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Nuclear receptors in inflammation control: repression by GR and beyond

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Abstract

Inflammation is a protective response of organisms to pathogens, irritation or injury. Primary inflammatory sensors activate an array of signaling pathways that ultimately converge upon a few transcription factors such as AP1, NFκB and STATs that in turn stimulate expression of inflammatory genes to ultimately eradicate infection and repair the damage. A disturbed balance between activation and inhibition of inflammatory pathways can set the stage for chronic inflammation which is increasingly recognized as a key pathogenic component of autoimmune, metabolic, cardiovascular and neurodegenerative disorders. Nuclear Receptors (NRs) are a large family of transcription factors many of which are known for their potent anti-inflammatory actions. Activated by small lipophilic ligands, NRs interact with a wide range of transcription factors, cofactors and chromatin-modifying enzymes, assembling numerous cell- and tissue-specific DNA-protein transcriptional regulatory complexes with diverse activities. Here we discuss established and emerging roles and mechanisms by which NRs and, in particular, the glucocorticoid receptor (GR) repress genes encoding cytokines, chemokines and other pro-inflammatory mediators.

Keywords

Inflammation; transcriptional repression; nuclear receptors; glucocorticoid receptor

Inflammation is the response of the host innate immune system to infection, irritation or injury that involves the production of cytokines and chemokines, changes in vascular permeability, activation and mobilization of specialized immune cells to the affected area and, ultimately, elimination of the infectious agents and the repair of damaged tissue. Inflammation is a broad and relatively non-specific response usually initiated upon the recognition of conserved microbial components by pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), Rig-I-like receptors (RLRs) and Nod-like receptors (NLRs). TLRs reside either on the cell surface or endosomal membranes and recognize a

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wide range of structures such as lipopolysaccharides (LPS), lipopeptides, proteins and single- and double-stranded nucleic acids. TLRs trigger an array of downstream signaling events that converge upon the transcription factors Nuclear Factor (NF) κB, activator protein-1 (AP-1), interferon response factors (IRF) and signal transducer and activator of transcription (STAT) (Takeuchi and Akira 2010) that induce the transcription of key immune modulators such as TNFα, interleukins (IL)-1α, -1β, -6, and chemokines CXCL10, CCL2 among others. The production of cytokines and chemokines, particularly by resident macrophages and dendritic cells at the site of inflammation, enables the influx and activation of neutrophils, which release additional inflammatory mediators such as oxygen-independent antimicrobial effectors (*e.g.,* defensins, cathepsins, lactoferrin) and reactive oxygen and nitrogen species ultimately aimed at clearing the infection and initiating tissue repair (Nathan 2006).

Activators of inflammatory gene expression programs

Since their discovery over 25 years ago, the NFκB/Rel transcription factors have been established as primary regulators of innate immune responses. The members of this family share the Rel homology domain that participates in DNA binding and protein-protein interactions. Five mammalian members have been identified: p65 (RelA), RelB, cRel, p50 and p52. In addition to the Rel domain p65, RelB and cRel each contain the N-terminal transactivation domain (TAD). The NFκB subunits form either homo- or heterodimers with different transcriptional activities; the p65:p50 heterodimer (Fig. 1A) is the most potent activator whereas the p50:50 and p50:52 dimers that lack TAD often confer repression (Saccani, et al. 2003; Smale 2012; Yan, et al. 2012). In unstimulated cells, the majority of NFκB is sequestered in an inactive cytoplasmic complex with the Inhibitor of κB (IκB) proteins. Induction of TLR pathways activates the IκB kinases (IKK), which in turn phosphorylate IκB thereby marking it for ubiquitn-mediated proteasomal degradation (Hayden and Ghosh 2012). Free NFκB translocates into the nucleus and binds specific recognition (κB) sites containing the consensus sequence, 5'-GGGRNWYYCC-3' (Fig. 1A) (Kunsch, et al. 1992; Siggers, et al. 2011). DNA bound NFκB recruits additional cofactors with chromatin remodeling and histone modifying activities that promote formation of a transcriptionally permissive chromatin structure (Zhong, et al. 2002).

In addition to activating NFκB TLR ligation also results in phosphorylation of downstream signaling adapters such as TRAF6, leading to sequential activation of TAK1 followed by MAP kinases JNK and p38 that phosphorylate serine/threonine residues on cJun and cFos, commonly referred to as AP-1 proteins (Johnson and Lapadat 2002). AP-1 transcription factors belong to a large family that share a conserved bZIP domain responsible for DNA binding and dimerization. AP-1 proteins (cJun, cFos, Fra-1, Fra-2, FosB, JunB and JunD) homo- and heterodimerize (Chinenov and Kerppola 2001) and bind to AP-1 (TGA(C/G)TCA) or CRE (TGACGTCA) elements (Fig. 1A) in target promoter regions often adjacent to NFκB, IRF, PU.1 or nuclear factor of activated T-cells (NFAT) to coordinately induce transcription (Chinenov and Kerppola 2001; Pascual and Glass 2006).

