Developmental Ontology: Computational modeling of Retinoic Acid in Development of Spina Bifida

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Retinoic acid during development

The concentration of retinoic acid (RA) is tightly controlled over time and location during embryogenesis. RA is considered a morphogen. RA may serve as an excellent starting point for the elucidation of adverse effects associated with a wide variety of developmental defects.
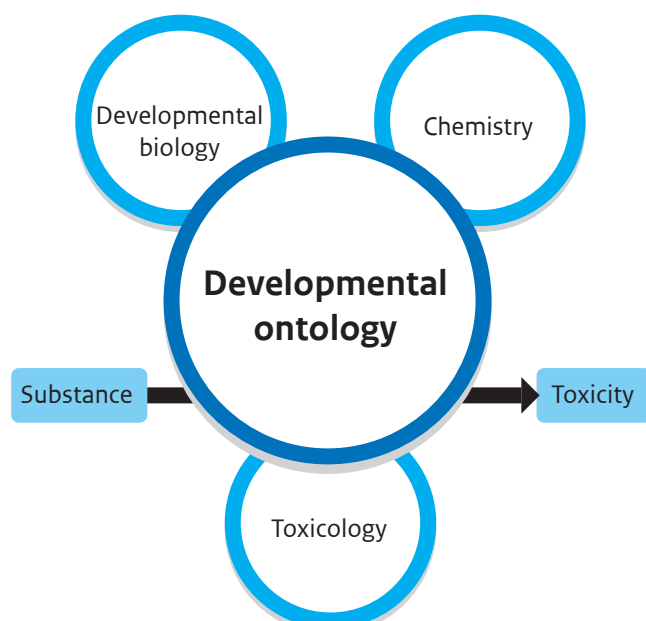
Spina bifida

Spina bifida has a prevalence of 0.03% in newborns and is the most prevalent caudal neural tube defect. RA balance during embryonic development plays an important role in neural tube closure and may play a role in the development of spina bifida.

Computational modelling

Based on available data, the molecular regulation of neural tube closure was mapped, from the perspective of RA as a central morphogen. We expanded an earlier AOP relating RA perturbation to neural tube and axial malformations in mammalian development. We employed text mining tools that allowed rapid identification of relevant literature related to human embryonic neural tube closure. Our aim is to model biological knowledge for mechanistic understanding of spina bifida and predict adverse effects.

Focus: RA metabolism leading to spina bifida

Figure 1. Our aim is to integrate knowledge from biology, chemistry and toxicology into an ontology based computer model, that will be used to assess prenatal developmental toxicity.
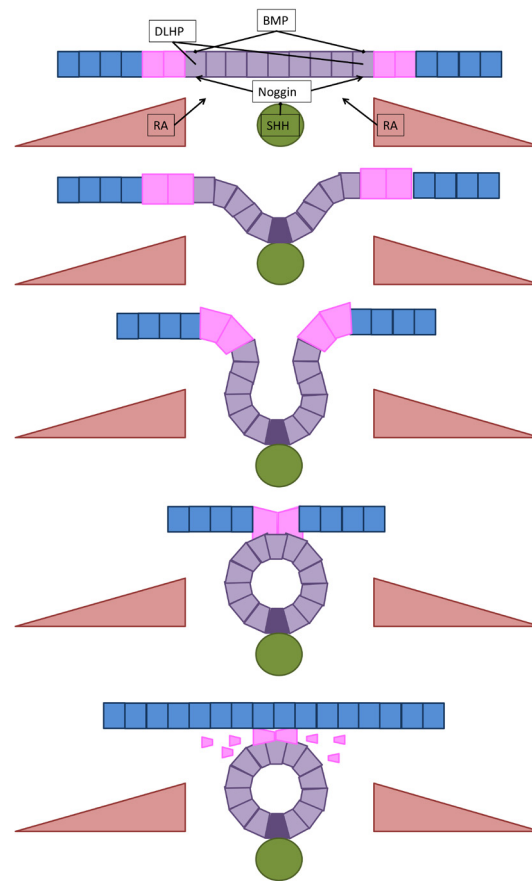
Neural tube closure

Figure 2. Schematic visualization (top to bottom) of neural tube closure. BMP inhibits dorso-lateral hinge point (DLHP) formation, whereas this is stimulated by Noggin. Noggin is inhibited by Shh, which is produced by the notochord. RA is produced by somites and regulates this process through FGF signaling.

