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The Interplay between the Glucocorticoid Receptor and Nuclear Factor-κB or Activator Protein-1: Molecular Mechanisms for Gene Repression

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The inflammatory response is a highly regulated physiological process that is critically important for homeostasis. A precise physiological control of inflammation allows a timely reaction to invading pathogens or to other insults without causing overreaction liable to damage the host. The cellular signaling pathways identified as important regulators of inflammation are the signal transduction cascades mediated by the nuclear factor-κB and the activator protein-1, which can both be modulated by glucocorticoids. Their use in the clinic includes treatment of rheumatoid arthritis, asthma, allograft rejection, and allergic skin diseases. Although glucocorticoids have been widely used since the late 1940s, the molecular mechanisms responsible for their antiinflammatory activity are still under investigation. The various molecular pathways proposed so far are discussed in more detail. (*Endocrine Reviews* 24: 488–522, 2003)

I. Introduction

THE INFLAMMATION PROCESS was first described by Cornelius Celsus (30 BC–38 AD) who mentioned that "rubor et tumor cum calore et dolore" (redness and swelling, accompanied with heat and pain) are the cardinal symptoms of inflammation. The inflammatory response can be interpreted as notification of a threatening agent or organism and subsequent activation of the defense system developed to eliminate these threats. Immunity and inflammation are physiological processes of profound importance to the organism; without these processes, a host would quickly succumb to invading pathogens or damaging stimuli, whereas excessive or inappropriate activation of these responses causes tissue and cell damage and even death. Therefore, maintaining immune homeostasis is critical for the survival of an organism. Both pro- and antiinflammatory mechanisms must be present and functional for a cell (organism) to survive in the face of environmental stimuli that elicit an immune response. These pathways provide homeostasis by pulling the cell in opposite directions (1–4). Over the last 10 yr, the transcription factors nuclear factor (NF)-κB and activator protein (AP)-1 have been shown to be crucial for the induction of genes involved in inflammation, as well as in a wide range of diseases originating from chronic activation of the immune system, including asthma, atherosclerosis, inflammatory bowel disease, and autoimmune diseases such as multiple sclerosis and rheumatoid arthritis (5–8). A plethora of immunoregulatory genes coding for cytokines, cytokine receptors, chemotactic proteins, or adhesion molecules, such as TNF-α, IL-1β, IL-2, IL-6, IL-8, macrophage chemotactic protein (MCP-1), regulated on activation, normal T cell expressed and secreted (RANTES), interferon (IFN)-β, granulocyte-macrophage colony stimulating factor (GM-CSF), intercellular adhesion molecule-1 (ICAM-1), vascular cellular adhesion molecule-1 (VCAM-1), and E-selectin, contain NF-κB and/or AP-1 sites in their promoters or regulatory regions. Therefore, both transcription factors represent an obvious target for immunosuppressive therapies (9–15). Glucocorticoids (GCs) and catecholamines, the major stress hormones, counteract the production of (pro)inflammatory cytokines, such as IL-12, IL-6, and TNF-α, whereas they stimulate the production of antiinflammatory cytokines such as

Abbreviations: AF, Activation function; AP, activator protein; AR, androgen receptor; Bcl, B cell lymphoma; BRG-1, brahma-related gene-1; CARM, coactivator-associated arginine methyltransferase; CBG, corticosteroid-binding globulin; CBP, CREB-binding protein; COX, cyclooxygenase; CREB, cAMP response element-binding protein; DBD, DNA-binding domain; DEX, dexamethasone; DRIP, vitamin D receptor-interacting protein; ER, estrogen receptor; FKBP, FK-binding protein; GC, glucocorticoid; GILZ, GC-induced leucine zipper; GM-CSF, granulocyte-macrophage colony stimulating factor; GR, GC receptor; GRE, GC response element; HAT, histone acetyltransferase; HDAC, histone deacetylase; hsp, heat shock protein(s); ICAM, intercellular adhesion molecule; IFN, interferon; IκB, inhibitory protein κB; IKK, IκB kinase; JNK, Jun amino-terminal kinase; LBD, ligand-binding domain; LPS, lipopolysaccharide(s); LTR, long terminal repeat; MAPKKK, MAPK kinase kinase; MCP, macrophage chemotactic protein; MR, mineralocorticoid receptor; NCoR, nuclear corepressor; NF, nuclear factor; nGRE, negative GRE; NR, nuclear receptor; PK, protein kinase; POMC, proopiomelanocortin; PPAR, peroxisome proliferator-activated receptor; PR, progesterone receptor; PRL, prolactin; PRMT, protein arginine *N*-methyltransferase; P-TEFb, transcription elongation factor; RAR, retinoic acid receptor; RHD, Rel homology domain; RXR, retinoid X receptor; SMRT, silencing mediator of retinoid and thyroid receptors; SNF, sucrose nonfermenting; SRC, steroid receptor coactivator; STAT, signal transduction activator of transcription; TBP, TATA box-binding protein; TCR, T cell receptor; Th, T helper; TPA, tetradecanoylphorbol acetate; TR, thyroid receptor; TRAP, thyroid receptor-activated protein; TSA, trichostatin A; VCAM, vascular cellular adhesion molecule.

IL-10, IL-4, and TGF-β (16–19). Systemically, by activation of the stress system, an excessive immune response stimulates an important negative feedback mechanism, which protects the organism from an overshoot of proinflammatory cytokines and other tissue-damaging products (3, 20–24).

A. NF-κB

Transcriptional regulators of the NF-κB/inhibitory protein (I)κB family promote expression of more than 100 target genes, the majority of which participate in the host immune response (4, 25–28) (for a recent update, visit http://people.bu.edu/gilmore/nf-kb/). Gene knockout and other studies established roles for NF-κB in the ontogeny of the immune system and demonstrated that NF-κB participates at multiple steps during oncogenesis and regulation of programmed cell death (5, 8, 29–31). The involvement of the ubiquitous transcription factor NF-κB in the pathogenesis of the inflammatory response has been well documented by experiments, both *in vitro* and *in vivo* (5–7, 10, 32). NF-κB is a heterodimer, typically consisting of p50 and p65 monomeric proteins. A targeted disruption of the genes encoding p50 or p65 leads to extreme immunodeficiencies, and even to lethality in the case of p65 knockout mice (28, 33, 34). The mammalian NF-κB/Rel family includes five members: p65 or RelA, RelB, c-Rel, NF-κB1 (p50/p105), and NF-κB2 (p52/p100). All members are characterized by a conserved stretch of 300 amino acids, designated as the Rel homology domain (RHD). This domain is important for DNA binding and mutual interactions between the different Rel family members. It also serves as an interaction surface for the IκB. NF-κB is latently present in the cytoplasm, under tight control of the associated protein IκB-α. The IκB protein family comprises the following members: IκB-α, IκB-β, IκB-γ/p105, IκB-δ/p100, IκB-ε, and B cell lymphoma (Bcl)-3. They are characterized by several 30- to 33-amino acid motifs called ankyrin repeats. Potent inducers of NF-κB include the proinflammatory cytokines IL-1 and TNF, byproducts of microbial, fungal, and viral infections such as lipopolysaccharides (LPS), sphingomyelinase, double strand (ds)RNA, Tax protein from human T cell leukemia/lymphoma virus (HTLV), and proapoptotic and necrotic stimuli, such as oxygen-free radicals, UV irradiation, and γ irradiation. The first step in the activation process of NF-κB is an IκB kinase complex (IKK)-dependent phosphorylation of IκB-α at serines 32 and 36. Subsequently, ubiquitinylation at lysines 21 and 22 takes place by a specific ubiquitin ligase belonging to the SCF (Skp-1/Cul/F box) family and tags IκB-α for degradation by the 26S proteasome complex. The actual recognition of N-terminally phosphorylated IκBs is carried out by a WD repeat- and F box-containing protein called β-TrCP (35). This finally leads to release of the NF-κB protein, which migrates to the nucleus to exert its effects on gene regulation (25, 27, 35–42). Many groups focused on the identification of the serine-specific IκB kinase complex IKK, which comprises multiple subunits (43, 44) and acts as an integrator of multiple NF-κB-activating stimuli (41, 45, 46).

The differential activity of the two IKK kinases on different IκB family members probably also results in a differentially regulated downstream NF-κB response and activity (47). Further examination of these proteins confirmed the involvement of IKK-β in proinflammatory cytokine-induced activation of NF-κB, whereas IKK-α was found to be crucial for B cell maturation, formation of secondary lymphoid organs, increased expression of certain NF-κB target genes, processing of the NF-κB2 (p100) precursor, and NF-κB activation in the limb and skin during embryogenesis (48–50). Results from IKK-α and IKK-β double-deficient mice confirmed the importance of IKKs for NF-κB activation *in vivo* and further demonstrated a neuroprotective role for these kinases during development (51). Antagonistic effects of IKK-α and IKK-β have recently also been described in Wnt signaling depending on β-catenin phosphorylation and localization, thus integrating signaling events between the NF-κB and Wnt pathways (52). A third component, IKK-γ (also known as NEMO/IKKAP/FIP-3), was designated as a scaffold platform for the assembly of the IKK complex (53–56). Several studies indicate that the IKK complex consists of two IKK-α/IKK-β heterodimers held together by one IKK-γ monomer. Many proteins have been reported to activate the IKK complex, but so far there is no full understanding of their specificity and redundancy; they include protein kinase (PK)C isozymes, MAPK kinase kinase (MAPKKK) family members, NIK, AKT/TPB, MEKK-1, MEKK-2, MEKK-3, COT/TPL-2, TAK-1 and NAK (46, 57, 58). Many of the previous reports regarding the ability of kinases to activate IKK and induce NF-κB DNA binding activity may be the result of overexpression studies and have not necessarily been confirmed by knockout studies (59).

Alternative IKK complexes causing NF-κB activation were also identified (42, 60, 61). Besides the classical IκB metabolism, variations have also been described at the level of phosphorylation (Ser32, Ser36, Thr273, Tyr42) and degradation (nonproteosomal, lysosomal, or caspase-dependent) (62–71). Both the release and activity of NF-κB are subject to different control mechanisms. IκB-α expression itself is controlled by NF-κB, establishing an autoregulatory feedback loop and shutting down activation of NF-κB (72). Furthermore, NF-κB activation can be negatively regulated by a SUMO-1 (small ubiquitin-like modifier-1 or sentrine) modification of unphosphorylated IκB-α. This leads to a degradation-resistant IκB molecule (73) which may relocalize to particular subcellular compartments (74). Another level of regulation of NF-κB is imposed by the catalytic subunit of PKA, which has been demonstrated to form a cytosolic complex together with NF-κB and IκB (75). p65 phosphorylation by PKA at Ser276 affects its transcriptional activity and was reported to mediate a functional interaction of NF-κB with the cofactor cAMP response element-binding protein (CREB)-binding protein (CBP) (76, 77). Phosphorylation at various other amino acid residues in p65 was also found to contribute to the transcriptional activity of NF-κB (28, 42, 77–86).

