

The miR-17-92 cluster consists of six miRNAs, miR-17, -18a, -19a, -19b-1, -20a and 92a-1, which are derived from a precursor RNA transcribed from chromosome 13 (114). This complex targets the PTEN tumor suppressor, which regulates inositol phosphate signaling, and a pro-apoptotic member of the Bcl-2 protein family, Bim which regulates cytochrome c-induced apoptosis (115,116). According to several studies, GCs function as inhibitors of this cluster, thus exerting several therapeutic effects on lymphoma, while the failure of GCs to inhibit the miR-17-92 cluster resulted in resistance to apoptosis. In conclusion, the miR-17-92 cluster plays an important role in regulating responses to pro- and anti-apoptotic signals (116,117).

Finally, two miRNAs that have been linked to GC-induced apoptosis resistance in multiple myeloma (MM) are miR-221/222 (118) and miR-125b (119). The increased expression of these miRNAs has been shown to be associated with the attenuation of cell death pathways, such as apoptosis led by tumor protein 53. miR-125b expression levels are regulated by GCs as part of a possible self-limiting mechanism of GCs

Table II. lncRNAs and glucocorticoid activity.

lncRNAs	Type of interaction	Metabolism-related	Immune/inflammatory-related	Cancer-related	Other
GR-related					
GAS5	GR regulator	(14)	(144-145,147)	(148)	(146)
EDN1-AS	Regulated by GR				(15,149-150)
PSORS1C3	Regulated by GR				(152-154)
Related to other receptors					
SRA	AR, ER, GR and PR regulator			(156)	(155)
PRNCR1, PCGEM1	AR regulators			(157)	

Type of interaction between the lncRNAs and corresponding receptors, and references (numbers in parentheses) to lncRNAs related to GR or to other NR in metabolism-related, immune/inflammatory-related, cancer-related or other diseases. lncRNA, long non-coding RNA; GC, glucocorticoid; GR, glucocorticoid receptor; growth arrest-specific 5; PSORS1C3, psoriasis susceptibility 1 candidate 3; SRA, steroid RNA coactivator; AR, androgen receptor; ER, estrogen receptor; PR, progesterone receptor.

pro-apoptotic effects (119). On the other hand, a detailed analysis of miR-221 expression demonstrates the specificity of its expression in different types of cancer. More specifically, the increased expression of miR-221 in MM has been shown to induce resistance to GC-induced apoptosis (118), contrary to certain types of ALL, where resistance to GC-induced apoptosis is due to the reduced expression of miR-221 (120).

Performing RNA-sequencing and microarray expression analysis of male and female mouse hearts with a cardiomyocyte-specific knockout of the GR, Cruz-Topete *et al* (121) were able to identify 130 miRNAs whose expression was sex- and GR-dependent. Of these miRNAs, 25 were responsible for the vast majority of the differences observed between male and female hearts, including prominent heart failure biomarkers, such as miR-1-3p, miR-128, miR-370 and miR-28. miR-29a and miR-340 overexpression in L929 cells was previously found to be associated with a significant reduction in GR expression, suggesting a direct binding role for both miRNAs and the GR receptor transcript (122). Of note, in another study, the overexpression of miR-29a *in vivo* ameliorated GC-induced bone tissue destruction (123), while miR-340 overexpression decreased GR protein levels in the mouse placenta and affected sensitivity against activity-based anorexia (124).

Last but not least, a few recent studies have also identified GR as a potential miRNA regulator. In an *in vitro* study, miR-22 expression was shown to be elevated in AR42J cells following the induction of apoptosis. A GR binding site was identified in the promoter region of miR-22, while GR was shown to be able to repress miR-22 expression (125). In addition, a recent profiling study in triple-negative breast cancer suggested the ability of GR to influence multiple miRNA expression profiles (126), while in the study by Tejos-Bravo *et al* (127), neuron-specific GR knockout mice exhibited altered miRNA expression profiles in a sex-dependent manner. Such effects exhibit the great complexity inherent in miRNA regulation of GC activity, but also suggest an additional fine-tuning potential via the possible integration of feedback loops.

miRNA regulation of GR-chaperone proteins. As previously mentioned, until the moment of GC activation GR remains located in the cytoplasm, forming a complex with various chaperone proteins. As such, a number of secondary-degree regulatory potential exists via miRNA-mediated regulation of these chaperone proteins. While not thoroughly investigated, such effects have already been identified. miR-511, whose effects were previously discussed, was found to be able to directly bind the 3'UTR of *FKBP5*, suppressing GC-induced FKBP51 expression, while increasing neuronal development (128). In a similar manner, miR-124 was also shown to be able to target *FKBP5* (129). Of note miR-142 and miR-340, miRNAs with the established binding of GRα transcript, were predicted also to target the 3'UTR of *FKBP5* (128). Taking into account the numerous chaperone proteins that GRα interacts with, as well as the indicative gene regulatory network already established (Fig. 1), it is clear that the miRNA-mediated regulation of GC response is a very complex and multilayered process, which has only begun to be explored.

