



**Karolinska
Institutet**

Department of Biosciences and Nutrition

Molecular mechanisms of Glucocorticoids - Anti-inflammatory implications

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska
Institutet offentligen försvaras i 4U Solen, Alfred Nobels allé 8,
Karolinska Institutet, Huddinge

Onsdagen den 28 Mars, 2012, kl 09.15

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Stockholm 2012

ABSTRACT

Glucocorticoids (GCs) play important roles in many biological processes including inflammatory responses. The study of this process has involved investigations of cross-talk abilities by GC receptor (GR) with cellular signaling pathways that have been associated with inflammatory disorders or implicated as contributory for the adverse effects observed with GC therapy. This thesis aims to provide additional insights into this area of research and contains studies made to investigate aspects of GC-cross-talk with some of these signaling pathways, in particular the MAPK, NF- κ B and Wnt signaling pathways.

MKP-1, an anti-inflammatory feed-back inhibitor of MAPK-signaling, has also been shown to be up-regulated by GCs. In **paper I**, we demonstrate that GCs stimulate expression of MKP-1 through a positive “tethering” mechanism involving the GR and the promoter-bound transcription factor C/EBP, without GR itself contacting the DNA. This study emphasizes the multiple mechanisms that exist by which agonist-bound GR can affect gene expression, also in the anti-inflammatory response.

GR mutants are powerful investigative tools that can be used to study cross-talk between GCs and the pro-inflammatory canonical NF- κ B pathway. In **paper II**, we demonstrate that a “loss of function” GR mutant is able to repress NF- κ B activated by TNF α , but not by TPA, whereas the wild-type receptor inhibits NF- κ B in both cases. This study highlights that the ability of the GR to repress NF- κ B not only relies on gene and cell context but also depends on the signaling pathway that is employed to activate NF- κ B.

The non-canonical NF- κ B pathway is emerging as a key player in various inflammatory diseases, but a cross-talk between this pathway and GCs have not been described. In **paper III**, we demonstrate for that GCs inhibit non-canonical NF- κ B signaling and that the GR physically interacts with RelB and inhibits the transcriptional activity of RelB/p52 heterodimers in a hormone-dependent manner.

GC-induced hippocampal damage and osteoporosis have been suggested to be caused by the inhibition of the Wnt-signaling pathway by GCs. In **paper IV**, we demonstrate that GC stimulation of DKK-1, a Wnt-antagonist, inhibits proliferation of neuronal progenitor cells. The agonist-bound GR binds to a GRE in the regulatory promoter region of the DKK-1 gene and induces its expression. Restoring the activity of Wnt-pathways that are inhibited by GCs may be valuable to limit some of the side-effects observed with GC therapy.

In conclusion, the studies in this thesis give additional insight into the complexity, reciprocity and variety of cross-talk mechanisms involving GR and several signaling pathways, thereby providing an increased understanding of the molecular mechanisms behind GC effects with emphasis on their anti-inflammatory actions.