AIMT5 Summary

Embryo development follows a strictly orchestrated program, which leads from a fertilized egg to a newborn individual. Malformations are the consequence of adverse interference with this program. The program of embryo development is driven by a complex interplay among many processes that direct the proliferation, migration and differentiation of cells in a time- and space-dependent way. Many of these developmental processes are regulated by retinoic acid balance in the embryo.

The retinoic acid (RA) pathway controls retinoid homeostasis, which plays an important role in cell differentiation and cell growth in the embryo. Disturbances in RA signaling can result in malformations of the embryo. The disruption of the RA pathway, leading to defects in neural tube closure, was the basis for the construction of a developmental toxicity ontology. The ontology can be considered a network of developmental processes, described as adverse outcome pathways, including feedback loops representing homeostasis. In the construction of the ontology existing information from developmental biology, chemistry and toxicology is combined. Basic elements in the ontology are subjects (enzymes, receptors, cell types) and their quantitative relationships (response-response relationships), together forming a network of biological interactions that can be mapped to a vulnerable window for teratogen-induced neural tube defects such as spina bifida. We have searched literature using text-mining tools that allowed rapid identification of relevant information. We collected known molecular interactions, genetic signals and responses that: (a) play a crucial role in neural tube cellular differentiation; (b) establish anterior-posterior gradients (FGF and RA signaling) and dorsal-ventral gradients (zinc factors (Zic) and BMP signaling) for regional specification. Xenobiotic compounds potentially affect molecular initiating events that are important for RA balance (like CYP26 enzymes and RALDH2). High-throughput screening data was used to connect these molecular initiating events with toxicological data on the development of posterior neural tube defects. Compounds that are known to cause posterior neural tube defects (2-methoxyethanol, valproic acid and retinoic acid) indeed showed different gene regulation compared to a compound not causing such effects (nitrofen). Ultimately, this network can be dynamically modeled in silico, providing an integrated computational systems model with which toxicity predictions can be made at the level of adverse outcomes in the intact individual. A follow-up LRI project aimed at implementing the ontology in an in silico model will start in 2019.