5. lncRNAs in glucocorticoid signaling

As already mentioned, GC signaling involves various signal transduction cascades in the cell. In recent years, studies focusing on the roles of ncRNAs have increased, including their roles in regulating the transcriptional activity of GR and other NRs (Table II). lncRNAs are a class of ncRNAs, which consist of >200 nucleotides and are derived from various regions in the genome, such as promoters, enhancers, introns, UTRs, overlapping or non-coding isoforms of coding genes, antisense to other transcripts and pseudogenes (130,131). According to previous studies, lncRNAs have been observed in the majority of organisms, such as animals (132), plants (133), fungi (134) and even viruses (135), without however evolving conservation among species. Following technological advancements and novel laboratory techniques, numerous data related to the roles of lncRNAs in a variety of vital biological processes have been gathered (136) and more specifically in transcription (137), alternative splicing (138), translation, cell cycle (139), apoptosis (140) and heat shock response (141). Several lncRNAs create RNA-protein, RNA-DNA and RNA-RNA complexes, while they have also been associated

with chromatin modification and guiding transcription factors to specific genomic DNA targets. Last but not least, a number of lncRNAs have been found to be associated with various diseases, including cancer, myocardial infractions and Alzheimer's disease (142,143).

GAS5 is a lncRNA that has been of immense interest to researchers in recent years and is involved in GR activity. As its name suggests, GAS5 inhibits cell growth caused by a lack of nutrients or growth factors. In the study by Kino *et al* (14), it was shown that GAS5 functions as an inhibitor of the transcriptional activity of GR and other steroid receptors (SRs). More specifically, the sequence of GAS5 contains two GC response elements-mimetic sequences at nucleotides 539-544 (GRE-1) and 553-559 (GRE-2). Thus, GAS5 acts as a competitor for GR binding through the GRE regions, decreasing GR-mediated gene activation and ultimately affecting cell survival and metabolic activity during nutrient deficiency. GAS5 overexpression significantly inhibits the transcription of GR target genes, including genes encoding the cellular inhibitor of apoptosis 2 and serum/GC-responsive kinase 1 (14).

However, an interesting observation was the fact that during growth inhibition or lack of nutrients in cells, the accumulation of GAS5 was reported in the organs of mice which are involved in metabolism, i.e., in the liver and adipose tissue, by modifying the mTOR signaling pathway, contrary to organs involved in the immune system, such as the thymus gland, spleen and the brain. Recent studies have demonstrated that the levels of GAS5 in cells can vary. In particular, it has been suggested that GAS5 exerts regulatory activity on GR in the immune system, independently of nutrient availability. This is evidenced by the different expression of GAS5 in leukocytes of patients with inflammatory or autoimmune diseases (144), as well as its role in the GC response of children with diseases, such as inflammatory bowel disease (145), multiple sclerosis (146), human beta cell dysfunction (147) and acute myeloid leukemia (148).

EDN1-AS is a lncRNA, which appears to interact with GR. This lncRNA is located antisense of the endothelin 1 gene, which is a peptide hormone that acts on the vascular system as a vasoconstrictor, while in the kidneys it affects blood pressure through diuretic and natriuretic effects (15). Its aberrant quantity has been shown to be associated with pathological conditions, such as hypertension (149) and chronic kidney disease (150). EDN1-AS is expressed in multiple human cell types, including the kidneys. In the study by Douma *et al* (15) in a human kidney proximal tubule cell line (HK-2), the promoter of lncRNA EDN1-AS appeared to have a GRE sequence, which could be recognized and bound by GR, as well as the MR, representing a new mechanism for regulating ET-1 expression. Using CRISPR/Cas9 for the deletion of the GRE element from the EDN1-AS promoter, abolished the binding of GR to EDN1-AS and resulted in increased EDN1-AS expression with a concomitant increase in endothelin 1 expression and cell proliferation. The inhibitory effect of GR binding to the EDN1-AS promoter is therefore inferred (15).