Rapid activation of NFκB, AP-1 and IRFs amplifies the initial response to TLR ligands by activating the transcription of multiple cytokine genes including IL-6, IFN α and β that bind their cognate cell surface receptors and initiate the Janus kinase (JAK)-STAT signaling cascade (Flammer and Rogatsky 2011; O'Shea, et al. 2013; Yu, et al. 2009). Ligated cytokine receptors change their conformation and bring associated JAK tyrosine kinases in close proximity inducing their self-phosphorylation. Activated JAKs phosphorylate specific tyrosine residues of the cytokine receptors thus creating recognition sites for the STAT family of transcription factors. There are at least seven eukaryotic STAT proteins that upon receptor binding undergo tyrosine phosphorylation which induces conformational

rearrangement and dimerization via SH2 domains which recognizes phosphotyrosines (Mao, et al. 2005; Ota, et al. 2004). Most STAT proteins (1, 3, 4, 5 and 6) form homodimers, whereas STAT1 and 2 form heterodimers that further interact with IRF9 to form a heterotrimeric ISGF3 complex (Flammer and Rogatsky 2011). STATs have also been proposed to exist as inactive dimers in the absence of cytokine signals. Activated STAT dimers translocate into the nucleus, bind DNA and induce the transcription of cytokine genes, thereby ensuring secondary amplification of the inflammatory signal (Shuai and Liu 2003).

Nuclear receptors and control of inflammation

Although effective at rapidly stopping infection, most innate immune effectors are relatively non-specific and do not distinguish well between the host and pathogens which can lead to inflammation-associated tissue damage. Indeed, excessive cytokine production, sometimes referred to as “cytokine storm” (Ferrara, et al. 1993), results in pathologies of varying severity from fever, hypoglycemia and weight loss to organ damage and, in extreme circumstances, death (Clark, et al. 1987; Spriggs, et al. 1988; Tracey, et al. 1986). Furthermore, a wide range of autoimmune diseases including rheumatoid arthritis, psoriasis, inflammatory bowel disease and many others have been associated with augmented cytokine production and signaling (Palucka, et al. 2005). Hence, numerous local and systemic regulatory pathways have evolved to control inflammation and promote postinflammatory tissue repair and remodeling (Lee and Mazmanian 2010; Medzhitov 2008). Locally, innate immune and surrounding cells in the affected tissue produce antiinflammatory cytokines and suppressor proteins, such as IL-10, TGFβ and SOCS family members, initiate degradation of cytokine mRNAs, and induce the synthesis and release of small inhibitory molecules such as neuropeptides, lipoxins, prostaglandins and eicosanoids (Medzhitov and Horng 2009). Systemically, circulating cytokines either directly or via stimulation of the *vagus* nerve initiate a hormonal stress response (Webster, et al. 2002) and production of steroid molecules such as glucocorticoids described in subsequent sections.

Many anti-inflammatory steroids are recognized by the nuclear receptor (NR) superfamily of transcription factors. NR are modular proteins containing the C4-Zn-finger DNA binding and Ligand binding domains (DBD and LBD) linked by a short disordered (or flexible) hinge region in the center of the molecule (Fig. 1B). The highly variable N-terminal regulatory domain encompasses the activation function-1 (AF1) whereas the C-terminal domain including a portion of LBD forms ligand-dependent activation function-2 (AF2). NRs that participate in regulation of inflammation may reside in the nucleus or translocate from the cytoplasm into the nucleus upon ligand binding. Once in the nucleus, NRs either bind directly to specific DNA sequences to induce or repress target genes or become ‘tethered’ to DNA by unrelated DNA-bound transcription factors via protein:protein interactions and typically repress associated genes in ‘trans’ (a.k.a. transrepression). This process is mechanistically and functionally distinct from repression by the same receptor when bound to DNA (‘cis’) and has been well characterized particularly for estrogen receptors (ER), peroxisome proliferator-activated receptors (PPAR), liver-X receptors (LXR) and glucocorticoid receptor (GR) in the context of inflammation (Fig. 1B). Below, we will provide a few examples of the roles of ER, PPAR and LXR in the regulation of inflammation via tethering followed by a more detailed discussion of GR-mediated transrepression.

Estrogen receptors

Estrogens exhibit either pro- or anti-inflammatory activities, depending on the cell type, immune stimulus, hormonal concentration and relative amounts of the predominant ER subtype (α or β) (Cutolo, et al. 2010; Straub 2007). Tethering of either ERα or ERβ to other

transcription factors has been proposed as a major mechanism mediating the 'ERE-independent' effects of estrogen (Heldring, et al. 2007). In particular, ER interacts *in vivo* and *in vitro* with multiple AP-1 family members including cFos, cJun, JunD, JunB, small Maf proteins, ATF2 and CREB1 (Eferl and Wagner 2003; Heldring, et al. 2011; Yang-Yen, et al. 1990), and genome-wide studies demonstrate extensive co-localization of ER and AP-1 binding sites in estradiol-stimulated MCF7 breast cancer cells (Carroll, et al. 2006; Kininis, et al. 2007). More recently, genome wide ChIP-chip experiments in HeLa cells with reintroduced ERα (Heldring et al. 2011) have shown a strong enrichment of ERα at AP-1 sites following estradiol treatment. Liganded ERα recruitment promoted activation of AP-1-driven native genes and enhanced promoter occupancy by cFos and CREB1 suggesting that ERα stabilizes relatively weak DNA binding by AP-1 by an unknown mechanism. Conversely, ER binding to NFκB repressed transiently transfected NFκB-driven IL-6 reporters in estradiol-treated HeLa cells (Ray, et al. 1994). Similarly, in microglia and astrocytes, two cell types involved in the innate immune responses in the brain, liganded ERβ isoform repressed the endogenous production of pro-inflammatory cytokines IL-1β, IL-6 and IL-23 p19. The molecular mechanism of repression involved initial ERβ tethering to phosphorylated cFos followed by ERβ-mediated recruitment of CtBP co-repressor (Fig. 1C). Consequently, treatment with ERβ-specific ligands conferred neuroprotection against experimentally induced autoimmune encephalomyelitis (EAE), a murine model for multiple sclerosis (MS) (Saijo, et al. 2011). Thus, the progression of MS, and possibly other autoimmune disorders of the brain, could potentially be linked to a dysregulated ERβ transrepression pathway (Gosselin and Rivest 2011).

