ROLE OF THE AH RECEPTOR IN TUMOR PROMOTION

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2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), the prototype dioxin, shows strong tumor promoting activity in rat liver, an effect that is assumed to be Ah receptor mediated. Tumor promoters are generally believed to enhance the net growth rate of intermediate (initiated) cells. In rat liver, these cells can be visualized by their expression of the marker enzyme glutathione-S-transferase P (GST-P). GST-P-positive hepatocytes show ~10-fold higher rates of cell division and apoptosis compared to their normal counterparts. Exposure of rats to TCDD had only very moderate effects on division of GST-P-positive liver cells, as estimated by BrdU-labeling indices, while the agent strongly inhibited apoptosis of tumor precursor cells, in particular upon prolonged exposure times. The effects of TCDD on liver cell homeostasis have also been investigated under diverse experimental settings by various other groups, both *in vitro* and *in vivo*. The results, which will be reviewed, are partly conflicting. The mechanisms that lead to suppression of apoptosis by TCDD are not clear. Signalling through Raf-1 kinase-dependent pathway does not appear to play a role in this process. Other possible mechanisms will be discussed. Since the survival probability of single GST-P-positive preneoplastic cells and very small GST-P-positive cell clones is comparatively low, due to their

high rate of spontaneous apoptosis, the majority of these cells will become extinct in the absence of tumor promoters. Inhibition of apoptosis by TCDD and other tumor promoters will give these cells a chance to survive and develop into larger clones. Consequently, TCDD not only promotes the growth of already existing clones of 'initiated' cells but will also increase their number, an effect which may not be easily distinguishable from initiating activities of genotoxic hepatocarcinogens.