B. AP-1

The transcription factor AP-1 is encoded by protooncogenes and regulates various aspects of cell proliferation and differentiation (12, 14, 87). AP-1 can be composed of either homodimers or heterodimers between members of the Jun

(c-Jun, v-Jun, Jun-B, and Jun-D), Fos (c-Fos, Fos-B, Fra-1, and Fra-2), activating transcription factor (ATF-2, ATF-3/LRF-1, B-ATF, JDP-1, JDP-2) or Maf (v-Maf, c-Maf, Maf-A/B/F/G/K, Nrl) families; they all belong to the class of the basic zipper (bZIP) family of sequence-specific dimeric DNA-binding proteins. The protein products of the *fos* and *jun* gene families, *i.e.*, the so-called immediate-early genes that are directly activated and require no new transcription or translation for their induction, are transcription factors that activate and repress other genes, thereby producing secondary transcriptional reprogramming appropriate to the stimulus used (88–90). The regulation of AP-1 activity is complex and first occurs by changes in *jun* and *fos* gene transcription and mRNA turnover; secondly, by effects on Jun and Fos protein turnover; thirdly, by posttranslational modifications of Jun and Fos proteins that modulate their transactivation potential; and fourthly, by interactions with other transcription factors that can either synergize or interfere with AP-1 activity (12, 88–92). AP-1 was originally identified to interact with the control regions of genes containing promoter elements responsive to tetradecanoylphorbol acetate. Today, various stimuli, such as physiological agents (growth factors, mitogens, polypeptide hormones, cell-matrix interactions, and inflammatory cytokines), bacterial and viral infections, pharmacological compounds (anisomycin, phorbol esters, and okadaic acid), cellular stress (ultraviolet or ionizing radiation), as well as hyperosmotic and heavy-metal stress, have been shown to induce AP-1 activity. These stimuli activate MAPK cascades [mostly p38, Jun amino-terminal kinase (JNK), and ERKs] that enhance AP-1 activity by phosphorylating distinct substrates. The transcriptional activity of c-Jun is enhanced by amino-terminal phosphorylation at Ser63 and Ser73 by JNK (93). This inducible phosphorylation step is required to recruit the transcriptional coactivator CBP, which leads to transcriptional enhancement (94, 95). In addition to positive regulatory effects, the AP-1 complex has been shown to confer negative regulation, for instance of GC receptor (GR) (96). The growth-promoting activity of c-Jun is mediated by repression of tumor suppressors, as well as up-regulation of positive cell cycle regulators. c-Jun is a mostly positive regulator of cell proliferation, whereas Jun-B has the adverse effect. However, the ability of c-Jun and Jun-B to elicit opposite transcriptional responses in the presence of apparently similar AP-1 recognition sites, found in the control regions of different genes, remains enigmatic (14). Knockout studies indicated a biological role for c-Fos in survival during bone development and homeostasis, gametogenesis, and neuronal functions, besides its role in cell proliferation and differentiation. For c-Jun, a role has also been demonstrated in development, hepatogenesis, and liver erythropoiesis (12).

C. Glucocorticoid (GC) hormones

1. Molecular aspects and physiology. GCs exert their effects by binding to the GR, a transcription factor capable of regulating several genes in a positive or negative way (for a comprehensive list, see Ref. 1). GR belongs to the family of steroid hormone receptors, comprising structurally similar modular proteins, such as GR, progesterone (PR), mineralocorticoid (MR), androgen (AR), and estrogen (ER) receptor forms, which further belong to the nuclear receptor (NR) superfamily (97). Other classes of NRs include thyroid (TR), retinoid and orphan receptors [retinoic acid receptor (RAR)/retinoid X receptor (RXR)]. In general, the receptor members share a variable amino-terminal transactivation domain (98), a central and well-conserved DNA-binding domain (DBD), and a moderately conserved carboxy-terminal domain responsible for ligand binding. The latter domain also contains activating functions (1, 99–102).

In vivo, GC hormones are synthesized stepwise from cholesterol by a series of cytochrome P450-catalyzed reactions within the adrenal cortex (zona fasciculata). The synthesis and secretion of cortisol, the major GC hormone in man, is tightly controlled by the balance of adrenocorticotropin (secreted from the anterior pituitary gland) and CRH (secreted from the hypothalamus during stress) in a pulsatile and circadian way (103, 104). The most widely accepted mechanism for GC entry into the cell is by free diffusion of the lipophilic molecules across the lipid bilayer of the cell into the cytoplasm. In its unliganded resting state, in the absence of GC hormone, GR is present in the cytoplasm in an inactive complex (*i.e.*, DNA binding-incompetent) with chaperones and cochaperone molecules (105, 106). The most important chaperones in NR action are heat shock protein (hsp)90 and hsp70. Their action is further positively or negatively regulated by cochaperones such as immunophilins (FK506-binding proteins FKBP1/2), dynein, p23, hsp40/hdj1, hip, carboxy terminus of hsp70-interacting protein (CHIP) and BAG-1 (Bcl-2 binding athanogene-1) (105, 107–109). Receptor activation and hyperphosphorylation occurs upon ligand binding, which initiates substitution of one immunophilin (FKBP-51) for another (FKBP-52), and concomitant recruitment of the transport protein dynein, but leaving hsp90 unchanged. Immunofluorescence and fractionation revealed hormone-induced translocation of the hormone-generated GR-hsp90-FKBP-52-dynein complex from cytoplasm to nucleus, a step that precedes dissociation of the complex within the nucleus and conversion of GR to the DNA-binding form (109, 110). From recent studies, it has become apparent that the role of the (co)chaperones is not only restricted to the cytoplasm. Apart from inhibiting hormone binding to GR, they can also regulate the regulatory functions of the receptors in the nucleus (108) by dynamic (dis)assembly of various transcription complexes (111–113). Activated GR binds to specific DNA sequences as a homodimer. Genes positively regulated by GR are characterized by GC-response elements (GRE) in the promoter (Fig. 1A and Table 1), whereas negatively regulated genes contain either a negative GRE (nGRE) (Fig. 1B) or are inhibited by direct or indirect interference of GR with the transcriptional activity of other DNA-bound transcription factors [such as NF-κB, AP-1, CREB, CCAAT enhancer binding protein (C/EBP), signal transduction activator of transcription (STAT), p53, Smad, *etc.*] (Fig. 1C–N).

2. Biological effects of GCs. GCs are of major importance for protection of the body against stress by regulating glucose metabolism and blood pressure. They are also involved in lipid metabolism and deposition of glycogen in the liver. Besides the metabolic actions, GC effects have also been

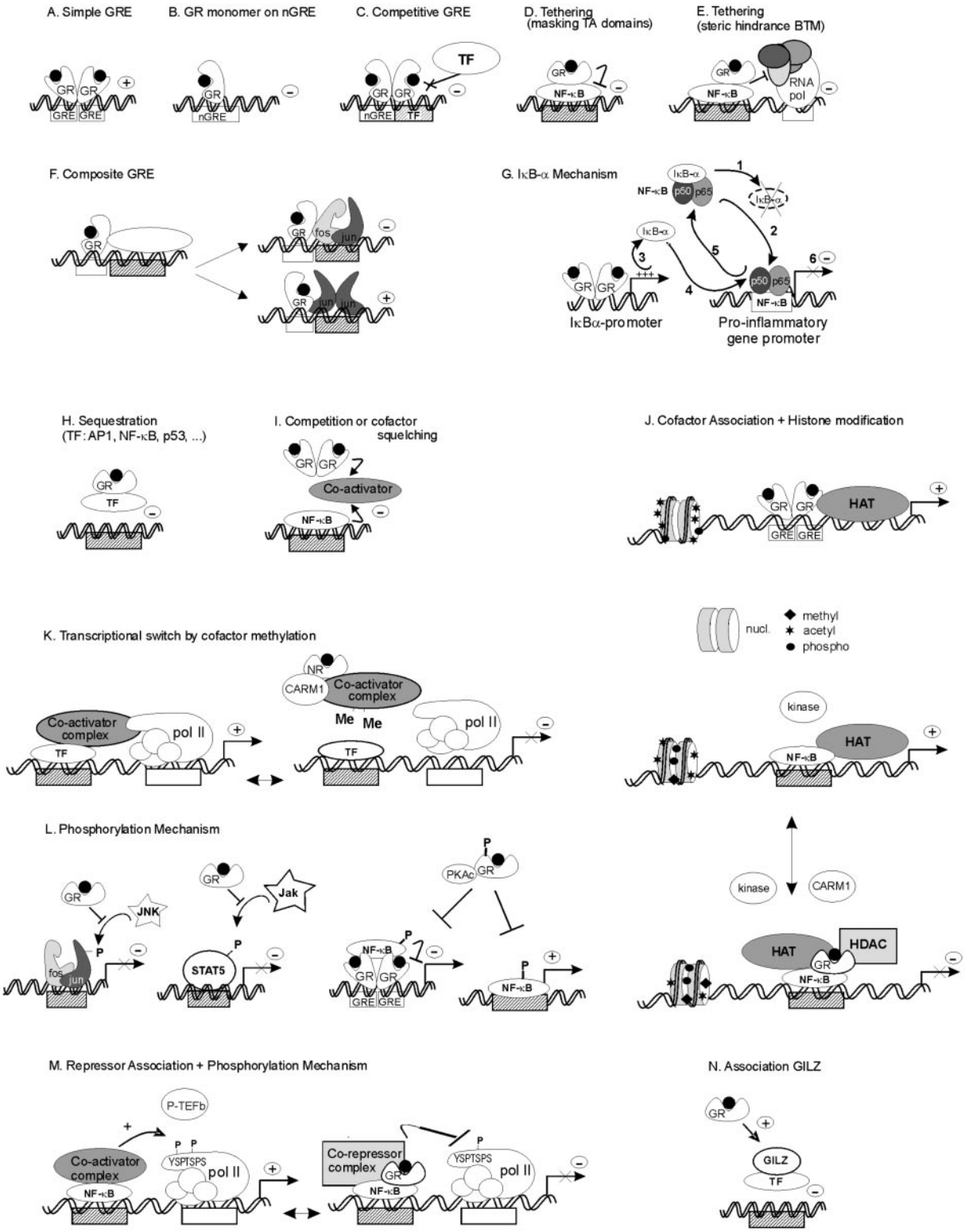

FIG. 1. Cartoons of the proposed models as described throughout the text are drawn in Fig. 1 and represented in Table 1, explaining interactions of GR with DNA/transcription factors and corresponding effects on gene regulation (represented by + or − sign). BTM, Basal transcription machinery; nucl., nucleosome; P-TEFb, transcription elongation factor; pol, polymerase; TA, transactivation domain; TF, transcription factor.

described with respect to behavior and brain function (114–118). Furthermore, GCs affect organ development, tissue maturation, wound healing, and calcium reabsorption (104, 119). Highly important is the role of GCs in the dynamic modulation of inflammatory and immune responses. This involves cross-talk with transcription factors and signaling

TABLE 1. Overview of the different models for GC activation or suppression of genes

Model	Gene	Transcription factor	Ref.
A	TAT, PEPCK, lipocortin	GR	775–777
BC	Keratin	GR monomer	213–215, 778, 779
	Osteocalcin, POMC	GR-TBP	
	Type 1 vasoactive intestinal polypeptide receptor	GR-basal factor	
DE	IL-6, IL-8, E-selectin, COX-2	NF-κB	212, 217, 227, 240, 260, 321–323, 760, 780–782
	Collagenase	AP-1	
	POMC	Nurr-77	
	Prolactin	Pit-1	
	Glycoprotein-α subunit	CREB	
	Type 1 plasminogen activator inhibitor	Smad-3/4	
F	Proliferin	AP-1	222, 223, 783–785
	α-Fetoprotein	AP-1	
	c-fms	AP-1	
	Prolactin	Pit-1	
G	NF-κB-driven genes (see Table 3)	NF-κB	250, 251
H	IL-2 and other NF-κB-driven genes	NF-κB	228, 786, 787
	Bax, bcl-2, $p21^{WAF1/CIP1}$	p53	
	IL-2R, Jak3	STAT5	
I	E-selectin	NF-κB	347, 357, 506
	Collagenase	AP-1	
J	GRE-driven genes	GR	472, 571, 572, 788
	NF-κB- or AP-1-driven genes	NF-κB/AP-1	427, 476, 477
K	CBP-sensitive genes	CREB-CBP	492
L	AP-1-driven genes	AP-1	283, 286, 326, 786
	STAT5-driven genes	STAT5	
	GRE-driven genes	GR	
	NF-κB-driven genes	NF-κB	
M	NF-κB-driven genes	NF-κB	603
N	IL2-R	NF-κB/AP-1	645, 647

pathways, effects on cytokine receptor expression (120, 121), regulation of thymocyte and lymphocyte survival, selection, and functions (122–126), as well as interference with eosinopoiesis (127) or erythropoiesis (128). If optimally balanced, GC-dependent functions will contribute to a resolution of infection, trauma, or other immunologically related stressors. However, disruption or malfunction of these dynamic interactions may result in a fatal outcome of acute inflammation or may predispose for autoimmunity or atopic reactions (129). An understanding of the true role of endogenous GCs in host defense can open new avenues for the treatment or prophylaxis of immune-mediated diseases.