Psoriasis susceptibility 1 candidate 3 (PSORS1C3) is a lncRNA whose sequence is adjacent to the octamer-binding transcription factor 4 (*OCT4*) gene. As is well known, the transcription factor OCT4 plays regulatory roles in oncogenesis, stemness and in response to stress. PSORS1C3 has shown to be associated with diseases, such as psoriasis (151) and other immune-mediated diseases, such as acute anterior uveitis (152), as well as major depressive disorder (153). According to the study by Mirzadeh Azad *et al* (154), this lncRNA has two endogenously active promoters, promoters 0 and 1 and two sets of transcripts, small and large variants. A GRE sequence was identified upstream of promoter 0 of PSORS1C3, where GR binds and acts as either an enhancer or a repressor of the expression of target genes. More specifically, that study demonstrated the positive effect of GR on the expression level of *OCT4* and small variants of PSORS1C3, which may reflect a new regulatory pathway of cell proliferation and the stress response through the regulation of expression levels of *OCT4*. On the other hand, the binding of GR to promoter 0 of large variants of lncRNA PSORS1C3 exerted an inhibitory effect, suggesting its function as a pro-inflammatory factor. Thus, GR functions as a regulator of the expression of the lncRNA PSORS1C3, which in turn regulates and moderates the expression of the OCT4 factor in non-multipotent cells, as the PSORS1C3 promoter 0 region acts as an enhancer for the neighboring *OCT4* gene (154).

In general, several lncRNAs have been recorded to regulate the transcriptional activity of several SRs, including GR. A prototype lncRNA is the steroid RNA coactivator (SRA) which increases the transcriptional activity of the androgen receptor (AR), estrogen receptor, GR and progesterone receptor. The SRA regulates the transcriptional activity by binding to the SRA stem-loop-interacting RNA binding-protein and the RNA-induced silencing complex complex (155,156). In addition, according to Yang *et al* (157), lncRNAs PRNCR1 and PCGEM1, which are expressed primarily in the prostate gland, bind AR to its DNA binding domain, and suppress receptor activity, playing a significant role in the development of prostate cancer. In summary, lncRNAs appear to regulate the expression levels of various target genes of NRs, including GR. For this reason, future research is required to elucidate the function of lncRNAs in regulating gene expression through their interaction with transcription factors, such as GR in GC signaling pathways.

6. Discussion

The stress response system is related to the production of endogenous GCs. This system, particularly the interaction between cortisol and GR, which is described by the GR pathways, has attracted increasing attention in recent years due to its medical interest in developing therapeutic approaches. Although GR is derived from a single gene, its function differs based on the different isomers which are produced due to alternative splicing and alternative translation initiation mechanisms. It has been shown that GCs bind in a similar manner to all the isomers (158); however, GRs differ in their subcellular distribution and gene regulatory profiles, affecting the human organism via multiple mechanisms. It should be noted that some GR polymorphisms have been linked to GC resistance and a healthier metabolic profile, whereas others seem to be associated with GC hypersensitivity increasing cardiovascular risk (159). It has been proposed that the regulation of GC signaling is related

to pathological conditions, such as cancer, heart diseases, diabetes and other metabolic disorders.

Recently, numerous studies have implicated GC signaling in cancer progression or prevention, depending on the cell type. In one case, animal models of human breast cancer revealed that GCs inhibit tumor cell apoptosis, while in other cases, synthetic GCs are used to induce apoptotic cell death in malignant lymphoid cells (e.g., lymphoma). Even though pharmacologic GC therapy is frequently administered to cancer patients to reduce the associated side effects of chemotherapy, further investigations on the results of the treatment on patients need to be conducted as GC application may contribute to tumor growth (160). Other studies have suggested that GR signaling in cardiomyocytes is critical for the normal development and function of the heart (161,162). In a previous study (161), cardiomyocyte-specific GR overexpression led to bradycardia, while GR inhibition resulted in cardiac hypertrophy, systolic dysfunction, and impaired maturation. Further research is required in order to determine the precise molecular pathways and genes through which cardiomyocyte GC signaling can either promote or protect against heart pathology (161). It should also be mentioned that, apart from the endogenous GCs, studies have suggested the use of dexamethasone for the treatment of post-operative nausea and vomiting, as it is a synthetic GC with anti-inflammatory and immunosuppressant properties, with 20- to 30-fold the binding affinity for GR of endogenous cortisol (163).

