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Tissue glucocorticoid resistance/hypersensitivity syndromes☆

Tomoshige Kino*, Massimo U. De Martino, Evangelia Charmandari, Marco Mirani, George P. Chrousos

Pediatric and Reproductive Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892-1583, USA

Abstract

Glucocorticoids have a broad array of life-sustaining functions and play an important role in the therapy of many diseases. Thus, changes of tissue sensitivity to glucocorticoids may be associated with and influence the course and treatment of many pathologic states. Such tissue sensitivity changes may present on either side of an optimal range, respectively as glucocorticoid resistance or hypersensitivity, and may be generalized or tissue-specific. Familial/sporadic glucocorticoid resistance syndrome caused by inactivating mutations of the glucocorticoid receptor (*GR*) gene is a classic monogenic disorder associated with congenital, generalized glucocorticoid insensitivity, while several autoimmune, inflammatory and allergic diseases are often associated with resistance of the inflamed tissues to glucocorticoids. On the other hand, glucocorticoid hypersensitivity has been suggested in visceral obesity-related insulin resistance associated with components of the metabolic syndrome, and in the acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency virus type-1 (HIV-1) infection. Here, we have reviewed the molecular analyses of five familial and three sporadic cases of the familial/sporadic glucocorticoid resistance syndrome and discussed the possible contribution of newly identified molecules, such as HIV-1 accessory proteins Vpr and Tat, FLICE-associated huge protein (FLASH) and chicken ovalbumin upstream promoter-transcription factor II (COUP-TFII), on the molecular regulation of GR activity, as well as their possible contribution to changes in tissue sensitivity to glucocorticoids in pathologic conditions. Published by Elsevier Science Ltd.

Keywords: Glucocorticoid; Accessory proteins; HIV-1

1. Introduction

Glucocorticoids are crucial for the regulation of basal and stress-related homeostasis. These steroid hormones influence and are necessary for maintenance of many important biologic activities, such as the homeostasis of the central nervous system, the cardiovascular system, the intermediary metabolism and the immune/inflammatory reaction [1,2]. In addition, at "pharmacologic" doses, glucocorticoids are potent immunosuppressive and anti-inflammatory agents that make them irreplaceable therapeutic means for many inflammatory, autoimmune, and lymphoproliferative diseases [3].

The actions of glucocorticoids are mediated by a ubiquitous intracellular receptor protein, the glucocorticoid receptor (GR), which functions as a hormone-activated transcription factor of glucocorticoid target genes. These genes probably represent up to 10–20% of the human genome and can be influenced by the ligand-activated GR directly or indirectly [4]. The gene of the GR consists of nine exons and is located in chromosome 5 [5] (Fig. 1A). It encodes two 3′ splicing variants, GRα and β, from alternative use of a different terminal exons 9α and β. The GRα encodes a 777 amino acid protein, while the GRβ contains 742 amino acids. The first 727 amino acids from the N-terminus are identical in the two isoforms. GRα possesses an additional 50 amino acids, while the GRβ encodes an additional 15 non-homologous amino acids in their C-terminus. GRα is the classic GR that binds with glucocorticoids and transactivates or transrepresses glucocorticoid-responsive promoters. On the other hand, hGRβ does not bind glucocorticoids and its physiologic and pathologic roles are not well known [6].

The classic GR consists of three domains, the N-terminal or "immunogenic" domain, the central, DNA-binding domain (DBD), and the C-terminal, ligand-binding domain (LBD) [5,7] (Fig. 1A). The GR in its unliganded but ligand-friendly state is located primarily in the cytoplasm, as part of hetero-oligomeric complexes containing heat shock proteins 90, 70 and 50, and, possibly, other proteins as well [8]. After binding to its agonist ligand, the GR undergoes conformational changes, dissociates from the heat shock proteins, homodimerizes, and translocates into the nucleus through the nuclear pore via an active process.

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* Corresponding author. Tel.: +1-301-496-6417; fax: +1-301-480-2024.
E-mail address: kinot@mail.nih.gov (T. Kino).