3. Tissue specificity of GC effects. Because GR is expressed in the vast majority of tissues, it is reasonable to assume that GCs affect nearly all cells in the body (130). The regulation and action of GC-mediated effects further depend on other tissue-specific factors, on the bioavailability of the hormone, and on tissue-specific hormone-modifying enzymes. At one level, the biological sensitivity of GCs is achieved by binding to circulating proteins present in plasma and blood, such as corticosteroid-binding globulin (CBG) (131). During a stressful situation (*e.g.*, septic disorder), CBG levels drop due to an IL-6-dependent hepatic posttranscriptional blockade. This results in enhanced exposure of cells and tissues to free GC hormone to suppress the inflammatory response, which would otherwise lead to death. CBG homeostasis is normally restored after 1 or 2 d (132, 133). In kidney, liver, brain, and pancreas cells, 11β-hydroxysteroid dehydrogenases can convert cortisol to a biologically inactive form or reactivate it from hormone precursors in a cell-specific manner (134–136). At another level, GC sensitivity is determined by expression levels of the transporter protein LEM1 or multidrug resistance protein MDR1 (137, 138). The expression levels of GR are also cell- and tissue-specific. GR levels are themselves negatively regulated by GCs, contributing to the fact that long-term treatment with GCs results in a decrease of the physiological response (139, 140). Other levels of regulation that determine GC sensitivity include variations in the receptor protein (mutations, polymorphisms, isoforms) (141–147), alternative receptor dimerization (GR heterodimerization has been described with MR, PR, and AR) (144, 148–151), presence of GC modulatory element binding proteins (152–155), receptor cochaperones (111, 112, 156, 157), DNA-bending (158), altered expression levels of hsp proteins (159, 160), effects of signaling cascades (141, 161–163), and posttranslational modifications (phosphorylation, nitrosylation, ubiquitinylation, sumoylation, and acetylation) (141, 159, 164–173). Finally, it is now clear that differences between endogenous GCs (produced by the adrenal glands) and synthetic GCs, in terms of their regulatory mechanisms, are crucial for their biological actions. For example, synthetic GCs differ from endogenous GCs in binding to CBG, tissue-specific metabolism, affinity for various GRs, and interaction with transcription factors (174).

4. GCs in the clinic. GCs belong to the most commonly and effectively used drugs in the clinic to relieve inflammation and various immune disorders (1, 104, 175–178). Inflammatory diseases, for which administration of GCs are a standard treatment, include rheumatoid arthritis, inflammatory bowel diseases, systemic lupus erythematosus, sarcoidosis, and nephrotic syndrome. Local treatments with GCs are applied against dermatitis, ophthalmological disorders, asthma, and

conjunctivitis (179–183). Furthermore, GCs are used to suppress the immune system post transplantation. GCs are also used to treat brain edema, shock conditions, and certain cancers (*e.g.*, hematological malignancies), as well as conditions involving adrenal cortex insufficiency (*e.g.*, Addison's disease). There is a huge drawback, however, to the beneficial use of GCs, because treatments with high doses for longer periods cannot only cause resistance to the steroid-based therapy (184, 185), but can also be accompanied by a range of detrimental side-effects (178, 186–188). These include diabetes, impaired wound healing, skin atrophy, muscle atrophy, increased susceptibility to infections, activation of latent infections, hypothalamus-pituitary-adrenal axis insufficiency, cataracts, peptic ulcers, hypertension (due to activation of the MR), metabolic disorders (resulting from hyperglycemia and a decreased carbohydrate tolerance), retention of water and sodium and excretion of potassium (disturbing the water household balance of the body), and loss of mineral from bone (leading to osteoporosis) (104, 176, 178, 189–195). To date, physicians attempt to minimize these side-effects with local therapies, intervals, supplementation with calcium, vitamin D3, and estrogens, and using specific GCs with a minimum of mineralocorticoid agonistic effects (178).

5. GCs and inflammation. GCs have been described to inhibit leukocyte migration to the sites of inflammation and to interfere with the functions of endothelial cells, leukocytes, and fibroblasts. They suppress the production and effects of humoral factors involved in the inflammatory response (104, 196). From a mechanistic point of view, it is generally assumed that the beneficial, antiinflammatory potential of the GR resides in a negative modulation of proinflammatory cytokines and that its side-effects are mainly the consequence of its transactivating capacities (197). Nevertheless, other compounds have not matched the clinical use of GCs as a potent immune suppressive and antiinflammatory agent.

To explain the repressive action of GCs on immune target genes, the role of GCs in inhibiting the activity of the transcription factors NF-κB, AP-1, or CREB has been widely investigated. Table 2 lists a number of proinflammatory genes and the main transcription factors contributing to their up-regulation. It would be an improvement for many steroid-treated patients if one could redesign GR function and reduce its side-effects while retaining the antiinflammatory characteristics (198). To that end, many investigators are currently trying to elucidate how GCs exert their mechanism of action (177, 199). The final goal is to reach a more effective and targeted immunosuppressive therapy. In this respect, the development and characterization of so-called dissociating GCs, which separate transrepression from transactivation, have been the holy grail of steroid pharmacology for years, although they did not live up to their expectations *in vivo* so far (198, 200–208).

The main purpose of this review is to discuss currently proposed mechanisms responsible for the antiinflammatory properties of GCs. Different experimental settings and cell systems have indeed led to many different, sometimes conflicting conclusions. We will focus on discrepancies in the proposed hypotheses and on the concomitant controversy in the actual mechanism explaining the cross-talk between the GR and genes driven by NF-κB or AP-1.

II. Molecular Mechanisms

A. GC receptor (GR) activity and direct DNA binding

Activated GR binds to specific DNA sequences as a homodimer. The dimerization domain (DBD) consists of two zinc ions coordinated with eight cysteine residues to form two zinc fingers. Each zinc finger is followed by an amphipathic α-helix. GR DBDs bind cooperatively to specifically spaced target half-sites in the DNA (the consensus sequence is 5′-GGTACAnnnTGTTCT-3′); the N-terminal zinc finger is involved in specific DNA interaction, whereas the C-terminal zinc finger mainly provides DNA-dependent dimerization (209, 210). One function of the DBD is to discriminate between different response elements and determine which target genes are activated. This function is achieved by a few crucial amino acids localized in the C-terminal part of the N-terminal zinc finger, the so-called P-box (211).

TABLE 2. Proinflammatory genes down-regulated by GCs independently of the presence of a nGRE

Proinflammatory genes	Main transcription factor(s)	Ref.
Cytokines		
IL-2	NF-AT, AP-1, NF-κB	251, 741, 742
IL-6	NF-κB, C/EBP-β (= NF-IL6), AP-1	80, 226, 233, 351, 554
TNF-α	NF-κB	743–745
IL-1β	CREB, NF-IL6, NF-κB	746, 747
GM-CSF	NF-κB	748
IFN-γ	AP-1	749
Chemokines		
IL-8	NF-κB	750
CINC/gro	NF-κB	751
RANTES	NF-κB	752
Enzymes		
iNOS	NF-κB	753–755
COX-2	NF-κB	227, 323, 756, 757
Collagenase	AP-1	96, 758
Adhesion molecules		
ICAM-1	NF-κB	227, 321
E-selectin	NF-κB	759–761
VCAM-1	NF-κB	762

Direct transcriptional repression by GCs can be achieved by the interaction of GR with a site on the DNA, designated nGRE, of which the actual sequence is poorly defined. This mechanism of action was proposed to account for repression of the proopiomelanocortin (POMC) gene (precursor of ACTH), type 1 vasoactive intestinal polypeptide (VIPR1), keratin, prolactin (PRL) and proliferin genes, as well as the vitamin D-induced osteocalcin gene (212) (Fig. 1, B and C). Detailed footprinting revealed that the function of nGREs is to instruct GR to bind as a monomer (213). In addition, for some of these genes the mechanism was also found to involve GR-dependent displacement of another factor (for example TATA-binding protein TBP) or DNA-independent tethering by GR of another transcription factor (214, 215) (Fig. 1, D and E). GR tethering of the transcription factors CREB, AP-1, or the orphan NR Nurr-77 has been studied in detail in the human glycoprotein hormone α-subunit (216, 217), the collagenase gene (96, 218), and the POMC gene (212, 219), respectively. A variation on this theme is observed for the proliferin gene, in which a composite GRE/AP-1 site, termed pflG, was defined; the GR can regulate activated AP-1 and enhance transcription of proliferin if AP-1 consists of c-Jun homodimers, but represses when AP-1 consists of c-Jun/c-Fos heterodimers (220, 221) (Fig. 1F). A similar regulation was reported for α-fetoprotein (222). Finally, a nGRE/Pit1/XTF composite element was detected in the PRL3 gene (223).

B. Protein-protein cross-talk

Because no nGRE could be detected in the majority of inflammatory genes, transcriptional interference was discovered to mostly result from cross-talk between the GR and other transcription factors, such as NF-κB or AP-1 (Table 2) (224, 225). GC repression by a direct physical association between GR and NF-κB was supported by several research groups, but these conclusions relied on *in vitro* data (226–228). Only recently, Adcock *et al*. (229) succeeded in showing an interaction between endogenous p65 and GR, using IL-1β- and dexamethasone (DEX)-costimulated A549 cells, which contain a considerable amount of immunoreactive GR. It remains to be investigated whether such a complex is also formed during GR-mediated repression in other cell lines, whether ligand binding can play a modulatory role, and whether other factors or modifications are also involved. To further understand how GR interferes with the activity of NF-κB and AP-1, several groups focused on delineating the relevant domains by mutation analysis or domain swapping experiments. Essentially, exchanging the DBD between different NRs (*viz*. GR, ER, and TRβ) has proven the importance of the GR DBD both in transactivation and transrepression (102, 211, 230). Deleting the ligand-binding domain (LBD) diminished transrepression, whereas replacing it with an unrelated β-galactosidase moiety greatly restored the transrepressive action, arguing for an exclusively steric role of the LBD (231). However, depending on the cell type and/or the NF-κB-dependent promoter tested, some conflicting results were found regarding the requirement of the GR DBD (232) or the C-terminal zinc finger in NF-κB transrepression (211, 233). The presence of a different subset of cofactors or GR function-modulating chaperones, or distinct signaling mechanisms in the different cell lines may explain particular discrepancies (1, 234, 235). Alternatively, the promoter context or effector site may also determine whether a specific NR can interfere with NF-κB activity (236–238). NF-κB-dependent up-regulation of ICAM-1 in human tracheal smooth muscle cells was found to be largely refractory to DEX inhibition, whereas simultaneous NF-κB stimulation of the COX-2 gene did respond to the inhibitory action of DEX (239). Similarly, GR-mediated NF-κB repression was found to be highly dependent on the core promoter and/or TATA-box environment (240, 241). For some hepatic acute-phase reactant genes, *e.g.*, angiotensinogen, it appears that NF-κB and GR positively interact at the acute phase response element to activate transcription (242–244).

Complementary to mapping the GR domains involved in NF-κB repression, domains of p65 important in repressing the GR activity have also been mapped (245). Extensive mutational analysis illustrated that both the N-terminal RHD and the C-terminal domain of p65 are required for repression of GR transactivation. *In vitro,* a physical interaction could be demonstrated between GR and the RHD of p65, but not with the C-terminal part of p65 (228, 245). p50 Has also been shown to interact *in vitro* with GR, supporting the notion that there is an interaction with the homologous RHD. However, because p50 lacks transactivation domains, it cannot, in contrast to p65, reciprocally repress the transcriptional activity of the GR (228). Remarkably, c-Rel, which does contain a transactivation function, is also incapable of inhibiting GR-mediated transactivation. These data suggest that the presence of a conserved RHD alone is not sufficient to mediate repression and that an additional input is given by the unique transactivation functions of p65 (227).