Peroxisome proliferator-activated receptors

PPAR isoforms α, γ and δ (Fig. 1B) have been implicated in regulating inflammation in numerous physiological contexts ranging from atherosclerosis to encephalitis (Li and Yang 2011; Schnegg, et al. 2012) PPARs regulate inflammatory responses through multiple mechanisms including both activation of genes encoding anti-inflammatory mediators, such as IκB (Delerive, et al. 2002), soluble IL-1 receptor antagonist (Stienstra, et al. 2007) and TGFβ, and repression of inflammatory genes via tethering to AP-1, NFκB and STAT1 (Ricote, et al. 1998; Wahli and Michalik 2012). In macrophages, PPAR agonists induce a number of genes related to glucose and lipid metabolism and repress a large subset of genes induced by inflammatory stimuli (Welch, et al. 2003) suggesting that PPARs integrate the two processes making these receptors highly relevant in metabolic diseases including type-II diabetes and atherosclerosis (Varga, et al. 2011). Indeed, in human aortic smooth muscle cells, PPARα inhibits production of IL-6, a key cytokine involved in the pathogenesis of atherosclerosis, by directly tethering to p65 and cJun (Delerive, et al. 1999). Interestingly, PPARα was also proposed to attenuate inflammation indirectly, by potentiating the anti-inflammatory activities of glucocorticoids. Although the mechanistic details are scarce, in a proposed model, PPARα interferes with GR DNA binding at palindromic GREs thereby increasing the pool of free GR available to be tethered to DNA by NFκB or AP-1 (Bougarne, et al. 2009). Co-treatment of L929sA mouse fibrosarcoma cells with the synthetic glucocorticoid, dexamethasone (Dex) and PPARα ligand GW647 resulted in greater suppression of NFκB- and AP-1-dependent inflammatory genes than Dex alone.

PPARγ transrepression of inflammatory genes has been proposed to be regulated by receptor SUMOylation. In this model, AP-1 and NFκB at the IL-8, Mmp12 and iNOS promoters are basally bound by NCoR/SMRT:HDAC3 co-repressor complexes (Hoberg, et al. 2004; Ogawa, et al. 2004). In the presence of ligand, PPARγ undergoes SUMOylation at the conserved Lys-365, which targets PPARγ to promoter-bound NCoR complexes and prevents LPS-induced recruitment of ubiquitin ligase Ubc5 to NCoR (Fig. 1C). This in turn precludes proteasomal degradation and clearance of the co-repressor complex, thereby attenuating

LPS-induced transcription (Pascual, et al. 2005). It has been proposed that the NCoR-dependent repression by PPARγ is protective against inflammation-induced insulin resistance associated with obesity and type-II diabetes (Olefsky and Glass 2010).

Liver X receptors

LXR α and β that recognize oxysterols are central to the regulation of cholesterol and lipid metabolism in hepatocytes. In macrophages, LXRs repress a number of atherogenic inflammatory mediators including TNFα, IL-6, CCL2 and iNOS (Pourcet, et al. 2011; Zelcer and Tontonoz 2006). Moreover, inflammatory gene repression by LXRs is not a macrophage-specific phenomenon and has been observed in other cell types such as astrocytes (Lee, et al. 2009) and hepatocytes (Venteclef, et al. 2010). Thus, similar to PPARs, LXRs integrate the maintenance of lipid homeostasis with inhibition of inflammation (Kidani and Bensinger 2012). Despite a significant overlap between inflammatory genes repressed by LXRs and PPARs, a large subset of genes was sensitive to only one receptor (Ogawa, et al. 2005). Furthermore, although the repression of inflammatory genes by both LXR and PPAR involves SUMOylation, each receptor relies on a different E3 ligase (HDAC4 and PIAS-1, respectively) that conjugates distinct SUMO proteins (SUMO-2/3 and SUMO-1, respectively) and are functionally independent of each other (Ghisletti, et al. 2007). Similar to PPARs, SUMOylated LXRs repress inflammatory genes by preventing NCoR and SMRT (Fig. 1C) co-repressor clearance from promoter regions of LPS-stimulated genes in macrophages (Ghisletti, et al. 2009). Resident NCoR/SMRT complexes recruit several chromatin modifying enzymes with “repressing” activities, including HDAC1, HDAC3 and histone methyltransferase SMYD5 that trimethylates H4 K20 (Gao, et al. 2005; Stender, et al. 2012). NCoR promoter clearance is mediated by CORO2A, an actin-binding subunit of the NCoR complex that also harbors a conserved SUMO-interaction motif. The SUMOylated LXR binds CORO2A and prevents the actin-dependent NCoR release that is required for transcription activation (Huang, et al. 2011).

Glucocorticoid-mediated suppression of inflammation

Of the NR superfamily, GR is the most widely known target of anti-inflammatory therapy. Indeed, since the Nobel Prize winning discovery of their anti-inflammatory actions (Hench, et al. 1950; Reichstein 1951), glucocorticoids have remained among the most commonly prescribed drugs to treat a multitude of autoimmune and inflammatory diseases including rheumatoid arthritis, asthma, lupus, inflammatory bowel disease, and multiple sclerosis.

