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Review

Molecular Interaction between the Glucocorticoid Receptor and MAPK Signaling Pathway: A novel link in Modulating the Anti-inflammatory Role of Glucocorticoids

Banteiskhem Kharwanlang and Ramesh Sharma*
Department of Biochemistry, North-Eastern Hill University, Shillong 793 022, India

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Glucocorticoids (GCs) have a broad spectrum of life-sustaining functions and play an important role in health and diseases. At pharmacologic doses, GCs are potent immunosuppressive and anti-inflammatory agents. Inflammation and its related diseases present a huge ever increasing burden on the health and disease management. A plausible link of inflammation with aging, cardiovascular diseases and cancer makes matter even worst and calls for a better understanding to resolve the mechanisms associated with the cause and cure of inflammation. Understanding the physiological and molecular interlinks is an utmost importance in designing novel therapeutic strategies in combating inflammation. Advancement in research related to the mitogen-activated protein kinase (MAPK) signaling pathway and its regulation on inflammation has open up new and promising avenues in targeting inflammation as well as understanding the anti-inflammatory property of GCs. Molecular interaction between the ligand-activated glucocorticoid receptor (GR) and the MAPK signaling at different junctions inhibit the latter and thus may account for the anti-inflammatory role of GCs. Therapeutic application of GCs in combination with the recently added class of GR modulators having greater transrepresssion over transactivation (dissociative property) might overcome the clinical side effects associated with GCs.

Keywords: Glucocorticoids, Glucocorticoid receptor, MAPK signaling, Molecular interaction, Anti-inflammatory.

Introduction

Glucocorticoids (GCs) are synthesized in the adrenal cortex and act on various tissues. They influence wide spectrum of biological activities like intermediary metabolism[1], immune/inflammatory reaction[2], stress[3], central nervous system[4] and cardiovascular system[5]. GCs are regularly used in the treatment of various diseases associated with inflammation such as asthma, chronic obstructive pulmonary disease and arthritis. Recently, inflammation is also found to be associated with several physiological impairments and pathological conditions associated with old age. Many diseases associated with old age are mediated by the inability of the body to control inflammation and homeostasis. Inflammation during aging can be reduced by following a healthy lifestyle like maintaining a restriction on diet[6,7].

Findings in our laboratory have shown an increased level of glucocorticoid receptor (GR) in aged mice during dietary restriction. Higher expression of GR might result in greater efficiency of GCs in maintaining an anti-inflammatory condition and homeostasis, giving rise to a healthy longevity[8,9]. Inflammation is a healing process sets in with the aim of restoring and healing damaged tissues, as well as clearing off microbial infection. However, overshooting of inflammation can be harmful, leading to a cohort of pathological conditions characterized by chronic inflammation[10]. Hence, combating the cause and finding a cure on chronic inflammation is the key in treatment of such diseases.

GCs execute their anti-inflammatory action through the liganded-GR, in which the latter interact with various inflammatory signaling pathways mediating inflammation like the mitogen-activated protein kinase

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*Author for correspondence
Tel: +91-364-2722113; Fax: +91-364-2550108
E-mail: sharamesh@gmail.com

Abbreviations: AFs, activation functions; DBD, DNA binding domain; ERKs, extracellular signal-regulated kinases; GC, glucocorticoid; GR, glucocorticoid receptor; GREs, glucocorticoid response elements; HR, hormone-glucocorticoid receptor complex; GTFs, general transcription factors; JNK, c-Jun N-terminal kinase; MKK7, mitogen activated protein kinase kinase 7; MCP-1, monocyte chemoattractant protein-1; MAPK, mitogen-activated protein kinase; MAPKK, MAPK kinase; MAPKKK, MAPK kinase kinase; MKP-1, MAPK phosphatase-1; MSK1, mitogen and stress-activated protein kinase 1; SAPKs; stress-activated protein kinases.

(MAPK), resulting in their inhibition[11-13]. Thus, understanding the relationship of GC signaling pathway with MAPK pathway at the level of molecular interaction between GR and various components of MAPK cascade may be beneficial in designing modulators with dissociative property capable of enhancing GR inhibition on MAPK, while reducing the transactivation associated with side effects.

