Computational Modeling of Limb-Bud Dysmorphogenesis: Predicting Cellular Dynamics and Key Events in Developmental Toxicity with a Multicellular Systems Model

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1. COMPUTATIONAL EMBRYOLOGY & PREDICTIVE TOXICOLOGY

HYPOTHESIS:
A computer model that simulates cellular function in a growing embryo can be used to predict the potential impact of chemical exposure during early limb development.

2. SIGNALING NETWORK: spatial information processing

Query of Mouse Genome Informatics database (www.informatics.jax.org/) by ‘abnormal limb bud morphology’ (MP:0005650) returned genes for 132 relevant genotypes.

An e-Library developed from these genes (31,701 PubMed records annotated by MsIH terms for limb development) returned 81 genes regulating early limb morphogenesis.

Apical Ectodermal Ridge (AER) and Zone of Polarizing Activity (ZPA) are major signaling centers; pivotal signaling pathways fibroblast growth factor (FGF), sonic hedgehog (SHH), bone morphogenetic protein (BMP) and retinoic acid (RA) were modeled in CellDesigner (www.celldesigner.org/).

3. CELLULAR DYNAMICS: translation of spatial information

CELL AGENT-BASED MODEL (ABM): multicellular and signaling dynamics were modeled in CompuCell3D (www.compuCell3D.org/); the small working prototype simulated mouse hindlimb-bud development between Thielers stages 16-19 (~42h) in ~42,000 Monte Carlo Steps (MCS).

4. TOXICODYNAMICS: predicting key events

Example: 5-Fluorouracil, a teratogen that disrupts digit formation, perturbed 13 of 650 ToxCast HTS assays at ≤15 μM; impaired differentiation and increased cell loss (excessive apoptosis); p53 induction, mitotic arrest and cell death. These effects can be fed into the model for translation into predicted outcomes.

5. PRACTICAL APPLICATIONS OF A MULTICELLULAR SIMULATION

Example:
- Model reacts quantitatively to transitive mitotic arrest and/or excessive apoptosis
- Virtual models can rapidly sweep many ‘what-if’ exposure scenarios to predict response

Note: This is a preliminary computational framework for modeling limb bud morphogenesis and predictions may need further validation. For more information, visit www.informatics.jax.org.