Abstract

The aryl hydrocarbon receptor (AHR) is a ligand activated transcription factor best known for mediating the toxic actions of environmental contaminants, such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). The aryl hydrocarbon receptor repressor (AHRR) is an AHR regulated gene and a negative regulator of AHR. Although the mechanism of AHRR-dependent repression of AHR is not clear, one of the proposed mechanisms is through direct competition with AHR for binding to DNA sequences termed aryl hydrocarbon response elements (AHREs). This thesis aimed to compare the genome-wide binding profiles of AHR and AHRR in MCF-7 cells treated for 24 h with 10 nM TCDD using ChIP-seq. We identified 3915 AHR- and 2811 AHRR-bound regions, 969 of which were common to both datasets. These regions corresponded to 2647 AHR, 2417 AHRR and 1064 AHR/AHRR co-bound or potentially regulated genes. AHRR-bound regions mapped closer to promoter regions compared with AHR-bound regions. The AHRE was overrepresented in both AHR- and AHRR-bound regions, and de novo motif discovery also identified an AHRE motif in both datasets. Candidate unique AHR- and AHRR-bound regions were validated by ChIP-qPCR. Luciferase assays confirmed the AHR- or AHRR-independent
regulation of the identified genes. This work is the first genome-wide mapping of AHRR-bound regions ever performed and provides insight into novel functions for AHRR.