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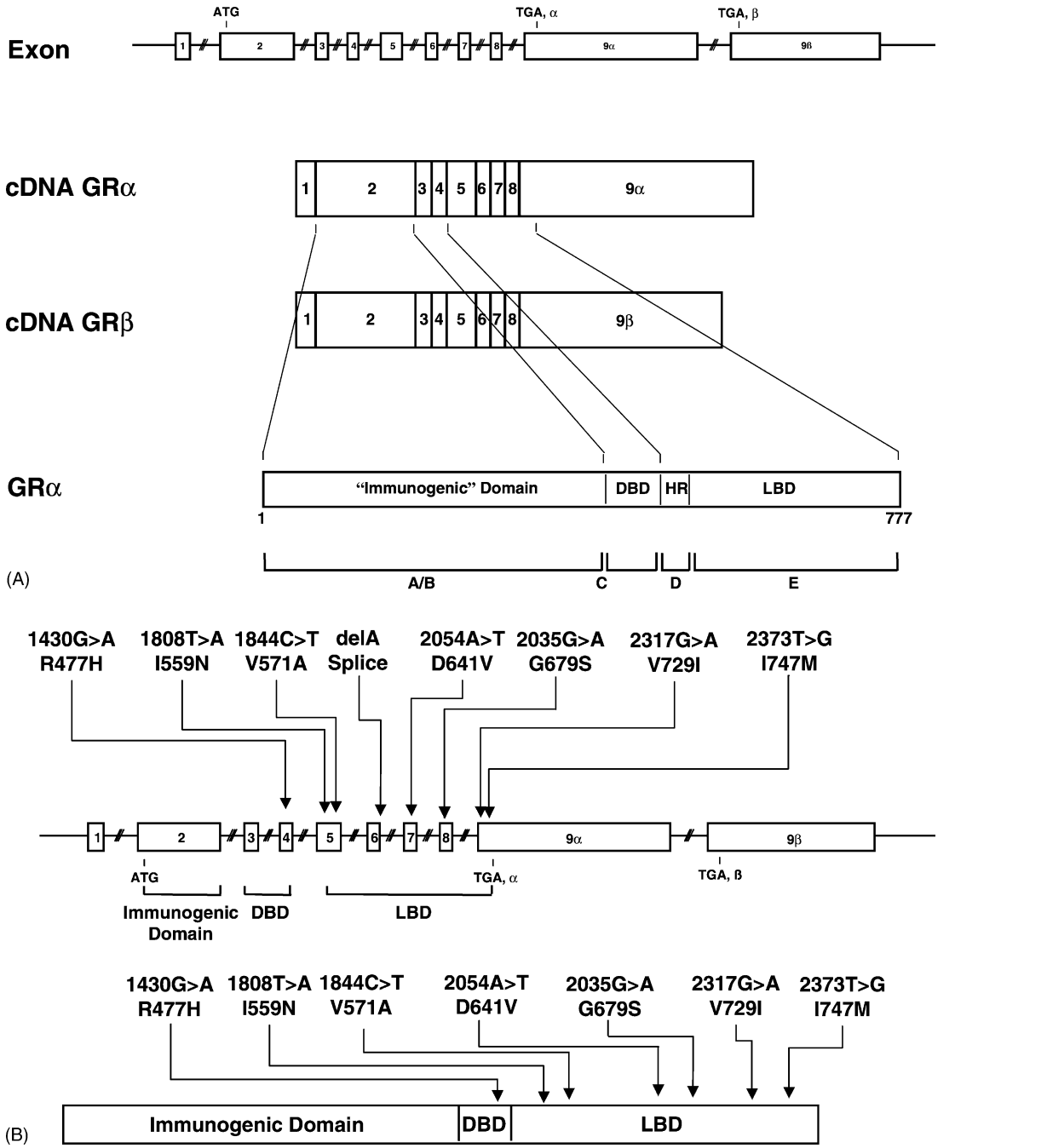

Fig. 1. (A) Genomic and complementary DNA, and protein structures of the human glucocorticoid receptor. The human glucocorticoid receptor gene consists of 10 exons; A/B: exon 1 is untranslated region, exon 2 codes for the immunogenic domain, C: exons 3 and 4 for the DNA-binding domain, D: exons 5–9 for the hinge region, and E: the ligand-binding domain. The glucocorticoid receptor gene contains two terminal exons 9 (exons 9α and 9β) alternatively spliced to produce the classic GRα and the non-ligand-binding GRβ. C-terminal gray colored domains in GRα and GRβ show their specific portions. GR: glucocorticoid receptor; HR: hinge region; DBD: DNA-binding domain; LBD: ligand-binding domain. (B) Location of the known mutations of the glucocorticoid receptor in its genomic and protein structures.

There, the ligand-activated GR directly interacts with DNA sequences, the glucocorticoid-responsive elements (GREs), in the promoter regions of target genes, or with other transcription factors via protein–protein interactions, indirectly influencing the activity of the latter on their target genes [8].

The GRE-bound GRα stimulates transcription rate of responsive genes by facilitating the formation of the transcription initiation complex, including RNA polymerase II and its ancillary factors [9]. In addition to these molecules, GRα, via its two transactivation domains attracts several proteins and protein complexes, the coactivators, which

help transmit the glucocorticoid receptor–ligand complex to the transcription initiation complex. In addition to serving as "bridging" factors, coactivators contain intrinsic histone acetyltransferase (HAT) activity, through which they loosen the chromatin structure and facilitate access and/or binding of transcription machinery components to DNA [10]. They include molecules, consisting of the homologous p300 and cAMP-responsive element binding protein (CREB)-binding protein (CBP) and the family of p160 nuclear receptor coactivators. p300/CBP coactivators also serve as macromolecular docking "platforms" for transcription factors from several signal transduction cascades, including, in addition to nuclear receptors, CREB, activator protein (AP)-1, nuclear factor (NF)-κB, p53, Ras-dependent growth factor, and signal transducers and activators of transcription (STATs) [11]. Because of their central position in many signal transduction cascades, the p300/CBP coactivators are also called as co-integrators. p300/CBP-associated factor (p/CAF), originally reported as a human homologue of yeast Gcn5 that interacts with p300/CBP is also a broad coactivator with HAT activity [12,13].

