Computational Embryology and Predictive Toxicology of Cleft Palate

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Capacity to model and simulate key events in developmental toxicity using computational systems biology and biological knowledge steps closer to hazard identification across the vast landscape of untested environmental chemicals. In this context, we chose cleft palate as a model defect to integrate four orthogonal approaches into a systems biology framework for predictive toxicology. The first approach utilized a semi-automated method to mine 20,000 PubMed cleft palate articles based on curated MeSH annotations. This returned a matrix of articles addressing relationships to genes, proteins, molecular pathways, and chemicals. Overall, 816 chemicals were co-annotated in 2,000 PubMed articles, of which 397 chemicals were additionally associated with toxicity, poisoning, or adverse effects. Furthermore, 100 proteins and 2,800 protein-protein combinations were co-annotated within cleft palate articles. Next, we utilized univariate associations between 3.2 million in vitro data points from high-throughput and high-content screening techniques on chemical-biological interactions and in vivo data from traditional guideline studies in EPA's ToxCast and ToxRefDB databases, respectively. Among the ~1000 chemicals evaluated, we identified 70 orofacial disrupting chemicals that could be statistically linked to disruption of biological pathways involving: retinoic acid receptor, pregnane X receptor, cytochrome P450s, aminergic GPCRs, matrix metalloproteinases, and ephrins. All this information was then used to develop an adverse outcome pathway (AOP) framework linking potential molecular initiating events, altered cellular behaviors (changes in ECM production, proliferation, apoptosis, adhesion, differentiation), tissue morphogenesis (mesenchymal mass, ECM remodeling, and medial edge degeneration) and organogenesis (altered palatal growth, reorientation, fusion). Finally, a multicellular computer simulation model capable of rendering key events in palatal fusion was built in the CompuCell3D environment. The simulation model incorporated key signals (e.g., TGFb, FGF10, BMP4) and cellular behaviors (eg, selective adhesion, apoptosis) in palatogenesis. The prototype model successfully represented the persistence of a midline epithelial seam following in silico disruption of TGFb signaling. Overall, this approach has the potential to integrate a vast array of knowledge and multidimensional data to predictively model the complexity of developmental toxicity, leading to novel hypotheses and mechanistic understanding of adverse developmental outcomes. *This abstract does not necessarily reflect US EPA policy.*