Computational Embryology and Predictive Toxicology of Hypospadias

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Abstract # 418a

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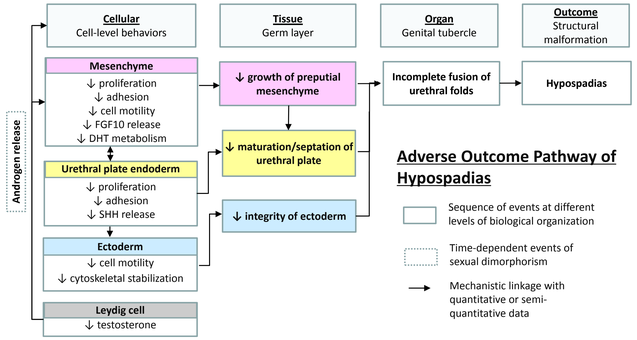
Introduction

Hypospadias, one of the most common birth defects in human male infants, is a condition in which the urethral opening is misplaced along ventral aspect of the penis. We hypothesized that a cell-level computer simulation composed of key events in adverse outcomes could predictively model the pathogenesis of hypospadias using *in vitro* data (*1*), starting with disruption of cell signaling and structural targets of the fetal testis and genital tubercle during embryogenesis.

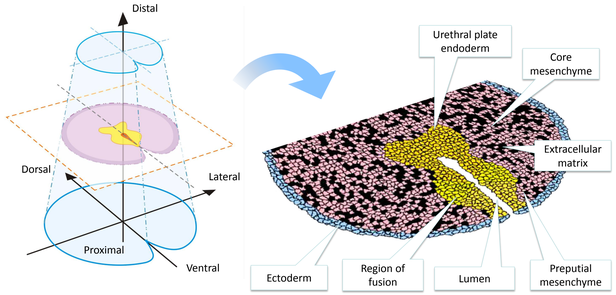


Method

- Semi-automated literature mining was first utilized to identify PubMed articles based on MeSH annotations for chemicals and proteins (*2*).
- 312 chemicals and 293 proteins were co-annotated within the literature on hypospadias. This information was then used to develop an AOP framework.
- A cell-level computer simulation was built with a CompuCell3D model (*3*) by incorporating key signals (e.g. sonic hedgehog (SHH), fibroblast growth factor 10 (FGF10), and androgen) and cellular behaviors (e.g., differential adhesion and selective growth) in mouse genital tubercle development .
- Patterns of mesenchymal growth and urethral remodeling were visualized and compared to normal development.

Genital tubercle development is modeled at the cellular level

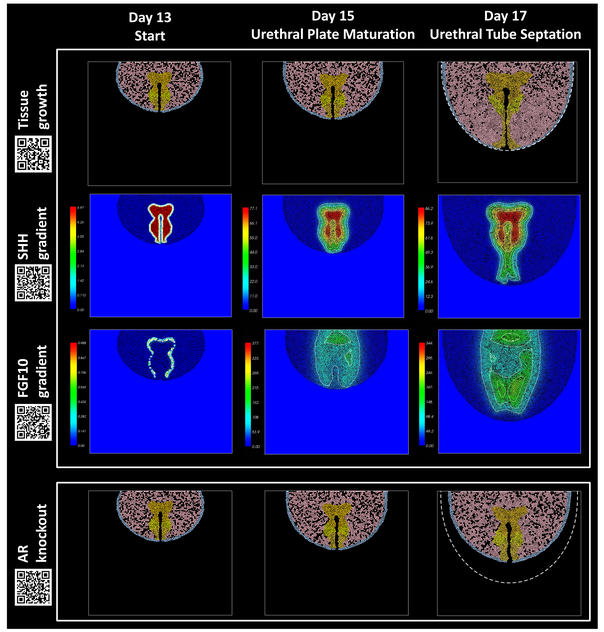
- The model covered urethral plate maturation and urethral tube septation during gestation day 13 – 17 of mouse embryo development with 5,000 Monte Carlo Step calculations (*3*).
- The initial structure was captured from the morphological development of the urethral plate endoderm (*4*,*5*).
- The three-dimensional structure of the developing genital tubercle was modeled in an idealized two-dimensional cross-section plane.



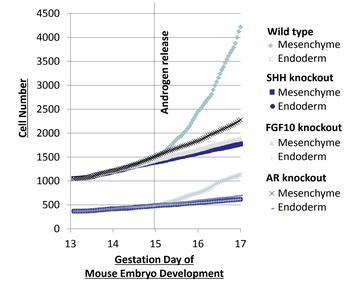
- The current model captured the interaction between urethral plate endoderm, mesenchyme, ectoderm through sonic hedgehog (SHH), fibroblast growth factor 10 (FGF10), and androgen receptor (AR) signaling in CompuCell3D as follows:

Source	Produces	Acting on	Effects
Urethral plate endoderm	SHH	Core and preputial mesenchyme	Growth and FGF10 secretion
Core and preputial mesenchyme	FGF10	Urethral plate endoderm	Growth
Core and preputial mesenchyme	FGF10	Core and preputial mesenchyme	Growth
Leydig cell	Androgen	Urethral plate endoderm and preputial mesenchyme	Increase FGF10 response

Morphogenetic changes with SHH, FGF10, and androgen are visualized during sexual dimorphism

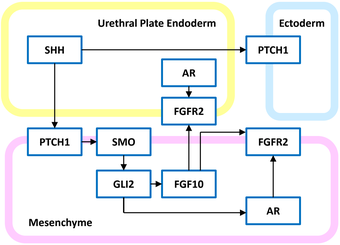


- The current simulation visualized the mesenchymal-endodermal interaction through SHH-FGF10 signaling and physical (cell-level) events.
- SHH had a narrower spatial gradient than FGF10 since it was transported through transcytosis (*6*).
- Sexual dimorphism of the genital tubercle was driven by androgen-dependent ventral growth of preputial mesenchyme from gestation day 15.
- The simulation demonstrated ventral urethral plate endoderm septation, but urethral fold fusion remained incomplete through gestation day 17, possibly due to missing key events such as EphB2 signaling (*7*,*8*).
- The androgen-dependent mesenchymal growth resulted from an increase in both sensitivity and response to FGF10.
- This behavior was consistent with the presence of androgen response element in the FGFR2 promoter (*4*); it also suggested the involvement of other molecular targets downstream to AR signaling.



Conclusions and Future Directions

- The current results support the hypothesis that a cell-level computer simulation can be used to model the high-level morphogenetic events that result in hypospadias.
- The simulation also demonstrates the time-dependent interaction between SHH, FGF10, and AR signaling in genital tubercle development.
- Further simulations will address the missing key events (e.g. EphB2) and model the chemical disruption of genital tubercle development using *in vitro* data (*1*,*9*).



Cell Signaling in Genital Tubercle Development

Reference

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