In the current review, we have attempted to present an overview on the molecular interaction between GR and MAPK signaling, in order to find out a link that can modulate GCs activity and reduce side effects while using them in health and diseases.

GC action mechanism

GCs exert their action through a cascade of regulatory events initiated by binding to their intracellular receptor called glucocorticoid receptor (GR) (Fig. 1). Multiple isoforms of GR have been identified[14], of which GRα is functionally active, whereas GRβ is transcriptionally inactive. A new variant GRγ has also been identified[15]. The GR is bound to a protein complex that includes two subunits of the heat shock protein (hsp90) acting as molecular chaperones preventing the nuclear localization of the unliganded GR[16]. Other associated proteins include a 59 kDa immunophilin protein[17] and various other modulatory proteins[18]. Hsp90 is necessary for ligand binding to GR and may facilitate the proper folding of the GR in an optimal DNA-binding conformation[19]. Once GCs bind to unactivated GR, hsp90 dissociates permitting the nuclear localization of the activated hormone-receptor complex (HR-complex) and it's binding to DNA or interaction with co-activator complexes[18].

Recently, GR translocation to the mitochondria has also been reported, in addition to its distinctive nuclear translocation[20]. Activated GR binds to the major groove of DNA at consensus sequence sites termed glucocorticoid responsive element (GRE) in upstream[21] and/or downstream promoter regions of GC-responsive genes[22]. This interaction changes the rate of transcription, resulting in either induction[23] or repression of GC-responsive genes[24]. The GRE is a 15 bps sequence GGTACAnnnTGTTCT, although for repression, the negative GRE (nGRE) has a more variable sequence (ATYACnnnTnATCn)[18].

The GR contains a N-terminal domain carrying a transactivation region[25], a central Zn^{2+}-finger DNA binding domain (DBD) responsible for binding to

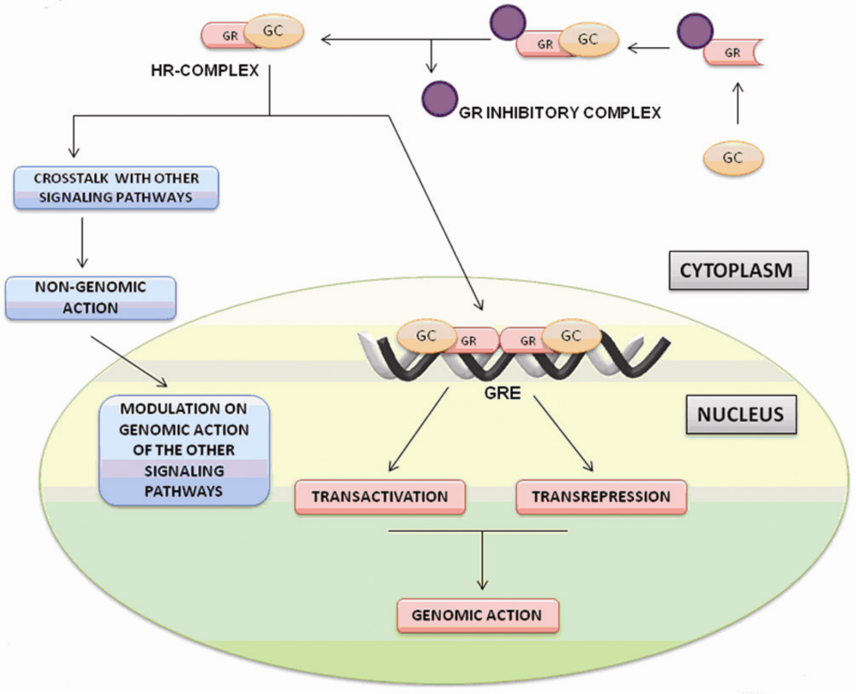

Fig. 1—Schematic illustration of the signaling pathway of gluccoorticoid action [Binding of glucocorticoid (GC) to glucocorticoid receptor (GR) leads to activation of GR complex by dissociation/removal of GR inhibitory complex. The hormone-glucocorticoid receptor (HR) complex monomers perform non-genomic action by interacting with other signaling pathways, thereby modulating their genomic action or after nuclear translocation bind to specific DNA sequences termed glucocorticoid response elements (GREs) as dimers performing genomic action, leading to either transactivation or transrepression]

GRE and nuclear export, and a C-terminal ligand binding domain containing ligand-dependent transcriptional activation function (AF-2) domain and responsible for receptor dimerization[26]. The DBD consists of two highly conserved zinc fingers, which are crucial for the binding to the GRE. In addition, the second DBD zinc finger mediates receptor dimerization[27] and the first zinc-finger of DBD binds NF-κB and AP-1[28], suggesting that GCs modulate either the binding or activation by these transcription factors, thereby modifying the expression of inflammatory genes[29] via non-genomic effect.

