A transcriptional regulatory switch underlying B-cell terminal differentiation and its disruption by dioxin

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Introduction

- Background
  - The terminal differentiation of B-lymphocytes into antibody-secreting plasma cells upon antigen stimulation is a crucial step in the humoral immune response.
  - A bistable switch arising from the coupled double-negative feedback loops involving Bcl-6, Blimp-1 and Pax5 forms the basis of the B-cell to plasma cell differentiation program and its disruption by dioxin.

- Hypothesis
  - A bistable switch arising from the coupled double-negative feedback loops involving Bcl-6, Blimp-1 and Pax5 forms the basis of the B-cell to plasma cell differentiation program and its disruption by dioxin.

Results

- Model Structure
  - In a deterministic model, the occurrence and timing of differentiation are uniquely determined by the LPS dose.

  - In stochastic simulations, fluctuations in the content of regulatory proteins impart a distributional characteristic to the occurrence and timing of differentiation.

- Deterministic vs. stochastic model
  - “Forward” and “backward” dose-response surfaces generated from the stochastic model by starting simulation from B-cell state and plasma-cell state respectively.

Conclusions

- The architecture of the B-cell transcriptional regulatory network consists of coupled mutually-repressive feedback loops involving the three transcription factors Bcl-6, Blimp-1 and Pax5. This structure forms the basis of an irreversible bistable switch directing the B-cell to plasma-cell differentiation process – i.e., the switch remains on after the activating stimulus (antigen) is removed.

- Using a kinetic model and bifurcation analysis, we suggest that TCDD may regulate the proportion of B-cells that differentiate into plasma cells by raising the threshold dose of antigen (lipopolysaccharide (LPS)) required to trigger the bistable switch in individual cells.

- The model also indicates that TCDD could cause some plasma cells to “de-differentiate” into B cells as the LPS dose is reduced.

- This would imply that TCDD disrupts the maintenance of the humoral response by causing long-lived plasma cells to de-differentiate to B cells.

References