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Review Article

Glucocorticoid receptor modulators in inflammation and oncology

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Abstract

Glucocorticoid hormones produce a diverse array of immunological and metabolic effects. Their antiinflammatory properties are commonly utilized in the treatment of inflammatory diseases and cancer, but they often cause severe side effects. In recent years, we have gained a greater understanding of the hormone, together with the ubiquitously expressed glucocorticoid receptor (GR) and downstream effector pathways. This hydrophobic hormone diffuses across the plasma membrane to gain access to the cytoplasmic GR. The activated GR subsequently translocates to the nucleus to modulate target gene and transcription factor activity. It is now clear that the GR is responsible for modulating target genes in a number of discrete and dissociable ways. This has allowed selective targeting of particular subsets of genes by mutated GRs, and by novel, synthetic ligands, in a manner analogous to the selective estrogen receptor modulators (SERMs) used in breast cancer treatment. It is clear that the antiinflammatory effects of glucocorticoids are mediated by binding to and interference with the function of other transcription factors, notably NF-κB, also an important factor in cell survival signaling. A concerted effort is now under way to find selective GR modulators that retain these beneficial properties while showing an improved side effect profile.

Introduction

Glucocorticoid receptor (GR) modulators represent a vital group of medicines frequently used in the treatment of inflammatory diseases and cancer. However, their potent benefits are accompanied by a wide range of significant, and in some cases irreversible, side effects that limit their therapeutic utility. These adverse effects include osteoporosis, cardiovascular disease, diabetes and visceral fat deposition. As the mechanisms of glucocorticoid action are elucidated, the possibility of introducing specificity has been raised. In this way, new molecules capable of engaging more selectively with the downstream targets of glucocorticoid action have been sought, and indeed some have been described. This report will review glucocorticoids and their mode of action, and report on recent developments in the search for therapeutically optimized selective glucocorticoid modulators.

Glucocorticoid production and release

Glucocorticoid production by the adrenal gland is under the control of the hypothalamic–pituitary–adrenal (HPA) axis. Corticotropin-releasing hormone (CRH) is secreted in the hypothalamus and portal system and results in the stimulation of adrenocorticotropin (ACTH) from pituitary corticotroph cells. Circulating levels of ACTH trigger the production of cortisol in the adrenal gland. The HPA axis is under cortisol-controlled negative feedback at pituitary, hypothalamic and higher center levels (1). Only 5% of circulating cortisol is in the “free form”, with the majority of the hormone bound to cortisol-binding protein (CBP) or albumin (2). Activation of the HPA axis with increased secretion of glucocorticoids is a well-established response to physical or mental stress, and is thought to be important in the adaptive response to such stress. In addition, the activity of the HPA axis shows a strong circadian rhythm, which now seems to be important for synchronizing the local, peripheral rhythms of body organs and tissues to the central clock within the suprachiasmatic nucleus (SCN) of the brain (3).

In humans, the circadian rhythm of cortisol production shows a peak in the early morning, before waking, and a

subsequent steep decline to low levels in the late evening and overnight. In noctural animals, this phase is reversed, with the peak occurring before the dark phase, or the phase of maximal physical activity. Additionally, ultradian rhythms of cortisol exist, with a pulse of cortisol production every 1-2 h (4, 5). These pulses have a variable frequency and amplitude, and thus result in mean serum concentrations showing a circadian oscillation. These diurnal and ultradian fluctuations arise from signaling between the SCN and the adrenal gland, and consist of both the autonomic nervous system and hormonal regulation of the HPA axis. Recent evidence suggests that the temporal aspects of glucocorticoid release may play a critical role in the subsequent downstream effects.

Physiological effects of glucocorticoids

Glucocorticoids, named after their effect on carbohydrate metabolism, play a vital role in physiology, including endocrine, immune, neural and renal systems. The diverse effects of the hormone are particularly evident in clinical conditions of excessive production (Cushing's syndrome) or insufficiency (Addison's disease), resulting in a plethora of symptoms including alteration of metabolic and psychological states and musculoskeletal abnormalities (1).

Glucocorticoids play an important role in metabolism via the control of gluconeogenesis, glucose conservation and lipolysis. Glucocorticoids upregulate several enzymes involved in gluconeogenesis. In the fasted state, this process enables the synthesis of glucose from non-hexose organic molecules, such as pyruvate, lactate, glycerol and amino acids (6). Glucocorticoids limit glucose uptake in muscle and adipose tissue, whereas increased uptake is directed to the nervous system. The stimulation of lipolysis in adipose tissue releases both glycerol, an important substrate in gluconeogenesis, and fatty acids, used in muscle ATP production (7).

