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Nuclear receptors and inflammation control: molecular mechanisms and pathophysiological relevance

Wendy Huang and **Christopher K. Glass**
Department of Cellular and Molecular Medicine Department of Medicine University of California, San Diego 9500 Gilman Drive La Jolla CA, 92093-0651

Abstract

Tissue inflammation is a tightly regulated process that normally serves to recruit the immune system to sites of infection and injury and to facilitate tissue repair processes. When an inflammatory state is excessive or prolonged, local and systemic damage to host tissues can result in loss of normal physiological functions. Here, we briefly review recent studies that advance our understanding of signaling pathways involved in initiation of inflammatory responses at the level of transcription and counter-regulation of these pathways by selected members of the nuclear receptor superfamily. Studies of the intersection of nuclear receptors and inflammation have revealed mechanisms of positive and negative transcriptional control that may provide new targets for pharmacological intervention in chronic diseases such as atherosclerosis.

Inflammation Overview

Inflammation is a biological process that represents the initial response of an organism to infection and injury[1]. A disturbance that is successfully cleared results in a return to basal homeostatic set points. When conditions that induce inflammation are persistent, or resolution mechanisms fail, a state of chronic inflammation ensues that can lead to loss of normal physiological functions. The initiation and maintenance of immunity is a metabolically costly process. The interdependency of inflammatory responses and metabolic control systems are well-conserved evolutionarily. The two pathways share many signaling-mediator and responder molecules [2]. Innate immune responses typically promote a transient decrease in insulin sensitivity that has been suggested to allow the redistribution of glucose from skeletal muscle to leukocytes and other cell types with increased energy demands [3]. While malnutrition conditions impair immune functions, chronic metabolic overload and excess inflammation lead to immune imbalance and significantly contribute to chronic human diseases, including atherosclerosis, diabetes, fatty liver disease, airway inflammation, and cancers [2].

Local tissue inflammation involves four major components, including the inducers, the sensors, the responding mediators, and the effects of the mediators on the surrounding tissue (reviewed in 4). Tissue-resident macrophages, mast cells, endothelial cells, and barrier epithelial cells function to monitor tissue homeostasis, regulate tissue metabolism, and control inflammatory responses. These cells use extracellular and intracellular receptors to sense endogenous inducers of inflammation produced by stressed, damaged or

Correspondence to CKG: ckg@ucsd.edu.

malfunctioning cells and tissues, as well as exogenous inflammatory inducers that signal for infection.

Pattern-recognition receptors (PRRs) represent a class of receptors that sense both exogenous and endogenous inflammation stimulus. Four main families of PRRs have been described, including the nucleotide-binding oligomerization domain-like receptor family (NOD receptors and NALPs), Toll-like receptors (TLRs), C-type lectin-like molecules (including the mannose receptor and the β-glucan receptors), and a family of receptors with RNA-helicase and caspase-recruitment domains (RIG-1 and MDA5) [4, 5]. PRRs detect exogenous inducers by recognizing structurally conserved lipid, carbohydrate, peptide and nucleic-acid molecules that are components of microbial and viral pathogens. Endogenous inducers, such as ATP, K^+ ions, uric acid, HMGB1, and heat-shock proteins released from abnormal necrotic cell death commonly found in diabetic adipose tissue and atherosclerotic plaques, are also sensed by PPRs, including NALP3 and TLR4 (reviewed in 4). Furthermore, TLRs are also activated by fatty acids 6 and oxidized lipid-lipoproteins 7 in metabolically disturbed tissues, as well as heparin sulfates released from the extracellular matrix in response to infection and complement-coagulation cascades upon tissue injury 8.

Activation of the PRRs has diverse effects on the host, including alteration in metabolic states, protein production/secretion/processing, and induction of genes that function in innate and acquired immune responses 9. These effects are achieved by coupling receptor ligation to downstream signaling molecules that regulate the activities of several classes of signal-dependent transcription factors, including NFκB and AP-1 (reviewed in 10), illustrated in Figure 1. These transcription factors work in a combinatorial manner to recruit multiple transcriptional coregulators that remodel local nucleosomes, modify chromatin marks, and influence chromatin architecture required for initiating transcription and/or RNA polymerase elongation to rapidly alter the transcription program in the responding cells [11, 12] (Figure 2).