Steroid receptors preferentially interact with p160 family of coactivators: steroid receptor coactivator-1 (SRC-1); transcriptional intermediate factor-II (TIF-II) or glucocorticoid receptor-interacting protein-1 (GRIP-1), also called SRC-2; and the p300/CBP/co-integrator-associated protein (p/CIP), activator of thyroid receptor (ACTR) or receptor-associated coactivator-3 (RAC3), also called SRC-3 [10,14]. p300/CBP and p160 family coactivators contain one or more copies of the coactivator signature motif sequence LXXLL where L is leucine and X is any amino acids through which they directly bind the GR [14,15]. p160 coactivators are firstly attracted to the DNA-bound steroid receptor and help accumulate p300/CBP and p/CAF to the promoter region through their mutual interactions, indicating that p160 proteins play a central role in the transactivation by steroid receptors [16].

Since glucocorticoids have a broad array of life-sustaining functions and play an important role in therapeutic interventions, changes of tissue sensitivity to glucocorticoids may be associated with and influence the course of many pathologic states (Table 1) [17]. Such changes may present on either side of an optimal range, respectively as glucocorticoid resistance or hypersensitivity, and may be a generalized or tissue-specific. Primary generalized glucocorticoid resistance has been described as a rare familial or sporadic syndrome mostly due to inactivating mutations of the *GR* gene, while several autoimmune/inflammatory states, such as rheumatoid arthritis, osteoarthritis, Crohn's disease, ulcerative colitis and asthma, are often associated with resistance of the inflamed tissues to glucocorticoids [8,18,19]. In addition, septic shock and respiratory distress syndrome have been associated with systemic glucocorticoid resistance [20].

On the other hand, glucocorticoid hypersensitivity has been suggested in visceral obesity-related insulin resistance associated with components of the metabolic syndrome, and in the acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency virus Type-1 (HIV-1) infection [7,21,22]. The mechanisms, which potentially cause change of tissue sensitivity to glucocorticoids may be considered in each step of the GR signaling cascade described above (Fig. 2). Indeed, many molecules change GR activity at different steps of GR signaling pathway and some of them may have a direct link to the pathogenesis of glucocorticoid resistance/hypersensitivity syndromes (Table 2).

Table 1
Reported pathologic states associated with changes in tissue sensitivity to glucocorticoids (from [17])

Resistance
Familial/sporadic glucocorticoid resistance syndrome
Rheumatoid arthritis
Osteoarthritis
Systemic lupus erythematosus
Crohn's disease
Ulcerative colitis
Septic shock/respiratory distress syndrome
Bronchial asthma
Hypersensitivity
Visceral-type obesity-related hypertension and insulin resistance
Acquired immunodeficiency syndrome (AIDS) (human immunodeficiency virus type-1 infection)

In this review, we will focus on an update on the familial/sporadic glucocorticoid resistance syndrome and the cellular mechanisms, which potentially influence the tissues' sensitivity to glucocorticoids.

1.1. Familial/sporadic glucocorticoid resistance syndrome

Familial/sporadic glucocorticoid resistance syndrome was first described in 1976, as a glucocorticoid receptor-mediated disorder characterized by hypercortisolism without Cushingoid features [23,24]. Since then, over 10 kindreds and sporadic cases with abnormalities of the GR concentration, affinity for glucocorticoids, stability, and/or translocation into the nucleus have been reported [25–38]. However, the molecular defects have been elucidated only in five kindreds and three sporadic cases (Fig. 1B, Table 3). The propositus of the original kindred was a homozygote for a single non-conservative point mutation, replacing aspartic acid with valine at amino acid 641 in GR LBD; this mutation reduced binding affinity for dexamethasone by three-fold and caused concomitant loss of transactivation activity [31]. The proposita of the second family had 4-base deletion at 3′-boundary of exon 6, removing a donor splice site. This resulted in complete ablation of one of the GR alleles in affected members of the family [32]. The propositus of the third kindred had a single homozygotic point mutation at amino acid 729 (valine to isoleucine) of the LBD, which reduced both the affinity and transactivation activity of the GR [34]. There was also an interesting sporadic case of a man with a de novo, germ-line, heterozygotic GR mutation at amino acid 559 (isoleucin to asparagine) also of the LBD

