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Meeting abstract

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TCDD deregulates contact inhibition in rat liver oval cells via Ah receptor, JunD and cyclin A

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The aryl hydrocarbon receptor (AhR) is a transcription factor involved in physiological processes, but also mediates most, if not all, toxic responses to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Activation of the AhR by TCDD leads to its dimerization with ARNT and transcriptional activation of several phase I and II metabolising enzymes. However, this classical signalling pathway so far failed to explain the pleiotrophic hazardous effects of TCDD such as developmental toxicity and tumour promotion. Thus, there is an urgent need to define genetic programmes orchestrated by AhR to unravel its role in physiology and toxicology. Treatment of rat liver oval cells with TCDD leads to a release from contact-inhibition. Loss of contact-inhibition is one characteristic hallmark in tumourigenesis. We have recently shown that TCDD-exposure leads to an elevation of JunD protein levels and to transcriptional activation of Cyclin A in an AhR-dependent, and probably ARNT-independent way. Ectopic expression of Cyclin A in confluent cultures overcomes G1-arrest indicating that increased Cyclin A levels are indeed sufficient to bypass contact-inhibition. Elevation of JunD precedes that of Cyclin A suggesting a role of JunD in Cyclin A induction. Indeed, down-regulating JunD by siRNA blocks TCDD-induced expression of Cyclin A. DNA affinity purification assays and reporter gene analysis indicate that JunD binds to an ATF/CRE consensus sequence in the rat Cyclin A promoter. Using in vitro DNA affinity purification assays, we also revealed binding of ATF2, but not Fra- or Fos-proteins, to the ATF/CRE consensus sequence. Down-regulating ATF2 by siRNA blocks TCDD-dependent Cyclin A induction indicating that ATF2 is the interaction partner of JunD mediating Cyclin A expression. In summary, we have discovered in rat liver oval cells a novel AhR-dependent and probably ARNT-independent signalling pathway involving JunD/ATF2 and Cyclin A, which mediates deregulation of contact-inhibition by TCDD.

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