It has been suggested that transcriptional activators such as GR use their transcriptional activation domain as surface to recruit chromatin remodeling factors and to interact with general transcription factors (GTFs) or adaptor proteins often termed coactivators that serve to link enhancer-bound transcription factors to the GTFs, thereby inducing transcription[30]. Several lines of evidence support this model of transcriptional modulation by GR. At least two regions of GR possess intrinsic transcriptional activation functions (AFs). AF-2 which maps to the C-terminus is GCs dependent, with ligand binding promoting the formation of a surface that permits protein-protein contacts between AF-2 and additional transcriptional regulator factors. On the contrary, AF-1 located at the GR N-terminus is GCs independent and constitutive and cofactors that associate with GR-AF-1 remain largely unidentified[31,32]. Thus, GR's stimulatory or inhibitory influences on gene expression are determined by the cell context, nature of the response element, composition of interacting sequence-specific transcription factors[33] and the differential transcription output after the transcription machinery assembly[34].

MAPK signaling pathway

Multicellular organisms from yeast to mammals have a well-characterized and highly conserved family of MAPKs that control a vast array of physiological processes, including gene induction, cell survival/apoptosis, proliferation and differentiation as well as cellular stress and inflammatory responses. There are three major classes of MAPKs in mammals- extracellular signal-regulated kinases (ERKs) and two stress-activated protein kinases (SAPKs) families i.e. c-Jun N-terminal kinase (JNK) and p38, which are a series of serine/threonine protein kinases regulated by a relay of phosphorylating events[35] that phosphorylate other target proteins, a bulk of which are transcription factors. A fourth cascade called the BMK1 (ERK5) is also categorized under MAPK[36].

Activation of MAPKs depends on the upstream induction of MAPKs kinase (MAPKK) and MAPKs kinase kinase (MAPKKK). MAPK enzymes are also negatively regulated by a feedback mechanism comprising of MAPK phosphatases, thereby maintaining inflammation at physiological level[35]. MAPKs are susceptible to regulatory inputs at multiple levels via several mechanisms like expression pattern, modification of MAPK responses via activators, inhibitors, crosstalk among MAPK and other signaling pathways[37]. Activation of MAPK leads to the production of various inflammatory cytokines including TNF-α, IL-1, IL-6 and IL-12[38] which are the mediators in inflammation. NF-kB, a trancription factor regulating the expression of inflammatory genes serves as a target of MAPKs (p38, ERK1/2 and JNK)[39]. JNK was originally identified as the major kinase responsible for the phosphorylation of c-Jun, leading to increased activity of AP-1[37], another transcription factor controlling the expression of inflammatory molecules[40]. Thus, elucidation of MAPK signaling will enhance our understanding on molecular basis of inflammatory diseases.

GC's anti-inflammatory action

GCs are widely used for the suppression of inflammation in chronic inflammatory diseases such as asthma, rheumatoid arthritis, inflammatory bowel disease and autoimmune diseases. Their anti-inflammatory property is mediated via a cohort of mechanisms. They may increase the transcription of genes coding for the anti-inflammatory proteins like lipocortin-1, IL-10, IL-1 receptor antagonist and neutral endopeptidase, but this is unlikely to account for all of the widespread anti-inflammatory actions of GCs. They also inactivate the expression of inflammatory molecules. One possible way is by interacting with GREs, but these binding sites are absent from promoter regions of inflammatory genes[41]. However, as mentioned before, GCs may modulate the binding or activation of NF-kB and AP-1, thereby modifying the expression of inflammatory genes via molecular binding between GR and these transcription factors.

