National Institute for Public Health
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Ministry of Health, Welfare and Sport

An AOP-based Ontology for Neural Tube Closure Caused by Disturbance in Retinoic Acid Signaling

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Retinoic acid (RA) balance and leading to neural tube defects

Retinoid signaling plays an important role in embryo-fetal development and its disruption is teratogenic. The biology of the RA pathway, leading to defects in neural tube closure was the basis for the construction of an ontology for developmental toxicity.

We are constructing an ontology from an AOP network that incorporates feedback-loops, which can be used for risk assessment.

Cellular behavior

For each cell type information on its behavior was collected from the available literature to map molecular interactions and genetic signals.

Table 1: example of information on cellular behavior for neuroectoderm fusion.

Cell type	Behavior	Signal	
....	....	....	....
neuroectoderm	fusion	inhibited by	BMP
neuroectoderm	fusion	requires	Grhl2
neuroectoderm	fusion	requires	correct cell polarity
neuroectoderm	fusion	inhibited by	RhoA
neuroectoderm	fusion	requires	Lrp6
neuroectoderm	fusion	involves	Ephrin
neuroectoderm	fusion	requires	Grhl2
neuroectoderm	fusion	requires	Lrp6
neuroectoderm	fusion	requires	Traf4
neuroectoderm	fusion	requires	Cdx2
neuroectoderm	fusion	requires	Pax3
....	....	....	....

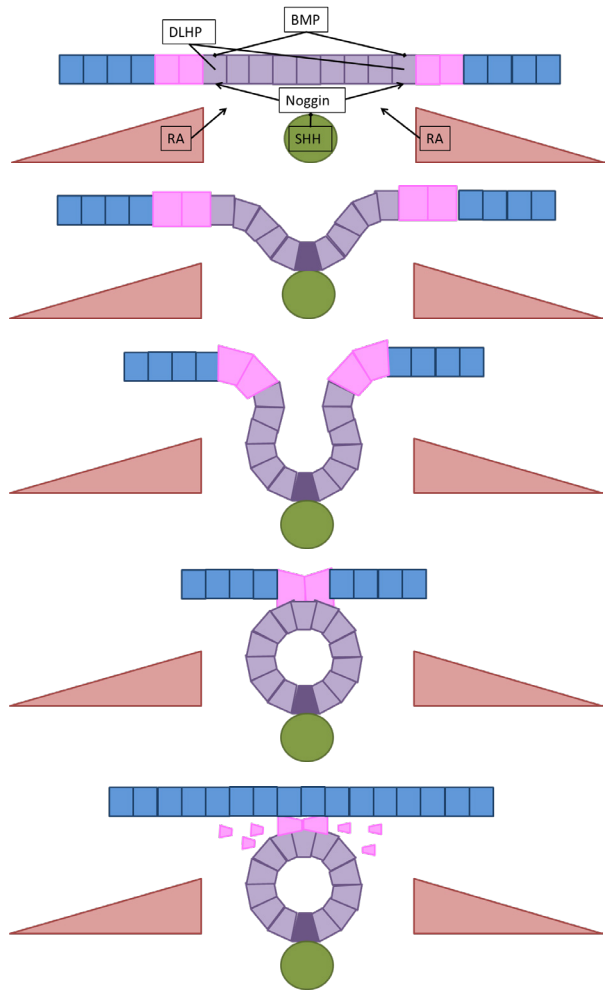

Fig 1: Schematic visualization (top to bottom) of neural tube closure. BMP inhibits dorso-lateral hinge point (DLHP) formation, whereas this is stimulated by Noggin. Noggin is inhibited by Shh, which is produced by the notochord. RA is produced by somites and regulates this process through FGF signalling.