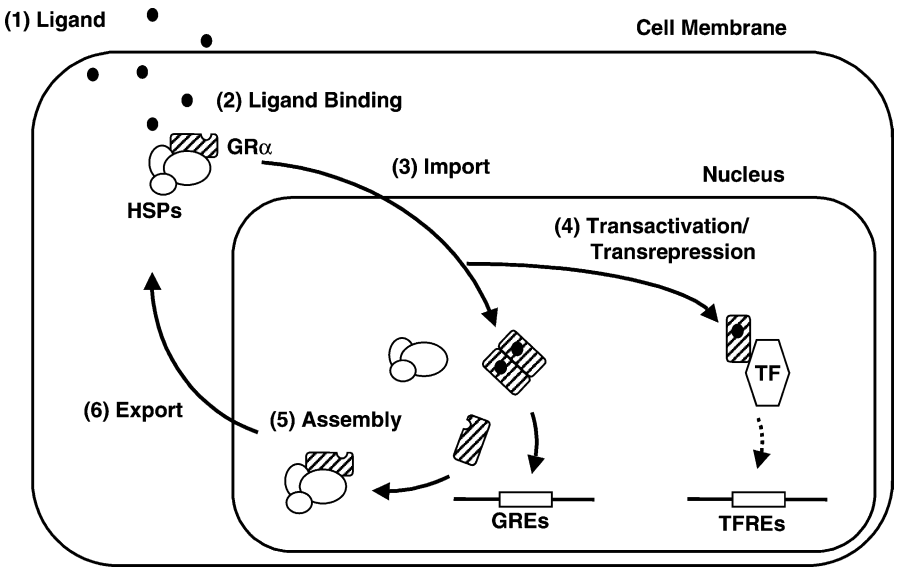

Fig. 2. Shuttling of GRα between the cytoplasm and the nucleus and its transactivating or transrepressive activities. Possible sites of intervention, which may change the activity of GRα are indicated by numbers. GR: glucocorticoid receptor; GREs: glucocorticoid-responsive elements; TFREs: transcription factor responsive elements; HSP: heat shock proteins; TF: transcription factor.

close to nuclear localization signal 1 (NL1). This mutant GR bound no ligand but exerted dominant negative activity on the wild type receptor by forming heterocomplex with and retarding the translocation of the wild-type receptor into the nucleus [33,35].

A fifth case/kindred with glucocorticoid resistance and a heterozygotic GR mutation in the LBD (amino acid 747, replacing isoleucine with methionine) was described [36]; the mutant receptor had mildly reduced affinity for dexamethasone and markedly decreased transactivation activity; interestingly, it also had dominant negative activity on the wild-type receptor. The mutation is located just several amino acids prior to the helix 12 of the LBD. This mutant receptor has an inactive activation function 2 (AF2) and cannot bind to the nuclear coactivator signature motif LXXLL of the p160 type nuclear receptor coactivators, but still associates with another site of this coactivator through its intact AF-1 domain. Overexpression of the p160 coactivator diminishes dominant negative activity of the mutant receptor, suggesting that the defective interaction of the mutant receptor with p160 coactivators may explain its dominant negative activity on the wild type receptor. Indeed, it appears that amino acid 747 of the GR LBD plays a critical role in the transactivation activity of the GR, but not in its ligand-binding activity; introduction of an artificial mutation, replacing the isoleucine to threonine at amino acid 747 resulted in marked decrease in the transactivation activity of the molecule [39,40].

The sixth and seventh sporadic cases were also due to heterozygous mutations, replacing arginine to histidine at amino acid 477 and glycine to serine at amino acid 679, respectively [38]. The former is located in the second zinc finger in the DBD. This mutant receptor has no transactivation activity due to impaired binding to GREs. The latter mutation is found in the LBD, outside of the ligand-binding pocket. This mutation causes 50% reduction of ligand-binding affinity

Table 2
Factors and molecules, modulating the action of the glucocorticoid receptor

Signaling system step	Molecules
Ligand and ligand-binding	Membrane transporters for glucocorticoids 11β-HSD, glucocorticoid agonists or antagonists (RU 486), other chemical compounds (ursodeoxycolic acid, cortivazol, thioredoxin, carnitine)
Modification of GR	Nitrosylation, acetylation, methylation
GR intracellular trafficking	Heat shock proteins, RAP46, FKBPs, 14-3-3s
Receptor isoform	GRβ
Transcriptional regulators	Coactivators/corepressors, SWI/SNF, TRAP/DRIP complex viral proteins (adenovirus E1A, HIV-1 Vpr and Tat), FLASH
Transcription factors	NF-κB, COUP-TFII, AP-1, STATs, CREB, C/EBP, Nur77, HNF-6, p53, GATA-1, SP1, Oct-1, NF1

11β-HSD: 11β-hydroxysteroid dehydrogenase; RAP46: receptor-associating protein of ∼46 kDa; FKBPs: FK506-binding proteins; GRβ: glucocorticoid receptor β; SWI: mating-type switching; SNF: sucrose non-fermenting; TRAP: thyroid hormone receptor-associated protein; DRIP: Vitamin D receptor-interacting protein; FLASH: "FLICE-associate huge" protein; NF-κB: nuclear factor-κB; COUP-TFII: chicken ovalbumin upstream promoter transcription factor II; AP-1: activator protein-1; STATs: signal transducers and activators of transcription; CREB: cAMP-responsive element-binding protein; C/EBP: CAAT/enhancer-binding protein; HNF-6: hepatocyte nuclear factor-6; Oct-1: octamer factor-1; NF1: nuclear factor 1.