Many of these inducible genes encode for critical inflammatory cytokines, chemokines, major histocompatibility complex, and co-stimulatory molecules involved in innate and acquired immunity. Together, these mediator molecules help to promote vascular permeability, upregulate expression of cell-adhesion molecules on vascular endothelium, and allow plasma proteins and leukocytes to gain access to extravascular tissue at the site of insult. The recruited neutrophils have enhanced phagocytic abilities and can release reactive oxygen and nitrogen intermediates, as well as toxic contents of their granules to facilitate the killing of microorganisms [13]. After the initial insult has been removed, tissue macrophages facilitate inflammation resolution and tissue repair, at least in part, through secretion of transforming growth factor beta (TGFβ), growth factors, and anti-inflammatory lipid mediators, including lipoxins, resolvins, and protectins [14]. When the acute inflammatory response fails to eliminate the initial disturbance, the inflammatory process acquires new characteristics, including pathological tissue remodeling, fibrosis, reduced normal tissue functions, and even persistent tissue metaplasia.

Sensors of inflammatory stimuli have well-documented roles in chronic inflammatory diseases, including atherosclerosis, diabetes mellitus, arthritis, inflammatory bowel diseases, and neurodegenerative diseases in human patients and animal models [15-19]. Elevated PRRs expression and their activation by local endogenous and exogenous mediators correlate with the pathological states of obesity, diabetes, and coronary artery diseases in human [20-23]. Single nucleotide polymorphisms in genetic loci coding for various PRRs have been linked to differential risks for the development and progression of these inflammatory diseases in human population studies [24]. Animal models revealed that deletion of PRRs are protective against diet induced insulin resistance [25] and artherosclerosis progression [17, 26]. In contrary,

administration of PRR agonists enhances local and systemic inflammation, increasing disease burden [18, 27].

In addition to PRRs, local tissue metabolic stresses, such as excess saturated fatty acids and free cholesterol, are sensed by intracellular lipid chaperone proteins, and cellular organelles, including the endoplasmic reticulum (ER) and mitochondria [28] . ER stress and mitochondrial activation can lead to increased inflammatory ROS production. ROS oxidation of high-density lipoproteins and low-density lipoproteins can convert these molecules into secondary inflammatory inducers. Malfunctioning of fatty acid chaperone proteins, ER, and mitochondria have been implicated in chronic inflammatory diseases, including type 2 diabetes and cardiovascular diseases in human 2, 29. Overall, the emerging picture suggests that receptors for inflammation inducers play quantitatively important roles in the initiation and progression of chronic inflammatory diseases.

Inflammation regulators: nuclear receptors

Tissue inflammation is a tightly regulated process. Given the need to resolve inflammation following eradication of the inciting stimuli and the importance of preventing excessive inflammation and the resulting tissue dysfunction, it is not surprising that inflammation is subject to counter-regulation at multiple levels. Signaling molecules downstream of TLR, Trif/MyD88, IRAKs/TRAFs, and NFκB, are negatively regulated in the cytoplasm by SARM/sMyD88, CYCLD/A20/Trim30a, and BCL1/ATF3 respectively (reviewed in 30). Members of the nuclear receptor superfamily of ligand-dependent transcription factors play diverse roles in the regulation of development, homeostasis and immune responses by positively and negatively regulating gene expressions. Many are found to crosstalk with the inflammatory signaling pathways and regulate the innate and adaptive immune system, contributing to inflammatory diseases in vivo 31, 32. We highlight below the roles of the ligand-binding glucocorticoid receptor (GR), peroxisome proliferator-activated receptors (PPARs), liver x receptors (LXR), and the orphan receptor, Nurr-1, in the physiology and pathology of inflammation and some of the recent advances in our understanding of the molecular mechanisms underlying their anti-inflammatory functions (illustrated in Figure 3). Several other members of the nuclear receptor family also contributed significantly to inflammatory processes, their roles in inflammatory diseases and the underlying mechanisms are briefly summarized in Table 1.