Molecular interactions

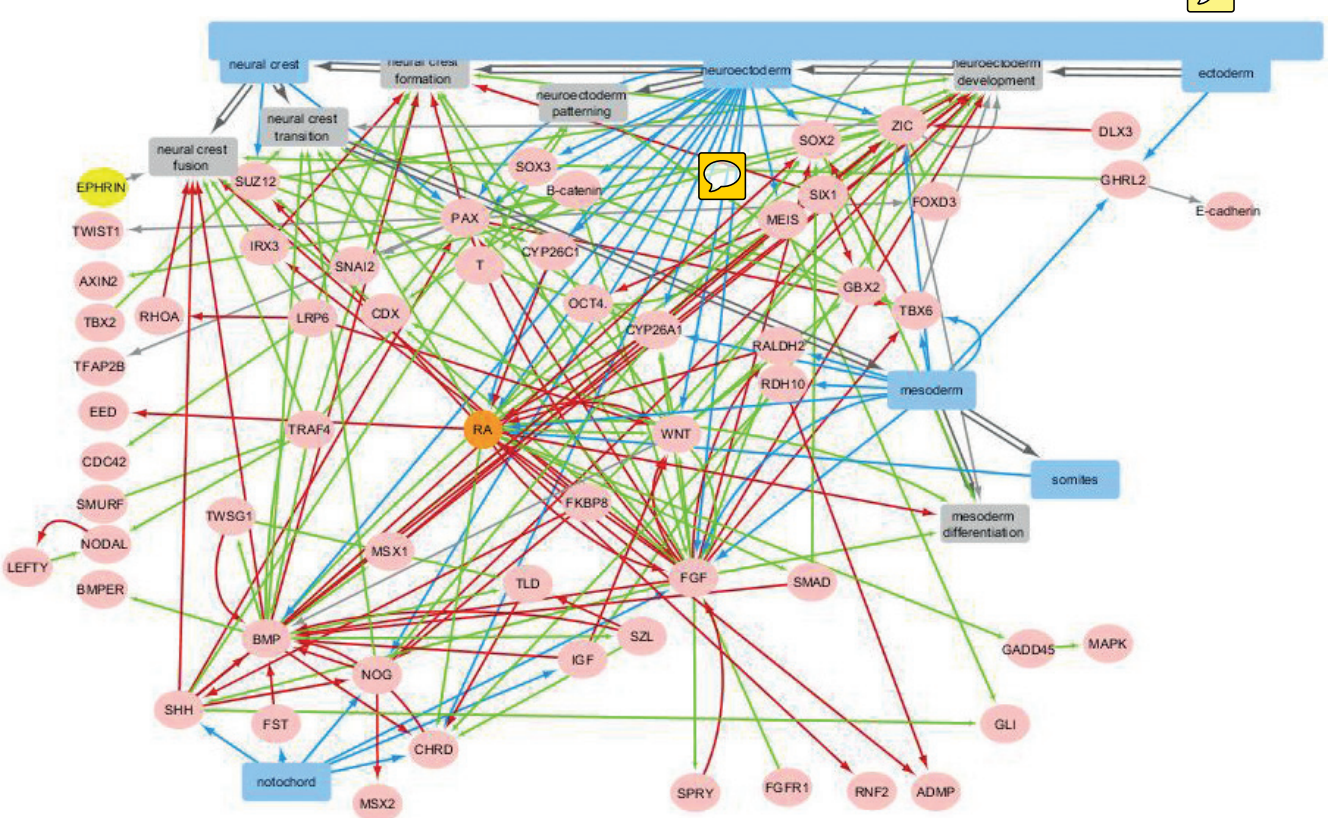

Fig 2: Network of genes and proteins that are required for normal neural tube closure. The upper blue bar represents the ectoderm, which partly differentiates in neuroectoderm and neural crest. The notochord is in the bottom left of the images and the mesoderm developing into somites and differentiating into other cells and tissues. All circles represent genes. Blue lines indicate that this gene or protein is produced by this cell type. Green lines indicate stimulation and red lines indicate inhibition.

Conclusions and future perspective

The network:

- includes the genes and pathways that are expected to respond by compounds interfering with the RA balance or lead to neural tube defects.
- Can be modelled using an integrated computational systems model with which toxicity predictions can be made at the level of adverse outcomes in the intact individual.

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