In addition to the inhibitory property of GCs on gene transcription, their ability to interfere with post-transcriptional gene regulation may also result in quick anti-inflammatory responses. An increasing number of inflammatory genes which are altered by turnover and/or translation of their mRNA include IL-1, IL-6, IL-8 and GM-CSF[42]. The ability of GCs to inhibit the inflammatory genes by modulating their transcription factors, gene transcription or post-transcriptional regulation exhibits a plausible molecular link between the GR and the components of MAPK signaling cascade.

Anti-inflammatory property of GCs mediated by molecular interaction between GR and MAPK signaling pathway

Components of MAPK cascade are increasingly recognized as “general switches”, whose modulation by other signaling pathways can have far reaching effects on inflammatory gene expression[42]. Apart from NF-kB and AP-1, molecular crosstalk between the GR and components of MAPK like JNK, Raf and MSK1 (Fig. 2) provides better explanation for role of GCs in mediating anti-inflammatory property.

GR interaction with Raf

GCs have been reported to have an inhibitory effect on the Raf-1-Ras signaling pathway[49]. GR protein-protein interaction with Raf-1-Ras may provide a mechanistic explanation on GCs anti-inflammatory property. A specific immunoaffinity chromatography purification of GR from liver cytosol of adrenalectomized rats has been used to identify hitherto unknown cytosolic proteins interacting with GR. Raf-1, a downstream effector of Ras and a protein 14-3-3 have been detected as GR co-purifying proteins. Liganded/activated GR shows a remarkably strong interaction with Raf-1 and 14-3-3, which can withstand even an extensive wash by 2.4 M salt. However, 14-3-3 has also been found to co-purify with GR in a non-liganded/non-activated state. As of now, it is not clear whether GR interaction with Raf-1 is mediated by 14-3-3 or GR directly binds to Raf-1[11]. However, this interaction could be one of the mechanisms of GCs inhibition on the MAPK signaling pathway.

GR interaction with MSK1

Another mechanistic explanation on GCs anti-inflammatory activity is the interaction between GR and MSK1. Mitogen and stress-activated protein kinases (MSKs) are serine/threonine kinases that are activated downstream of the ERK and p38 MAPK[43] to regulate gene transcription at multiple levels. Transcription factor like NF-kB and c-AMP response

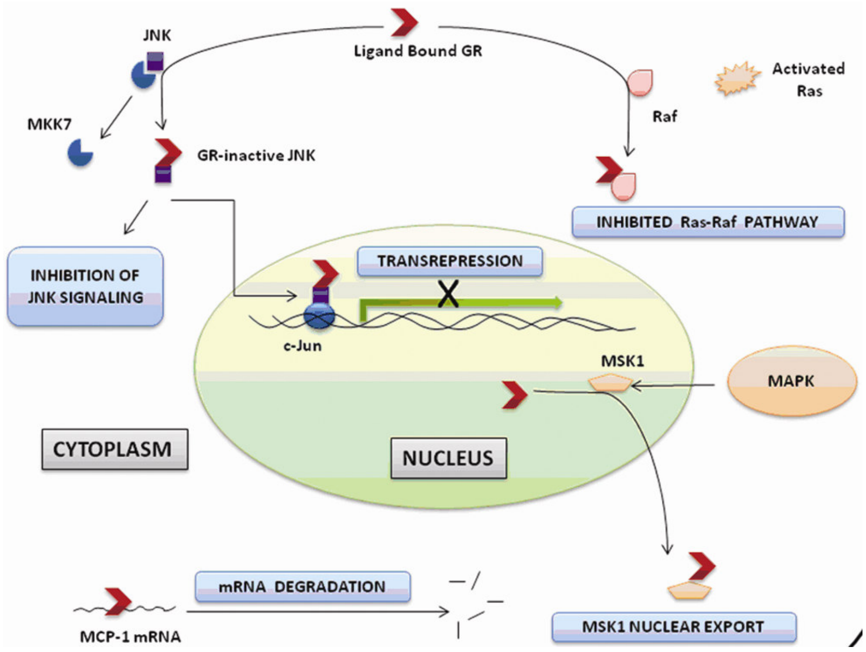

Fig. 2—Schematic representation of the protein-protein interaction between GR and various components of the MAPK signaling pathway [Ligand bound GR on one hand inhibits JNK signaling by protein-protein interaction or by transrepression. On the other hand, GR interaction inhibits Ras-Raf pathway. GR also induces MSK1 nuclear export, thereby inhibiting the latter’s action. Post-transcriptional degradation of MCP-1 mRNA, an inflammatory response mediator is achieved by direct interaction of GR. MKK7, mitogen activated protein kinase kinase 7; MSK 1, mitogen- and stress-activated protein kinase 1; MCP-1, monocyte chemoattractant protein 1]

element binding protein (CREB) are targets of MSKs. MSKs also regulate histones activity by phosphorylation, thereby inducing chromatin relaxation and recruitment of additional regulatory proteins[44].