Due to the ability of miRNAs to regulate multiple targets, while every 3'UTR can harbor multiple binding sites for different microRNAs, it is easily apparent that post-transcriptional regulation via miRNAs forms a highly complex and sensitive network. Under physiological conditions, the miRNA-mediated modulation of GR expression is mainly involved in fine-tuning GC responses during CNS development. However, a number of pathological responses have implicated the interaction between the mRNA transcript of GR protein and different miRNAs, as observed in brain disorders, as well as in cancer development and treatment. Taking into account the negative role of miRNAs in steroidogenesis, the association between miRNAs and GR expression warrants further in-depth investigations. Currently, numerous miRNAs have already been identified that have the capacity to directly bind *NR3C1* 3'UTR and exercise their regulatory effects, such as miR-124-3p and miR-142-3p, among several others. Nevertheless, the concept of a single cause-single target, while beneficial for past drug development, is gradually being pushed aside, as the multi-factorial nature of regulation becomes more and more apparent. These types of interactions offer increased sensitivity and fine-tuning potential to environmental changes. More systematic approaches are therefore necessary that will offer a holistic regulatory view. Combining existing target prediction tools with network generation packages, their complexity instantly emerges (Fig. 2). Additional regulatory levels are also exercised through alternative splicing and the production of other GR isoforms. This is the case for miR-124-3p, where differential splicing produces the GRb isoform, no longer harboring its binding site, which in turn acts as a negative inhibitor of GRα (90,162). Tying this to recent studies, demonstrating that the GR can itself influence miRNA expression profiles (125-127), the intricacies of miRNA-GR regulation and response to GCs are becoming exponentially complex.

Similar to miRNAs, lncRNAs have a variety of regulatory roles in gene expression. Their ability to form RNA-protein, RNA-DNA and RNA-RNA complexes enable them to be involved in cellular processes, such as apoptosis, translation, cell cycle and heat shock response. They play key roles in various disease cases, such as numerous types of cancer, myocardial infraction and neurodegenerative diseases, such as Alzheimer's disease (142,143). lncRNAs are further involved in various biological processes, including GC signaling, which connects to extensive pathways related to the immune, nervous and metabolic systems. An example is lncRNA GAS5, which regulates the GR response via direct binding through its GRE sequences, thus having an impact on the gene expression of the GR target-genes (14). EDN1-AS and PSORS1C3 are two additional lncRNAs whose expression is regulated by the GR. In both cases, these lncRNAs are bound with the GR via GREs, which in turn acts as their inhibitor, affecting the expression of genes that interact with them, the *EDN1* (15) and *OCT4* (154) genes, respectively.

It thus becomes clear that GC signaling has extensive and important functions in the immune, nervous system and related metabolic responses in the context of homeostasis. Its activity has been associated with numerous pathological conditions, such as cancer, metabolic and neurodegenerative diseases. It is easily apparent that GC signaling is part of an intricate regulatory network, heavily involving post-transcriptional regulation via ncRNAs, in an effort to maintain the fine-tuning potential the body needs to respond to ever-shifting environmental conditions. Such a network is comprised of numerous miRNAs, lncRNAs and potentially yet unverified actors. Their complex associations are just beginning to be unraveled, but are already demanding new analysis paradigms to be adopted. To this aim, combinatory bioinformatic approaches need to be employed and new tools developed that can investigate such effects in a more systematic manner. Only then can a better understanding of GC activity be obtained and the utilization of its therapeutic potential can effectively be achieved.

7. Conclusions

ncRNAs are an intriguing field of study. Their unique properties, as well as their ability to be involved in vital cellular processes, render them suitable pharmaceutical targets and biomarkers. GC signaling participates in a regulatory network that includes post-transcriptional regulation via ncRNAs, including various miRNAs and lncRNAs. These molecules can either act as regulators of GR activity or be regulated by endogenous GCs, affecting the expression of GC-mediated genes. Generally, GC activity is associated with several pathological conditions, including cancer, neurodegenerative and metabolic diseases. Therefore, the development of more effective therapies for these diseases requires a better understanding of GC signaling that includes interacting regulatory ncRNAs.

Acknowledgements

Not applicable.

Funding

The authors would like to acknowledge funding from the following organizations: i) AdjustEBOVGP-Dx (RIA2018EF-2081): Biochemical Adjustments of native EBOV Glycoprotein in Patient Sample to Unmask target Epitopes for Rapid Diagnostic Testing. A European and Developing Countries Clinical Trials Partnership (EDCTP2) under the Horizon 2020 'Research and Innovation Actions' DESCA; and ii) 'MilkSafe: A novel pipeline to enrich formula milk using omics technologies', a research co-financed by the European Regional Development Fund of the European Union and Greek national funds through the Operational Program Competitiveness, Entrepreneurship and Innovation, under the call RESEARCH-CREATE-INNOVATE (project code: T2EDK-02222).

Availability of data and materials

Not applicable.

Authors' contributions

All authors (KP, LP, TM, EP, ID, SL, MS, KD, DAS, FB, GPC, GNG, EE and DV) contributed to the conceptualization and design of the study, as well as in the writing, drafting, revising, editing and reviewing of the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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