Glucocorticoid Receptor

GR is prototypic of a subset of the ligand-dependent nuclear receptors that integrate host immune responses with physiological circuits that are required for maintenance of necessary organ functions. Glucocorticoids have potent anti-inflammatory effects and have been used clinically to treat inflammatory diseases since mid 1900s (reviewed in 33). Similarly, animal studies have supported its protective role against cholesterol induced atherosclerosis 34. The ability of GR to repress inflammatory responses is thought to result, at least in part, from its ability to interfere with the activities of other signal-dependent transcription factors, including those of NF-κB and activator protein-1 (AP-1) 35, by direct interactions with NF-κB components 36, induction of negative regulators that target signaling molecules involved in activating NF-κB and AP-1, including IL-10, GILZ, MKP-1, and IκBα 37, 38, disruption of activator/coactivator complexes [35], blockage of transcriptional elongation [39], and/or alteration of the epigenetic states of chromatins on target gene promoters through MSK1 and GRIP-1 [40-42].

PPARs

PPARs play important roles in regulating metabolism, cell differentiation, and tissue inflammation that contributes to metabolic disorders and cardiovascular diseases [43]. Two classes of clinical drugs for increasing insulin sensitivity in type II diabetes and lowering circulating fatty acids and triglycerides, thiazolidinediones (TZDs) and fibrates, target PPARγ and PPARα respectively. In animal models, deletion of PPARγ from macrophages results in insulin resistance in lean animals and a loss of the full antidiabetic effects of synthetic PPARγ agonists in obese and insulin resistant mice [32]. These findings are consistent with important functions of PPARγ in macrophages in controlling the production of pro-inflammatory mediators that help promote the insulin-resistant state. Deletion of PPARα from macrophages results in elevation of NFκB expression and increased atherosclerotic lesion formation 44. Similarly, PPARδ has been suggested to negatively regulate inflammatory responses implicated in chemical induced colitis, experimental autoimmune encephalomyelitis, and atherosclerosis 45.

Multiple mechanisms have been described to account for the anti-inflammatory action of PPARγ. In endothelial cells and vascular smooth muscle cells, activation of PPARγ inhibits the phosphorylation of NFκB, decreasing its transcriptional activities [46, 47]. In the adaptive immune system, PPARγ activation decreases the capacity of dendritic cells to prime naïve T lymphocytes and its ability to interact with critical transcription factor, NFAT, reduces the production of pro-inflammatory molecules in T lymphocytes 48, 49. In cells of the innate immune system, PPARγ activation promotes expression of anti-inflammatory mediators, including IL-10 and LXR, and contributes to the phenotype of alternatively activated macrophages that exert suppressive effects on inflammation 50. In classically activated macrophages, PPARγ inhibits the transcription of genes coding for pro-inflammatory molecules, including MCP-1, NOS2, IL-1β, IL-12, and MMP9. The molecular mechanism underlying the repression of these inflammatory genes has been recently identified. In macrophages, many of the inflammatory responsive genes are kept at a “repressed but poised state” by the Nuclear Receptor Corepressor (NCoR/SMRT) checkpoint, (reviewed in 9), summarized in Figure 2. The dismissal of these corepressor complexes from inflammatory response genes is a prerequisite for their transcriptional activation by PRRs [51-53]. Ligand activation of PPARγ induces an allosteric change that enables PIAS1-dependent SUMOylation of PPARγ by SUMO1 [54]. SUMOylated PPARγ binds to NCoR complexes on PPR-inducible gene promoters and prevents the signal-dependent turnover of NCoR. As a consequence, NCoR complexes continue to exert repression functions, resulting in attenuated transcription activation and dampened subsequent inflammatory responses [54].

Similar to PPARγ, PPARα activation also decreases NFκB and AP-1 activities in liver and endothelial cells [55]. Three major mechanisms have been described for the anti-inflammatory actions of PPARβ/δ, including the induction of anti-inflammatory co-repressor BCL6 protein, inhibition of NFκB, and induction of anti-inflammatory mediators, such as TGFβ and RSG4 and RSG5 [45].