GCs anti-inflammatory actions have also been linked to MSK1 nuclear-cytoplasmic ratio. Dexamethasone instigates the export of MSK1 from the nucleus. However, GR antagonist RU486 blocks the MSK1 nuclear translocation, which is also exhibited when gene knockdown on GR protein is implemented. These studies clearly suggest that MSK1 translocation from the nucleus to cytoplasm is GR-dependent[12]. The shift in nuclear-cytosolic ratio of MSK1 could inhibit the activity of NF-kB, thereby transrepressing NF-kB driven gene expression as well as inducing a closed chromatin environment via reduced H3 phosphorylation, as a consequence producing a reduced inflammed condition.

GR interaction with JNK

An alternative explanation for inhibitory effect of GCs on MAPK is the GR-mediated interference with the signaling pathway feeding into the AP-1 driven gene expression. MAPKs contribute to AP-1 induction in response to a series of extracellular stimuli[45]. GCs transrepresses AP-1 activity by inhibiting JNK. GR-AP-1 complex formation prevents AP-1 binding to DNA and also induces MAPK phosphatase-1(MKP-1), resulting in GC-induced inhibition of JNK[13].

Bruna et al[13] reported a new mechanism whereby GCs are able to disassemble JNK association with MAPK kinase 7 (MKK7) and promoting JNK-GR association. A JNK docking site within GR is found to be responsible for mediating JNK-GR interaction. This interaction results in the inhibition of JNK and activation of inactive JNK nuclear transfer. Though MKK7-JNK dissociation is accountable for AP-1 inhibition, however, loading of an inactive JNK on AP-1-bound response element may protect activation of AP-1 by keeping a JNK-deficient status and masking the AP-1 from successive activated JNK generated by subsequent MAPK activation.

GR and post-transcriptional regulation of pro-inflammatory signals

GCs inhibit the secretion of monocyte chemoattractant protein-1 (MCP-1), an inflammatory response mediator in arterial smooth muscle cells (SMCs) by markedly decreasing MCP-1 mRNA stability. MCP-1 plays an important role in attracting monocytes to the sites of inflammation and is the dominant mediator of macrophage accumulation in atherosclerotic plaques. Dhawan et al[46] reported destabilization of MCP-1 mRNA which is mediated by direct binding of GR to the mRNA. GR binding to inflammatory mRNA causing acceleration in their degradation could be a mechanistic option for rapid effect of GCs (Fig. 2). Their studies suggest that effect of dexamethasone (Dex) on MCP-1 mRNA stability is mediated by the GR. RU486, an antagonist blocks the effect of Dex on MCP-1 mRNA stability in cultured SMCs and also antibodies to the GR block the ability of cytoplasmic extracts from Dex-treated cells to rapidly degrade MCP-1 mRNA. The addition of exogenous recombinant human GR blocks the ability of extracts from Dex-treated SMC to degrade MCP-1 mRNA, suggesting that a complex of proteins is required for the degradation of mRNA. Their study have also demonstrated that the effect of Dex on MCP-1 mRNA stability is independent of the AU-rich elements or 3'-UTR, but is dependent on the presence of three stem loops at the 5' end of mRNA[46].