The increase in serum level of glucocorticoids during the immune response has been first noted in the mid-1970s (Besedovsky, et al. 1975) and was linked to the increased serum concentration of cytokines such as IL-1 (Besedovsky, et al. 1986; Woloski, et al. 1985). The level of circulating glucocorticoids is globally controlled by the hypothalamic-pituitary axis (HPA) whereby in response to various stresses, corticotropin-releasing hormone (CRH) produced in paraventricular nucleus of the hypothalamus activates the production of adrenocorticotropic hormone (ACTH) by the anterior lobe of the pituitary ultimately triggering the synthesis and release of glucocorticoids by the adrenal cortex (Silverman and Sternberg 2012; Webster et al. 2002). The regulation of the *CRH* and *POMC* genes encoding CRH and ACTH, respectively, is complex and integrates multiple signaling pathways (Kageyama, et al. 2011; Kariagina, et al. 2004). IL1, IL6, TNFα and LIF can each stimulate transcription of the *CRH* and *POMC* genes in cell culture directly (Katahira, et al. 1998; Liu, et al. 2008; Wei, et al. 2002). In vivo, however, the contribution of direct activation via cytokines in circulation vs. the hypothalamic stimulation through afferent neuronal circuitry remains to be fully elucidated (Watts and Sanchez-Watts 2002). In a classic example of a feed-back loop regulation, glucocorticoids inhibit *POMC* transcription and ACTH production (Bilodeau, et al. 2006; Gagner and Drouin 1985). The effect of

glucocorticoids on *CRH* expression is more complex: although glucocorticoids inhibit the transcription of *CRH* in pituitary cell cultures (Adler, et al. 1988) in placenta, the effect is opposite (Robinson, et al. 1988).

Unliganded GR resides in the cytoplasm as a part of a large aporeceptor complex with chaperon proteins including heat shock protein (HSP) 70, HSP90, HSP40 co-chaperones p23 and Hop, and immunophilin FKBP51. Upon glucocorticoid binding, structural changes in GR result in the complex rearrangement and exchange of FKBP51 for FKBP2, binding to a motor-protein dynein that translocates GR to the nucleus where it activates or represses target gene transcription (Echeverria and Picard 2010). GR can directly bind specific palindromic glucocorticoid response elements (GREs) that contain consensus AGAACA half-sites arranged as an inverted palindrome separated by 0–3 bp providing a binding site for the GR homodimer. Liganded GR then recruits various co-factors, such as the NCoA/p160 family of co-factors (SRC1, SRC2/GRIP1/TIF2 and SRC3/AIB1/ACTR/Rac3), which in turn recruit histone modifiers including histone acetyltransferases CBP/p300; histone methyltransferases CARM1, G9a (York and O'Malley 2010) and ATP-dependent chromatin remodellers, *e.g.*, BRG1 (Burd, et al. 2012; Trotter and Archer 2008). Several GR-induced genes encode anti-inflammatory molecules such as Dusp1 (Imasato, et al. 2002; Vandevyver, et al. 2012), Tsc22d3 (GILZ) (Cannarile, et al. 2009; Mittelstadt and Ashwell 2001) and IκB (Scheinman, et al. 1995a). The role of these factors in inflammation is beyond the scope of this review and has been extensively discussed elsewhere (Clark 2007). Recently, GR binding at GREs with atypical spacers of 1–2 nucleotides was shown to result in transcriptional repression (Surjit, et al. 2011). Although the mechanism and biological relevance of this phenomenon remains to be explored, the recent crystal structure of GR DBD bound to such a site revealed an unusual binding orientation that precluded GR dimerization (Hudson, et al. 2013) suggesting that the repressive activity of GR at nGREs relies on monomeric GR.

At “tethering” GREs GR does not directly bind DNA but instead interacts with other DNA-bound factors and modifies their transcriptional activity. Indeed, GR interacts with several AP-1 family members such as cJun, cFos (Konig, et al. 1992), JunD, JunB and CREB1 (Matsumoto, et al. 2012), NFκB subunit p65 (Nissen and Yamamoto 2000), STAT3 (Langlais, et al. 2012), SMAD3 (Li, et al. 2003), p53 (Sengupta, et al. 2000; Sengupta and Wasylyk 2001) and C/EBPα (Rudiger, et al. 2002) and represses transcription of their target genes. The initial analysis of the repression function of GR mutants with disrupted dimerization interface suggested that at tethering sites GR dimerization may not be required (Reichardt, et al. 2001), however, later studies indicated that the importance of dimeric GR needs to be analyzed on a case by case basis for activated and repressed GR targets alike (Chen, et al. 2013; Rogatsky, et al. 2003). This review will focus on the mechanisms and physiological consequences of GR-mediated transrepression.

GR interactions with AP-1

The first evidence of GR-mediated antagonism of AP-1 activity emerged two decades ago when GR activation was shown to inhibit transcription from transfected AP-1 reporters (Jonat, et al. 1990; Yang-Yen et al. 1990). Subsequently, these *in vitro* observations were extended to endogenous genes demonstrating by nuclear run-on assays that GR repressed transcription of AP-1-driven collagenase I (Mmp1) gene in human skin fibroblasts treated with Dex. This glucocorticoid-dependent repression did not interfere with AP-1 DNA binding *in vitro* based on electrophoretic mobility shift assays (EMSA), and did not involve chromatin remodeling as evidenced by the lack of any Dex-induced changes in genomic dimethyl sulfate footprinting at the AP-1 binding sites (Konig et al. 1992). Moreover, mutations affecting GR DNA binding had no effect on its ability to repress AP-1 (Heck, et al. 1994). Later, the advent of ChIP assays enabled a direct quantitative assessment of GR

recruitment to genomic AP-1 sites associated with the Mmp13 and IL-8 genes along with cJun and cFos (Kassel, et al. 2004; Rogatsky, et al. 2001) thus solidifying the model for GR tethering to AP-1 and inhibiting its activity. Furthermore, the analysis of overrepresented binding sites within GR binding peaks identified by ChIP-seq in mammary epithelial cells revealed an enrichment of AP-1 motifs. Interestingly, over 90% of AP-1 binding sites, including those coinciding with GR sites, have been associated with constitutively "open" chromatin as shown by DNase-seq assays. Thus, most of the GR binding sites enriched for AP-1 display constitutive GC-independent DNase I hypersensitivity (Biddie, et al. 2011; John, et al. 2011). GR binding to the majority of these sites required intact AP-1 binding activity and was disrupted by cFos DNA binding-deficient mutants when used instead of the WT cFos (Biddie et al. 2011). Taken together, these findings demonstrate the ubiquitous nature and functional importance of GR tethering to AP-1 in modulating its activity.