The hormones also influence the cardiovascular system, controlling blood pressure by altering the vascular reactivity to vasoactive substances such as angiotensin II and noradrenaline. The importance of glucocorticoids in vasoregulation is demonstrated in the resulting hypotension of both adrenalectomized animals and patients with glucocorticoid deficiency (8).

Glucocorticoids alter bone and cartilage production via the modulation of insulin-like growth factor I (IGF-I), IGF-binding protein, growth hormones and thyroid hormones. There are multiple effects, which include altered differentiation of osteoblast precursor cells from the bone marrow into an adipocyte phenotype, increased osteocyte apoptosis and effects on the osteoprotegerin/RANK (receptor activator of nuclear factor kappa B) signaling system. The net result is a decline in osteoblast number and function, with a resulting imbalance in the rates of bone resorption and bone deposition that is manifest in osteoporosis.

The antiinflammatory actions of glucocorticoid hormones were first discovered by Hench *et al.* in 1950, and subsequent investigations have provided huge insights into the molecular pathways responsible for these clinically harnessed properties (9). Several genes involved in inflammatory and immune responses are downregulated by glucocorticoids, including, cytokines, chemokines and adhesion molecules. Elevated cytokine production, in particular circulating interleukin-6 (IL-6), during inflammatory reactions initiates HPA axis-driven glucocorticoids. This initiates an important homeostatic negative feedback loop, with glucocorticoids suppressing the inflammatory and immune responses in many cell types, including T cells, macrophages and neutrophils (9-11).

Adverse effects associated with glucocorticoid administration

Long-term use of glucocorticoids is associated with several side effects that vary in severity and persistence. Glucocorticoids induce osteoporosis in 50% of patients on long-term glucocorticoid treatment, representing the most common form of secondary osteoporosis. This is a result of a rapid deterioration in bone mineral density and a subsequent increase in bone fragility. The underlying biochemical cause is the reabsorption of calcium from the bone due to increased osteoclastic activity and a suppressive effect on osteoblastogenesis (12). The detrimental physiological outcome is enhanced by the underlying inflammatory disease and associated risk factors such as elevated inflammatory mediators and immobility.

In childhood, glucocorticoid use causes profound stunting of growth. This may be exacerbated by the nature of the underlying disease. This action appears to be due to both impaired secretion of growth hormone by the pituitary and opposition to growth hormone action in target tissues.

Glucocorticoids can induce elevations in blood sugar, together with insulin resistance in peripheral tissues, resulting in steroid-induced diabetes. Glucocorticoids reduce the function of the glucose transporter GLUT-4, thereby reducing insulin-mediated glucose disposal, and also act on the liver to stimulate gluconeogenesis and hepatic glucose production. This results in hyperinsulinemia and insulin resistance, thereby contributing to the increased risk of atherosclerosis and cardiovascular disease associated with the systemic therapeutic use of glucocorticoids.

The immunosuppression induced by glucocorticoid administration places the patient at risk of opportunistic infections. Masking of severity and presentation of infection often occurs due to the antiinflammatory effects of glucocorticoids, resulting in a delayed diagnosis and worse prognosis (12).

Molecular mechanisms of glucocorticoid actions

Target cells respond to glucocorticoids via the GR, which is a member of the nuclear receptor superfamily with the conventional domain structure: *N*-terminal transactivation domain, central DNA-binding domain and a

