Role of Dual Specificity Phosphatases in Biological Responses to Glucocorticoids*5

Published, JBC Papers in Press, June 9, 2008, DOI 10.1074/jbc.R700053200
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The powerful anti-inflammatory effects of glucocorticoids (GCs) have been known for more than sixty years, but their molecular mechanisms are still incompletely understood and hotly debated. The GC receptor (GR) was cloned in 1985 and shown to be a transcription factor. Initially, the anti-inflammatory actions of GCs were explained in terms of genes that were up-regulated by the receptor. However, none of these putative mediators seemed able to account for the spectrum of anti-inflammatory responses to GCs. The discovery of a negative regulatory function of GR then shifted the focus away from GC-induced genes as anti-inflammatory mediators. In recent years, attention has begun to move back toward the idea that the anti-inflammatory response to GCs is partially dependent on the positive regulation of gene expression by GR.

Classical Model of Glucocorticoid Action

Synthetic GCs inhibit expression of many immune and inflammatory mediators in several cell types. For this reason, they are of great use as immunosuppressants and in the treatment of chronic inflammatory diseases (1, 2), yet they can also give rise to a number of side effects of varying severity (3). Both the therapeutic and undesired effects of GCs are mediated by GR, a member of a large family of transcription factors, the nuclear hormone receptors. GR activates or inhibits gene expression via mechanisms known as transactivation and transrepression. According to the current paradigm, the side effects of GCs are largely dependent on dimerization of GR, binding to palindromic GC-response elements, and activation of expression of genes (for example, regulators of gluconeogenesis). On the other hand, anti-inflammatory effects are thought to be largely due to the dimerization-independent transrepression of NF-κB, AP-1, and other transcription factors that contribute to pro-inflammatory gene expression (3–5). Hence, novel GR ligands that selectively promote transrepression rather than transactivation might retain anti-inflammatory effects but cause fewer side effects (6, 7).

This model of GC action is based largely on the in vivo and in vitro properties of dimerization-defective GR mutants (8). A re-examination of this model (9, 10) has been prompted by several recent findings. (i) Anti-inflammatory functions of GR are not, as originally thought, independent of dimerization (8, 11). (ii) Activation of gene expression by GCs is not invariably dependent on palindromic GC-response elements or on dimerization of GR (9, 12–16). (iii) A growing number of anti-inflammatory mediators have been shown to be up-regulated by GCs (9, 10). Among these factors are phosphatases that inactivate MAPKs.

MAPKs and Phosphatases

In response to extracellular stimuli, MAPKs become activated via the phosphorylation of threonine and tyrosine residues within short activation motifs. The activated MAPKs then modulate cellular responses by phosphorylating a variety of substrates, including transcription factors and downstream effector kinases. Activation of ERK frequently mediates proliferative or anti-apoptotic responses, whereas JNK and p38 MAPK often mediate transcriptional and post-transcriptional responses to stressful and/or pro-inflammatory stimuli (17). Among other mechanisms, JNK phosphorylates and activates the c-Jun component of AP-1 to induce transcription of many inflammatory effectors. Stimulation of the p38 MAPK pathway results in the transient stabilization of many inflammatory mediator mRNAs that contain destabilizing adenylate/uridylic-rich elements in their 3′-untranslated regions (18). The p38 pathway has also been implicated in regulation of NF-κB function, although the precise mechanism is disputed (19–21).

The timely inactivation of MAPKs is essential for the generation of appropriate cellular outcomes and for restoration of responsiveness. Such inactivation can be carried out by tyrosine-specific, serine/threonine-specific, or dual specificity (DUSP) phosphatases. The DUSP family includes ~10 members that catalyze dephosphorylation of both threonine and tyrosine residues within MAPK activation motifs (22, 23). These enzymes are also known as MAPK phosphatases.

The roles of DUSPs in cellular responses to external stimuli are determined by their different patterns of expression, subcellular localization, and substrate specificity. A few such as DUSP2 appear rather cell type-restricted in expression, whereas others are widely expressed. Some are constitutively expressed, whereas others are inducible and contribute to negative feedback regulation of the MAPK pathways. Some, like DUSP1 and DUSP4, are reportedly restricted to the nucleus and may modulate cellular responses not only through inactivation but also by nuclear sequestration of their substrates (24). DUSP5–DUSP7 appear to be highly specific for dephosphorylation and inactivation of ERKs, whereas others are less selective. According to some reports, DUSP1 knock-out results in disregulated p38 MAPK and/or JNK but not ERK signaling (12, 24).
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FIGURE 1. Black box of DUSP-mediated responses to GCs. It is not known (i) whether GC-mediated induction of DUSP1 is dependent on dimerization of GR, (ii) to what extent other DUSP proteins are up-regulated by GCs, (iii) under what circumstances DUSP1 inhibits ERK signaling, (iv) at what level(s) DUSP1-mediated inhibition of MAPKs influences gene expression, and (v) whether DUSP1 contributes to side effects as well as anti-inflammatory effects of GCs. TF, transcription factor.