Although AP-1 transrepression displays a lot of similarities to NF-κB repression, some important differences are to be noted. Recently, a GR mutated in the first zinc finger (S425G) of the GR DBD was found to lose its capacity to repress NF-κB without affecting AP-1 transrepression (246), allowing discrimination between both types of repression. Along the same line, the GC antagonist ZK98299 is not able to repress NF-κB activity, whereas it efficiently inhibits AP-1 (211, 247). Repression specificity toward NF-κB, AP-1, or other GR targets may be codetermined by distinct signaling mechanisms toward the various transcription components (see Section II.E.4, 7, and 9). Similarly, as for NF-κB, repression of AP-1 activity was also shown to be strictly dependent on promoter, receptor, and cell type (248, 249).

C. Up-regulation of IκB-α

The alteration or induced expression of a regulatory protein capable of inhibiting NF-κB activity may lie at the basis of GC repression of NF-κB-mediated gene expression. One such candidate is the cytoplasmic inhibitor of NF-κB, *viz*. IκB-α. GC-dependent repression of NF-κB-driven genes has been proposed to be mediated by increased synthesis of IκB-α, which would then sequester NF-κB in an inactive cytoplasmic form (Fig. 1G) (250, 251). However, the involve-

TABLE 3. Presence of up-regulation of IκB-α in GC-mediated repression

NR	Cell type	Repressed gene or origin of NF-κB site	NF-κB inducer	NF-κB binding	Ref.
GR	HeLa (human cervix carcinoma) THP-1 monocytes	H-2Kb region I enhancer	TNF-α	Decreased	250
GR	FJ8.1 (murine T cell hybridoma) Jurkat T lymphocyte Lymph node, spleen, thymus tissue	IL-2	TNF-α TPA	Decreased N.D.	251
AR	LNCaP prostate carcinoma cells HeLa	IL-6	PMA	N.D.	258[a]
GR	Rat hepatocytes	iNOS (NOSII)	TNF/IL-1/IFN-γ mix	Decreased	763
GR	GCA (giant cell arteritis tissue)	IL-6	*In vivo* inflamed	N.D.	764
GR	rCI8 derived from sympathetic precursor-like PC12 cells	Ig-κ light chain	High constitutive NF-κB	Equal	765
GR/PR	A549 (human pulmonary epithelial cells) T47D (breast carcinoma)	ICAM-1 COX-2 HIV-LTR	IL-1β	Equal	323[b]
GR	Rat mesangial cells	iNOS	LPS + TNF	N.D.	327
GR	PBMC (peripheral blood mononuclear cells)	IL-2	Mitogen	N.D.	766
GR	Vascular endothelial cells from Crohn's disease patients	–	*In vivo* inflamed	N.D.	315
GR	Rat mesangial cells	MMP-9	IL-1β	Decreased	767

N.D., Not determined.
[a] The authors did not see up-regulation of IκB-α, only maintenance of IκB-α levels.
[b] The authors propose a dual mechanism for GC-mediated repression.

TABLE 4. Absence of up-regulation of IκB-α in GC-mediated repression

NR	Cell type	Repressed gene or origin of NF-κB site	NF-κB inducer	NF-κB binding	Ref.
ER	Osteoblast U2-OS	IL-6	IL-1β	N.D.	688
GR	Aortic primary endothelial cells (BAEC and PAEC)	E-selectin	TNF, LPS	Equal	260
GR	A549/8 alveolar epithelium-like	iNOS (NOSII)	Cytokine mix	N.D.	756
GR	NRK-52E rat kidney epithelial cells	CINC/gro	IL-1β	Decreased	751
AR	COS-1, CV-1	$p\kappa B_6$-tk-LUC	p65 plasmid	N.D.	257
GR	TC10 mouse endothelial cells L929sA mouse fibroblast cells	IL-6	TNF-α	Equal	322
VDR/GR	G-361 human melanoma-derived cells	IL-8	TNF-α		768
ER/GR	MCF-7 human breast carcinoma cells	HIV-LTR or IL-6	TNF-α	N.D.	256[a]
AR	Mouse fibroblast cells LNCaP prostate carcinoma cells	HIV-LTR	TNF-α	N.D.	256
GR	A549 human pulmonary epithelial cells	E-selectin	IL-1β	N.D.	769[a]
GR	L929sA	NF-κB reporter	TNF-α	N.D.	324
GR	A549, BEAS-2B (airway epithelial cells)	NF-κB reporter	IL-1β	Equal	770
GR	Human placenta cytotrophoblasts	IL-6, IL-8, TNF-α	*In vivo* inflamed	N.D.	771
GR	Lamina propria biopsies from Crohn's disease patients	–	*In vivo* inflamed	N.D.	772
GR/PR	A549 T47D	ICAM-1, COX-2 HIV-LTR	IL-1β	N.D.	323[b]
GR	A549	GM-CSF	IL-1β	N.D.	229
GR	1321N1 human astrocytoma SK.N.SH human neuroblastoma	IL-8 VCAM-1, ICAM-1	IL-1β	N.D.	773
GR	Plasma blood	PAF	LPS	N.D.	774[a]
GR	Infiltrating mononuclear cells from Crohn's disease patients' lamina propria biopsies	–	*In vivo* inflamed	N.D.	315

N.D., Not determined.
[a] The authors observed upregulated IκB levels, but no correlation with GC repression.
[b] The authors propose a dual mechanism for GC-mediated repression.

ment of this mechanism cannot be generalized and seems to be strongly cell type and target gene dependent (Tables 3 and 4). Interestingly, other antiinflammatory signaling pathways (*i.e.*, TGF-β, IL-10, *etc.*) that inhibit NF-κB activity through up-regulation of the IκB-α protein have also been described (8, 252–255).

1. Transcriptional regulation of the IκB-α promoter by GCs. DEX is able to stimulate synthesis of IκB-α in HeLa cells by directly activating IκB-α gene transcription. The newly synthesized IκB-α, induced by DEX treatment, was suggested to associate with newly released NF-κB, thus further preventing NF-κB-dependent gene transcription (250). Experiments using ac-

tinomycin D, which blocks *de novo* synthesis, suggested that the effect of DEX on IκB-α gene expression is mainly at the transcriptional level (251, 256).

The mechanism by which DEX stimulates the IκB-α promoter is still unresolved. The pIκB-α-Luc (−623 to +11) promoter construct, transiently transfected in HeLa cells and induced with tetradecanoylphorbol acetate, showed a twofold increase in luciferase activities when DEX was included (256); this is in agreement with data previously obtained in HeLa cells (250). Mutational analysis demonstrated that homodimerization of the GR is a prerequisite for induction of the IκB-α gene, which would argue for a classical GRE in the promoter (256). The same response element is also recognized by PR, in accordance with the fact that progesterone can also induce IκB-α synthesis (256). However, AR and ER are not able to enhance IκB-α synthesis in LNCaP prostate cancer cells and MCF-7 cells, respectively (256), or in AR-transfected COS-1 cells (257). On the other hand, an androgen-mediated increase in IκB-α synthesis was reported with endogenously present AR in LNCaP cells (258). The reason for these discrepancies remains unresolved. The suggestion of direct binding of GR to the IκB-α promoter DNA is complicated by the fact that no classical GRE can be detected up to 600 bp upstream of the start site of transcription. However, a related motif at positions −93 to −73 with a conserved one half of the normally palindromic hexanucleotide motif AGTTCT might suffice to carry out this induction (256). It would therefore be interesting to test the functionality of this putative GRE in HeLa cells by mutational analysis. Detailed DNase I footprinting recently confirmed a GR half-site at position −91/−81, although the results were obtained in breast cancer cells overexpressing GR (259).

The IκB-α promoter also contains three elements responsive to NF-κB, which ensures a negative feedback loop for activation of NF-κB. It is intriguing why this promoter does not show repression by DEX as observed with other NF-κB-dependent promoters. In fact, a stably integrated pIκB-α-Luc (−623 to +11) construct in L929 sA cells showed no enhancing effect of DEX alone or DEX + TNF on promoter activity, but was clearly repressed (202). Likewise, the porcine IκB-α promoter construct −600 to +20 coupled to luciferase and transiently transfected in BAEC cells showed induction with LPS or TNF, but was not induced by DEX (260). The basis for the apparent cell-specific opposing responses may be a cell-specific subset of cofactors (261, 262) that may allow the GR to cooperate, perhaps even in a DNA-binding independent way, with other LPS- or TNF-activated transcription factors in the IκB-α-promoter. This type of regulation is not without precedent, because a cooperative effect between the GR and NF-IL6 has previously been demonstrated for activation of the α_1-acid glycoprotein gene (263, 264). Also, induction of the c-IAP2 promoter (containing two NF-κB response elements and one GRE) by DEX and TNF results in a more than additive increase of the promoter activity. A c-IAP2 promoter variant in which the GRE site had been mutated resulted not only in loss of GC-mediated induction, but also, surprisingly enough, in loss of GC repression of the NF-κB activity (238). In addition, synergistic stimulation of the IκB-α promoter can also be observed under conditions of activated NF-κB and peroxisome proliferator-activated receptor PPAR-α or the retinoid-related orphan receptor (ROR)-α (265, 266). Interestingly, PPAR-α ligand-dependent recruitment of vitamin D receptor-interacting protein (DRIP)/thyroid receptor-activated protein (TRAP) complex together with Sp1-flanking NF-κB lies at the basis of the observed transcriptional synergy (265, 267). Whether this mechanism can be generalized for the GR and/or other cell types needs to be investigated further (268). The diversity of NR interactions with cofactor complexes may further be codetermined by chaperone proteins (107, 111–113, 154, 269, 270).

2. IκB-α expression vs. NF-κB/DNA binding. Conflicting results have been published on the relationship between IκB expression levels and NF-κB/DNA binding. A few groups found an elevated IκB-α protein level after a combined treatment with DEX and an inflammatory stimulus, concomitantly with a redistribution of p65 from the nucleus to the cytoplasm and a reduction in NF-κB/DNA-binding, deemed responsible for gene repression (Fig. 1H and Table 3). In complete contrast, we and others observed DEX-mediated repression in the complete absence of IκB-α induction, without release of the TNF-induced NF-κB complex from its response element in various cell types (Table 4). Similar observations were recorded for another NR, *viz.* the PR, which also antagonizes NF-κB activity. This indicates that NRs can repress DNA-bound NF-κB via tethering, without actually affecting DNA binding itself. *In vivo* footprinting experiments of the NF-κB site in the ICAM promoter further proved that GC repression occurs by changing the conformation of the protein complex binding to the NF-κB-binding site, without apparent perturbation of NF-κB binding (87, 271). Sustained NF-κB/DNA binding and resynthesis of IκB may coexist if resynthesized IκB is simultaneously degraded (272). Finally, repressive effects of DEX have also been described to appear with increased IκB levels (but without a parallel decrease in NF-κB/DNA binding) or with unaffected IκB levels (with decreased NF-κB expression levels) (Tables 3 and 4).

Intriguingly, in the neuronal cortex of DEX-treated rats, the levels of IκB-α are lower than in untreated animals, whereas the levels of IκB-α are enhanced in peripheral cells from the same animal. It would be interesting to investigate the underlying basis and the reason for the variations observed between related cell types in the same animal (273, 274). Apparently, there is no exclusive relationship between NF-κB relocalization from nucleus to cytoplasm, reduced NF-κB/DNA binding, and elevation in expression levels of IκB-α during GC repression.