Dorsal-Ventral axis

Figure 3. Molecular mapping of RA signaling on the DV axis.

Next steps

Ontologies describing the molecular network underlying morphogenesis will be used for computational modeling. Extracted information on RA related molecular regulators and biomarkers is structured in an ontology software environment. This work aims at:
- the identification of critical events leading to adverse effects
- a description of the molecular network of developmental pathways
- Integration of toxicological and chemical data
- proof of principle for prediction of adverse outcomes

Summary

Retinoic acid regulates the development of many organs and tissues throughout vertebrate embryogenesis, and plays a crucial role in neural tube closure.

Retinoic acid homeostasis offers a wealth of biomarkers that may be employed to detect a wide variety of embryotoxic responses.

An ontology of the molecular pathways of neural tube closure can be integrated in computational visualization of embryonic development, allowing the generation of predict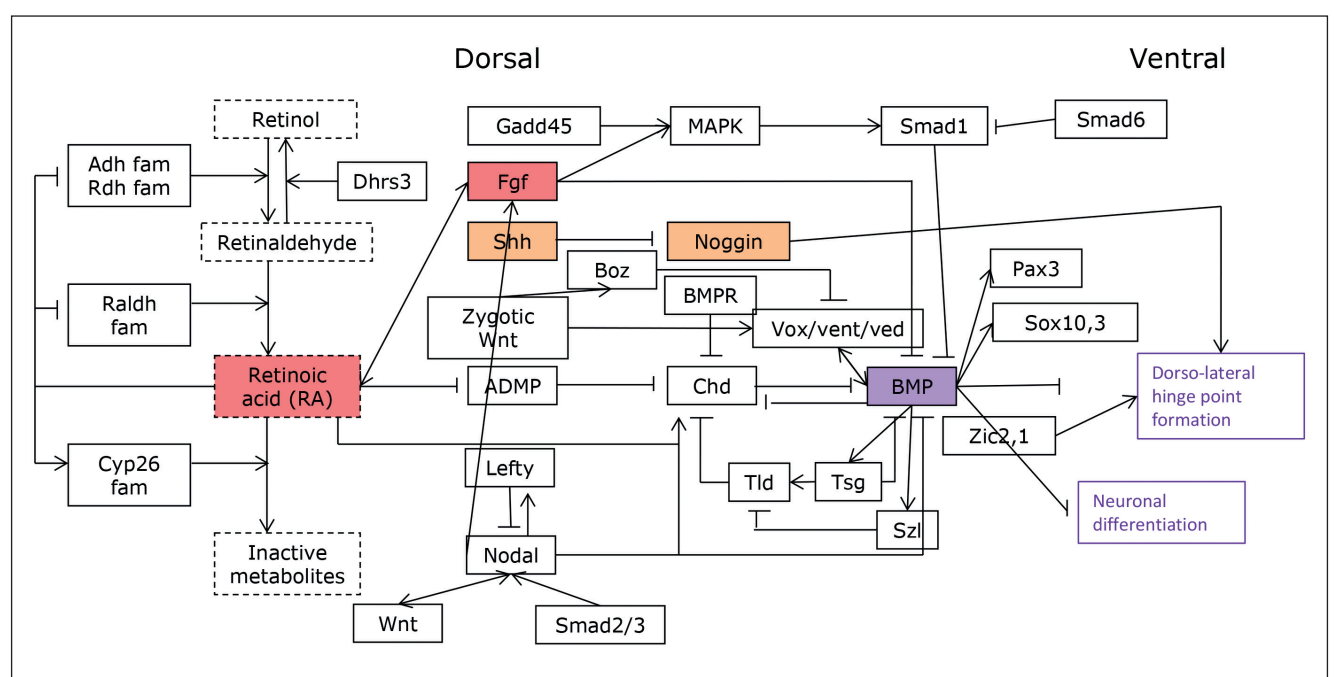ive tools for e.g. spina bifida.