Published in final edited form as:

Differentiation. 2010 ; 80(0): 79–80. doi:10.1016/j.diff.2010.08.004.

Urogenital Development: A Four-Part Story of Mesenchymal-Epithelial Interactions

Gerald R. Cunha

Division of Pediatric Urology, University of California, San Francisco, CA 94143

Gerald R. Cunha: cunhag@urology.ucsf.edu

The Cunha lab began in 1970 at Stanford University, moved to the University of Colorado in 1976, and was at UCSF from 1982 to 2005 when I “retired”. The lab was noted for epithelial-stromal interactions, hormone action, and developmental and cancer biology in organs of the male and female urogenital tracts and mammary gland in species as diverse as mice, rats, rabbits, humans and spotted hyenas. Particularly productive periods for the Cunha lab were in the mid-1980s when Yoshiki Sugimura was present and also around 2000 when amongst others Axel Thomson and Takeshi Kurita were in attendance. These three independent investigators have moved on to established their own labs and in the case of Sugimura to become Chairman of Urology. It is with pleasure that I introduce their research papers in this Urogenital Development Mini-Series. In addition to papers from Sugimura, Thomson and Kurita, this Mini-Series also contains a review authored by Gregory Tasian from Larry Baskin’s lab at UCSF. Since my “retirement” in 2010, I have been occupying part of my time in the Baskin lab working on differentiation of bladder smooth muscle, development of external genitalia, and spotted hyena developmental biology.

The common theme of the 3 papers in this mini-series is urogenital development. All organs of male and female urogenital tracts (with the exception of the gonads) develop as a result of reciprocal mesenchymal-epithelial interactions. Male and female urogenital systems can be subdivided into separate urinary and genital organs. Genital organs (epididymis, vas deferens, prostate, seminal vesicle, penis, oviduct, uterus, cervix, vagina and clitoris) are hormonally dependent and/or hormonally responsive for their development. In contrast, most urinary organs (kidney, ureter, bladder) are identical in males and females and are hormone-independent for development. The common theme for all of these urogenital organs is that mesenchyme (embryonic connective tissue) induces and patterns epithelial morphogenesis and differentiation, a concept amply demonstrated in the prostate by decades of publications from the Cunha lab (Cunha et al., 1987; Marker et al., 2003). Papers from the Sugimura and Thomson laboratories deal with the chemical mediators of mesenchymal-epithelial interactions in the prostate. The paper by Yoshio from the Sugimura laboratory documents the effect of transforming growth factor alpha (TGF α) in urogenital gland development in the mouse. Such TGF α overexpression failed to induce carcinogenesis or

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

hyperplasia in urogenital organs, but increased the number of p63-positive basal cells in epithelium of certain lobes of the prostate, and elicited bladder outlet obstruction causing bladder distension in 19/20 TGF α transgenic mice. The paper by Ashley et al from Axel Thomson's lab demonstrates a role for EphB3 and EphrinB1 as mediators of paracrine signaling from mesenchyme to epithelium in regulating prostate organogenesis, specifically implicating EphrinB signaling in regulation of prostatic growth.

The paper by Tasian et al deals with hormone-independent development, patterning and differentiation of smooth muscle of the urinary bladder, an organ whose development is dependent upon reciprocal mesenchymal-epithelial interactions. This review summarizes years of collaborative work between the Baskin and Cunha labs. In the developing bladder, the epithelium induces smooth muscle differentiation in the mesenchyme. This process is mediated at least in part by sonic hedgehog, even though other mediators are also at play (see Table 1, page 6 in Tasian et al). A fascinating aspect of bladder smooth muscle is its patterning. Bladder smooth muscle is consistently located some distance from the inducing epithelium, being separated from the epithelium by a thick connective tissue layer. This pattern (which is similar to that in the uterus) is controlled by epithelial signals yet to be discovered.

The third paper in this series, authored by Takeshi Kurita, deals with the derivation of vaginal epithelium (see the Editorial in this issue). The vagina is a target principally of estrogen and progesterone, whose actions are mediated via mesenchymal epithelial-interactions (Cunha et al., 2004).

Male and female urogenital tracts provide unparalleled opportunities for investigating mesenchymal-epithelial interactions. Interaction between tissues can be initiated or curtailed at will by introduction or removal of trophic hormones or anti-hormones. Development of male and female urogenital organs occurs during embryonic as well as postnatal periods. Indeed, developmental processes in reproductive tracts occur naturally throughout adult reproductive life, for example in estrous or menstrual cycles in which organs are substantially remodeled in cyclic fashion throughout reproductive life and experimentally even beyond. Morphogenesis, growth, cell differentiation, secretory protein production and malignant processes occur in urogenital organs, but only under appropriate hormone action, making urogenital organs ideal subjects for the endocrinologist and pathologist.

References

- Cunha GR, Cooke PS, Kurita T. Role of stromal-epithelial interactions in hormonal responses. Arch Histol Cytol. 2004; 67:417–434. [PubMed: 15781983]
- Cunha GR, Donjacour AA, Cooke PS, Mee S, Bigsby RM, Higgins SJ, Sugimura Y. The endocrinology and developmental biology of the prostate. Endocrine Rev. 1987; 8:338–362. [PubMed: 3308446]
- Marker PC, Donjacour AA, Dahiya R, Cunha GR. Hormonal, cellular, and molecular control of prostatic development. Dev Biol. 2003; 253:165–174. [PubMed: 12645922]