3. Discriminating conditions determining a possible up-regulation of IκB-α by GCs. Tables 3 and 4 show that IκB-α up-regulation is predominantly and consistently observed in lymphocytes and monocytes, whereas no such mechanism can be retrieved for endothelial or fibroblast cells *in vitro*. How can GCs achieve an up-regulation of IκB-α in some cell types and not in others? Different cell types may use alternative pathways to mediate GC effects. For example, in cells of lymphoid origin unique redox-sensitive NF-κB signaling pathways requiring lipoxygenases or glutathione have been described (275, 276). In this respect, GC effects on oxidative stress and

on lipoxygenase and glutathione levels have already been demonstrated for cells of lymphoid origin, arguing for the fact that unique redox-sensitive modes could have developed during evolution that may affect IκB stability (277–281). Along the same line, JNK has been reported to mediate degradation of IκB in a redox-dependent manner (282); because GCs were found to block JNK activity, IκB-α degradation may similarly be delayed (283–286). Further evidence for this concept is provided by the fact that various links between IKK and JNK signaling have now been established (287, 288).

Besides cell-dependent variations in particular redox pathways, sensitivity to GC-induced apoptosis is also a cellular response known to be highly cell type- and stimulus-dependent (125, 289, 290). Cellular injury induces a differential adaptive response depending on the nature of the insult, whether physical (*e.g.*, heat, radiation), chemical [*e.g.*, reactive oxygen species (ROS), GCs], infectious (*e.g.*, bacteria), or inflammatory (*e.g.*, LPS, TNF). Recent data indicate that the cross-talk between various responses is not predictable and that permutations in triggering can have opposite effects on the outcome after injury (291, 292). For example, although it is well known that a prior heat shock can protect cells against inflammatory stress both *in vitro* and *in vivo*, it has also been shown that induction of a heat stress in cells primed by inflammation can precipitate cell death by apoptosis. This ability of heat shock to induce cytoprotection and cytotoxicity is therefore also known as the heat shock paradox. Experimental data currently link the heat shock paradox to induction of the NF-κB inhibitor IκB (293). Indeed, hsp proteins have currently been found to connect death receptor signaling, steroid activities, and inflammatory responses (112, 157, 160, 294–301); besides its chaperone function in GR activity, hsp90 was recently found to be a functional component of the IKK complex, required for TNF signaling (302–304). Whether GC treatment relocates hsp90 association from GR to IKK complexes remains to be demonstrated, but this might explain why GCs modulate IκB levels in particular cell types (112).

Besides hsp, ras chaperone proteins, proteasomes, and caspases have also been described as targets for GCs, which may in turn affect IκB-α turnover rates (169, 305–307). As such, GR/Raf1-Ras signaling toward a subclass of ras chaperone proteins was found to affect IκB half-life (306–308). Proteasome inhibitors were found to sensitize leukemia cells for GC therapy (309). Furthermore, IκB has been described as a caspase target both *in vitro* and *in vivo* (63, 70), whereas various caspases are required to mediate GC effects during apoptosis (310–312). Finally, differences in cell-culturing conditions and cell proliferation rate have been found to induce variations in GC-induced IκB gene expression, depending on gene clusters involved in energy metabolism (313, 314).

From another point of view, cell culture experiments *in vitro* may not exactly reflect GC effects *in vivo*. In vascular endothelial tissue from patients suffering from Crohn's disease, elevated levels of IκB-α were found after GC treatment, whereas in mononuclear cell infiltrates no such GC-induced up-regulation could be demonstrated (315). It was therefore concluded that up-regulation of IκB-α in these endothelial cells might correlate with the beneficial effects of GC treatment in Crohn's disease. One should consider that, in chronic inflammatory disease models *in vivo*, the continuous induction of proinflammatory responses as well as the treatment last much longer (days to months) than investigations performed in *in vitro* cell lines (minutes to hours). In addition, in *in vivo* situations, many more parameters have to be taken into account. This includes signal transduction cascades elicited by different cell-cell contacts, systemic signals, GR metabolism, and neuroendocrine effects (178, 203, 316, 317).

4. Are GC-mediated transrepression and IκB-α up-regulation uncoupled phenomena? The aforementioned observations raise the assumption that up-regulation of the IκB-α protein is not the main mechanism by which GCs can suppress immune genes. This view is further corroborated by various genetic approaches. First, the DNA-binding capacities of the GR itself do not determine transrepression, arguing against the induction by DEX of IκB-α as an element in transrepression (227). Furthermore, a dimerization-defective mutant rat GR (D4X, with the exchanges N454D, A458T, R460D, and D462C) (247) that does not bind DNA and does not transactivate GC-responsive genes or enhance IκB-α synthesis is still able to repress NF-κB activity. These results have now been confirmed by experiments using mice with a dimerization-defective $GR^{dim/dim}$ mutant (A458T), which demonstrates that GR/DNA binding and IκB gene activation are dispensable for the antiinflammatory activity of the GR (197, 318–320). Reciprocally, the GC analogs ZK57740 and ZK077945, selected for their lack of antiinflammatory activities *in vivo*, do not repress NF-κB-regulated genes but can still enhance IκB-α synthesis (256). Similar results were obtained with a GR mutant (S425G) lacking NF-κB-repressing activity, but leaving enhanced IκB synthesis intact (246). Second, repressive effects by the GR remain apparent in the presence of the protein synthesis inhibitor cycloheximide (321–323). Third, experiments with the GC antagonist RU486 or dissociated compounds RU24782 and RU24858 lacking GR transactivation activities demonstrated that GR-mediated transcription is not required for the inhibition of p65 transactivation (202, 228, 245). Moreover, the activity of constitutively nuclear Gal4-p65 chimeric proteins can efficiently be repressed by GCs, demonstrating that repression can occur in a promoter-independent way (322). Along the same line, a study comparing the activity of various clinically important GCs showed that it is possible to prevent TNF-induced degradation of IκB-α to various extents without affecting the NF-κB/DNA-binding activity (324). Finally, comparable GC repression of NF-κB has been observed in wild-type and $I\kappa B\text{-}\alpha^{-/-}$ mouse embryonic fibroblasts (325, 326). These findings demonstrate that up-regulation of IκB-α and the phenomenon of GC repression are in many cases two independent processes.

If GC repression of NF-κB activity and GC-mediated up-regulation of the IκB-α protein are uncoupled phenomena, the question remains what the biological significance is for the latter event. That two independent mechanisms of NF-κB repression by GR may exist within the same cell suggests that maintaining negative control on NF-κB-signaling pathways is of real physiological importance. IκB-α up-regulation rep-

resents a roundabout route to achieve effective repression, whereas a direct interference between preexisting, activated GR and NF-κB proteins is a direct and quicker way to immediately repress proinflammatory excesses. The need for induction of IκB-α could, for instance, provide a molecular explanation for the limited efficacy of GCs in the therapy of septic shock (327). DEX-induced up-regulation of IκB-α has mainly been described for monocytes and T-lymphoid cells, which are sensitive to GC-induced apoptosis. In this respect, GCs are frequently used as therapeutic agents in the treatment of B or T cell lymphomas (328–330). Alternatively, in T cells, stimulation of IκB-α in response to GCs could have evolved to counter the antiapoptotic effects of constitutive NF-κB levels by reducing its DNA binding (331). The first genetic evidence for NF-κB in antiapoptotic events was found in p65-deficient embryos dying from massive liver apoptosis (33, 332–334). Analysis of mice carrying a dimerization-defective GR highlighted the importance of gene-inducing effects for subsequent apoptosis (197, 320). Interestingly, IκB-α induction was found in GC-induced apoptosis-sensitive cells, but not in resistant human leukemic T cells (335). Along the same line, variations in GC sensitivity and IκB induction may also be caused by variations in GRα/GRβ ratio (336, 337). Overall, these data imply that particular cell types (such as T lymphocytes) need, in order to survive, threshold levels of NF-κB transcriptional activity to maintain cell cycle progression (338–341). This threshold may be subject to modulation by GCs via regulation of IκB-α expression during apoptosis (342, 343). This feedback mechanism may act as a back-up or final checkpoint to efficiently induce apoptosis in cells that sensed too much damage and to prevent an avalanche of systemic immune responses capable of inducing a life-threatening septic shock.

D. Cofactor competition model

Coactivator molecules are characterized by an intrinsic histone acetyltransferase (HAT) activity, believed to result in a more relaxed chromatin environment, which promotes gene activation (344). Hence, it may be assumed that competition between nuclear transcription factors for limited amounts of coactivator molecules leads to gene repression. The NR LBD has been shown to interact, in a ligand-dependent way, with coactivator proteins such as CBP, p300, and steroid receptor coactivator (SRC)-1 (345, 346). Because the same coactivators are also implicated in bridging p65, AP-1, or GR to the factors of the basal transcription machinery (347–351), transrepression was suggested to result from a competition between different transcription factors for a limited amount of cofactors (Fig. 1I). This model was first investigated for RAR- and GR-mediated repression of AP-1-dependent transactivation (347) and was supported by data from a number of other groups investigating negative cross-talk between various transcription factors and NRs (352–355). Similarly, a competition between p65 or AP-1 and GR for limiting amounts of CBP or SRC-1 was proposed to account for transrepression of NF-κB- and AP-1-dependent genes, respectively (356–358). However, a number of experiments and arguments counter the involvement of cofactor squelching in transrepression. First, an increase in coactivator concentrations (CBP, p300, SRC-1) in the cell generally leads to an increase in absolute gene expression levels of NF-κB- or AP-1-driven promoters (which, in the presence of GR, was misinterpreted as relief of repression), but relative levels of GR-mediated transrepression remain unaffected. Notably, under conditions of GC repression, the physical association between p65 and CBP is not disrupted by repressing amounts of activated GR, both *in vivo* and *in vitro* (224, 240, 359). Second, if NR-mediated repression of both AP-1 and NF-κB activities occurs through a general squelching for common cofactors, then RAR should also be able to mediate repression of NF-κB. However, this NR only represses AP-1 activity, disfavoring a general competition model (360). Third, the existence of dissociating ligands (200, 202) as well as the availability of various receptor point-mutants of GR, which either separate transactivation and transrepression (197, 211, 320) or distinguish between NF-κB and AP-1 repression (246), is not compatible with competition for a general cofactor (361, 362). Actually, GR may adopt a different conformation when working as a monomer in "trans" to inhibit NF-κB activity or when it is bound to DNA as a homodimer to transactivate (319, 320, 363–367), requiring different cofactor configurations. In this respect, ligand-dependent allosteric effects of DNA-bound GR have recently been observed (368). Fourth, mutants of AP-1 that lack the N-terminal transactivation domain still repress NRs, whereas the interaction with CBP is lost (95, 96). Along the same line, the NF-κB mutant Ser276C, defective in CBP recruitment (76), is as efficiently repressed as the wild-type molecule (240). In contrast, DNA-binding deficient mutants of p65, but with an intact predicted coactivator-recruiting transactivation domain, could no longer repress GC-mediated transactivation (245). These results suggest that competition for common cofactors is probably not a valid mechanism underlying mutual repression between GR and p65 or AP-1 (369). Finally, because various transcription factor families converge to the level of CBP/p300 for their transcriptional activities, the competition model struggles with a lack of specificity. If a cell were to inactivate the entire cellular pool of a given coactivator or activator in response to one signal, such a mechanism would preclude responsiveness by other activators or cooperativity at other genes in response to additional signals. As such, posttranslational modifications (*e.g.*, phosphorylation, acetylation, methylation) (370–375) or accessory chaperone proteins (*e.g.*, SNIP-1, INHAT, DREAM, $p35^{rsj}$) (376–380) may selectively regulate cofactor access for specific transcription factors. Alternatively, CBP access may depend on dynamic nucleosome positioning around the target promoter of interest (381–386).