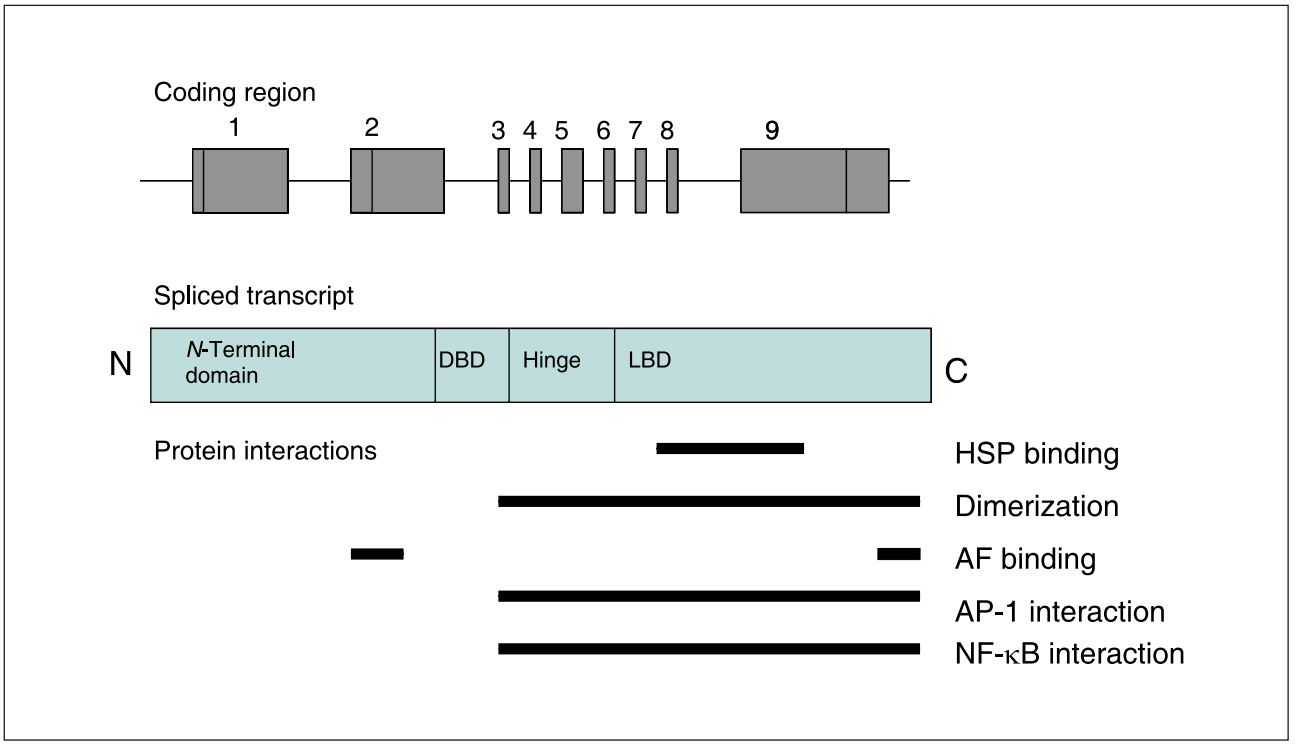


Fig. 1. Genomic and functional structure of the glucocorticoid receptor (GR). The receptor is encoded by 9 exons, with alternative splicing of exon 9 producing the GRα and GRβ isoforms The *N*-terminal domain contains the hormone-independent activation function domain (AF-1) important in recruiting both positive and negative gene regulation. The DNA-binding domain (DBD) is important in receptor dimerization, nuclear translocation and binding to glucocorticoid response elements (GREs) and subsequent transactivation. The ligand-binding domain (LBD) undergoes a conformational change upon binding of glucocorticoids, allowing interactions with coregulators. Upon ligand binding, the heat shock protein (HSP) complex dissociates from the receptor, which subsequently translocates to the nucleus, where it exerts its multifaceted effects via homodimerization or acting alone. Functional domains in the receptor are indicated (12).

C-terminal hormone-binding domain (Fig. 1). Four splice variants exist, with the conventional GRα receptor responsible for the majority of synthetic glucocorticoid actions. The GRβ, a *C*-terminal variant, does not bind ligand and has been reported to have dominant negative activity on GRα (13). The functions of GRδ and GRγ are currently under investigation (14). Further receptor diversity is generated via the use of alternative translational start sites (A-D) (15).

Glucocorticoids (endogenous or synthetic) diffuse across target cell membranes to bind to cytoplasmic GRs, triggering the release of chaperones (two molecules of heat shock protein HSP90, one molecule each of HSP70 and HSP56), and subsequent nuclear translocation and target gene modulation (16). Activated GRs can induce differential expression of genes via homodimer binding to glucocorticoid response elements (GREs). Initially, GREs were thought to only be involved in enhancing gene expression, but subsequent studies have identified negative GREs (nGREs) that repress promoter activity in several genes, including osteocalcin and prolactin (17-19). The complex regulation of genes involves the recruitment of several transcription factors and co-modulators, resulting in chromatin remodeling. This process requires the posttranslational modification of histones, with acetylated histones driving a “relaxed” chromatin conformation permissive for transcription, and deacetylated histones having the opposite effect. The “relaxed” chromatin conformation allows the recruitment of coregulators and subsequent RNA polymerase II initiation of target gene transcription. Conversely, the “closed” chromatin structure results in occlusion of DNA by densely packed histone structures (20, 21). Several of these co-modulators have now been identified and altered expression has been shown to affect hormone sensitivity.

