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Selective modulation of the glucocorticoid receptor can distinguish between transrepression of NF-κB and AP-1

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Abstract

Glucocorticoids (GCs) block inflammation via interference of the liganded Glucocorticoid Receptor (GR) with the activity of pro-inflammatory transcription factors NF-κB and AP-1, a mechanism known as transrepression. This mechanism is believed to involve the activity of GR monomers. Here, we explored how the GR monomer-favouring Compound A (CpdA) affects AP-1 activation and activity. Our results demonstrate that non-steroidal CpdA, unlike classic steroidal GCs, blocks NF-κB- but not AP-1-driven gene expression. CpdA rather sustains AP-1-driven gene expression, a result which could mechanistically be explained by the failure of CpdA to block upstream JNK kinase activation and concomitantly also phosphorylation of c-Jun. In concordance and in contrast to DEX, CpdA maintained the expression of the activated AP-1 target gene *c-jun*, as well as the production of the c-Jun protein. As for the underlying mechanism, GR is a necessary intermediate in the CpdA-mediated gene expression of AP1-regulated genes, but seems to be superfluous to CpdA-mediated JNK phosphorylation prolongation. The latter phenomenon concurs with the inability of CpdA to stimulate DUSP1 gene expression. ChIP analysis demonstrates that DEX-activated GR, but not CpdA-activated GR, is recruited to AP-1-driven promoters. Furthermore, in mice we observed that CpdA instigates a strong enhancement of TNF-induced AP-1-driven gene expression. Finally, we demonstrate that this phenomenon coincides with an increased sensitivity towards TNF lethality, and implicate again a role for JNK2. In conclusion, our data support the hypothesis that a ligand-induced differential conformation of GR yields a different transcription factor cross-talk profile.

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Biography

Ilse Beck has completed her PhD in Biotechnology at Ghent University (Belgium) in 2009, after obtaining a MSc in Biology at the age of 22 years from the Catholic University of Leuven. She performed a fellowship at the Karolinska Institute (Sweden). She continued in the Laboratory of Experimental Cancer Research at Ghent University, as a postdoctoral fellow of the Research Foundation - Flanders (FWO). She has published more than 15 papers in reputed journals. Her long-standing research focus in nuclear receptors is currently concentrated towards effects on an by nuclear receptors in solid and hematological tumors.