Today, a number of observations are more consistent with the notion of territorial subdivision rather than a competition for factors (387–391). If transcription factor complexes are assembled within segregated nuclear compartments, then cofactor effects may be restricted to the designated compartment without affecting the same factors in other compartments associated with different genes (391–401). A specific nuclear matrix targeting signal has been identified within GR, including part of its DBD and transactivation domains (402–404). In addition, sumoylation, proposed to play a role in protein targeting, has now been observed for NF-κB/IκB

(73, 74) as well as for GR (167, 170, 171). Of special interest is the cytoplasmic sequestration of nuclear corepressor (NCoR) and silencing mediator of retinoid and thyroid receptors (SMRT) corepressors upon complexation with IκB/p65 RHD (405, 406). Nucleocytoplasmic shuttling is finally also affected by cofactor phosphorylation (407, 408).

Besides the spatial dimension of transcription, temporal aspects also argue against the cofactor competition model. Biological systems are highly dynamic, and transcription factors only transiently associate with their cognate DNA recognition sites and cofactor targets (368, 409–412). In contrast to static transcription models supporting ordered recruitment of huge coregulator complexes (372, 413–417), more recent views propose very dynamic cofactor modules [(dis)assembly of distinct configurations depends on hsp chaperone molecules] that hit the promoter in a cyclic way during transcription (111–113, 418, 419). One study surprisingly revealed that ligand-dependent promoter remodeling, coactivator association, and target gene transcription induced by NRs are remarkably transient (minutes), despite continuous receptor association with the target DNA (hours) (420–422). Importantly, at a fixed DNA concentration, DEX-bound GR dissociates from DNA 10 times faster than does ligand-free GR or RU486-bound GR (368). Various experimental approaches (such as transient transfection, microinjection), which overload cells with transcription components (transcription factors, cofactors) neglect the dynamic stoichiometry of cofactor complexes and may not reflect appropriate regulation with respect to nuclear architecture (391, 393, 419, 422–425). New RNAi approaches combining multiple somatic knockouts of transcription components in a single cell may soon shed new light on various aspects of NR and coregulator functions (235, 422).

E. New perspectives

1. Histone vs. (co)factor acetylation. Because simple competition for common coactivators is probably not the main mechanism of GC repression, the question remains what the effective mechanism is. As an alternative to cofactor competition, a coactivator repulsion model, based on transcription factor domains that prevent enhanceosome-dependent recruitment of the CBP-PolII holoenzyme complex by repulsion, was suggested (415, 426). However, we and others found no disruption of p65-CBP interaction under repressive conditions with the GR (240, 427). Over the last 10 yr, a vast amount of novel proteins interacting with members of the NR superfamily were identified by two-hybrid screening, functional complementation studies, far-Western blotting, and expression cloning (101, 262). Most of these proteins appear to be ubiquitously expressed and to interact with multiple members of the NR superfamily, although specificities and different affinities have also been detected (261, 268, 428–432). It should be noted that a correlation between levels of histone acetylation and transcriptional activity of specific loci has been established (433). Similarly, targeted deacetylation of chromatin may contribute to transcriptional repression in mammals (434, 435). Some members of nuclear hormone receptors, such as TR, actively silence gene expression in the absence of hormone. Corepressors, which bind to the receptors silencing domain, are involved in this repression (436, 437). A histone deacetylase (HDAC)-containing corepressor complex consisting of NCoR, SMRT, mSin-3, and RPD-3/HDAC-1 was identified to be associated with unliganded RAR/RXR and TR (438, 439). Upon ligand binding, this silencing complex is displaced by a HAT-containing coactivator complex comprising CBP, p300/CBP-associated factor (p/CAF) and SRC-1 (440, 441). Thus NR-dependent transcription may be regulated by an acetylation/deacetylation flip-flop mechanism (442, 443) (Fig. 1J). Of particular interest is the possibility that multiple ligands for NRs influence the biological activity of the receptor by selectively affecting the recruitment of coregulator complexes (361, 362, 397, 444–446). Cocrystal structures have revealed that antagonist-bound and agonist-bound ER display a different position of helix 12 in the LBD (447, 448). Similarly, antagonist-bound PR was shown to interact *in vitro* with the corepressor NCoR (449). Furthermore, NCoR and SMRT associated only with antagonist-bound PR and ER, as assessed by a two-hybrid screen (450–452). A novel coregulatory protein, template-activating factor Iβ associates with ERα and regulates transcription of estrogen-responsive genes by modulating acetylation of histones and ERα (453). In a molecular dynamics study, it has recently been shown that the GR DBD can exist in two conformational states, a transcriptionally active and a transcriptionally inactive state (454). The transactivating DNA-bound homodimeric GR may, as opposed to the repressing non-DNA-bound monomer, adopt a different conformation, favoring interactions with NR coactivator or corepressor complexes (363, 365, 368). In this respect, the crystal structure of the human GR LBD, bound to DEX and a coactivator motif, derived from the transcriptional intermediary factor 2 (TIF-2), adopts a surprising dimer configuration involving formation of an intermolecular β sheet; an additional charge clamp determines the binding selectivity of cofactors, whereas a distinct ligand-binding pocket explains its selectivity for endogenous steroid hormones (198, 364, 455). The synergism between GR and c-Jun homodimers is not easily explained; it would require a GRE-bound GR conformation in a composite element context. The allosteric model does, however, not suffice to explain why the nontransactivating form of GR actively hinders the activity of the Jun/Fos heterodimer (456), unless one assumes that a GR-bound corepressor molecule can also negatively influence the neighboring Jun/Fos heterodimer. An important challenge for future experiments will be to provide the currently lacking experimental connection between *in vitro* data (overexpression) and *in vivo* behavior of the receptor [chromatin immunoprecipitations, real-time imaging by means of green fluorescent protein (GFP), fluorescence resonance energy transfer (FRET), fluorescence recovery after photobleaching (FRAP), fluorescence loss in photobleaching (FLIP), bimolecular fluorescence complementation (BiFC), *etc.*] with respect to its cofactor partners (274, 392, 457, 458). The physiological relevance of predominantly *in vitro* observations can ultimately be answered only in knockout mice of individual coactivators, like that of SRC-1 (459), or in combined somatic knockouts (*e.g.*, NCoR, SMRT, SRC-1, CBP) by means of RNAi (235, 460).

There is no doubt that GR will recruit specific coactivators

to enable transactivation. The key question to be addressed is whether a distinct GR cofactor configuration is involved in repression of NF-κB-mediated gene expression (361, 362, 443, 461). Recently, GR has been found to be associated with HDAC-2 *in vivo*. In addition, GR antagonist was able to abrogate this interaction (462). Blocking HDAC-2 activity by cigarette smoke in alveolar macrophages was further found to block GR transrepression and increase cytokine expression (463). Interestingly, HAT and HDAC activities coexist within the same complex in the presence of p65 and GR, and they can each act independently without competing with each other, as revealed by *in vivo* chromatin immunoprecipitations (77, 427). A different histone acetylation pattern was observed in the presence of p65 alone, as compared with p65 and GR. In addition, GR was able to block specific histone acetylation and CBP phosphorylation under particular conditions, which may be tightly linked to gene repression (427, 464–466). In this configuration, the HDAC inhibitor trichostatin A (TSA) again relieves GR-mediated repression. However, similarly as for CBP overexpression experiments, reporter gene activities in response to the GR ligand DEX+TNF+TSA should be compared with the response to TNF+TSA, demonstrating that relative repression is conserved under conditions of inhibited deacetylases (357, 427, 462, 463). In addition, promoter responsivity to TSA does not necessarily reflect sensitivity to GCs because IL-8 and HIV promoter activity can be similarly increased with TSA, whereas only the IL-8 promoter shows a strong repression in the presence of DEX. This proves that the dynamic balance of acetylation/deacetylation can be uncoupled from GR-mediated repression (224). It still remains to be established how liganded GR recruits HDAC-2 to the p65-CBP HAT complex. Besides HDAC-2, association of NF-κB with HDAC-1 and HDAC-3 has also been observed recently (77, 467, 468). Because histones (465, 469, 470), NRs (172, 173), NF-κB (468), as well as cofactors (370, 371, 420, 471) can be (de)acetylated, it will be interesting to understand cross-talk of the various modifications under conditions of gene activation and GC repression (372, 442, 472–474).

2. Methylation of histones, (co)factors and DNA. Besides acetylation, other posttranslational modifications such as phosphorylation and methylation also do occur in core histone tails (465, 466, 469, 470, 475). Different hormone-dependent histone H3- or H4-specific methyltransferases, *e.g.*, coactivator-associated arginine methyltransferase (CARM-1), protein arginine *N*-methyltransferase (PRMT-1), and SUV39H-1 (472, 476–478), synergizing with acetylases and kinases, have now been characterized (472, 479–483) and play an important role in transcriptional regulation. Recent results reveal an extensive interplay between histone acetylation, methylation, and phosphorylation in transcriptional control by nuclear hormone receptors (NHR) (472) (Fig. 1J). Because the inflammatory response of NF-κB target genes was found to strongly depend on its histone modifications (H3/H4 acetylation, H3 phosphorylation, and H3 methylation) (484–488) (Fig. 1J), the potential interference of GCs in histone regulation will remain a hot research issue for the coming years (489–491).

In addition, hormone-dependent CARM-1 recruitment has also been shown to methylate the cofactor CBP/p300 (which causes destabilization of its KIX domain), disabling the interaction with the transcription factor CREB (492–494). Furthermore, PRMT-1 has been reported to affect transcription by methylation of the transcription factor STAT1 (495), which further regulates its dephosphorylation by phosphatases (496). To what extent methylation of either CBP, GR, AP-1, or NF-κB/IκB contributes to hormone-dependent repression remains an open question (Fig. 1K). Finally, a role for DNA methylation in both GR transrepression and transactivation has been described (497, 498). Interestingly, DNA methylation was recently found to be guided by histone modifications (497, 499–501).

3. GR repression and histone/cofactor/transcription factor code. An emerging theme in cofactor complexes is the juxtaposition of distinct enzymatic activities and diverse functional domains (362, 479, 481, 502–504). These include (de)acetylases (CBP, p300, SRC-1, HDAC-1, HDAC-2), kinases [TIF-1, ribosomal S6 kinase (RSK), mitogen- and stress-activated protein kinase (MSK)], methyltransferase [CARM-1, PRMT-1, SUV39H-1, DNA methyltransferase (DNMT-1)], ubiquitin ligases (E6-AP), ATPases [brahma-related gene-1 (BRG-1), sucrose nonfermenting (SNF-2)], proteases (E6-AP) and coregulators (p/CAF, NCoR, SMRT), which all together orchestrate transcription by fingerprinting the DNA-chromatin interface (397, 427, 456, 466, 484, 485, 500, 504–507). RNA cofactor molecules may additionally act as scaffolding, catalyzing, or targeting platforms that confer further functional specificity on recruitment of multiprotein complexes by liganded receptors (440, 508–512). In parallel to modifications at the DNA-chromatin interface, a specific biological response also depends on the complete pattern of modifications present in the surrounding transcription factor or coregulators at a particular moment.

Tandem cofactor complexes (*e.g.*, CBP-kinase, CBP-methyltransferase) have now been found to modify both transcription factors, cofactors and histone components (83, 88, 479, 492, 503, 513–515), suggesting important cross-level regulation (transcription factor *vs.* cofactor *vs.* chromatin level). A balance in cofactor levels also plays a role. As such, it has been suggested that the ratio between the cofactors RIP140 (receptor-interacting protein 140) and GRIP1 (glucocorticoid receptor-interacting protein 1) codetermines a negative or positive transcriptional outcome on an AP-1-driven and estrogen-costimulated promoter (516). By analogy with histone code (465, 469, 470, 517), the interplay of modifications at the cofactor (370, 371) and transcription factor levels (418, 518–521) may similarly have important functional implications (such as, *e.g.*, localization, shuttling/trafficking characteristics, enzymatic activity, transactivation dynamics, affinity, and stability) in achieving specific transcriptional responses.