Future perspective of GR and its modulators in counteracting inflammation

GCs though are beneficial in the treatment of various inflammatory conditions, however, they represent a number of undesirable side effects. The identification of selective GR modulators having dissociative property i.e., separation of transactivation and transrepression properties represents an important research goal in steroid pharmacology. Such compounds are recognized to have the dissociative property. Compound A (CpdA), a plant-derived phenyl aziridine precursor, which does not fall in the steroidal class of GR-binding ligands mediates gene inhibitory effects by activating GR. However, it does not enhance expression of genes containing GRE or induce GR occupancy to such genes *in vivo.* CpdA exerts an anti-inflammatory property by down-regulating TNF-induced and NF-kB-dependent proinflammatory gene expression, such as IL-8 and IL-6. It also causes a reduction of the DNA-binding capacity of p65, thus interfering with the transactivation potential of NF-kB. CpdA is effective in downregulating acute inflammation as dexamethasone and does not cause hyperglycemic side effects as the latter[47]. It also induces a nucleoplasmic shift of MSK1[12]. CpdA transrepression of NF-kB-mediated gene expression by activating GR can thus be correlated to the nucleoplasmic shift of MSK1.

Yang et al[48] reported a series of 2,2-dimethyl-3,3-diphenyl propanamides as novel GR modulators displaying good agonist activity in GR-mediated transrepression assays and reduced agonist activity in GR-mediated transactivation assays. Compounds 17 and 30 of this series reduce transactivating property relative to steroidal agonists, whereas maintaining a good transrepression activity in (reporter) gene assays. This *in vitro* study is reflected on the *in vivo* anti-inflammatory efficacy to prednisolone by these compounds in the rat carrageenan paw edema assay and inducing little or no side effects with regard to blood glucose elevation and hepatic tyrosine aminotransferase (TAT) induction[48]. The discovery of CpdA and compounds 17 and 30 as a class of GR modulators and as anti-inflammatory agents with dissociative property might hold a great potential for therapeutic use of GCs in the future.

Recenly, Aoyagi et al[34] reported that curcumin differentially regulates the expression of two GR-dependent genes metallothioneine-2A (MT2A) and solute carrier family 19 member 2 (SLC19A2). Curcumin inhibits MT2A expression, but maintains the expression of SLC19A2 by interfering with the transcription output after transcription machinery assembly[34], indicating that it is emerging as a modulator with dissociative property.

Conclusion

Modulators that alter GR ligand binding capacity, activation, nuclear translocation and export, DNA binding, transcriptional regulation of GCs responsive genes and dissociation of transactivation from transrepression would consequently alter GCs-mediated physiological functions such as homeostasis, intermediary metabolism, anti-inflammatory, immunosupression and stress, thereby increasing the good effects of GCs and reducing the unwanted side-effects. Such modulators could in future find applications in combating diseases of old age, due to decreased efficiency of the endocrine system with age. Furthermore, these regulators that could potentiate a wanted GC effect in one tissue and reduce the unwanted effect in another tissue will be a boon to hormone therapy in health and diseases.

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References

1 Sharma R & Timiras P S (1997) Age-dependent regulation of glucocorticoid receptor in the liver of male rats. *Biochim Biophys Acta* 930, 237-243

2 Barnes P J (1996) Mechanism of action of glucocorticoids in asthma. *J Respir Crit Care Med* 154, S21-27

3 Munck A, Gurye P M & Holbrook N J (1984) Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocr Rev* 5, 25-44

4 Glezer I & Rivest S (2004) Glucocorticoids: Protector of the brain during innate immune responses. *Neuroscientist* 10, 538-552

5 Giugliano G R, Giugliano R P, Gibson C M & Kuntz R E (2003) Meta-analysis of corticosteroid treatment in acute myocardial infarction. *Am J Cardiol* 91, 1055–1059

6 Chung H Y, Cesari M, Anton S, Marzetti E, Giovannini S, Seo A Y, Carter C, Yu B P & Leeuwenburgh C (2009) Molecular inflammation: Underpinnings of aging and age-related diseases. *Ageing Res Rev* 8, 18–30

7 Sharma R (2004) Dietary restriction and its multifaceted effects. *Curr Sci* 87, 1203-1210

8 Dutta D & Sharma R (2005) Age-dependent dietary regulation of glucocorticoid receptors in the liver of mice. *Biogerontology* 5, 177-184

9 Sharma R & Dutta D (2006) Age-dependent decrease in renal glucocorticoid receptor function is reversed by dietary restriction in mice. *Ann NY Acad Sci* 1067, 129-141

10 Medzhitov R (2010) Inflammation 2010: New Adventure of an Old Flame. *Cell* 140, 771-776

11 Widén C, Zilliacus J, Gustafsson J & Wikström A (2000) Glucocorticoid receptor interaction with 14-3-3 and Raf-1, a proposed mechanism for cross-talk of two signal transduction pathways. *J Biol Chem* 275, 39296-39301

