Computation Modeling of TCDD Disruption of B Cell Terminal Differentiation

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Alteration of immune function is among the earliest and most sensitive responses to TCDD and dioxin-like chemical exposure. One aspect of TCDD-induced immunotoxicity is the disruption of B cell terminal differentiation into plasma cells and consequent suppression of humoral immunity. In this study, we established a computational model describing the molecular circuit underlying B cell terminal differentiation and how TCDD may affect this process by impinging upon various molecular targets. It has long been suggested that cell differentiation in general is driven and sustained by bistable or multistable molecular circuits that are able to switch between different states in response to environmental differentiating cues. With such a memory switch, cells can remain in the differentiated states even after the initial cue no longer exists. We identified and confirmed, *in silico*, that the mutual transcriptional inhibition between Bcl-6 and Prdm1 may be at the core of a molecular switching circuit governing irreversible B cell differentiation into plasma cells. In addition to repressing gene expression of immunoglobin heavy chain directly, TCDD appears to interfere with the flipping of the switch by blunting antigen-induced c-Jun activation. As identified by our microarray study, TCDD exerts this inhibitory effect through transcriptionally inducing Mapk8ip1, a phosphotase that deactivates c-Jun. Our simulation also suggests that antigen-induced c-Jun activation is insufficient to flip the Bcl-6/Prdm1 switch, additional triggering sites, such as accelerated degradation of Bcl-6 protein by ERK may also be needed. In close collaborations with experimental biologists, our modeling efforts will help understand the molecular mechanism underlying B cell differentiation and eventually lead to quantitative prediction of TCDD immunotoxicity. *This abstract does not necessarily reflect offical policy of the U.S. EPA.*