Although ligand binding is essential for the activation of GR, the receptor is also subject to posttranslational modification by phosphorylation (522–525). GR is a phosphoprotein in the absence of ligand, with additional phosphorylation on hormone binding (ligand-dependent). Therefore, hormone-dependent phosphorylation of GR may help to determine target promoter specificity, cofactor interaction, dimeriza-

tion, GR activity, strength and duration of receptor signaling (recycling), and receptor stability (degradation) (168, 372, 522, 523, 526, 527). Cyclin-dependent kinases, MAPKs (p38, ERK, JNK), PKA, glycogen synthase kinase-(GSK)-3, and redox-sensitive enzymes were all demonstrated to affect directly or indirectly GR phosphorylation (163, 168, 326, 522, 523, 528–535). On the other hand, protein phosphatases 1, 2, and 5 have also been shown to associate with GR and affect GR phosphorylation and nucleocytoplasmic shuttling (536–539). By analogy with phosphorylation-dependent regulation of activation function (AF)-1 activity of ER (540–543), GR function may be similarly affected; conceivably, phosphorylation of AF domains may alter the receptor conformation or modulate interactions with coregulators (364, 527, 544, 545). Interestingly, GR phosphomutants of AF-1 showed reduced association with the AF-1 coregulator DRIP-150 (168, 546). Furthermore, immunofluorescence microscopy of different phospho-GR isoforms reveals distinct cytoplasmic, perinuclear, or nuclear populations of phospho-GR, suggesting that differentially phosphorylated receptor species are located in different subcellular compartments, likely modulating distinct aspects of receptor function (168, 534, 547). Considering the different phosphorylation kinetics observed for different GR residues, GR phosphorylation/function may be spatiotemporally controlled (168, 547). Whether differentially phosphorylated species have a distinct role in transrepression *vs.* transactivation remains to be investigated. Interestingly, in GC-resistant asthma patients, where GR has lost its antiinflammatory (transrepression) activity, the antiinflammatory function of the receptor can be restored if the therapy is combined with MAPK inhibitors. It is believed that hyperactivity of MAPK in asthma-resistant patients may desensitize transrepression because of reduced ligand or coregulator affinities due to GR phosphorylation (163, 544, 548, 549).

Besides GR, NF-κB (28, 42, 77, 80–83) and AP-1 (14, 225, 550, 551) are also subject to phosphoregulation via various signaling pathways including p38, ERK, JNK, MSK, RSK, PKA, PKC, phosphatidylinositol 3 kinase (PI3K), and Ras. Phosphorylation of NF-κB and AP-1 has been demonstrated to affect its function at multiple levels, *e.g.*, localization, dimerization, translocation, DNA binding, stability, transactivation, and cofactor recruitment. In this respect, GC inhibition of AP-1 was found to depend on interference of GCs with activation of JNK and ERK1/2 (via increased MKP1 levels), which prevented AP-1 phosphorylation (283, 286, 552, 553) (Fig. 1L). Negative cross-coupling between GCs and NF-κB was described to require PKA phosphorylation at NF-κB Ser276 in the RHD (326), but in our hands GR repression of NF-κB was independent of p65 Ser276 phosphorylation (240). Similarly, and although NF-κB transactivation strongly depends on MAPK activity (83, 554), MAPK inhibitors and GCs can independently repress NF-κB activity, suggesting distinct antiinflammatory mechanisms (our unpublished results). Although various nongenomic GC actions have now been described that are transmitted via multiple signaling pathways, it remains enigmatic how GCs inhibit kinases; one theory suggests that membrane-localized receptors coupled to G proteins may interfere with cytoplasmic signaling activities (see Section II.E.7). Recently, a genomic GC mechanism (requiring GR and *de novo* mRNA synthesis) was also described for the phosphatase MKP-1, which seems to be responsible for inhibition of p38 and/or ERK activities (552, 555, 556). It will be interesting to know the basis of the MAPK inhibition or the induction of MKP-1 in response to GC and its importance in inflammation relative to the mechanism of transcriptional interference (199).

Apart from phosphorylation, other posttranslational modifications (acetylation, ubiquitinylation, sumoylation, and nitrosylation) have also been shown to affect GR (141, 159, 164–173), NF-κB p65 (82, 224, 468, 557–559), and AP-1 function (559–561) and will further increase the complexity of transcription factor cross-talk. Considering the transcription factor p53 as a paradigm for interrelated modifications (562), it will be a real challenge to map all GR, NF-κB p65, and AP-1 modifications, as well as to understand their functional interplay in a spatiotemporal context.

4. GR repression and chromatin remodeling. Besides chromatin modifications, another type of structural alteration *in vivo* is often called chromatin remodeling. This refers to a dramatic, localized alteration in the fiber of chromatin in which a particular nucleosome, or several adjacent nucleosomes, undergo a receptor-controlled structural change. It is quite likely (although demonstrations *in vivo* are currently lacking) that such remodeling effected by liganded NRs occurs by recruitment of large ATP-using complexes (563). Several reports have already focused on the association of GR with components of the BRG-1 and/or SWI/SNF complex and showed that GR can alter chromatin-remodeling properties (564–570); recruitment was demonstrated to depend on surrounding histone H1 phosphorylation (506, 571, 572) and to require the transactivation domain and LBD of GR (573–579). Furthermore, GR effects in the presence of nucleosomes may strongly depend on rotational and translational positioning of the responsive elements (580, 581). As such, chromatin remodeling effects induced by GR can vary according to the chromosomal location (381, 582). When comparing transcriptional effects of GR on transient *vs.* chromatin-organized promoter templates, involvement of distinct GR domains was observed, depending on the chromatin status of the promoter (400). Also, nucleosome binding by the RHD of p65 can specifically be stimulated by SWI/SNF but not by BRG-1/BRG-1-associated factor (BAF)-155 complexes (583, 584). Whether mutual transrepression between GR and p65 has the chromatin-remodeling machinery as a target needs further experimentation and confirmation *in vivo*. Exposure of the HIV-long terminal repeat (LTR) to hormones was found to result in disruption of the nucleosomal array within the NF-κB/Sp1 promoter region (585). On the other hand, when investigating the chromatin structure of the IκB-α promoter on GC treatment, GCs did not affect the global nucleosome positioning, but rather allosterically interfered with DNA binding of transcription factors (259, 586). Similar allosteric changes were reported for the IL-2 and ICAM promoters (550, 587).

Note that both glucocorticoids and progestin can stimulate the IκB-α promoter, demonstrated to have an open chromatin structure, whereas only glucocorticoids can activate the mouse mammary tumor virus (MMTV) promoter, which has

a closed chromatin structure. At least one cofactor complex, the BRG-1 chromatin remodeling complex, is thought to contribute to this differential promoter activation (588).

5. GR repression and basal RNA polymerase II transcription. Another way for GR-mediated repression might be the targeting of non-HAT-containing cofactors, bridging p65 or AP-1 activation domains to the RNA polymerase holoenzyme (240, 589) (Fig. 1E). Although the DRIP complex was first thought to be specific for nuclear hormone receptors, essentially the same complex [called activator-recruited factor (ARC)] binds to and is required for transactivation by other transcription factors, *e.g.*, as the p65 subunit of NF-κB (261, 546, 590–593). Several DRIP/ARC subunits are also components of other potentially related cofactor complexes, such as cofactor required for Sp1 (CRSP) (594), TRAP (595, 596), negative regulator of activated transcription (NAT) (597), and Srb/mediator coactivator complex (SMCC) (598), indicating that unique classes of activators may share common sets or subsets of cofactors. Besides (in)direct contacts of GR with the RNA polymerase II holoenzyme, p65 and/or c-Jun can also contact basal transcription factors, such as TF-II-B, TBP, TBP-associated factor-(TAF)- II and TAF-II-105 (599–602). The possibility exists that GR represses NF-κB, or *vice versa*, by a steric hindrance mechanism, *i.e.* by disrupting the interaction of p65 or GR with one of these basal factors, or by modification of one of the basal machinery components to eliminate a transcriptionally active complex. In fact, exciting new evidence for the latter mechanism has emerged by demonstrating that GR interferes with phosphorylation of the C-terminal domain (CTD) of RNA polymerase II, without inhibiting the assembly of the preinitiation complex. These results suggest the existence of a novel corepressor, associated with the LBD of GR, possibly a serine-2-phosphatase or a serine-2 kinase inhibitor (603–605) (Fig. 1M). Furthermore, NF-κB was found to stimulate transcriptional elongation of RNA polymerase II by binding transcription elongation factor (P-TEFb), which phosphorylates RNA polymerase II CTD at Ser2 and Ser5 (606, 607). The activity of this transcription elongation factor P-TEFb, which comprises the kinase CDK9 and cyclin T, is regulated in a specific and reversible manner by small nuclear RNA molecules (608, 609). Because steroid receptor RNA cofactor molecules have also been described, it would be interesting to evaluate whether these molecules can modulate P-TEFb activities (508, 610). Whether this phenomenon is a general mechanism, also accounting for the reciprocal repression mechanism, *viz.* NF-κB-mediated repression of GRE-dependent transcriptional activity, is so far unexplored. Actually, recent evidence suggests that cofactor-mediated chromatin modifications may be coupled to RNA polymerase II phosphorylation and elongation during transcription (611–613).

6. GCs and T cell function. T lymphocytes are responsible for coordinating the immune response and thus form a major source of cytokines. Different cytokines induce various subsets of T cells or have divergent effects on proliferation within a particular subset. Recent studies suggest that the immune response is in fact regulated by the balance between T helper (Th)1 and Th2 cytokines. Th1 cells produce IL-2, IFN-γ, and TNF-β, whereas Th2 cells produce IL-4, IL-6, IL-10, and IL-13. These two pathways are often mutually exclusive. Deregulated chronic Th1 cell responses often result in autoimmunity, whereas prolonged Th2 cell responses can lead to allergy and atopy (2, 129, 614–616). Inflammation is upregulated after activation of Th1 cells, whereas Th2 cells may play a significant role in down-regulating Th1 proinflammatory responses by overproduction of Th2 cytokines. How helper T cells are directed toward either of these pathways has been an area of intense research (617). Various data indicate that GR, AP-1, and NF-κB participate in guiding these complex pathways (125, 618, 619).

GCs are used in treating immunity disorders such as transplant rejection, owing to their capacity to prevent T cell activation and apoptosis by a multitude of mechanisms; these include altered Th lineage development by favoring the generation of (antiinflammatory) Th2 cells (humoral immune response), suppression of the induction or activity of established (proinflammatory) Th1 cells (cellular immunity), and induction of the expression of the immunosuppressive cytokine TGF-β. To convert the immune response from a Th1- to a Th2-like phenotype, Th1 cytokine synthesis is inhibited and IL-10 production is stimulated (125, 457, 620–625). In view of the inducibility of TGF-β expression by GCs and the similarities of their inhibitory effects on cytokine expression and T cell activation with those induced by TGF-β, it was speculated that GCs mediate their antiproliferative effect by inducing TGF-β expression at the transcriptional and posttranscriptional level (626–628).

It is now accepted that lymphoid cells, especially $CD4^+CD8^+$ thymocytes, are among the few cell types that undergo apoptosis in response to corticosteroids. Despite the enormous efforts made in understanding GC-regulated cell death, the mechanisms are still largely unknown, although the proteasome, Apaf-1, caspase-9, and Bcl-2 family proteins have been demonstrated to be critical players (126, 629). Whether transactivation of death genes or transrepression of survival genes is required for GC-induced antiproliferative or apoptotic properties is not clear yet (124, 126, 630). Evidence in favor of either hypothesis has accumulated over the years. Multiple GR transcriptional regulatory mechanisms that use distinct receptor domains are used to elicit cytostatic and cytotoxic responses to GCs (631). In transgenic mice that have a dimerization-defective GR, thymocytes are fully resistant to GC-induced apoptosis, suggesting that this mode of cell death is likely to rely on the binding of GR to GREs (197, 320). In this respect, many attempts have been made to isolate steroid-induced genes that mediate cell death. Unfortunately, no convincing apoptotic target genes of GR have been reported so far (124, 126, 197, 314, 632), although a number of gene products are blocking GC-induced apoptosis, such as Bcl-2, Bcl-xL, as well as inhibitors of apoptosis (IAPs) (633–636). On the contrary, other experimental set-ups with GR mutants that lack transactivation but retain NF-κB and AP-1 transrepression capacity, point to an intact GC-induced apoptosis (637). Correspondingly, various target genes of AP-1 and NF-κB were identified as proliferative and apoptotic cellular responses (8, 14, 15, 28, 30).