GR interactions with NFκB

Resembling antagonism of AP-1, initial studies with NFκB showed that GR inhibited NFκB-dependent expression of reporter constructs driven by the IL-6 and ICAM1 proximal promoter regions, or tandem κB sites (Caldenhoven, et al. 1995; Ray and Prefontaine 1994; Scheinman, et al. 1995b). Interactions between GR and p65, p50 and Rel proteins have been further confirmed by *in vitro* pull-down and co-immunoprecipitation experiments (Ray and Prefontaine 1994; Scheinman et al. 1995b) Mutation analysis identified the GR LBD and DBD as being crucial for repression (Caldenhoven et al. 1995) and mapped the GR:p65 binding interface to the second zinc finger in GR DBD (Liden, et al. 1997; Nissen and Yamamoto 2000) and Rel homology domain (Wissink, et al. 1997). Curiously, a single point mutation in the second zinc finger of the rat GR (Arg488Gln) disrupts GR-mediated repression of NFκB reporters without affecting GR:p65 interactions (Bladh, et al. 2005). Using Bioluminescence Resonance Energy Transfer (BRET), interactions between GR DBD and NFκB have been observed in living cells (Garside, et al. 2004). GR recruitment to the IL-8, ICAM1, Mmp13, and IL-1 α and β κB sites did not alter p65 occupancy (Chinenov, et al. 2012; Kassel et al. 2004; Nissen and Yamamoto 2000) further corroborating the "tethering" model for GR inhibition of NFκB.

The physiological importance of GR-mediated repression in regulating p65-driven inflammation has been highlighted in several genome-wide studies. Microarray expression profiling of macrophages treated with LPS for 6 h in the absence or presence of Dex, revealed over 500 LPS-induced genes of which more than half were repressed by glucocorticoids at least two-fold (Ogawa et al. 2005). In our recent RNA-seq study, a 1-h LPS treatment upregulated over 350 genes >2 fold of which 150 were repressed by Dex, including key inflammatory mediators such as TNFα, IP10 and IL-1 a and β (Chinenov et al. 2012). In another study, co-treatment of HeLa cells with TNFα (a potent inducer of NFκB-driven transcription) and a synthetic glucocorticoid triamcinolone acetonide (TA) for 4 h resulted in the induction of 1033 novel GR binding sites (~12% of total GR binding) that were not induced by TA alone (Rao, et al. 2011). 572 of these "gained" sites overlapped with p65 binding sites induced by TNFα alone. Binding motif analysis revealed that NFκB and AP-1 elements, and not palindromic GREs, were overrepresented among the gained GR binding sites, consistent with the GR recruitment to DNA via tethering by NFκB or AP-1 (Rao et al. 2011). Furthermore, gained GR binding sites were associated with genes encoding cytokines, cytokine receptor families, MAP kinases and mediators of TLR signaling and apoptosis.

GR interactions with STAT3

GR interactions with several STAT family members, including STAT 3 and 5, result in either synergistic induction of STAT-bound genes or inhibition of the GR-bound genes

((Rogatsky and Ivashkiv 2006) and references therein). For example, the first evidence of STAT5:GR interaction was reported for the β-casein gene which lacks a known GRE but contains a STAT5 binding site. This interaction was shown to cooperatively induce β-casein expression relative to STAT5 alone (Stocklin, et al. 1996; Stoecklin, et al. 1997). GR and STAT5 have also been shown to induce the TLR2 gene in TNFα + Dex treated A549 cells, although whether this induction is due to direct protein:protein interactions remains to be determined (Hermoso, et al. 2004). STAT3:GR interaction results in an increased activation of the STAT3 target gene α2-macroglobin (Lerner, et al. 2003). Surprisingly, GR interaction with STAT3 was also reported to result in superactivation of GR targets with STAT3 operating as a GR co-activator at a GRE. Upon co-treatment of rat hepatoma H4IIE cells with IL-6 and Dex which stimulate STAT3 and GR binding, respectively, the two proteins could be co-precipitated. Moreover, in the EMSA experiment an IL-6+Dex-induced protein complex bound to a probe with a STAT3 binding site, and this could be inhibited by anti-GR and super-shifted by anti-STAT3 antibodies suggesting the presence of both proteins in the same DNA-bound complex (Zhang, et al. 1997). Interestingly, recent genome-scale studies have uncovered a widespread GR tethering to STAT3 which results in the negative regulation STAT3 target genes. Microarray-based expression profiling showed that Dex together with the STAT3-activating cytokine LIF, modulates the transcription of over 700 genes (Langlais et al. 2012). Moreover, cluster analysis of ChIP-seq data demonstrated that GR was recruited to over 300 STAT3-bound sites. Notably, the genes in this cluster were repressed by liganded GR in a LIF-dependent manner (Langlais et al. 2012). These results are consistent with a model whereby GR tethers to STAT3 and represses associated genes by as yet unknown mechanism.

