



Towards Building an AOP-based Prenatal Developmental Toxicity Ontology

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Background and Aim

Ontologies are a way to formalize domain-specific scientific knowledge. A **developmental ontology** would help researchers describe the pathways and processes critical to embryonic development and provide a way to link their chemical disruption to adverse outcomes. Designing one for developmental toxicology is scientific challenging, given the complexity of embryogenesis and the continuous changes at the molecular, cellular, tissue and organ levels occurring in time and location throughout gestation.

Our aim is to explore the construction of an ontology that integrates biological targets of toxicity with chemical structure-activity information and developmental trajectories by focusing on one important pathway as a prototype. We decided to start from the perspective of **retinoic acid (RA)**, which is a morphogen that regulates embryonic growth and differentiation and a known human teratogen.

Retinoid signaling includes elements in retinoid metabolism (e.g., RALDH, CYP26) and nuclear receptor (RAR, RXR) activation and thus serves as an excellent prototype for adverse outcome pathway (AOP) elucidation associated with developmental defects such as caudal regression.

Focus: RA metabolism leading to caudal regression

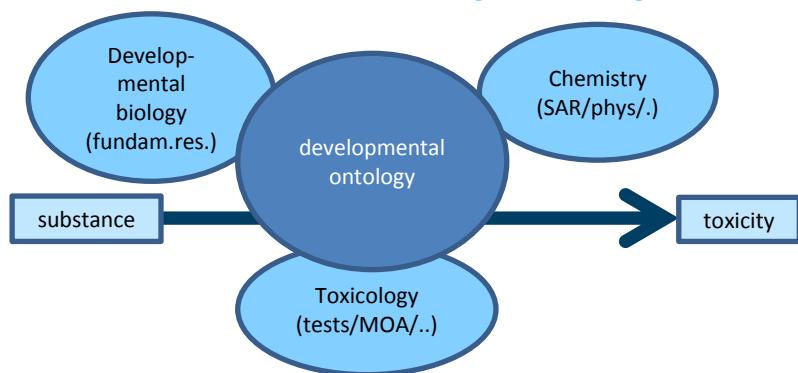


Fig 1: Combining knowledge from biology, chemistry and toxicology to build an ontology that will be used to assess prenatal developmental toxicity.

Methods

We will approach the ontology from two directions: biology and chemistry. The chemistry direction will focus on compounds that disrupt development through perturbation of the retinoic pathway. The biology direction will formalize the pathway players (genes, proteins, and endogenous chemicals) and the relationships to each other and their activity.

Chemistry: key steps

- Identify chemicals with known or predicted activity at retinoid pathway
- Define categories of chemical-biological interaction (mechanisms of action)
- Based on a decision tree for developmental toxicants (Wu et al., Chem. Res. Toxicol. 2013, 26, 1840–1861).
- Translate chemical activity into ontology entries

Biology & Toxicology: key steps

- Assess the available data in the literature using a HTP text mining tool
- Map interactions on the molecular level into ontology entries
- Focus on the **anterior-posterior axis** and the **dorsal-ventral axis**

RA	Cyp	Ald	RAR	RXR	Tox	pattern	caudal	axial	PMID	PubYr	Title
1									19243820	2009	Regulation of Hoxb4 induction after neuralization by somite signal and neural competence.
1									1207788	1991	Retinoic acid-binding protein, rhombomeres and the neural crest.
1									8079431	1994	Localization of CRABP-I and CRABP-II mRNA in the early mouse embryo by whole-mount in situ hybridization: implicat
1									1898738	2008	Ocular coloboma and dorsoventral neuroretinal patterning defects in Upk mutant eyes.
1									19086026	2009	Effects of retinoic acid on Dominant hemimelia expression in mice.
1									12050138	2002	The retinoic acid signaling pathway regulates anterior/posterior patterning in the nerve cord and pharynx of amphiox
1									13136149	2004	Independent roles for retinoic acid in segmentation and neuronal differentiation in the zebrafish hindbrain.
1									12872568	2007	CYP26A1 and CYP26C1 cooperatively regulate anterior-posterior patterning of the developing brain and the production
1									1895453	1996	Patterning the vertebrate neuraxis.
1									21955539	2013	Saltatory remodeling of Hox chromatin in response to rostrocaudal patterning signals.
1									7916256	1993	Molecular mechanisms of segmental patterning in the vertebrate hindbrain.
1									10655389	2000	Plasticity in mouse neural crest cells reveals a new patterning role for cranial mesoderm.
1									18926319	2008	Retinoic acid metabolizing factor <i>rCyp26c</i> is specifically expressed in neuroectoderm and regulates anterior neural pat
1									15614783	2009	Global analysis of RAR-responsive genes in the Xenopus neurula using cDNA microarrays.
1									18443282	2008	Modular patterning of structure and function of the striatum by retinoid receptor signaling.
1									18625063	2008	FGF15 promotes neurogenesis and opposes FGF8 function during neocortical development.
1									25454634	2014	3D reconstruction of the patterned neural tube from embryonic stem cells.
1									12949900	2003	Establishment of embryonic neuroepithelial cell lines exhibiting an epiplastic expression pattern of region specific m
1									16750825	2006	A retinoic acid-Hox hierarchy controls both anterior/posterior patterning and neuronal specification in the developi
1									28443947	2015	Deterministic HOX patterning in human pluripotent stem cell-derived neuroectoderm.

Fig 2: A sample of the literature mining output

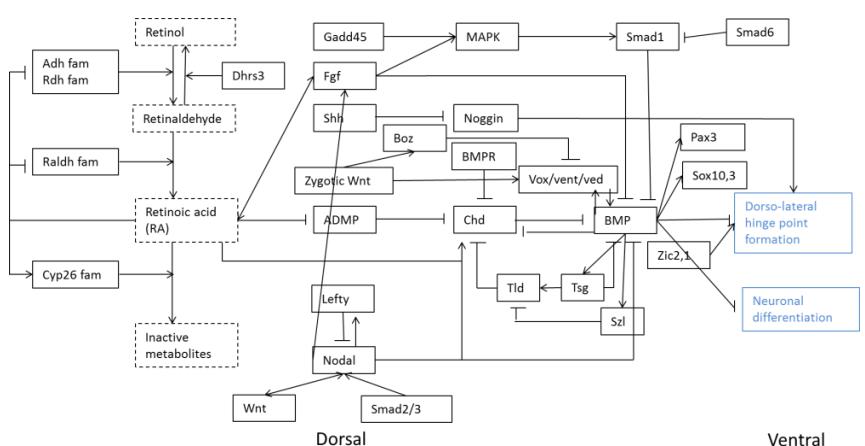


Fig 3: Gene and molecular interactions on the dorsal-ventral axis focusing on RA binding, and leading to caudal effects.

Extracted information from the chemistry and biology tasks will be structured in an **ontology software environment** in triple-store format. With this data and visualization tools, we will visualize perturbation of the caudal development by chemical disruptors of the retinoid system.

Summary

This prototype of ontology construction serves as an initial framework for a broader ontology using data from approximately 900 published developmental toxicity studies that contains information on putative molecular initiating events and key events that play roles in a number of critical developmental adverse outcome pathways.