Non-GRE-containing glucocorticoid target genes are indirectly modulated via a “tethering” mechanism whereby the GR is bound to other transcription factors, themselves bound to DNA. These other transcription factors include activator protein AP-1, NF-κB and signal transducer and activator of transcription 5 (STAT5) (22-24).

In recent years, nongenomic mechanisms of glucocorticoid action have become evident. Rapid effects of GRα activation that are insensitive to inhibitors of transcription make a transcriptional mode of action unlikely. Reported nongenomic effects are postulated to involve the activation of signaling cascades involving the proto-oncogene tyrosine protein kinase Src, phosphoinositide 3-kinase (PI3K) and mitogen-activated protein (MAP) kinase (25, 26).

Glucocorticoid receptor interactions with inflammatory mediators

The antiinflammatory response elicited by glucocorticoids is the result of an accumulative effect on different transcription factors and target genes. Direct interaction with transcription factors, such as NF-κB and AP-1, results in suppression of their activity. NF-κB is a heterodimeric complex of transcription factors containing the Rel homology domain, and is the major signaling system for the inflammatory response. RelA interaction with the GR results in a mutual inhibition of transcriptional activation. A similar mutual inhibition is present with AP-1, with glucocorticoid binding at c-jun/c-fos heterodimers. Both transcription factors regulate many inflammatory response genes, including cytokines (*e.g.*, IL-6), enzymes (*e.g.*, inducible nitric oxide synthase, iNOS) and cell adhesion molecules (*e.g.*, intercellular adhesion molecule 1, ICAM-1). The mechanism whereby the tethered GR can alter the transcriptional effect of other transcription factors is not completely understood, but may involve recruitment of co-modulatory proteins, such as members of the p160 family (GRIP1 or SRC-2). These co-modulators appear to be capable of both enhancing and inhibiting gene transcription, depending on the conformation of the GR and whether the GR is bound to DNA as a homodimer or to other transcription factors as a monomer (27).

Glucocorticoids inhibit MAP kinase phosphorylation cascades, another major signaling pathway in inflammation. Two of the MAP kinases, c-jun *N*-terminal kinase (JNK) and p38, demonstrate reduced activity in the presence of the hormone (28). The precise mechanism is unclear, although recent data demonstrate glucocorticoid upregulating MAP kinase phosphatase (MKP), an enzyme that inactivates, via dephosphorylation, both JNK and p38 (29).

Glucocorticoid receptor and cancer

Glucocorticoids are part of the treatment regimen for several malignancies, including prostate cancer and lymphoproliferative disorders such as leukemia and Hodgkin's disease. They are also commonly used as part of chemotherapy for advanced cancers, due to their antiemetic effects and potent ability to reduce edema. The GR is present in most lymphoid malignancies and solid tumors. Glucocorticoids may exert direct effects on tumor cell proliferation, either promoting apoptosis or slowing cell cycle progression through effects on prokinetic protein expression. In addition, glucocorticoids may act to prevent chemotherapy-induced apoptosis in some tumor cells, indicating a complexity of action dependent in part on the target cell phenotype.

Several studies involving both *in vitro* and *in vivo* model systems have indicated that glucocorticoids induce differentiation and prevent proliferation of cancer cells. Activated GR induces a G1 cell cycle arrest in rat mammary tumors, which can be reversed upon glucocorticoid removal. Glucocorticoids alter the intricate balance between growth-promoting and growth-inhibiting factors of the cell cycle. This process involves the downregulation of several growth-promoting genes, including c-Myc, cyclin D3 and cyclin-dependent kinase (CDK). Furthermore, a GRE in the promoter of the CDK inhibitor p21 triggers upregulation and as a consequence exerts an antimitogenic effect (30).