Mechanisms of GR-mediated repression

Although the physiological relevance of GR-mediated repression of AP-1- and NFκB-induced transcription is well established, the underlying molecular mechanisms remain to be determined. Conceivably, a single unifying mechanism does not exist rather, distinct processes contribute to repression in a gene-, cell type- and tissue-specific manner with the regulatory outcome ultimately determined by the relative concentrations, activities and repertoire of the context-specific components. Several models of GR action have been proposed over the years and are discussed below.

GR competition for limited co-activators

Regulators of different families rely on a defined repertoire of co-regulators to control the basal transcriptional machinery and chromatin dynamics. Thus, cofactors utilized by both GR and AP-1 or NFκB may in principle become limiting such that activation of GR would sequester them away from AP-1 and NFκB thereby attenuating transcription of genes dependent on these regulators. One example of such shared co-regulators are the histone acetyltransferases CBP/p300, which are used by NRs as well as p65 and Jun. Indeed, introduction of CBP was shown to alleviate GR-mediated repression of AP-1- and NFκB-driven synthetic reporters (Kamei, et al. 1996; Sheppard, et al. 1998). This model was later debated when similar CBP ‘rescue’ experiments had no effect on GR-mediated repression of IL-6 reporters driven by either p65 or Jun (De Bosscher, et al. 2001; De Bosscher, et al. 2000). This suggests that perhaps, competition for co-activators as the basis of GR-mediated repression might be gene-specific and requires validation on a genome-wide scale.

Consistent with the mutually exclusive cofactor utilization mechanism, in macrophages, sequestration of the p160 protein GRIP1 by GR may account for glucocorticoid inhibition of transcription regulated by members of the IRF family (reviewed in (Flammer and Rogatsky 2011)). IRF3 and IRF9 are responsible for anti-viral defenses by activating transcription in response to TLR3 ligands and type I interferons, respectively. GRIP1 was found to interact

with several IRF proteins including IRF3 and 9 (Bhandare, et al. 2011; Flammer, et al. 2010; Reily, et al. 2006) in a glucocorticoid-sensitive fashion. In macrophages, knockdown of GRIP1 or Dex treatment both markedly attenuated transcription of IRF3 and IRF9 target genes, whereas GR antagonists that interfere with GR:GRIP1 complex formation reversed Dex-mediated inhibition. These findings were consistent with the role of GRIP1 as a rate-limiting co-activator for IRF proteins, which is sequestered away by the agonist-bound GR. Interestingly, this effect was determined by the total amount of cellular GRIP1: in fibroblasts that, unlike macrophages, express GRIP1 at high levels, IFN-induced transcription was refractory to Dex (Flammer et al. 2010), illustrating how a specific cellular context influences the regulatory outcome.

Contextual “gain of function”

Reportedly, NRs utilize over 300 different co-regulators (Lonard, et al. 2007) that form a combinatorial interaction network participating in gene-, cell- and signal-specific complexes with varying, sometimes opposite, activities. Surprisingly, unlike LXR and PPAR, GR transrepression does not seem to involve the NCoR complex and, at least in macrophages, is unaffected by NCoR depletion (Ogawa et al. 2005). Alternative cofactors have been implicated in GR-mediated transrepression, including GRIP1 and TRIP6.

Similar to several other GR cofactors (Bittencourt, et al. 2012), GRIP1 was first identified as a co-activator of the p160 family with a typical multidomain structure encompassing a centrally located NR interacting domain, the N-terminal bHLH-PAS domain and several C-terminal domains involved in protein:protein interactions. In the context of palindromic GREs, GR-bound GRIP1 activates transcription by recruiting several co-activators such as CBP/p300 and CARM1 (York and O'Malley 2010). GRIP1 also interacts with several nonreceptor transcription activators including MEF2C and MyoD (Chen, et al. 2000; Wu, et al. 2005) and, as discussed above, several IRF proteins. The first indication for an additional role of GRIP1 in GR signaling was its ability to potentiate glucocorticoid repression of the human Mmp13 gene via the AP-1 response element in a GR agonist- and GR recruitment-dependent manner (Rogatsky et al. 2001). GRIP1 repression activity was associated with a unique Repression Domain (RD), located immediately downstream of the NR interacting domain. RD does not have any discernible sequence or structural motifs suggestive of function and is absent in the other p160 proteins (Rogatsky, et al. 2002). Consistently, other members of p160 family (SRC1 and SRC3) fail to potentiate GR-mediated repression of AP-1- or NFκB-dependent transcription. In mouse macrophages, GRIP1 is recruited to NFκB binding sites concomitantly with GR upon co-treatment with Dex and LPS. Furthermore, in macrophages derived from mice conditionally lacking GRIP1 in hematopoietic cells, genes encoding inflammatory mediators such as TNFα, IL-1β and CCL4 were less susceptible to GR-mediated repression than those in wild-type macrophages (Chinenov et al. 2012). Remarkably, GRIP1 depletion attenuated GR-mediated repression of nearly half of the LPS-induced, Dex-repressed genes including a large number of mediators of inflammation (TNFα, IL-1 α and β, CCL2, 3 and 4, LIF, IP10 and IFNβ) thus illustrating a broad role of GRIP1 in controlling the inflammatory transcriptome in macrophages. Furthermore, the GRIP1-deficient mice were more sensitive to a systemic inflammatory challenge *in vivo* succumbing to endotoxin shock due to augmented levels of serum inflammatory cytokines relative to wild-type mice (Chinenov et al. 2012).