12 Beck I M E, Berghe W V, Vermeulen L, Bougarne N, Cruyssen B V, Haegeman G & De Bosscher K (2008) Altered subcellular distribution of MSK1 induced by glucocorticoids contributes to NF-kB inhibition. *EMBO J* 27, 1682–1693

13 Bruna A, Nicolás M, Munöz A, Kyriakis J M & Caelles C (2003) Glucocorticoid receptor-JNK interaction mediates inhibition of the JNK pathway by glucocorticoids. *EMBO J* 22, 6035-6044

14 Lu N Z & Cidlowski J A (2004) The origin and functions of multiple human glucocorticoid receptor isoforms. *Ann NY Acad Sci* 1024, 102-123

15 Rivers C, Levy A, Hancock J, Lightman S & Norman M (1994) Insertion of an amino acid in the DNA-binding domain of the glucocorticoid receptor as a result of alteranative splicing. *J Clin Endocr Metab* 84, 4283-4286

16 Bresnick E H, Dalman F C, Sanchez E R & Pratt W B (1989) Evidence that the 90-kDa heat shock protein is necessary for the steroid binding conformation of the L cell glucocorticosteroid receptor. *J Biol Chem* 264, 4992-4997

17 Tai P K, Albers M W, Chang H, Faber L E & Schreiber S L (1992) Association of a 59-kilodalton immunophilin with the glucocorticosteroid receptor complex. *Science* 256, 1315-1318

18 Truss M & Beato M (1993) Steroid hormone receptor: interaction with deoxyribonucleic acid and transcription factors. *Endocr Rev* 14, 459-479

19 Picard D, Khursheed B, Garabedian M J, Fortin M G, Lindquist S & Yamamoto K R (1990) Reduced levels of hsp 90 compromise steroid receptor action *in vivo*. *Nature* 348, 166-168

20 Scheller K, Seibel P & Sekeris C E (2003) Glucocorticoid and thyroid hormone receptors in mitochondria of animal cells. *Int Rev Cyto* 222, 1-61

21 Winter L A, Stewart M J, Shean M L, Dong Y, Poellinger L, Okret S, Gustafsson J & Duester G (1990) A hormone response element upstream from the human alcohol dehydrogenase gene *ADH2* consists of three tandem glucocorticoid receptor binding sites. *Genes* 91, 233-240

22 Hao H, Rhodes R, Ingbar D H & Wendt C H (2003) Dexamethasone responsive element in the rat Na, K-ATPase $ß_1$ gene coding region. *Biochim Biophys Acta* 1630, 55-63

23 Jantzen H M, Strahle U, Gloss B, Stewart F, Schmid W, Boshart M, Miksicek R & Schutz G (1987) Cooperativity of glucocorticoid response elements located far upstream of the tyrosine aminotransferase gene. *Cell* 49, 29-38

24 Meyer T, Gustafsson J A & Carlstedt Duke J (1997) Glucocorticoid-dependent transcriptional repression of the osteocalcin gene by competitive binding at the TATA box. *DNA Cell Biol* 16, 919-927

25 Ford J, McEwan I J, Wright A P H & Gustafsson J A (1997) Involvement of the transcription factor IID protein complex in gene activation by the N-terminal transactivation domain of the glucocorticoid receptor *in vitro*. *Mol Endocrinol* 11, 1467-1475

26 Black B E, Holaska J M, Rastinejad F & Paschal B M (2001) DNA binding domains in diverse nuclear receptors function as nuclear export signals. *Curr Biol* 11, 1749-1758

27 Reichardt H M, Kaestner K H, Tuckermann J, Kretz O, Wessely O, Bock R, Gass P, Schmid W, Herrlich P, Angel P & Schutz G (1998) DNA binding of the glucocorticoid receptor is not essential for survival. *Cell* 93, 531-541

28 Tao Y, Williams-Skipp C & Scheinman R I (2001) Mapping of glucocorticoid receptor DNA binding domain surfaces contributing to transrepression of NF-κB and induction of apoptosis. *J Biol Chem* 276, 2329-2332