Table 3
Pathologic mutations in the glucocorticoid receptor gene

References	Position of mutations		Biochemical phenotype	Genotype/transmission
	cDNA	Amino acid		
Hurley et al., 1991 [31]	2054A > T	D641V	Affinity ↓ Transactivation ↓	Homozygote/autosomal recessive
Karl et al., 1993 [32]	Δ4 at the 3′-boundary of exon and intron 6		GR number ↓ Inactivation of the affected allele	Heterozygote/autosomal dominant
Malchoff et al., 1993 [34]	2317G > A	V729I	Affinity ↓ Transactivation ↓	Homozygote/autosomal recessive
Karl et al., 1996 [33,35]	1808T > A	I559N	Number ↓ Transactivation ↓ Dominant negative activity	Heterozygote/sporadic
Vottero et al., 1999 [36,94]	2373T > G	I747M	Affinity ↓ Transactivation ↓↓ Dominant negative activity	Heterozygote/autosomal dominant
Ruiz et al., 2001 [38]	1430G > A	R477H	Transactivation (–)	Heterozygote/sporadic
Ruiz et al., 2001 [38]	2035G > A	G679S	Affinity ↓ Transactivation ↓	Heterozygote/sporadic
Mendonca et al. [37]	1844A > T	T571C	Affinity ↓ Transactivation ↓↓	Homozygote/autosomal recessive

with comparable reduction of the transactivation activity. Since these two mutant receptors are found in the heterozygous condition, they might behave as dominant negative mutants, suppressing the biologic activity of the wild type receptor.

The proposita of the eighth familial case had a homozygotic point mutation replacing valine by alanine at amino acid 571 of the LBD [37]. The mutant receptor had six-fold reduction in its binding affinity to dexamethasone and 10–50-fold less transactivation activity than the wild type receptor. Interestingly, this baby born with ambiguous genitalia also suffered from 21-hydroxylase deficiency, suggesting that this congenital disease exacerbated the hyperandrogenism and virilization potential of the glucocorticoid resistance syndrome.

1.2. New regulators of the glucocorticoid receptor activity

1.2.1. Human immunodeficiency virus type-1 accessory proteins Vpr and Tat

Patients with AIDS, which is caused by infection with HIV-1, have several manifestations compatible with increased activity of the glucocorticoid receptor. For instance, they develop reduction of innate and T helper 1-directed cellular immunity, which is also seen in conditions of glucocorticoid excess. AIDS patients also frequently develop muscle wasting and myopathy as well as dyslipidemia and visceral obesity-related insulin resistance, also seen in hypercortisolemic states [22,41–46]. Therefore, it is possible that some unknown factor(s) might modulate the GR function in AIDS patients.

In agreement with above clinical evidence, one of the HIV-1 accessory proteins, Vpr, a 96-amino acid virion-associated protein with multiple functions [47,48], enhanced GR transactivation by functioning as a coactivator in vitro [49]. Indeed, Vpr contains a nuclear receptor signature motif LXXLL at amino acids 64–68, through which host nuclear receptor coactivators bind to nuclear receptors (Fig. 3A) [14]. Vpr directly bound to the GR through this motif and cooperatively enhanced its activity on its responsive promoters along with host p160 nuclear receptor coactivators and p300/CBP [49]. Vpr also directly bound p300 at its C terminal amino acids 2045–2191, at which host coactivator p160 proteins also bind, and functioned as an adaptor linking GR and the coactivator complex [50]. Since Vpr circulates at detectable levels in HIV-1-infected individuals and is able to penetrate the cell membrane, its effects may be extended to cells not infected by HIV-1 [51,52]. We found that extracellularly administered Vpr suppresses interleukin (IL)-12 production from peripheral monocytes by potentiating GR activity, possibly contributing to the suppression of innate and cellular immunity of HIV-1-infected individuals and AIDS patients [53].

Another HIV-1 accessory protein, Tat, which functions as a major transactivator of the HIV-1 long terminal repeat promoter [54] also moderately potentiates GR activity, by promoting the accumulation of the positive transcription elongation factor b (P-TEFb) [18,22,46,55–57] (Fig. 3A). Since, like Vpr, Tat also readily penetrates cell membranes [58], it may modulate GR activity irrespectively of infection of the cells by HIV-1.

