Multiscale Systems Modeling of Male Reproductive Tract Defects: From Genes to Populations

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The reproductive tract is a complex, integrated organ system with diverse embryology and unique sensitivity to prenatal environmental exposures that disrupt morphoregulatory processes and endocrine signaling. U.S. EPA's *in vitro* high-throughput screening (HTS) database (ToxCastDB) was used to profile the bioactivity of 54 chemicals with male developmental consequences across ~800 molecular and cellular features. The *in vitro* bioactivity on molecular targets could be condensed into 156 gene annotations in a bipartite network. These results highlighted the role of estrogen and androgen signaling pathways in male reproductive tract development, and importantly, broadened the list of molecular targets to include GPCRs, cytochrome-P450s, vascular remodeling proteins, and retinoic acid signaling. A multicellular agent-based model was used to simulate the complex interactions between morphoregulatory, endocrine, and environmental influences during genital tubercle (GT) development. Spatially dynamic signals (e.g., SHH, FGF10, and androgen) were implemented in the model to address differential adhesion, cell motility, proliferation, and apoptosis. Urethral tube closure was an emergent feature of the model that was linked to gender-specific rates of ventral mesenchymal proliferation and urethral plate endodermal apoptosis, both under control of androgen signaling. A systemic parameter sweep was used to examine the sensitivity of crosstalk between genetic deficiency and environmental disruption pathways. The *in silico* impact of subtle variations in SHH and FGF10 activity (simulating individual variability) with respect to dose-dependent androgen receptor insufficiency was modeled in a simulated population. Hypospadias could occur at 70% SHH and 70% FGF10 sufficiency with merely a 5% reduction in AR sufficiency. In conclusion, multiscale systems modeling provides a means to simulate population-level responses to reveal critical thresholds in teratogenesis for complex interactions between genetic (e.g., FGF10 polymorphism), environmental (e.g., androgen receptor disruption), and lifestyle (e.g., cholesterol deficiency for SHH) factors. (Disclaimer: this abstract does not reflect EPA policy).