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Glucocorticoid Receptor-Dependent Gene Regulatory Networks.

Phillip Phuc Le, Joshua R. Friedman, Jonathan Schug, John E. Brestelli¹, J. Brandon Parker, Irina M. Bochkis, Klaus H. Kaestner. PLoS Genetics. August 2005. Volume 1(2):e16.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1186734/>

Glucocorticoids are essential steroid hormones that affect multiple organ systems. The synthetic analogs of glucocorticoids are broadly prescribed for their immunosuppressive and anti-inflammatory effects, but they often cause unwanted side effects. Glucocorticoids and their receptor (GR) are involved in complex transcriptional regulation and multiple signaling pathways. The mechanism of the action of the ligand-bound GR remains unclear.

Investigators combined two high-throughput technologies to identify direct targets of the glucocorticoid receptor. The genes that interact with GR and their different expression patterns will provide a global network of the glucocorticoid signaling pathways. Hopefully this information will help improve glucocorticoid therapy.

Mouse liver lobes were collected from animals treated with synthetic glucocorticoid and from control groups. The samples were used in two parallel experiments. Expression profiling was performed with Agilent DNA oligonucleotide arrays. Location analysis, called ChIP-on-chip (chromatin immunoprecipitation followed by DNA array analysis), was also performed using an antiserum raised against GR. The immunoprecipitated DNA was then applied to the Mouse PromoterChip BCBC-3.0 promoter microarray. Quantitative real time PCR was used to validate the enriched genetic loci.

Expression analysis revealed that 445 genes were differentially expressed in the treatment versus control group. One hundred and eighty-two genes were able to bind to the GR promoter according to ChIP-on-chip analysis. Combining the results of the two analyses, 53 genes were classified as intersecting - that is, differentially expressed and bound to GR. Functional networks were generated from the 53 genes using IPA. Figure 6 in this paper shows the transcriptional regulatory network for GR. The network includes genes that were previously known to be targets of GR. Many of the other genes are candidate GR targets, including some novel GR target genes that may play critical roles in the glucocorticoid response.