Chapter 5: Conclusions

In the current study, we investigated the mechanisms by which TCDD mediates its immunotoxicity, particularly the thymic atrophy. Our data demonstrated that TCDD mediates its toxicity, in part by causing apoptosis of the thymocytes. The Fas\(^+\) wild-type mice were more susceptible to TCDD-induced thymic atrophy when compared to the Fas-deficient \((lpr/lpr)\) and the Fas-ligand defective \((gld/gld)\) mice. Administration of TCDD \textit{in vivo} caused significant apoptosis in wild-type mice which could be detected at early stages but not later on, due to the rapid clearance of the apoptotic cells by the phagocytic cells \textit{in vivo}. In the \textit{lpr} and \textit{gld} mice, apoptosis could not be detected following TCDD administration \textit{in vivo}. Also, TCDD-treatment caused significant alterations in the surface markers of thymocytes from wild-type mice, characteristic of cells undergoing apoptosis. In contrast, TCDD-treatment caused minimal phenotypic changes in thymocytes from \textit{lpr} and \textit{gld} mice. Because the detection of apoptosis in vivo is difficult, phenotypic alterations in the density of thymocyte surface molecules may serve as a useful biomarker for toxicity involving apoptosis.

The induction of apoptosis in thymocytes by TCDD can lead to altered T cell differentiation and decreased T cell functions in the periphery. In the human population, because the levels of Fas and FasL can vary, the immunotoxic effects of TCDD may also be different. The fact that TCDD up-regulates the density of TCR suggests that TCDD may enhance positive selection of T cells which in turn could lead to the induction of autoimmunity. The current study also demonstrates that the action of TCDD may be directed more towards cells and tissues that express high levels of Fas and Fas ligand. Lastly, the demonstration that caspase inhibitors can inhibit TCDD-induced apoptosis suggests that such inhibitors may serve as useful tools to neutralize the toxicity caused by TCDD.
Figure 5.1: TCDD-induced apoptosis of thymocytes is mediated by Fas-FasL interactions: TCDD administration could lead to increased expression of FasL on thymic stromal cells. These FasL expressing cells when in contact with the Fas+ thymocytes and mediate apoptosis leading to thymic atrophy. On the other hand, TCDD could increase the soluble FasL which in turn could mediate apoptosis and toxicity in Fas+ tissues.
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Master of Science in Microbiology, University of Bombay, India. 1992-1994.

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Apoptosis as a mechanism of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-induced immunotoxicity.
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- Second place in the Fourteenth Annual Virginia Tech Research Symposium, April 1998.

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- Merit certificate in the Carl Smith Mechanisms Award (students specialty awards section), Society of Toxicology Conference, Cincinnati, OH, 1997. Altered expression of T cell receptor and other adhesion molecules correlates with the induction of apoptosis in thymocytes of mice exposed to 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD).

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A. B. Kamath, I. Camacho, P. S. Nagarkatti and M. Nagarkatti. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) induced apoptosis in thymocytes maybe regulated
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PUBLICATIONS:


A. B. Kamath, I. Camacho, P. S. Nagarkatti and M. Nagarkatti. Role of Fas- Fas ligand interactions in 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)-induced immunotoxicity: increased resistance of thymocytes from Fas-deficient (lpr) and Fas-ligand defective (gld) mice to TCDD-induced apoptosis. Manuscript submitted to J. Immunol.
PROFESSIONAL EXPERIENCE:

Teaching Assistant: Assisted professors with grading of papers, setting up exams and also in drawing chemical structures on Chemdraw for a pharmacology course, 1995-1996.

Jr. Researcher at the Tata Institute of Fundamental Research, Bombay, India, 1992-1994. Worked in a molecular biology laboratory, on a project dealing with the malarial parasite and expression vectors in yeast.


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