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Perspective

Anti-inflammatory glucocorticoids: Changing concepts

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ABSTRACT

Despite being the most effective anti-inflammatory treatment for chronic inflammatory diseases, the mechanisms by which glucocorticoids (corticosteroids) effect repression of inflammatory gene expression remain incompletely understood. Direct interaction of the glucocorticoid receptor (NR3C1) with inflammatory transcription factors to repress transcriptional activity, i.e. transrepression, represents one mechanism of action. However, transcriptional activation, or transactivation, by NR3C1 also represents an important mechanism of glucocorticoid action. Glucocorticoids rapidly and profoundly increase expression of multiple genes, many with properties consistent with the repression of inflammatory gene expression. For example: the dual specificity phosphatase, DUSP1, reduces activation of mitogen-activated protein kinases; glucocorticoid-induced leucine zipper (TSC22D3) represses nuclear factor-κB (NF-κB) and activator protein 1 (AP-1) transcriptional responses; inhibitor of κBα (NFKBIA) inhibits NF-κB; tristraprolin (ZFP36) destabilises and translationally represses inflammatory mRNAs; CDKN1C, a cell cycle regulator, may attenuate JUN N-terminal kinase signalling; and regulator of G-protein signalling 2 (RGS2), by reducing signalling from Gαq-linked G protein-coupled receptors (GPCRs), is bronchoprotective. While glucocorticoid-dependent transrepression can co-exist with transactivation, transactivation may account for the greatest level and most potent repression of inflammatory genes. Equally, NR3C1 transactivation is enhanced by β_2-adrenoceptor agonists and may explain the enhanced clinical efficacy of β_2-adrenoceptor/glucocorticoid combination therapies in asthma and chronic obstructive pulmonary disease. Finally, NR3C1 transactivation is reduced by inflammatory stimuli, including respiratory syncytial virus and human rhinovirus. This provides an explanation for glucocorticoid resistance. Continuing efforts to understand roles for glucocorticoid-dependent transactivation will provide opportunities to improve glucocorticoid therapies.

1. Introduction

Glucocorticoids (corticosteroids) acting on the glucocorticoid receptor (NR3C1) (See Table 1 for list of gene symbols and function), a ligand-activated transcription factor, represent the most effective anti-inflammatory drugs currently available for the treatment of chronic inflammation (Barnes, 2006). Topical glucocorticoids are central to the management of multiple inflammatory conditions. Thus inhaled glucocorticoids, referred to clinically as inhaled corticosteroids, are used in asthma, and, typically as a combination with long-acting β_2-adrenoceptor agonists, in chronic obstructive pulmonary disease. Despite this, many individuals respond poorly to glucocorticoid therapy. In chronic obstructive pulmonary disease, severe asthma, asthmatics who smoke, and viral exacerbations of both diseases, inhaled glucocorticoids are of limited effect, necessitating, high-doses, or often oral therapy (Newton et al., 2010b; Barnes, 2013). While respiratory diseases account for the greatest patient numbers using oral glucocorticoids, inflammatory conditions of the skin, subcutaneous and musculoskeletal tissues, nervous and digestive systems are also significant (van Staa et al., 2000). However, glucocorticoids do not cure chronic disease, leading to long-term treatments and side-effects including osteoporosis, tissue wasting, cataracts, diabetes and hypothalamic-pituitary-adrenal axis suppression. Since, these are not off-target responses, but reflect NR3C1 physiology, the identification of anti-inflammatory NR3C1 ligands, which avoid resistance, and/or show reduced side-effect profiles, are goals of the pharmaceutical sector. Success requires a clear understanding of how glucocorticoids repress inflammation.

2. Repression of gene expression drives anti-inflammatory effectiveness

Of the many glucocorticoid-dependent responses, down-regulation of inflammatory gene expression is most critical for

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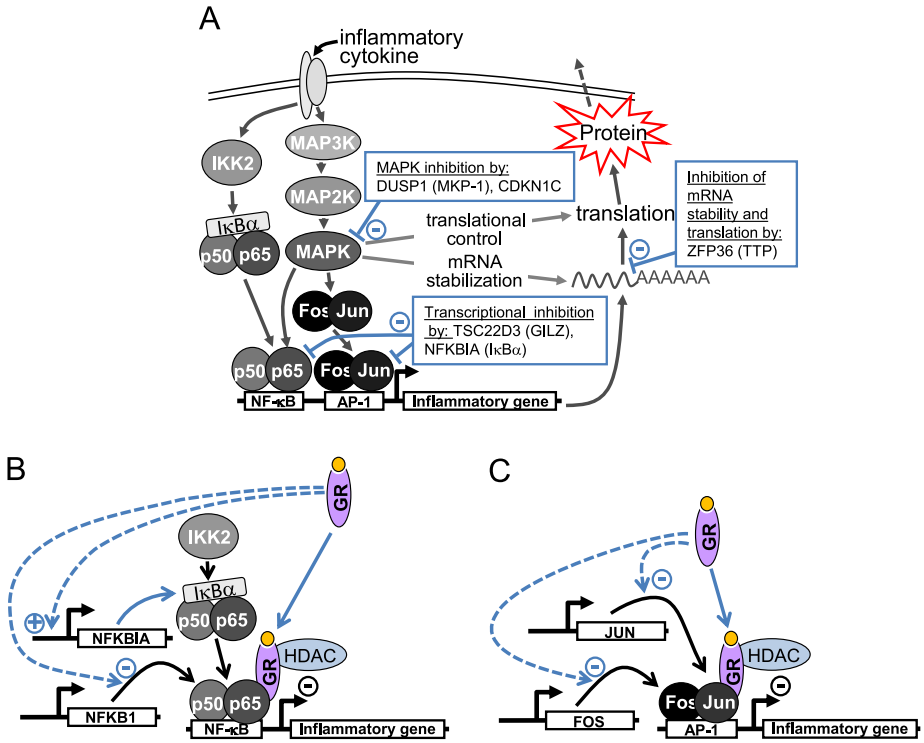