LXRs

LXRs are sensors of cholesterol metabolites in vivo [56]. In animal models, administration of synthetic LXR ligands can reduce atherosclerosis, while deficiencies in LXRs result in disturbed cholesterol homeostasis, promoting exaggerated inflammatory responses and accelerated diseases pathology [31, 57]. LXRs play a role in regulating immunologic synapse formation in dendritic cells and have anti-proliferative effects on T cells [58, 59]. In murine macrophages, ligand binding of LXRs promotes SUMOylation by SUMO2/3, using HDAC4 as the SUMO E3 ligase [60]. Similar to PPARγ, SUMOylated LXRs exert transcription repression activities by directing their interaction with corepressor complexes, NCoR and

SMRT, to inhibit a set of inflammatory genes in macrophages and other cell types [54, 60-62]. Studies of primary macrophages derived from genetic knockout mice indicate that the NCoR/SMRT corepressors are required for nearly all of the transrepression functions of LXRs in macrophages [52].

NR4A Family

Three members of the NR4A family, Nurr77, Nor1, and Nurr1, have been found to play important roles in regulating inflammatory diseases. These receptors are induced by atherogenic stimuli in macrophages and smooth muscle cells and are found in atherosclerotic plaques (reviewed in 63). Overexpression of these receptors decreases inflammatory cytokine and scavenger receptor expression, lowering LDL accumulation in macrophages and formation of foam cells 64. Nurr77 also inhibits smooth muscle cell proliferation and lowers inflammatory gene expression in smooth muscle cells, macrophages and endothelial cells 64, 65. In contrast, Nor1 induces VCAM-1 and ICAM-1 expression in endothelial cells, promote monocytes adhesion, and its deficiency decreases neointima formation in response to vascular injury[66]. Molecular mechanisms accounting for these divergent effects have not been established. Mutations in *Nurr1* are linked to familial Parkinson's disease, and this association has been suggested to be due, at least in part, to the diminished negative regulation of inflammatory responses by Nurr1 in microglia and astrocytes resulting in neurotoxicity in the brain [67]. Upon TLR activation, PIAS4 conjugates Nurr1 to SUMO2/3 [67]. SUMOylated Nurr1 and its associated CoREST corepressor complex interact with phosphorylated NFκB and dislodge it from gene promoters, attenuating the expression of NFκB-dependent inflammatory genes to help protect against Parkinson's disease in animal model [67].

Perspectives

Investigation of the intersection between an as yet small subset of nuclear receptors and inflammation pathways has led to new insights into basic transcriptional control mechanisms that are required for immunity and homeostasis. Systematic expression profiling experiments have documented the expression of 28 members of the nuclear receptor family in primary mouse macrophages, many of which exhibit dramatic changes in response to inflammatory stimuli [68]. Corresponding studies in other immune cells have not as yet been performed, but are likely to yield similarly complex patterns of nuclear receptor expression. In addition, the biological roles and mechanisms of action of most members of the nuclear receptor family in regulating inflammation and immunity remain poorly understood. Even for the most intensively studied receptors, such as GR and PPARγ, many questions remain regarding the relative importance of positive and negative regulation of gene expression. Mechanistically, how are these receptors recruited to their respective gene target promoters to exert repression in ‘trans’ How are concentrations of endogenous ligands controlled at the local level in normal and disease states? Additional questions include whether post-translational modifications and corepressor/coactivator interactions modulate nuclear receptor functions and whether chronic inflammatory signals inactivate their protective effects. The respective contribution of each of the above molecular mechanism in inflammatory conditions in vivo remains to be elucidated in future studies.

Recent technological advances in performing genetic association studies, genome-wide localization studies (ChIP-seq), and transcriptome sequencing (GRO-Seq, RNA-Seq) will likely catalyze rapid progress in our understanding of how nuclear receptors re-engineer nuclear chromatin architectures, modulate expression of inflammatory genes and non-coding small RNAs with immuno-regulatory roles, and contribute to human inflammation-related diseases. Of note, many of the previously described molecular mechanisms of nuclear receptor function are studied in particular cell types, including macrophages, microglia, and

endothelial cells. This begs the question of the generality of the described mechanisms. It is tempting to speculate that tissue-specific mechanisms should exist in vivo to facilitate different immunological and metabolic needs of different tissues in the context of an inflammatory response. It will therefore be of interest to use tissue-specific knockout animals in physiological and pathological contexts to evaluate the potential contribution of specific nuclear receptors in particular cell types in chronic inflammatory diseases.