29 Adock I M (2000) Molecular mechanisms of glucocorticosteroid actions. *Pulm Pharmacol Therapeut* 13, 115-126

30 Chen J L, Attardi L D, Verrijzer C P, Yokomori K & Tjian R (1994) Assembly of recombinant TFIID reveals differential coactivator requirements for distinct transcriptional activators. *Cell* 79, 93-105

31 Godowski P J, Rusconi S, Miesfeld R & Yamamoto K R (1987) Glucocorticoid receptor mutants that are constitutive activators of transcriptional enhancement. *Nature* 325, 365-368

32 Hollenberg S M & Evans R M (1988) Multiple and cooperative trans-activation domains of the human glucocorticoid receptor. *Cell* 55, 899-906

33 Starr D B, Matsui W, Thomas J R & Yamamoto K R (1996) Intracellular receptors use a common mechanism to interpret signaling information at response elements. *Genes Dev* 10, 1271-1283

34 Aoyagi S & Archer T K (2011) Differential glucocorticoid receptor–mediated transcription mechanism. *J Biol Chem* 286, 4610-4619

35 Thalhamer T, McGrath M A & Harnett M M (2008) Signalling, inflammation and arthritis. MAPKs and their relevance to arthritis and inflammation. *Rheumatology* 47, 409–414.

36 Chuderland D & Seger R (2005) Protein-protein interactions in the regulation of the extracellular signal-regulated kinase. *Mol Biotechnol* 29, 57-74

37 Cowan K J & Storey K B (2003) Mitogen–activated protein kinases: new signaling pathways functioning in cellular responses to environmental stress. *J Exp Biol* 206, 1107-1115

38 Zhang Z & Dong C (2005) MAP Kinases in immune responses. *Cell Mol Immunol* 2, 20-27

39 Chen Q, Wang Z, Xiong Y, Zou X & Liu Z (2010) Comparative study of p38 MAPK signal transduction pathway of peripheral blood mononuclear cells from patients with coal-combustion-type fluorosis with and without high hair selenium levels. *Int J Hyg Environ Hlth* 213, 381–386

40 Handel M L (1997) Transcription factors AP-1and NF-kB: Where steroids meet the gold standard of anti-rheumatic drugs. *Inflamm Res* 46, 282–286

41 Barnes P J (1998) Anti-inflammatory actions of glucocorticoids: molecular mechanisms. *Clin Sci* 94, 557-572

42 Stellato C (2004) Post-transcriptional and non-genomic effects of glucocorticoids. *Proc Am Thorac Soc* 1, 255–263.

43 Arthur J S (2008) MSK activation and physiological roles. *Front Biosci* 13, 5866-79

44 Vermeulen L, Berghe W V, Beck I M E, De Bosscher K & Haegeman G (2009) The versatile role of MSKs in transcriptional regulation. *Trends Biochem Sci* 34, 311-318

45 Karin M (1995) The regulation of AP-1 activity by mitogen-activated protein kinases. *J Biol Chem* 270, 16483-16486

46 Dhawan L, Liu B, Blaxall B C & Taubman M B (2007) A novel role for the glucocorticoid receptor in the regulation of monocyte chemoattractant protein-1 mRNA stability. *J Biol Chem* 282, 10146-10152

47 De Bosscher K, Berghe W V, Beck I M E, Molle W V, Hennuyer N, Hapgood J, Libert C, Staels B, Louw A & Haegeman G (2005) A fully dissociated compound of plant origin for inflammatory gene repression. *PNAS* 102, 15827-15832

48 Yang B V, Weinstein D S, Doweyko L M, Gong H, Vaccaro W, Huynh T, Xiao H, Doweyko A M, Mckay L, Holloway D A, Somerville J E, Habte S, Cunningham M, McMahon M, Townsend R, Shuster D, Dodd J H, Nadler S G & Barrish J C (2010) Dimethyl-diphenyl-propanamide derivatives as nonsteroidal dissociated glucocorticoid receptor agonists. *J Med Chem* 53, 8241-8251

49 Croxtall J D, Choudhury Q & Flower R J (2000) Glucocorticoids act within minutes to inhibit recruitment of signaling factors to activate EGF receptors through a receptor-dependent, transcription-independent mechanism. *Br J Pharmacol* 130, 289-298