whereas others describe increases in ERK activity in the absence of DUSP1 (29–31). An unexplored possibility is that substrate specificity might be modulated in a cell type-specific manner by means of post-translational modification such as phosphorylation or through interactions of MAPKs and their phosphatase with scaffold proteins.

Regulation of DUSP Gene Expression by GCs and Inflammatory Stimuli

Pro-inflammatory and stress stimuli typically induce rapid and transient expression of DUSP1 mRNA. JNK and/or p38 MAPK signaling pathways, NF-κB, and activating transcription factor 2 have been implicated in such responses (32–38). Being regulated by the same pathways that it suppresses, DUSP1 forms part of a classical negative feedback loop to limit cellular responses to noxious and pro-inflammatory stimuli. Hence, dusp1−/− mice showed exaggerated (sometimes lethal) inflammatory responses in experimental models of Gram-negative or Gram-positive sepsis (25–28), whereas others describe increases in ERK activity in the absence of DUSP1 (29–31). An unexplored possibility is that substrate specificity might be modulated in a cell type-specific manner by means of post-translational modification such as phosphorylation or through interactions of MAPKs and their phosphatase with scaffold proteins.

Role of DUSP1 in Anti-inflammatory Action of GCs

Cells of the myeloid lineage are central to the regulation of innate immune and inflammatory responses and are important targets for the anti-inflammatory effects of GCs. For example, targeted knock-out of GR expression in the myeloid lineage rendered mice highly sensitive to LPS-induced endotoxic shock, which was dependent on p38 MAPK activity (41). The synthetic GC dexamethasone induced the expression of DUSP1 and inhibited p38 MAPK function in wild-type macrophages but not in those lacking GR. Hence, endogenous GCs may prevent lethal macrophage-mediated inflammatory responses in part by inducing DUSP1 and inhibiting p38 MAPK. In rat microglia (resident myeloid cells of the nervous system), dexamethasone inhibited the activation of JNK and p38 MAPK, as well as the expression of monocyte chemotactic protein 1. Again, indirect evidence suggested that these anti-inflammatory effects of dexamethasone were mediated by DUSP1 (46).

Consistent with these findings, dexamethasone inhibited the late phase of LPS-induced activation of JNK and p38 MAPK in dusp1+/+ but not dusp1−/− macrophages (12). The anti-inflammatory effects of dexamethasone in these knock-out macrophages were partially impaired. Some inflammatory mediators such as inducible nitric-oxide synthase were equally sensitive to dexamethasone-mediated inhibition in dusp1+/+ and dusp1−/− cells, whereas others such as IL-1α were down-regulated by dexamethasone in an entirely DUSP1-dependent manner. Several inflammatory mediators showed an impairment but not loss of inhibition by dexamethasone in the absence of DUSP1, suggesting that both DUSP1-mediated and DUSP1-independent mechanisms operate together to regulate their expression.

GCs exert important anti-inflammatory effects on endothelial cells, reducing the expression of adhesion molecules and the ability of leukocytes to infiltrate to sites of inflammation. In human vascular endothelial cells, low doses of dexamethasone inhibited tumor necrosis factor-induced p38 MAPK signaling in a manner that was dependent on de novo gene expression, blocked by sodium orthovanadate (an inhibitor of DUSP1 and other phosphatases), and prevented by a DUSP1 antisense oligonucleotide. The same antisense oligonucleotide impaired the ability of dexamethasone to down-regulate the adhesion molecule E-selectin. Most compellingly, in endothelial cells differentiated from dusp1−/− embryonic stem cells, the inhibitory effect of dexamethasone on tumor necrosis factor-induced E-selectin expression was reversed (47).
The anti-inflammatory effects of GCs on ASMCs, mast cells, epithelial cells, and other targets in the lung are important in the treatment of asthma. GC-mediated reduction of chemokine expression by ASMCs may help to prevent the infiltration of eosinophils and other cells that contribute to airway inflammation and remodeling. DUSP1 was induced by dexamethasone in ASMCs, and its incomplete knockdown by RNA interference partially rescued the chemokine CXCL1 (CXC motif ligand 1) from dexamethasone-mediated inhibition (42). Dexamethasone inhibited the migratory response of mast cells to stem cell factor. Inhibition was accompanied by up-regulation of DUSP1 and inhibition of p38 MAPK, but a causal relationship between these effects has not yet been established (48).

