141 **TCDD-INDUCED DEGRADATION OF AH RECEPTOR BY THE UBIQUITIN-PROTEASOME PATHWAY**

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The aryl hydrocarbon receptor (AhR), a ligand-activated bHLH/PAS transcription factor, mediates a broad range of biological responses to halogenated aromatic hydrocarbons. TCDD, a potent agonist for AhR, induces a rapid reduction of the steady state AhR. In this study, we analyzed the mechanism of the agonist-induced down regulation of AhR. We show that TCDD shortens the half life of AhR, as measured by pulse-chase experiment. The TCDD-induced degradation of both unlabeled and pulse-labeled AhR is blocked by lactacystin and MG132, potent inhibitors of the 26S proteasome. Treatment with TCDD induces formation of ubiquitinated AhR. Furthermore, analyses of AhR degradation in cells bearing a temperature-sensitive mutation in the ubiquitin-activating enzyme (E1) reveal that degradation of AhR in both untreated and TCDD-treated cells requires functional E1. Collectively, these studies demonstrate that TCDD induces degradation of AhR via a ubiquitin-proteasome pathway. Lastly, we show that treatment with proteasome inhibitors enhances the induction of CYP1A1 gene expression by TCDD, suggesting that the ubiquitin-proteasome mediated degradation of AhR serves as a mechanism for controlling the activity of ligand-activated AhR.