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

Ilse M Beck[1,2], Karolien De Bosscher[1], Lien Dejager[1], Nadia Bougarne[1], Anthoula Gaigneaux[3], Sébastien Chateauvieux[3], Dariusz Ratman[1], Marc Bracke[2], Jan Tavernier[1], Wim Vanden Berghe[1,4], Claude Libert[1], Marc Diederich[5] and Guy Haegeman[1,6]

[1]Ghent University, Belgium
[2]Ghent University Hospital, Belgium
[3]Hôpital Kirchberg, Luxemburg, Luxemburg
[4]University of Antwerp, Belgium
[5]Seoul National University, S. Korea
[6]Mahidol University, Thailand

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. KDB, IMB, and LD are supported by FWO-Vlaanderen. DR and NB enjoy support of IWT-Vlaanderen. AG and SC S received grants from Télévie Luxembourg.

Biography

Ilse Beck has completed her PhD in Biotechnology at Ghent University (Belgium) in 2009, after obtaining an 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.

Ilse.Beck@UGent.be