These in vitro experiments suggest that expression of DUSP1 may contribute to anti-inflammatory actions of GCs. Evidence for such a role in vivo is equivocal so far, partly because the exaggerated inflammatory responses of dusp1−/− mice make direct comparisons of GC efficacy difficult. In a simple experimental model of acute, localized, macrophage-dependent inflammatory responses, therapeutic effects of dexamethasone were abrogated in dusp1−/− mice (12). The protective effects of GCs were reportedly also impaired in dusp1−/− mice subjected to endotoxic shock (cited as unpublished observations in Ref. 49). Another study did not make this comparison because of differences in LPS sensitivity between wild-type and dusp1-null mice (40). In experimental models of allergic airway inflammation, dusp1+/+ and dusp1−/− mice were equally sensitive to the therapeutic effects of GCs (40). The anti-inflammatory effects of GCs on mast cells may involve the induction of other phosphatases (40) and other negative regulators of pro-inflammatory signaling pathways (9).

The mechanism(s) by which GC-induced DUSP1 expression impairs inflammatory gene expression have not been defined in detail. In theory, the blockade of JNK and p38 MAPK signaling could cause inhibition of AP-1 and NF-κB. It has not been shown whether GCs exert different effects on AP-1 and NF-κB reporter constructs in DUSP1+/+ and DUSP1−/− cells. In HeLa cells, the p38 MAPK pathway was required for stabilization of cyclooxygenase-2 mRNA in response to IL-1α (50). Dexamethasone induced expression of DUSP1 (but not other DUSPs) and destabilized reporter mRNAs containing the cyclooxygenase-2 3′-untranslated region via phosphatase-dependent inhibition of p38 MAPK (34, 51). The implication is that dexamethasone induces DUSP1, down-regulates p38 MAPK, and destabilizes mRNAs that contain p38 MAPK-sensitive adenylic/uridylic-rich elements. A recent publication has provided evidence that GCs inhibit expression of IL-6 by such a mechanism in ASMCs (52). Other transcriptional or post-transcriptional mechanisms cannot be ruled out.

A small proportion of patients with chronic inflammatory diseases do not show a robust anti-inflammatory response to GCs and are often difficult to treat effectively (2, 53). If DUSPs contribute to the anti-inflammatory action of GCs, it is possible that defects in the expression or activity of DUSPs could contribute to GC insensitivity. Consistent with this hypothesis, persistent activation of p38 MAPK and JNK has been described in clinical samples from GC-resistant patients compared with GC-sensitive controls (54–56). More recently, GC insensitivity of alveolar macrophages was correlated with decreased expression of DUSP1 and increased activity of p38 MAPK in severe asthma (57). It should be noted that GR activity may be impaired by p38 MAPK (58–60); therefore, the chain of cause and effect is difficult to establish (61). Do excessive inflammation and activation of p38 MAPK lead to impairment of GR function and defective induction of DUSP1? Or does a defect in the expression of DUSP1 permit unchecked p38 MAPK activation and exaggerated inflammatory gene expression?

Role of DUSPs in Side Effects of GCs

Osteoporosis and consequent bone fractures are among the most frequent side effects of prolonged exposure to oral GCs (3, 62). The major underlying cause is thought to be a decrease in the survival and proliferation of osteoblasts. In primary osteoblasts and osteoblast cell lines, GCs induced DUSP1 expression and inhibited ERK, which is essential for survival and proliferation (63–65). Immunodepletion and RNA interference experiments suggested that DUSP1 is responsible for GC-mediated inhibition of ERK (30). Sodium orthovanadate, an inhibitor of DUSP1 and other phosphatases, prevented apoptosis of osteoblasts both in vitro and in vivo and protected rats from experimental GC-induced osteoporosis (66, 67). Therefore, induction of DUSP1 expression may contribute to one of the major side effects of GCs, although this remains untested so far in dusp1−/− mice.