The molecular mechanism of the GRIP1 co-repressor function awaits elucidation. GRIP1 contains several protein:protein interaction domains that recruit transcriptionally repressive chromatin-modifying enzymes such as methyltransferases G9a and Suv4–20h1 (Chinenov, et al. 2008; Lee, et al. 2006) that methylate H3 K9 and H4 K20, respectively. Curiously, in the context of LXR-mediated repression of TLR4 target genes, H4 K20 is trimethylated by

methyltransferase SMYD5 associated with the LXR/NCoR complex (Stender et al. 2012). Whether Suv4–20h1 plays a similar role in GR-mediated repression is unknown.

TRIP6 is another multifunctional protein whose role in transcription was overlooked at the time of the initial functional characterization (Wang, et al. 1999). TRIP6 is a LIM domain-containing protein from the zyxin family that was first discovered in focal adhesion contacts and later shown to shuttle between focal adhesion contacts and the nucleus (Nix and Beckerle 1997). In addition to TRIP6, several members of this family including paxillin and Hic-5 interact with GR and other NRs and typically act as co-activators (reviewed in (Hervy, et al. 2006). TRIP6 was first identified as a thyroid receptor binding partner activator recruited to palindromic GREs in a ligand-dependent manner (Diefenbacher, et al. 2010). Based on electrophoretic mobility TRIP6 exist as three different isoforms of which the fastest (nTRIP6) is localized to the nucleus (Kassel et al. 2004). Whether these isoforms are RNA splice variants or distinct protein species generated through posttranslational modifications is unknown. Interestingly, following AP-1 and NFκB stimulation, nTRIP6 is also recruited to AP-1 and κB sites (via interactions with cFos and NFκB) and potentiates transcription of endogenous Mmp13 and IL-8 genes. Notably, upon glucocorticoid treatment GR was recruited to the same binding sites, likely forming a complex with AP-1:nTRIP6 and NFκB:nTRIP6, which correlated with the repression of Mmp13 and IL-8. Indeed, TRIP6 depletion attenuated GR recruitment to these promoters and subsequent repression without affecting either AP-1 or NFκB loading (Diefenbacher, et al. 2008; Kassel et al. 2004). Similarly, the TRIP6 mutants interacting with cFos and p65 but not with GR, activated AP-1 and NFκB-driven reporters but failed to potentiate repression by GR (Kassel et al. 2004).

Transcription Initiation vs Elongation

Activation of transcription includes two sequential steps: initiation and elongation. Transcription initiation involves the assembly of RNA polymerase2 (Pol2) and general transcription factors at target promoters into the pre-initiation complex (PIC) which coincides with the phosphorylation of the Ser-5 residue of the heptapeptide repeats in the Pol2 C-terminal domain (CTD) by the cyclin H/CDK7 CAK kinase. The subsequent transition into productive elongation involves phosphorylation of the Ser-2 of the Pol2 CTD repeats by the Positive Transcription Elongation Factor (PTEF)-b complex (Nechaev and Adelman 2010). In principle, GR can target either or both steps to inhibit activation of transcription by AP-1 or NFκB.

For example, it was shown that GR represses the IL-8 and ICAM-1 genes in TNFα-stimulated A549 cells by inhibiting transcription elongation. Indeed, at the promoters of these genes, glucocorticoids did not affect TNFα-induced Pol2 recruitment and Ser-5 phosphorylation, thus implying that initiation occurred normally. However, the recruitment of PTEF-b to the IL-8 promoter, and hence, Ser-2 phosphorylation was blocked by Dex (Luecke and Yamamoto 2005; Nissen and Yamamoto 2000) resulting in the early elongation arrest of the initiated Pol2.

Recruitment of HDACs

Another potential target for GR is chromatin itself. Indeed, GR could inhibit transcription by changing either directly or via its co-regulators chromatin structure at the target promoters, making them inaccessible to the basal transcriptional machinery. For example, in A549 cells, glucocorticoids inhibit the IL-1β stimulated, p65-dependent expression of the GM-CSF gene which correlates with reduced histone H4 acetylation at the GM-CSF κB site. The potential enzyme responsible, HDAC2, was identified as a GR:p65 associated protein using co-immunoprecipitation assays. Both the inhibition and depletion of HDAC2 resulted in

elevated H4 acetylation of the GM-CSF promoter and increased GM-CSF production in the presence of Dex, implicating HDAC2 in GR-mediated inhibition of the GM-CSF gene (Ito, et al. 2000; Ito, et al. 2001; Ito, et al. 2006). Interestingly, GR itself is subject to hormone-dependent acetylation at Lys-494 and 495 in its DBD, and HDAC2 was able to reverse this process. Furthermore, HDAC2 depletion both inhibited GR deacetylation and also prevented GR:p65 interaction without affecting GR DNA binding (Ito et al. 2006). Thus, the requirement for HDAC2 in repression in this system might be due in part to its permissive effects on GR recruitment to the NFκB complexes rather than changes in H4 acetylation.