Glucocorticoids are potent inducers of T-lymphocyte apoptosis and are therefore widely used in chemotherapy for lymphoid malignancies. Typically, with prolonged use glucocorticoid-resistant clones arise and disease relapses. This process involves regulation of pro- and antiapoptotic Bcl-2 family members that are key to the so-called intrinsic cell death pathway. Proapoptotic Bcl-2 family members Bcl-2-binding component 3 (BBC3, also known as p53-upregulated modulator of apoptosis, or PUMA) and BIM (Bcl-2-interacting mediator of cell death) induce p53-dependent and -independent apoptosis in response to glucocorticoids. *Puma* and *Bim* knockout animals demonstrate the essential role these proteins play in the initiation of glucocorticoid-induced apoptosis (31). More recently, direct glucocorticoid activation of apoptosis has been described in small cell lung cancer cells (32), and also in osteosarcoma cells (33). However, dexamethasone induced a strong antiapoptopic effect in certain carcinoma cells and prevented cancer therapy-induced tumor reduction (34).

Angiogenesis is a fundamental event in the progression of tumor growth and metastasis. *VEGF* (vascular endothelial growth factor) and *IL8* are both proangiogenic genes that are repressed by glucocorticoids. NF-κB and AP-1 transcription factor inhibition is also shown to reduce angiogenesis. Prednisolone, a synthetic glucocorticoid, inhibits tumor-associated vascularization in mice with established tumors (35) (Fig. 2).

The potent antiinflammatory effects of glucocorticoids are of benefit in a range of inflammatory and immune conditions, and they are increasingly used as chemotherapeutic agents in the fight against cancer. A strong relationship exists between inflammation and carcinogenesis, with chronic inflammation playing a crucial role in the neoplastic process. Identification of the mechanisms and pathways involved in the inflammatory aspect of carcinogenesis has highlighted several potential targets for chemotherapy.

Several of the processes involved in inflammation, including leukocyte migration, vasodilatation and angiogenesis, contribute to tumor growth. Inflammation aids the initiation of carcinogenesis, with associated cytokines, chemokines and inflammatory cells increasing oxidative damage and the DNA mutation rate. Such damage promotes cell transformation to an oncogenic state.

Chronic inflammation enhances tumor progression. Tumor cells produce various inflammatory mediators that attract leukocytes (including neutrophils, macrophages, mast cells and lymphocytes), which in turn release cytokines (granulocyte–macrophage colony-stimulating factor, or GM-GSF, and IL-4) to stimulate further tumor cell proliferation. Metastasis of malignant tumor cells is

