Molecular mechanisms of gene repression by the glucocorticoid receptor

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The glucocorticoid receptor (GR) is a ligand-binding transcription factor, which resides in the cytoplasm as a huge protein complex containing several chaperones, adaptor and inhibitor molecules. Upon activation through ligand binding, GR is released from this complex and travels to the cell nucleus, where it acts as a true DNA-bound transcription factor or as a non-DNA-bound cofactor for gene induction or repression.
For most of the typical glucocorticoid-responsive genes, GR binds as a homodimeric factor onto the DNA at so-called GR-responsive elements, recruits the necessary co-factors for chromatin remodeling and activation of the basal transcription machinery, which all together lead to specific, glucocorticoid-mediated gene transcription.
In case of gene repression, GR does not bind to the DNA, but interferes, most probably as a monomeric factor, with other DNA-binding transcription factor complexes in order to shut off gene transcription. Although this GR effect is very important in many physiological conditions and diseases, the actual molecular mechanism(s) is at present not yet known. Several hypotheses to explain the gene-inhibitory effects of GR have already been proposed and published, but some of them are highly cell type-specific (and thus not generally valid) or rely on misinterpretation of the results obtained.
Based on our experimental work, we presently favor a model in which gene repression by GR is a fully nuclear event, in which a complete transcription-competent promoter complex at a given activated gene is inhibited at an ultimate step of the onset of gene transcription. Moreover, it should be noted that this inhibitory effect is highly gene-specific and promoter context-dependent. Furthermore, as GR does not interfere with the MAPK-MSK1 pathway, i.e. a necessary kinase cascade for chromatin relaxation in case of inflammatory gene induction, it also remains to be established how GR can counteract chromatin modification and opening, leaving the activating kinase pathway unaffected.

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