DOCTORAL THESIS

Study on the environmental contamination and mechanistic toxicology of 2,3,7,8-tetrachlorodibenzo-p-dioxin

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Study on the Environmental Contamination and Mechanistic Toxicology of 2,3,7, 8-Tetrachlorodibenzo-*p*-dioxin

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ABSTRACT

Polychlorinated dibenzo-*p*-dioxins, such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) has been recognized as the most toxic man-made pollutants. They are characterized by their persistent, fat-seeking and endocrine disruptive natures. Their ubiquitous occurrence in the environment can facilitate their bio-transfer and the subsequent bio-accumulation in different tropic levels, imposing health hazards to living organisms. It is well-known that the major route of human exposure to TCDD is through food consumption, resulting in about 1 – 3 pg TEQ (toxicity equivalents)/kg body weight uptake per day. With reference to TCDD, the mechanism of action is known to involve an interaction with cytosolic aryl hydrocarbon receptor (Ah-receptor), followed by heterodimeriztion with an Ah-receptor nuclear translocator (Arnt) and finally, bind on the *cis*-acting dioxin responsive element (DRE). The Ah-receptor pleiotropic response could lead to diverse pathological consequences, including the alteration of growth regulation, malignant cell transformation and reproductive functions. In this study, an integrative approach including environmental to mechanistic perspectives, was adopted to study and decipher the contamination profile and biological toxicities of TCDD.

For the environmental monitoring aspect, using human breast milk sample accompanied with H4IIE/EROD model, our results indicated that the dioxin contamination profile in Southeastern China was comparable to other studies conducted elsewhere in the world. Moreover our data indicated that samples collected from the Guangzhou population were in general with higher level of dioxin contamination than that of detected in Hong Kong. With the background information obtained, *de novo* biochemical interactions of TCDD

with endogenous hormones or some naturally purified/chemically synthesized compounds were examined in the same cell model. Our results identified that DEX had an additive effect on TCDD elicited CYP1A1/EROD expression. The interaction was glucocorticoids receptor dependent. Another novel pathway assessed was the receptor independent E_2-mediated suppression. It is hypothesized that the suppression was mediated by a direct hindrance of TCDD/Ah receptor complex formation. Furthermore, we have characterized the activity of a natural compound, SLY-1 that acted as a partial Ah receptor antagonist. Its action was mainly targeted at the post-transcription level. The outcome of these studies would be useful for our better understanding on the biochemical interactions of TCDD with natural hormones/compounds, shedding light on the issue of *de novo* modulation of TCDD elicited toxicities and the associated pathological consequences. In addition, the results support the notion that the natural product could be developed as an antidote for treatment of TCDD elicited diseases.

In the final part of the thesis, TCDD elicited reproductive toxicities, with special reference to the male reproductive system were investigated and discussed. It is well known that Sertoli and Leydig cells play crucial roles in regulating the process of spermatogenesis. Hence primary rat Sertoli and Leydig cell models were established for the investigation. Biological consequences evoked by direct TCDD intervention were elucidated. We have demonstrated that TCDD can modulate aromatase, MIS, sertolin and testin expressions as well as E_2 secretion in the Sertoli cells. The synthesis and secretion of progesterone and testosterone were considerably suppressed in TCDD treated Leydig cells. Along with this observation, a significant reduction of P450ssc was observed.

Collectively, this study demonstrated the crosstalk of TCDD with DEX, E_2 and SLY-1 in cellular level. Its toxicities to the male reproductive system are diverse and manifold.

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