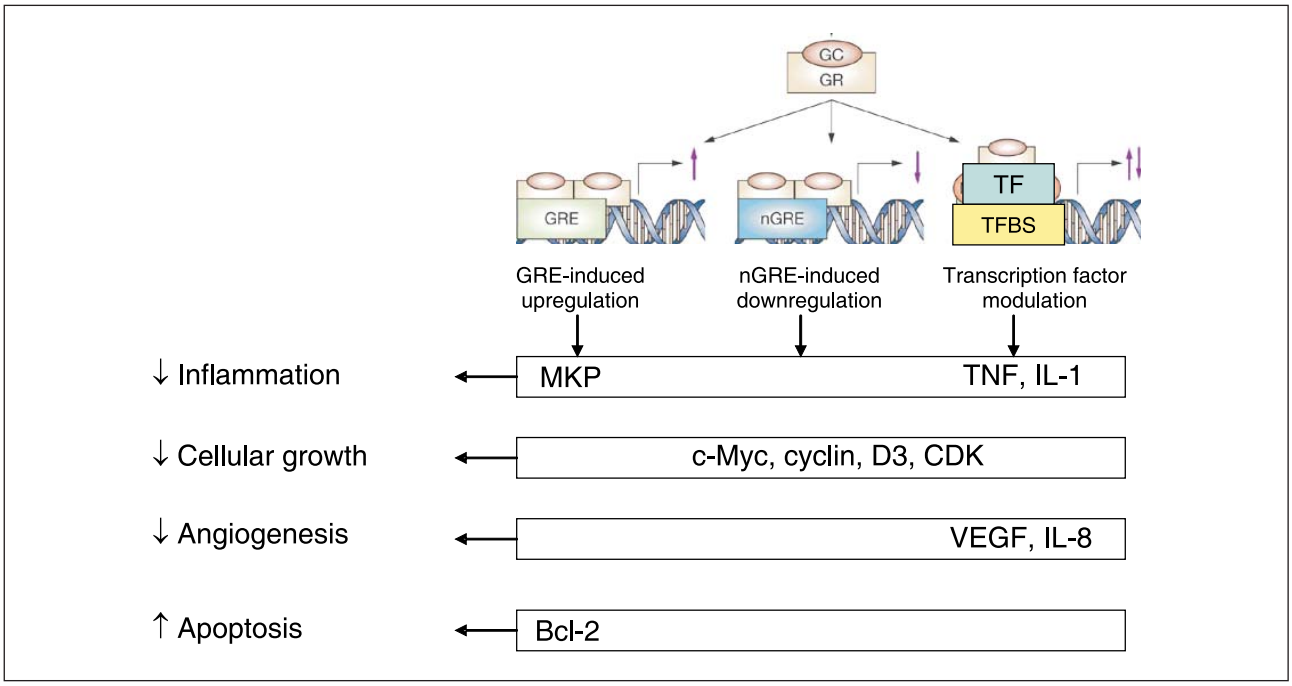


Fig. 2. Antiinflammatory and antineoplastic mechanisms of glucocorticoids. Glucocorticoids activate the cytoplasmic glucocorticoid receptor (GR), which then translocates to the nucleus to regulate gene expression. Activated GR homodimers can modulate transcriptional activation (via binding glucocorticoid response elements [GREs]) or transcriptional repression (via binding non-GREs). The GR achieves these effects by recruiting and interacting with other transcription factors and co-modulators, including those that can induce chromatin remodeling. The activated GR can also bind other transcription factors, altering their activity at transcription factor binding sites. The therapeutic effects of glucocorticoids in both inflammatory disease and cancer rely on each of these different mechanisms of steroid action. Examples of genes and transcription factors central to the therapeutic actions of glucocorticoids are listed, together with their mode of steroidal regulation.

also associated with inflammation. Leukocytes release cytokines and chemokines that promote cell motility and induce angiogenesis. Furthermore, vasodilatation and extravasation of tumor cells promote an increase in metastatic tumor cells (36-38). Hence, it has become evident that inflammatory cells in the tumor microenvironment are a critical factor in cancer formation, growth and spread. Therefore, glucocorticoid use, both by targeting the inflammatory component of the tumor and by potentially targeting the tumor cells directly, may be expected to play an important therapeutic role (Fig. 3).

Selective glucocorticoid receptor modulators and disease

Recent interest in novel glucocorticoid design aims to optimize therapeutic use by retaining beneficial effects while minimizing undesirable side effects. Such novel compounds can be grouped into several different classes: selective glucocorticoid receptor modulators, gene-selective compounds, soft steroids and dissociated compounds:

- *Selective glucocorticoid receptor modulators* - A selective glucocorticoid receptor modulator has antiinflammatory activity but does not activate transcriptional pathways involved in bone, glucose or lipid metabolism.
- *Gene-selective compounds* - Molecules that activate the receptor in a gene-specific fashion, resulting in a greatly reduced differential expression profile.
- *Dissociated compounds* - These molecules enable dissociation of transactivation from transrepression by the GR. These compounds only repress transcription on glucocorticoid-repressible genes.
- *Soft steroids* - Active compounds that are rapidly inactivated by enzymes, thereby reducing side effects caused by their presence in the systemic circulation (12).

The antiinflammatory pathways of glucocorticoids involve the transrepression of target genes and inhibition of transcription factors, whereas the molecular basis for a large number of side effects involves transactivation. The theory that repression alone may be sufficient for the antiinflammatory activity of glucocorticoids is supported by studies by Schütz *et al*. Using the $GR^{dim/dim}$ dimerization-deficient glucocorticoid receptor model that inhibited transactivation but did not affect repression, conventional glucocorticoids were shown to still exert antiinflammatory effects (28, 39). However, the Schütz group has recently reported that in contact hypersensitivity, an important rodent model for inflammatory disease, mice with the DNA binding-defective GR demonstrated an impaired response to glucocorticoids (40). This suggests that transactivation may play a role in the