A challenge of therapeutic interventions aimed at reducing inflammation is to tune down inflammatory programs that promote chronic disease processes without disarming the ability of the immune system to respond to infection or altering the homeostatic metabolic states of the organism. Although current therapeutic approaches that target members of the nuclear receptor super family have potent anti-inflammatory effects, many are associated with adverse side effects. For instance, glucocoticoids alter glucose homeostasis and inhibit the bone-forming activities of osteoclasts, among other adverse effects, resulting in hyperglycemia and osteoporosis that limit their use in treating chronic conditions in human patients. Long term exposure to LXR ligands could potentiate inflammatory responses by upregulating TLR4 expression and increase in triglyceride synthesis that could contribute to hepatic steatosis [69]. Therapeutic approaches that prevent activation of sensors of inflammatory signals, such as biologicals that specifically target inflammatory cytokines such as TNF and IL-1 [70] remain costly with delivery constraints and pitfalls of disease recurrences when treatment ceases. Together, the needs for novel therapeutics for treating chronic inflammatory conditions remain substantial.

One potential level of intervention is at the level of corepressor function, as illustrated by the anti-inflammatory activities of the nuclear receptors, PPARγ and LXRs. As discussed earlier, inflammation promoting genes are tightly regulated under basal conditions by the NCoR corepressor complexes that are recruited to broad sets of inflammatory response genes by members of the AP-1 transcription factor family member, c-Jun [51, 52, 71]. NCoR/SMRT clearance from inflammatory response genes is a prerequisite for their transcription activation in response to external inflammatory stimuli [51-53]. Recent studies identified several kinases, IKKα, JNK, IKKε and CaMKIIγ, downstream of cell surface receptor signaling that promote phosphorylation of components of the basal corepressor complex to facilitate corepressor turnover and activation of a subset of their respective target genes [72-74]. These kinases represent a potentially important class of pharmacological targets as their inhibitors will likely mimic nuclear receptor anti-inflammatory effects by blocking corepressor turnover and inflammatory gene activation, yet bypassing the clinically significant side effects associated with therapies that target the nuclear receptors systemically. Recently, small-molecule inhibitor for JNK has been shown to be effective in treating arthritis in animal models [70]. Better understanding of the process of inflammation and its natural regulatory pathways along with recent development of kinome-wide screens and tissue-specific drug delivery strategies will facilitate the identification of new therapeutic strategies for treating chronic inflammatory diseases in humans.