Through Vpr and Tat, HIV-1 may facilitate the transcription of genes encoding its own proteins by directly

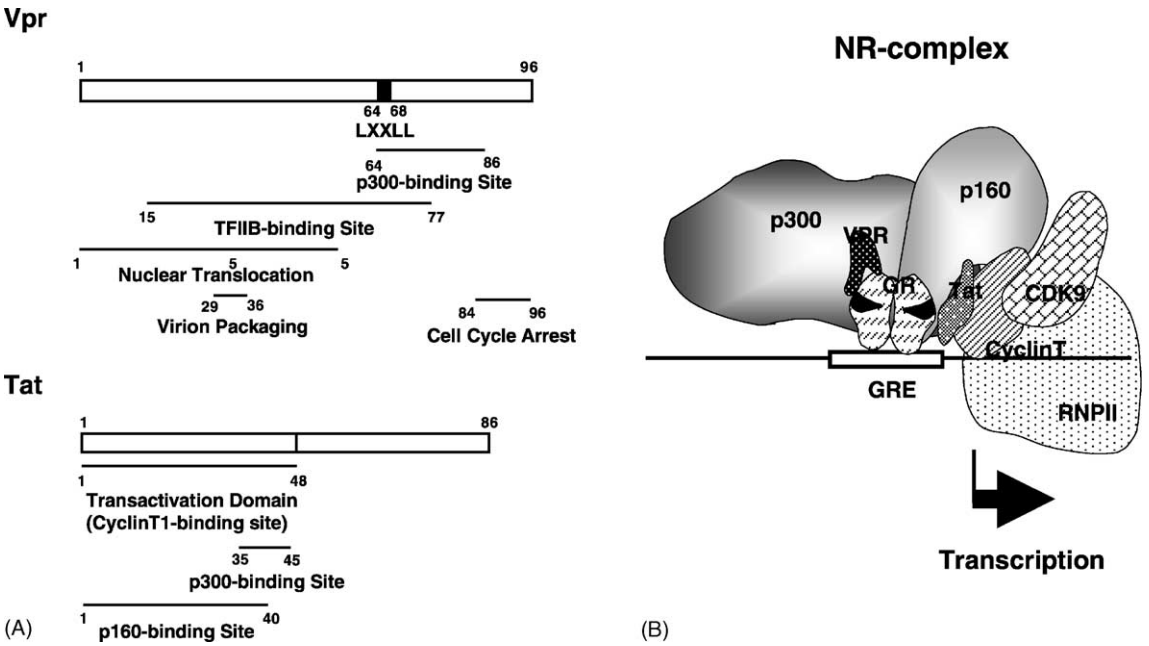

Fig. 3. (A) Linearized molecules and functional distribution of HIV-1 Vpr and Tat. (B) A simplified model of Vpr and Tat actions on glucocorticoid-responsive genes (from [22,55]). CDK9: cyclin-dependent kinase 9; RNPII: RNA polymerase II; GRE: glucocorticoid-responsive element.

stimulating viral proliferation. On the other hand, by enhancing transactivation of GR, these proteins may contribute to the proliferation of the virus indirectly possibly by suppressing the host immune system (Fig. 3B) [17,18,22,46,49,55,57].

1.2.2. Potential role of FLASH in Inflammation-associated glucocorticoid resistance

Several autoimmune/inflammatory/allergic diseases, such as rheumatoid arthritis, systemic lupus erythematosus, ulcerative colitis, Crohn's disease and glucocorticoid resistant asthma, are associated with glucocorticoid resistance (Table 1) [17]. Since inflammatory signals are mediated by numerous cytokines and growth factors, some of them or their combinations might contribute to the development of glucocorticoid resistance seen in these diseases [59,60]. Indeed, the glucocorticoid insensitivity in the majority of glucocorticoid resistant asthmatics appears to be associated with several changes in the glucocorticoid signaling system in certain immune cells, which can be induced in naïve white cells by incubation with IL-2 and -4 combined, or IL-13 alone [61,62]. These changes include decreases in the affinity of the nuclear fraction of the GR for its ligand and resistance of the cells to glucocorticoids in vitro. Similarly, tumor necrosis factor α (TNFα) has been shown to cause resistance of human mononuclear cells to glucocorticoids [59].

TNFα and its homologues play a central role in the development and maintenance of inflammation in many pathologic inflammatory states [60,63]. TNFα is produced by variety of immune and immune accessory cells, including monocytes, macrophages and dendritic cells, and exerts diverse effects on cell growth and differentiation, promotes inflammation, and may cause apoptosis [64]. The TNFα signal is mediated by its receptor, the TNFα receptor (TNF-R), which belongs to the Fas family of the cell surface receptors [64]. Binding of TNFα to its receptor induces its biologic activities through several other intermediate, receptor-associated proteins, such as TNFα receptor-associating factors (TRAF), receptor-interacting protein (RIP), and FLICE-associated huge protein (FLASH) [64–66]. These molecules also mediate signals from TNF-R to several transcription factors like NF-κB and AP-1, which may explain the negative effect of TNFα on the GR transcriptional activity [67–69].