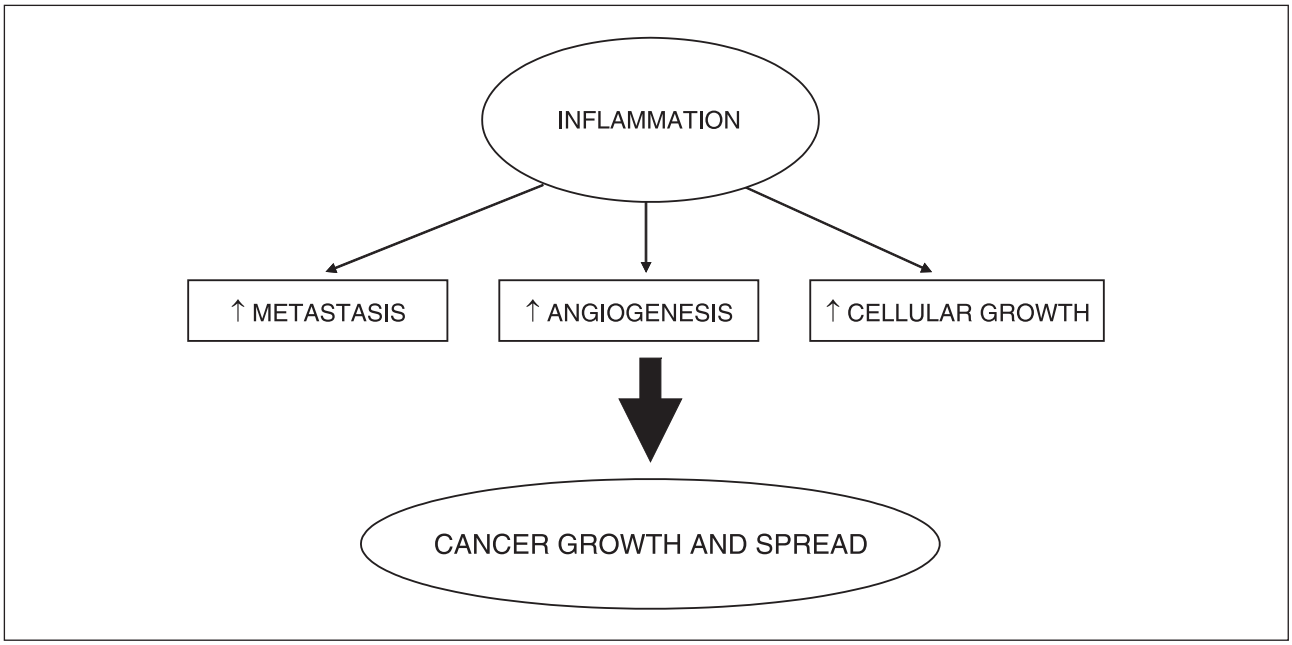


Fig. 3. The role of inflammation in cancer development. Inflammation can lead to an increase in apoptosis, angiogenesis and cellular growth, and therefore plays a central role in the pathogenesis of cancer. Glucocorticoid antiinflammatory actions exert a negative effect on cancer growth.

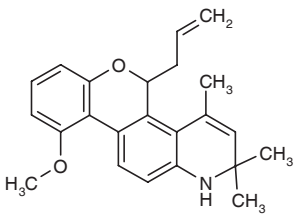
antiinflammatory actions of glucocorticoids in some inflammatory diseases.

The pathogenic involvement of inflammation in tumor formation results in a strong association of therapeutic GR signaling targets in both cancer and inflammatory disease. The established GR targets MAP kinase, AP-1 and NF-κB play important roles in inflammation, cell survival and tumorigenesis (28, 37, 39). The first reported dissociating GR ligand was produced by the former Roussel-Uclaf organization (now sanofi-aventis). Significant differences were observed between the test compound and conventional glucocorticoids, as determined in cell-based *in vitro* assays. These data suggested efficient inhibition of both AP-1- and NF-κB-mediated gene induction but negligible transactivation activity on several genes (41). However, these initial promising findings were not replicated by other investigators (27).

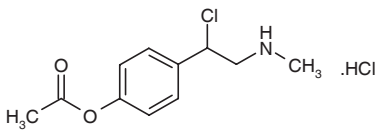
Transactivation assays showed that these compounds were similar to conventional full-agonist ligands such as hydrocortisone and they were found to have identical side effects to steroids *in vivo* (42, 43). There was no therapeutic advantage for this group of compounds in comparison with a conventional glucocorticoid. These novel compounds are still under investigation and recent reports suggest a different spectrum of activities compared to conventional glucocorticoids in specific cell types (44, 45).

Glucocorticoid control of target genes is dependent on concentration. For example, the concentration of dexamethasone required to repress proinflammatory cytokine expression in cells *in vitro* is significantly less than that required to activate target genes. Conventional glucocorticoids such as dexamethasone could therefore be regarded as having partially dissociated activity. Effects on transactivation and transrepression must be directly compared to characterize compound selectivity. Deflazacort is an example of a compound that was introduced into the clinic without complete experimental analysis. The compound was initially marketed as an antiinflammatory agent with decreased side effects. Indeed, at the manufacturer's suggested dose equivalents it did appear to be relatively free of side effects compared to prednisolone; unfortunately, it was subsequently found not to be therapeutically effective (46).