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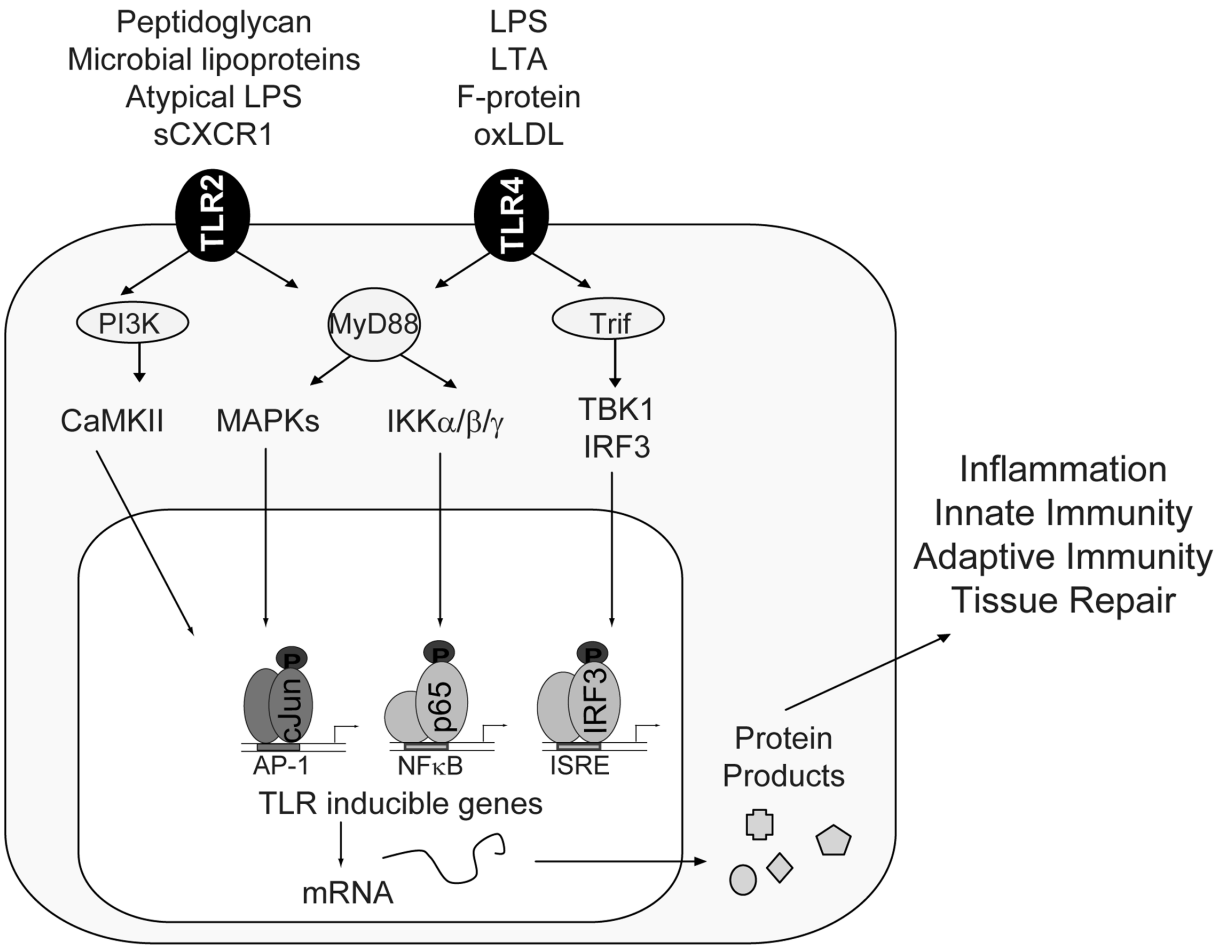

Figure 1. TLR signaling

Together with its accessory proteins, TLRs recognizes both exogenous and endogenous inflammatory inducers, including lipopolysaccharides (LPS) found in all Gram-negative bacteria, LTA derived from Myocobacterium tuberculosis, fusion (F) protein of respiratory syncytial virus, peptidoglycan from Gram-positive bacteria, bacterial lipoproteins, atypic LPS produced by *Leptospira interrogans* and *Porphyromonas gingivitis*, as well as soluble CXCR1 from inflammatory sites in the lung. All TLRs, except TLR3, signal through the adapter molecule, MyD88, to activate the MAP Kinase cascades and the IκB kinase (IKK) complex. Activated IKKs rapidly phosphorylate IκBα to promote its ubiquitination and degradation, releasing the activated NF-κB into the nucleus. Activation of TLR3 or TLR4 allows a different adaptor molecule, TRIF, to associate with TBK1 and induce the phosphorylation and nuclear translocation of IRF3. TLR1, 2, and 6 have a conserved phosphatidyl inositol 3 kinase (PI3K) binding motif not found in other TLRs. Activation of PI3K and consequent calcium mobilization is particularly important for TLR2 signaling.