During studies aimed at comparing activation- and GC-induced apoptosis of T cell hybridomas, it was unexpectedly

found that these lethal stimuli, when administered simultaneously, no longer caused cell death (638–640). This mutual antagonism was found to result from transcriptional interference between GR and AP-1/NF-κB, which modulate Fas ligand (Fas-L) expression (641–644) via the GC-induced leucine zipper GILZ (335, 640, 645–647). In addition, GILZ-mediated modulation of T cell receptor (TCR)-induced responses is part of a circuit, because TCR triggering can also down-regulate GILZ expression. Results indicate that GILZ can inhibit NF-κB-driven (p65, p52) and AP-1-driven (Fos, Jun) gene expression by direct protein-protein interaction and interference with DNA-binding. This particular mechanism has been demonstrated for repression of IL-2/IL-2R/Fas/Fas-L during TCR responses (642, 645, 647) (Fig. 1N). It is not clear yet whether GILZ may target other apoptosis-related transcription factors besides NF-κB and AP-1, such as p53 or STAT3, because crossreactivity of the latter factors with GR signaling has also been described (562, 648–651). In epithelial and breast cancer cells, the serum- and glucocorticoid-regulated kinase-(SGK)-1 (related to Akt/PKB family kinases) is protecting the cells from apoptosis in response to GCs and has been identified as a direct GR target gene. Whether this kinase is also important in GC-mediated T cell apoptotis or whether it affects GILZ function has not been explored yet (652–654).

7. Nongenomic GR actions. Because GRs are located in the cytoplasm, they need to enter the nucleus to alter gene expression. This typically takes less than 30 min (half-life with DEX is about 5 min) to result in biological effects (655, 656). Moreover, other regulatory actions are manifested within seconds to a few minutes. These time periods are far too rapid to be due to changes at the genomic level and are therefore termed nongenomic or rapid actions to be distinguished from the classical steroid hormone action of regulation of gene expression (657–659). Distinct GR forms might mediate the rapid actions of GCs (660–662); these may include either a unique gene product (such as for the progesterone receptor) (663), a specific isoform (664, 665), or a modified version of the classical GR capable of binding, associating, or integrating into the plasma membrane (657, 666). Alternatively, a cytosolic subset of GR may participate or interfere with signal transduction pathways usually associated with membrane receptor-signaling events (667). Many membrane-associated receptors are believed to signal via G proteins (1, 657, 664, 668–675). Although the cellular response to these rapid actions may ultimately affect gene expression, the response is distinguished mainly by its effect on components of signal transduction pathways. The rapid effects of steroid hormones are manifold, ranging from activation of MAPK, adenylcyclase (AC), PKC, PI3K, SGK-1, as well as heterotrimeric guanosine triphosphate-binding proteins (G proteins) (162, 283–286, 654, 657, 676–679). Some of the effects are also sensitive to classical steroid antagonists, whereas others are not. One function of the rapid action is to modulate the classical genomic action of the receptors. This is achieved in part by modification of the transactivation domains of the receptors. The rapid action of steroids is therefore an integral part of the genomic action and, like the latter, it can function in physiological and pathophysiological processes (161–163, 170, 529, 679).

8. Hormone selectivity by steroid receptors. GR belongs to the NR superfamily, which includes MR, ER, PR, AR, PPAR, vitamin D (VDR), and TR hormone receptors (1, 312, 680–682). Endogenous steroid hormones such as cortisol, testosterone, or progesterone share a similar core chemical structure but mediate distinct biological responses. Structural comparisons of GR, AR, PR, and ER start to provide insight into how functional specificity is achieved, because many subtle differences in the secondary structure and the topology of their ligand-binding pockets exist in these steroid receptors (364). Steroid selectivity appears to be achieved by the complementarity of shape and hydrogen bonding between ligands and the ligand-binding pocket in the receptors. Via alternative receptor dimerization of GR with MR, AR, or PR and/or binding to composite hormone response elements, functional diversity and cross-regulation can be further extended (144, 148–151, 683). In addition, transrepression of NF-κB and AP-1 by multiple NRs [*i.e.*, AR, ER, PR, GR, PPAR, ROR-α, arylhydrocarbon receptor (AhR), vitamin D, RAR/RXR] (257, 266, 353, 684–694) has now been demonstrated; this further increases the complexity of steroid specificity.

Evidently, hormone selectivity also depends on cell type-specific receptor expression, bioavailability of the hormone (systemic transport), and tissue-specific hormone-modifying enzymes (metabolism). From the accumulated studies of many laboratories, it has become increasingly obvious that the action of any hormone is much more than a simple single linear sequence of causes and effects. Rather, hormones and the regulatory pathways they control form interlocking networks. The interactive nature of the networks means that the concentration of each network molecule and the affinity of its molecular interactions determine the outcome of any hormonal effect at a given time in a particular cell type. New approaches using powerful gene array and proteomic tools may soon allow further unraveling of these dynamic circuitries (695–697).

9. Steroid resistance and combination therapy. GC resistance represents a serious clinical problem in various chronic inflammatory diseases. GC-responsive tissues with an activated inflammatory response (mediated by activated NF-κB) may become resistant to GC signaling because of a blocked GR function (180, 185, 698, 699). A small proportion of asthmatic patients are GC-resistant and fail to respond to even high doses of oral steroids; other chronic inflammatory diseases, such as inflammatory bowel disease, rheumatoid arthritis, and Crohn's disease, display similar incidences of impaired responsiveness (700, 701). This resistance is seen at the site of inflammation, where cytokines are produced, but not at noninflamed sites. This may explain why patients with GC-resistant asthma are not resistant to the endocrine and metabolic effects of GCs and thus develop GC side effects (702). Although some steroid-resistant patients have abnormally low numbers of GRs or demonstrate reduced ligand-binding affinity, others show no defects in their GRs or in steroid absorption or clearance.

It has recently been proposed that NF-κB may increase expression of the β-isoform of GR (GR-β), a truncated variant

of the α-isoform (GR-α) that neither binds steroid ligands nor transactivates steroid-responsive genes, but acts as an endogenous dominant-negative inhibitor of GR-α (336, 703–705). However, the biological significance of this dominant-negative effect by GR-β has been questioned, because it is expressed at rather low levels (706, 707).

Many proinflammatory cytokines, aberrantly up-regulated in chronic inflammatory diseases, require the concerted activation of NF-κB and AP-1, which are positively controlled by MAPK cascades (708, 709). Steroid-sensitive and steroid-resistant patients with Crohn's disease reveal a remarkably different cellular activation pattern of proinflammatory mediators; steroid resistance was found to correlate with increased epithelial activation of stress-activated protein kinases (MAPK) and NF-κB (161, 163, 710). Since we reported on the crucial role of p38 and ERK MAPK in TNF-dependent NF-κB transactivation (83, 554, 711), we have tested whether the p38 and ERK MAPK inhibitors SB20358 and PD098059 affect GR inhibition of NF-κB. Inhibition of gene expression by GR and by the MAPK inhibitors was additive, which may suggest that different mechanisms are involved in MAPK and GC-dependent modulation of NF-κB activity (our unpublished results). Interestingly, p38 MAPK has been shown to induce GR phosphorylation and to regulate ligand-binding and coregulator affinity (163, 544). Besides GR, also the TBP was found to be a direct substrate for p38 MAPK phosphorylation (712, 713) and may further co-determine steroid sensitivity during GR transrepression (599, 714–716). Enhanced JNK activation in steroid-resistant patients may contribute to steroid unresponsiveness by various mechanisms, either directly by inhibiting GR activity (by blocking its phosphorylation) or indirectly by increasing AP-1 activity, which transrepresses the GC effects (717, 718). Recent studies conducted at the whole animal level further extend the AP-1-GC cross-talk to a higher order, because JNK activity can modulate levels of circulating GCs (719).

Next to the stress-signaling aspects discussed above, other parameters have also been shown to contribute in steroid-resistant pathologies, *viz*. NR mutations affecting ligand binding or cofactor affinities, changed cofactor expression levels, NF-κB-dependent expression of the multidrug resistance protein MDR1, oncogenic activation of growth factor-signaling pathways, and altered circuitry in nongenomic NR pathways (549, 720, 721). Understanding which of these pathways dominates in steroid desensitization will further allow the development of strategies to overcome or bypass such resistance. Combinations of GCs with MAPK inhibitors or β-adrenergic agonists have already proven their therapeutic efficacy in the treatment of inflammatory pathologies (161, 163, 181, 182, 525, 698, 722). Finally, the detection of the activation state of mediators of the NF-κB and MAPK pathway could serve as a possible diagnostic tool for early recognition of steroid resistance, thereby protecting patients from the undesired severe side effects of prolonged and ineffective steroid treatment (161, 186, 188).

III. General Conclusion

Drug discovery efforts are presently aimed at selectively modulating the targets NF-κB and AP-1. So far, GCs are the most widely used antiinflammatory and immunomodulatory agents, the activity of which is based on the interference with these transcription factors. Understanding their precise mechanism of action has been clouded by numerous and sometimes conflicting hypotheses, which may result from differences in the target gene, receptor, or cell line investigated. This review highlights not only the massive work that has already led to the development of (at first sight plausible) models, but also pointed to some of the shortcomings of current dogmas. We would like to point out that the different mechanistic models discussed are not mutually exclusive. For instance, a direct interaction does not necessarily exclude the need for cofactors; also, it still leaves open the possibility for loss of transcriptional activity by changing the conformation of the DNA-bound complex, by steric hindrance of coactivator access, or by active silencing of an otherwise transcriptionally active factor. Besides the transcriptional effects discussed here, important GC effects have also been detected at the posttranscriptional level, such as mRNA destabilization of (pro)inflammatory gene (*viz*. iNOS, TNF-α, GM-CSF, COX-2, IL-1, IL-2, IL-6, IL-8) or cell cycle gene (*viz*. cyclin D3) transcripts, explaining why GC-mediated repression of promoter reporter gene constructs is often far less efficient than the inhibition observed for the corresponding endogenous genes (723–730).

In conclusion, cofactor(s) (domains) that specifically modulate interactions of GR with NF-κB, AP-1, and/or the RNA polymerase II holoenzyme in a particular promoter context, as well as dynamic subcellular localization of the various transcription components and spatiotemporal regulated signals that impinge on the corresponding promoter enhanceosomes, remain to be explored further and investigated, and they will become the prime focus of future investigations (80, 83, 398, 411, 444, 484, 485, 547, 731–736). Recent advances made in the field include the development and characterization of so-called dissociating ligands, in addition to the generation of mice defective in GR dimerization functions, both aiming at separating the yin and yang of GR functionality (197, 198, 200, 202–208, 320, 737). These new tools not only permit users to gain insight into the way GCs can suppress proinflammatory genes but also facilitate the development of a targeted strategy to combat inflammation and autoimmune diseases. They further provide perspectives to eliminate undesirable side effects. Because chromatin-embedded promoter enhanceosomes behave like sophisticated protein modules receptive to various signals, future GC therapies may benefit from combined structural (selective ligand or GR modifier) and signaling (selective inhibitors) approaches to establish harmless treatments (81, 162, 198, 383, 679, 738–740). Evidently, the molecular mechanisms involved in GR/NF-κB or GR/AP-1 cross-repression are far from being completely understood.

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