Summary and perspectives

NR ligands constitute 13% of unique FDA approved drugs (Overington, et al. 2006). Among them, potent anti-inflammatory properties of glucocorticoids ensured the widespread use of these compounds to treat a variety of immune and inflammatory disorders. 4000–5000 papers related to the use or mechanisms of glucocorticoid actions are published annually. Despite such intense scrutiny, how glucocorticoids inhibit inflammation remains a hotly debated topic. Numerous conflicting mechanisms are oftentimes based on data obtained in reductionist model systems that yield monofactorial readouts of a few “key” genes. Failed attempts to generalize these findings or translate *in vitro* results to more complex systems suggest that the discovery of the universal mechanism of anti-inflammatory actions of glucocorticoids may be an unattainable goal for not only technical but for broader biological reasons. Perhaps, much like the diverse inflammatory pathologies themselves, the anti-inflammatory approaches should be a disease- or condition-specific. Inflammatory disorders exhibit strikingly different profiles of pro- and anti-inflammatory gene expression and involve different cell types. For example, although rheumatoid arthritis and systemic lupus erythematosus both have a strong inflammatory component, the pathogenesis of the former is driven by TNFα (Feldmann 2002)whereas the latter is associated with dysregulated IFNα (Bennett, et al. 2003). Strikingly, in MS, another inflammatory autoimmune disease, IFNα is anti-inflammatory and is used therapeutically (Guarda, et al. 2011).The recognition of disease-specific pathogenic inflammatory cell types adds another layer of complexity to the design of anti-inflammatory strategies. Although “common” glucocorticoid-regulated genes certainly exist, system-specific regulatory events may drastically affect the kinetics of the response, relative activities of these genes and their products as well as their relevance to the pathogenesis of a specific disorder. Thus, it is difficult to predict whether “large” change in few genes observed in a given cell type would produce desired outcome in a unique disease settings. Conversely, minor, seemingly insignificant changes might initiate cooperative, cascading responses with profound biological consequences. Finally, data obtained in mouse models of human disease should be interpreted with caution given fundamental inter-species differences and well known strain-to-strain variations. Therefore, system-wide analyses in disease-relevant model systems and efforts to validate murine data in human are required to understand and ultimately manipulate GR regulatory circuits.

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Highlights

- Nuclear receptors inhibit inflammatory gene transcription via distinct mechanisms
- GR colocalizes with other regulators and represses their targets genome-wide
- GR utilizes cofactors as context-specific coactivators or corepressors

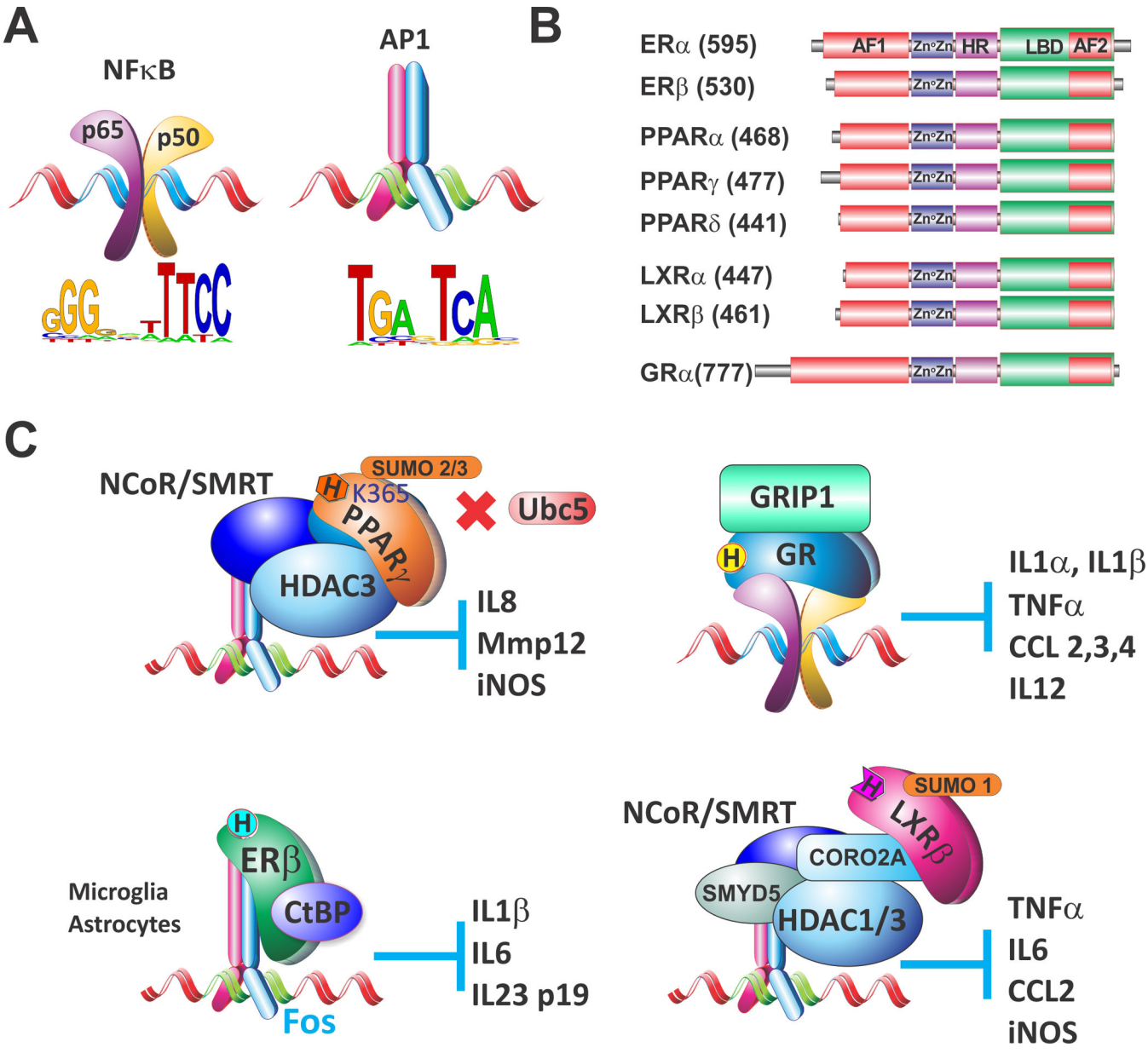

Fig. 1.
Nuclear receptor ‘transrepression’ complexes. Detailed descriptions appear in the text