Recently, a group of nonsteroidal molecules that promote DNA binding of the GR have been developed. Of particular interest is the potentially selective nonsteroidal GR modulator AL-438 (**1**). This compound was characterized *in vitro* using cell lines and was found to have antiinflammatory activity in a rat carrageenan-induced paw edema assay. AL-438 had the same binding affinity as prednisolone, but only weak agonist activity in a classical transactivation assay. Importantly, in an *in vivo* study, AL-438 did not result in impaired glucose tolerance, in contrast to biologically similar antiinflammatory doses of pred-



AL-438 (**1**)



Compound A (**2**)

nisolone. AL-438 demonstrated similar antiinflammatory activity to prednisolone and appeared to be free of the hyperglycemic side effects of full GR agonists. The effect of AL-438 on bone metabolism was studied by measuring mineralizing bone formation *in vivo*. Prednisolone was found to reduce bone mineralization rate, whereas AL-438 had no suppressive effect. This interesting compound demonstrated a lack of side effects without any detrimental effect on antiinflammatory activity (47).

Another promising molecule was isolated from the Namibian shrub *Salsola tuberculatiformis*. This compound, named compound A (**2**), downregulates NF-κB via binding to the GR. It completely failed to stimulate transactivation of target genes, suggesting that it was a dissociating compound. Both compound A and dexamethasone induced nuclear translocation of the GR. Compound A is believed to promote the GR to interfere with the transactivation potential of the p65 component of NF-κB. There appears to be a dual mechanism of action involving both a reduction in *in vivo* DNA binding capacity and in the transactivation potential of NF-κB. The compound demonstrated dissociative properties in fibroblast-like synoviocytes obtained from rheumatoid arthritis patients, resulting in reduced expression of several inflammatory mediators (48).

In vivo evidence supports the role of compound A as an effective antiinflammatory agent with equivalent potency to dexamethasone. In the murine collagen-induced arthritis model, compound A resulted in a potent antiinflammatory response comparable to dexamethasone, in the absence of hyperglycemic side effects (48).

The role of glucocorticoid-induced transrepression and transactivaton in apoptotic pathways remains uncertain. $GR^{dim/dim}$ mutant mice, which demonstrate impaired dimerization and subsequently decreased transactivation, have reduced levels of glucocorticoid-induced apoptosis and are therefore likely to display a reduced antitumor response to glucocorticoids (28). Surprisingly, compound A was associated with a reduced growth rate and initiated caspase-dependant apoptosis in GR-expressing prostate carcinoma cells. This study illustrated the potential role of GR-mediated transrepression in the anticancer effects of activated GR (49). The effect of compound A, and dissociative glucocorticoid compounds in general, on the control of apoptosis requires further investigation.

Arylpyrazole-like compounds bind the GR with high affinity and specificity, comparable to established agonists such as prednisolone or dexamethasone. However, these compounds differ in their effects in cell-based assays of proliferation, adipocyte differentiation or osteoblast differentiation. Furthermore, transcriptome profiling demonstrated that the different molecular structures had differential effects on individual target genes. Even very small changes in the structure of the ligand caused markedly distinct GR-regulatory effects in several cell lines. Further analysis indicated that the different compounds altered the relative affinity of the GR for specific DNA sequences. Chromatin immunoprecipitation suggested that the structure of the ligand-binding domain of the GR influences the interaction with specific DNA sequences and thereby results in a distinct profile of gene-regulatory events. These interesting findings suggest that an imperfect dissociating compound may offer an improved therapeutic index, offering the full antiinflammatory potency of glucocorticoids with a reduced side effect profile (50).

Conclusions

Glucocorticoids are potent antiinflammatory drugs used in the treatment of inflammatory diseases and cancer. Unfortunately, the widespread use of glucocorticoids is limited due to the spectrum of severe side effects. In recent years, an increase in our understanding of how glucocorticoids exert their pleiotropic effects has allowed the identification of new molecular targets which could limit adverse outcomes. The race is now on to find new synthetic agents capable of exerting the antiinflammatory actions of the hormones, while having reduced systemic side effects. Current theory suggests that selectively initiating transrepressive pathways could improve the therapeutic profiles of synthetic compounds. Only with the further development and characterization of such selective agents will we determine if these approaches will succeed. The search for GR modulators that can harness the therapeutic potential of glucocorticoids while limiting patient morbidity continues.

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