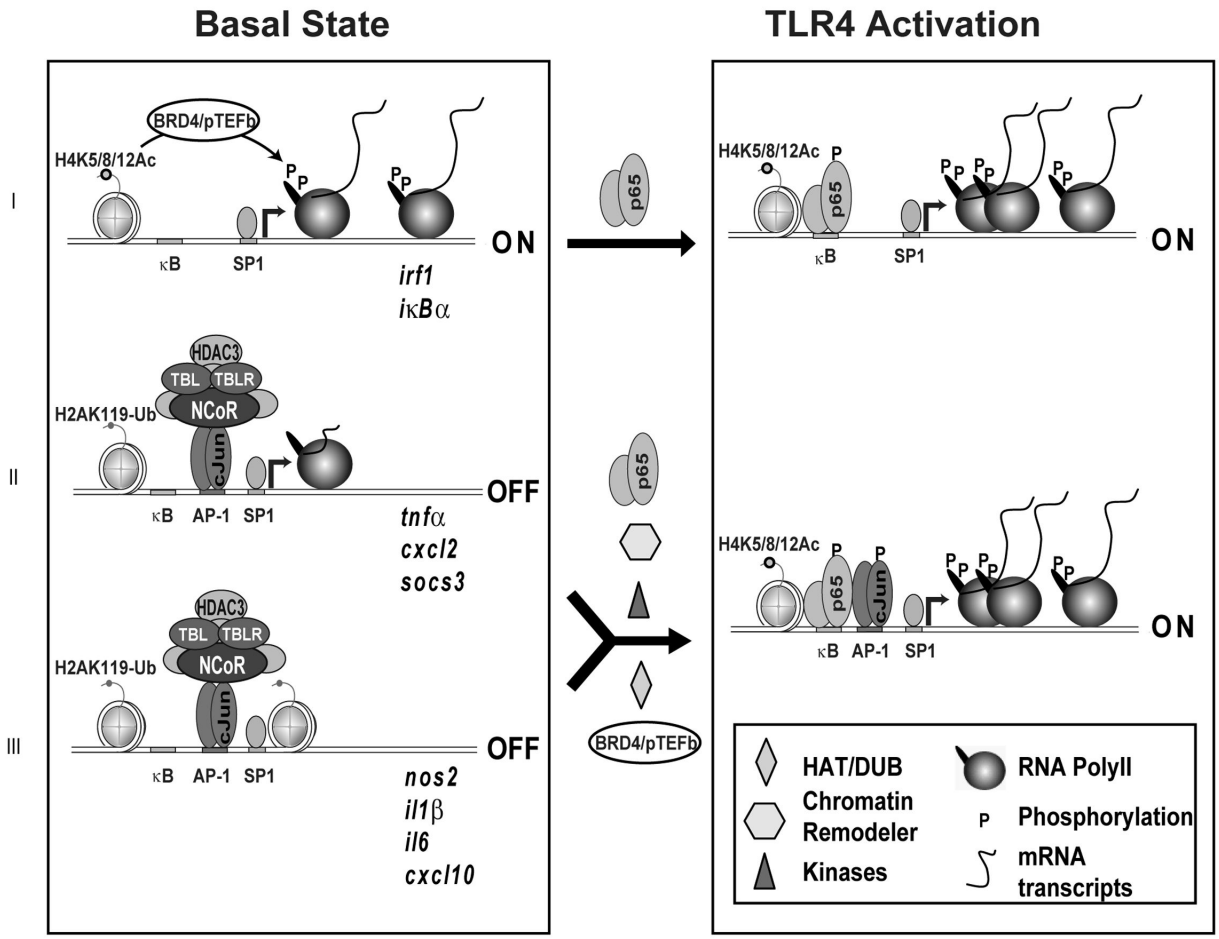

Figure 2. Three classes of inflammation responsive genes

Class I inducible genes are basally expressed, and are further activated upon inflammatory signal. Class II inducible genes are "poised" with RNA Polymerase II positioned on the promoter in a paused state. Class III inducible genes are not decorated by RNA Polymerase II and are kept at a repressed state basally. Activation of Class II and Class III inflammatory response genes require removal of the basal corepressor complexes (NCoR), recruitment of transcription activators (p65) and coactivators (various kinases for phosphorylating transcription factors and RNA Polymerase II), as well as additional histone modifiers (Histone acetylase, HAT, and deubiquitin enzymes, DUB) and chromatin remodeling machinery.