To further elucidate mechanism(s) that may contribute to glucocorticoid resistance associated with inflammation, we performed yeast two-hybrid screening using the nuclear receptor binding (NRB) domain of GRIP1 as bait. We successfully found that the C-terminal portion of FLASH specifically interacted with GRIP1 NRB at the region enclosed between the second and the third LXXLL motifs (Fig. 4A) [70]. FLASH is a CED4-homologous protein, involved in apoptosis induced by both TNFα and Fas ligand (FasL) [66,71]. This protein forms the death-inducing signaling complex (DISC) with the cytoplasmic portion of Fas, i.e. the receptor for FasL, and caspase-8, in response to FasL. FLASH also participates in the activation of NF-κB through direct interaction with TRAF2 [66].

Although FLASH was originally found as a component of a cytoplasmic complex located under the plasma membrane, it contains two putative nuclear localization signals (NLS) and one nuclear export signal (NES), findings that have led to the speculation that it might translocate into

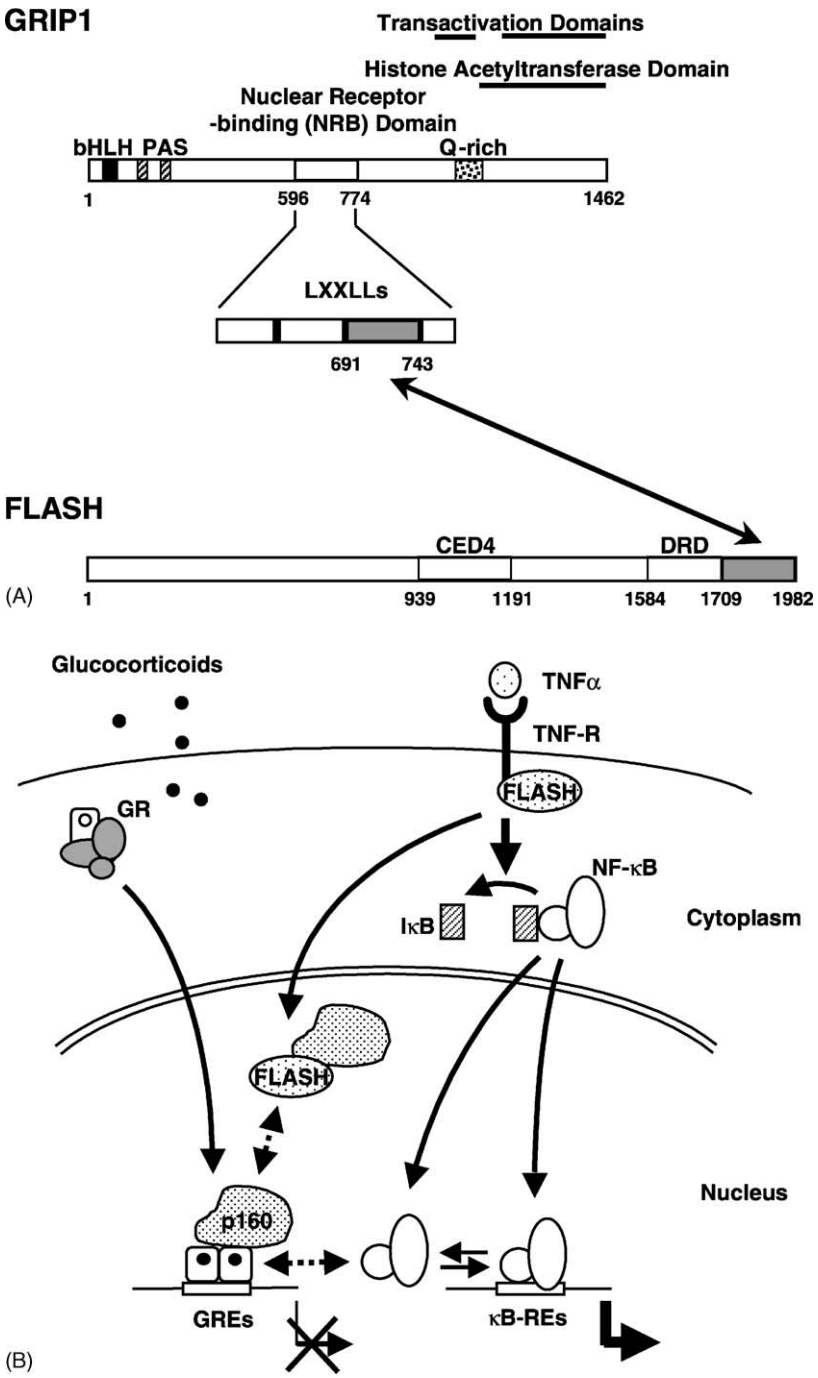

Fig. 4. (A) Localization of functional domains of GRIP1 and FLASH (from [70]). Mutual interacting domains in GRIP1 and FLASH are shown in grey. bHLH: basic helix–loop–helix sequence; PAS: period aryl hydrogen receptor and single-minded domain; CED4: CED4-homologous domain: DRD: death-effector domain-recruiting domain. (B) Schematic model of FLASH antagonism on GR-induced transactivation (from [70]). GR: glucocorticoid receptor; GREs: glucocorticoid-responsive elements; TNFα: tumor necrosis factor α; TNF-R: tumor necrosis factor receptor; NF-κB: nuclear factor-κB; κB-REs: κB-responsive elements.

the nucleus in response to certain stimuli [71]. We found that this molecule inhibited both GR transactivation and its enhancement by GRIP1 on a glucocorticoid-responsive promoter by interfering with GR binding to GRIP1 [70]. Incubation of cells with TNFα caused translocation of FLASH into the nucleus, blocking ligand-activated GR interaction with GRIP1 and suppressing transactivation. We suggest that the transcriptional activity of the GR is inhibited by TNFα at the level of p160 type coactivators through FLASH, independently of the parallel interaction with and interference by the transcription factor NF-κB signal transduction pathway (Fig. 4B) [70].

1.2.3. Chicken ovalbumin upstream promoter-transcription factor II: a potential mediator of metabolic activity of glucocorticoids

Glucocorticoids exert their extremely diverse effects through only one protein molecule, the classic GR. This becomes possible because they affect other signal transduction cascades through mutual protein–protein interactions with other transcription factors, which mediate the transcriptional effects of these cascades [8]. A mouse model harboring a mutant GR, which is active in protein–protein interaction but unable to dimerize and bind to GREs, survive relatively free of major clinical problems, in contrast to mice in which the entire *GR* gene is deleted, which die at birth from severe respiratory distress syndrome [72,73]. The former mouse model and additional in vitro data indicate that GR may interact with and influence the effect of other transcription factors in the forms of a monomer [72,74]. Glucocorticoid-induced suppression of transactivation through protein–protein interaction may be particularly important in the immunosuppressive and anti-inflammatory actions of glucocorticoids as described above [72,74]. Substantial part of glucocorticoid effect on the immune system may be explained by its interaction with NF-κB, AP-1 and probably STATs [20,75–77]. In addition, GR also mutually influences the transcriptional activity of other transcription factors, such as CREB, CAAT/enhancer-binding protein (C/EBP), Nur77, p53, hepatocyte nuclear factor (HNF)-6, GATA-1, Oct-1 and -2, nuclear factor (NF)-1 and Sp-1 [78–88].

To explore the presence of transcription factors, which bind to the GR and influence the GR metabolic activity, we performed yeast two-hybrid screening using the GR LBD as bait and found that the orphan nuclear receptor chicken ovalbumin upstream promoter-transcription factor II (COUP-TFII) specifically interacted with the GR (unpublished data). This orphan nuclear receptor plays an important role not only in the organogenesis, including limb, eye and neuronal development, during embryogenesis, but also in the regulation of glucose, cholesterol and xenobiotic metabolism [89,90]; COUP-TFII stimulates promoters of many key enzymes or signal molecules involved in these biologic activities, such as phosphoenolpyruvate carboxykinase (PEPCK), insulin, mitochondrial 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) synthase, cholesterol 7α-hydroxylase (CYP7A) and CYP3A by binding to its responsive sequences located in the promoter region of these molecules [90–93].

We found that the ligand-activated GR forms a complex with COUP-TFII and enhances its transcriptional activity on a COUP-TFII-responsive promoter in several cell lines (unpublished data). GR also enhanced the transcriptional activity of COUP-TFII on the promoter of the PEPCK, a key enzyme in gluconeogenesis, suggesting that their interaction may also be important in a well-known effect of glucocorticoids, such as glucose metabolism. Since COUP-TFII plays a critical role in the above-indicated activities, it is possible that the metabolic effects of glucocorticoids in the liver are partly mediated by COUP-TFII.

Since ligand-activated GR enhances transcriptional activity of COUP-TFII on its responsive promoters and COUPT-TFII suppresses GR transactivation activity, quantitative and/or qualitative changes of this orphan receptor may play a role in the development of glucocorticoid hypersensitivity/resistance in several pathologic situations, such as visceral obesity-related insulin resistance, carbohydrate intolerance, diabetes mellitus type 2 and dyslipidemia (unpublished data). Determination of changes in COUP-TFII signaling may help us understand the pathogenesis of glucocorticoid hypersensitivity/resistance in these pathologic states.

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