Endogenous GCs oppose the actions of insulin on adipocytes and other cells and are thought to contribute to insulin resistance and diet-induced obesity (68, 69). Clinically, both endogenous GC excess and prolonged exposure to exogenous GCs cause glucose intolerance and central obesity (3, 68, 69). The up-regulation of gluconeogenic enzymes has been considered a major cause of GC-induced diabetes (3), but this does not preclude other mechanisms. In 3T3-L1 adipocytes, dexamethasone induced the expression of DUSP1 and DUSP2, inhibited insulin-induced p38 MAPK activation, and impaired glucose uptake. Overexpression of DUSP1 mimicked the inhibitory effect of dexamethasone on glucose uptake (70). Interestingly, both dusp1 knock-out and adipocyte-specific blockade of GC signaling protected mice from diet-induced obesity (31, 71). In the case of the dusp1 knock-out, elevated basal activity of MAPKs was found in adipose tissue (31). Together, these observations suggest that there could be a link between the induction of DUSPs in adipose tissue, the altered regulation of MAPK signaling, and the metabolic syndrome caused by GC excess. It would be interesting to test the metabolic responses of dusp1+/+ and dusp1−/− mice to continued GC administration or adrenalectomy.

Another common side effect of GCs is cataracts. Two independent microarray studies of lens epithelial responses to GCs have demonstrated up-regulation of DUSP1 (72, 73). It has been speculated that DUSP1 (or other GC-induced signaling molecules) might perturb MAPK function and cause changes in epithelial cell proliferation or differentiation. As is the case for most putative roles of DUSPs in GC side effects, strong experimental evidence is lacking so far.
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DUSPs in Tumor Cell Responses to GCs

Disregulation of DUSPs has been described in several tumors, but there is little consistency as to whether they are silenced or overexpressed, reflecting the diverse roles of MAPKs in the regulation of proliferation, differentiation, and apoptosis (74). Similarly, the up-regulation of DUSPs by GCs could have either pro- or anti-apoptotic consequences.

GCs are commonly used in the treatment of childhood acute lymphoblastic leukemias (ALLs) and prostate cancers because of their anti-proliferative or pro-apoptotic effects. GCs have been found to modulate expression of DUSPs in primary leukemias or ALL cell lines, but with no consistent pattern (supplementary Table 1). RNA interference and overexpression experiments in one ALL line did not support a role for DUSP1 in the anti-proliferative response to GC (75). In prostate cancers resistant to hormone treatment, expression of GR (76) and DUSP1 (77) was low. Lentiviral expression of GR in a GC-resistant prostate cancer cell line restored the capacity of a GC to inhibit MAPK signaling and block proliferation (76), although it is not known whether expression of DUSP1 was restored. To summarize, there is not yet strong evidence that DUSPs mediate therapeutic responses to GCs in these cancers.

On the other hand, DUSP1 is postulated to be an important mediator of resistance of breast cancers to a variety of chemotherapeutic agents (78). Consistent with such a role, GC-induced up-regulation of DUSP1 was associated with impaired apoptotic responses of breast cancer cells to paclitaxel in vitro and in vivo (79–81), and blockade of DUSP1 expression by RNA interference prevented the anti-apoptotic effect of GC in a breast cancer cell line (79).

Conclusions

There is growing but not yet conclusive evidence that DUSPs, in particular DUSP1, contribute to biological responses to GCs in several tissues. DUSP1 appears to function as an important negative feedback regulator of MAPK signaling, and GCs can be considered to modulate the sensitivity and/or potency of this feedback loop. What this implies in terms of the control of DUSP1 gene expression by GCs and other agonists is not yet clear. GC-induced expression of other DUSP family members suggests that a degree of redundancy may exist in at least some cells. Still less is known about the regulation of these other phosphatases. Where the time course of induction is slow, it may involve a secondary response to GC-mediated up-regulation of other transcription factors.

It should be pointed out that changes in DUSP expression are only one aspect of the highly complex cellular response to GCs. This response also involves the induction of several modulators of intracellular signaling in addition to the DUSPs (9, 10), inhibition of transcriptional responses by means of transrepression (82), and non-genomic actions of GCs that have not been touched on here (5). It remains to be seen just how important a contribution is made by the up-regulation of DUSPs, in what cell types, and under what conditions.

A recent initiative in GC research has been to attempt to uncouple the therapeutic and harmful consequences of GR engagement, for example, by designing novel GR ligands that selectively mediate transrepression rather than transactivation (6, 7). Clinically valuable uncoupling may prove difficult to achieve if transactivation is required for GC-induced expression of anti-inflammatory mediators such as DUSP1 and others (9, 10) or if members of the DUSP family can contribute to both harmful and beneficial effects of GCs.

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