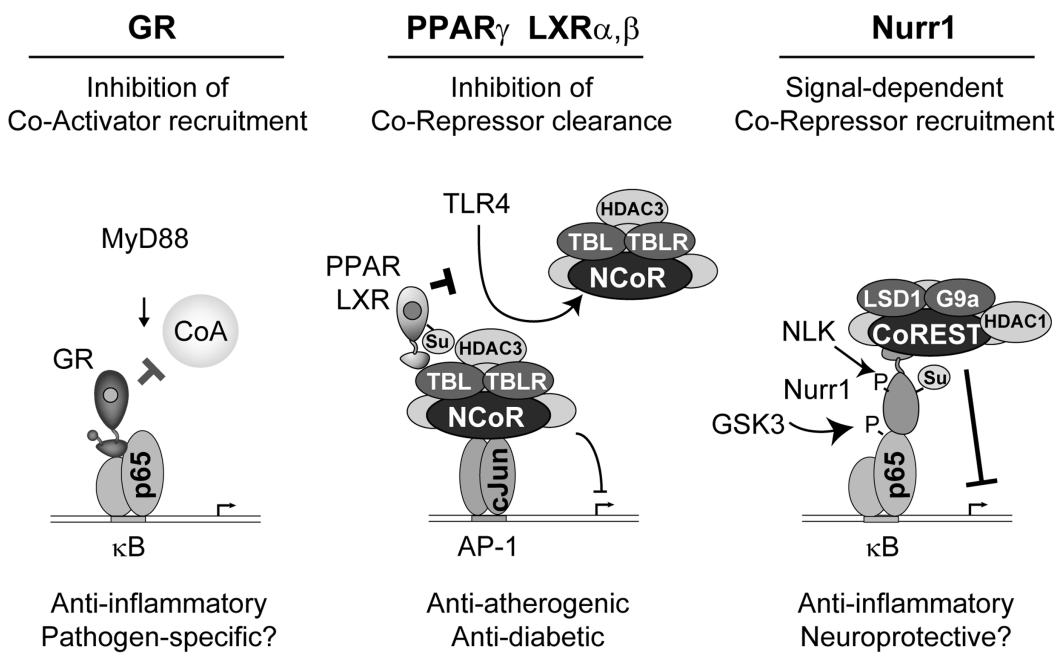

Figure 3. Nuclear receptor transrepression mechanisms

Nuclear receptors can interfere with numerous mechanisms required for signal-dependent gene activation so as to suppress inflammatory responses. Representative examples of these mechanisms are illustrated for Glucocorticoid Receptor (GR), PPARγ/LXRs and Nurr1. GR represses inflammatory responses by blocking coactivator (CoA) recruitment to inflammatory response genes. Upon ligand binding, PPARγ and Liver X Receptors (LXRs) are SUMOylated and inhibit induction of inflammatory response genes by preventing signal-dependent clearance of NCoR co-repressor complexes that maintain basal repression. SUMOylated Nurr-1 represses inflammatory gene induction by recruiting the CoREST corepressor complex to NFκB target promoters.

Table 1

Nuclear Receptor	Known Ligand	Disease Association	Known Molecular Mechanisms
Estrogen Receptors (NR3A1-2)	17b-estradiol	Vascular injury [75], chemical induced intestinal inflammation [76]	Decrease NFκB activation and increase TGFβ signaling [76] to modulate inflammation, growth factor expression, and oxidative stress [77].
Vitamin D Receptor (NR1I1)	Vitamin D metabolite: 1,25-dihydroxyvitamin D3	SLE [78 79, 80], type 1 diabetes [81 82], rheumatoid arthritis [83], inflammatory bowel disease [84], EAE [85]	Inhibits T cell proliferation and cytotoxicity, induces differentiation and expansion of regulator T cells, decreases the expression of chemokines and subsequent monocyte infilatration [85].
Retinoic acid receptors (NR1B1-3)	Vitamin A: metabolite – all-trans-retinoic acid and 9-cis-retinoic acid	Asthma [86], psoriasis, acne, photoaging and cancer [87]	Enhance cytotoxity and T cell proliferation, low concentration allows for Th17 cell differentiation, while high concentration favors the induction of regulator T cells [88].
LRH-1 (NR5A2)	Unknown	Inflammatory bowel disease [89], lipid absorption [90]	SUMO and NCoR dependent anti-inflammatory mechanism [62].