Fig. 1. Schematic showing the inhibition of inflammatory gene expression by glucocorticoids. (A) An inflammatory cytokine binding to its receptor activates kinase cascades. IκB kinase 2 (IKK2) activation leads to the phosphorylation of the inhibitor of κBα (IκBα) (NFKBIA), which leads to its rapid degradation and the release of active NF-κB (p50/p65). This translocates to the nucleus to activate inflammatory gene transcription. Activation of mitogen-activated protein kinase kinase kinase (MAP3Ks) leads to activation of the downstream MAPKs. MAPKs can enhance the transcriptional activity of NF-κB and AP-1, and also cause mRNA stabilisation and translational activation of inflammatory genes. While glucocorticoids may induce the expression of hundreds of effector genes, effects of selected glucocorticoid-inducible genes may include: dual-specificity phosphase 1 (DUSP1) (also known as MKP-1) inhibits MAPKs to prevent transcription, mRNA stability and translation; IκBα/NFKBIA inhibits NF-κB; Glucocorticoid-induced leucine zipper (GILZ/TCS22D3) can inhibit both NF-κB and AP-1; Tristetraprolin (TTP/ZFP36) promotes deadenylation, degradation and translational silencing of AU-rich element (ARE)-containing inflammatory mRNAs; CDKN1C is a cell-cycle kinase inhibitor and a potential inhibitor of JNK, which may prevent proliferative responses and the induction of pro-inflammatory genes respectively. (B) Activation of the NF-κB signal transduction cascade by IKK2 leads to rapid degradation of IκBα/NFKBIA and release of active NF-κB (p50/p65). Binding of glucocorticoid (yellow) to the cytoplasmic glucocorticoid receptor (GR) (NR3C1) causes translocation of the receptor to the nucleus where it can inhibit transcriptional activation by NF-κB. This may occur by up-regulating the expression of IκBα/NFKBIA (or other proteins indicated in (A)), reducing the expression of p50/p105 (NFKB1), or via transrepression, i.e. direct binding to NF-κB to recruit histone deacetylase 2 (HDAC2). (C) Ligand-activated GR/NR3C1 can inhibit AP-1-dependent transcription via the mechanisms indicated in (A) as well as by reducing the expression of the composite AP-1 factors, here FOS and JUN, or by via transrepression, i.e. direct binding to AP-1 (FOS/JUN heterodimer) to recruit HDAC2 and attenuate transcription.

anti-inflammatory effect (Barnes, 2006; De Bosscher et al., 2003). Reduced expression of chemokines, cytokines, inflammatory enzymes, adhesion molecules and other inflammatory proteins in, on or from epithelial, endothelial, smooth muscle, fibroblasts and other cell types, reduces recruitment, maturation, and/or survival of inflammatory cells. This lowers the inflammatory cell burden. Equally, acting on inflammatory cells, glucocorticoids produce similar repressive effects. However, mechanisms by which glucocorticoids repress inflammatory gene expression remain unclear (Clark and Belvisi, 2012). In this respect, inflammatory gene expression involves regulated mRNA stabilisation and translation, in addition to the more readily documented changes in gene transcription (Fig. 1A). Consequently, repressive mechanisms that solely address gene transcription can only represent one part of the picture. Thus, without NR3C1 over-expression, glucocorticoids may only partially repress transcription, yet reduce mRNA stability and translation, which together account for the repression of inflammatory gene expression (Fig. 1A) (Newton and Holden, 2007; Clark and Belvisi, 2012).

3. Repression of inflammatory gene transcription by glucocorticoids

That glucocorticoids repress the transcriptional activity of key inflammatory transcription factors, such as nuclear factor-κB (NF-κB) and activator protein (AP)-1, makes conceptual sense as their binding sites are both common in the promoters of inflammatory genes and crucial for transcriptional up-regulation (De Bosscher et al., 2003). Indeed, glucocorticoids can reduce the DNA binding ability of NF-κB and AP-1 to the their cognate DNA motifs (Yang-Yen et al., 1990; Mukaida et al., 1994). Such effects may be partly explained by the glucocorticoid-dependent down-regulation of the constituent transcription factor components, p50/p105 (NFKB1) of NF-κB, or c-Jun (JUN), c-Fos (FOS) and Fra1 (FOSL1) of AP-1 (Hass et al., 1991; Tacon et al., 2012; Newton et al., 1998), plus up-regulation of the NF-κB inhibitor, inhibitor of κBα (NFKBIA) (Scheinman et al., 1995) (Fig. 1B and C). However, many NF-κB-dependent genes are poorly, or even not, repressed by glucocorticoids (King et al., 2013). Furthermore, such genes may play roles in host defence or the resolution of inflammation, for which there could be an advantage to being spared the repressive effects of glucocorticoids (Stellato, 2007; Gilroy et al., 2004). Indeed this realisation implies a necessarily gene-specific, rather than activator-specific, aspect to the repressive actions of glucocorticoids. Furthermore, glucocorticoid-repression of inflammatory gene expression can be dissociated from up-regulation of NFKBIA and is not necessarily accompanied by reduced NF-κB or AP-1 DNA binding (Konig et al., 1992; Newton et al., 1998; Heck et al., 1997). Thus independent mechanisms of repression must also exist. For example, NR3C1 may directly bind NF-κB and AP-1, to promote transcriptional repression i.e. transrepression (Jonat et al., 1990;