Essential roles of androgen signaling in Wolffian duct stabilization and epipidal cell differentiation

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The epididymis is one of the male accessory organs derived from embryonic structure, Wolffian duct (WD). Although essential roles of androgen in the WD masculinization have been established, little is known about the cellular and molecular processes of WD masculinization. It is also unclear about the regulatory mechanisms of epithelial cell differentiation in the epididymis. The current study examined the cellular process of the WD stabilization controlled by androgen signaling via androgen receptor (AR). Analyses utilizing AR KO mice revealed that androgen signaling inhibits epithelial cell death in the WD. Further analysis on AP2α-Cre;ARfloX/Y mice, in which AR function is deleted in the WD epithelium, uncovered that epithelial AR is not required for the WD stabilization, but is required for the epithelial cell differentiation of the epididymis. Particularly, the loss of epithelial AR significantly reduced expression of p63 and we demonstrated that p63 is essential for basal cell differentiation in the epididymal epithelium. We also interrogated the possibility of regulation of p63 by AR in vitro and found that p63 is a likely direct target of AR regulation. We will also discuss some interactions between androgen and major growth factor signalings to understand the molecular mechanisms of WD masculinization mediated by androgen signaling.

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Sprouty genes are required for normal urethral formation in mouse

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Mammalian external genitalia organogenesis requires a tightly coordinated network of signaling molecules and transcription factors. Disruption of these signaling pathways can result in hypospadias, a congenital anomaly in which urethral development is defective. Hypospadias is one of the most common human birth defects, affecting approximately 1 in every 250 live male births, but the molecular mechanisms underlying hypospadias are incompletely understood. Mice lacking the FGF receptor Fgf10 have severe defects in genital morphogenesis, indicating that Fgf10 signaling is important in genital patterning. Sprouty (Spry) genes encode antagonists of FGF signaling and are expressed in the urethral epithelium during embryogenesis. To study the role of Sprouty genes in genital development, we examined mice carrying null alleles of Sprouty1 and Sprouty2 (Spry1−/−;Spry2−/−) and found that formation of the tubular urethra in males was perturbed. Abnormal urethral patterning was evident as early as embryonic day (E)14.5, and histological examination of serial sections from Spry1−/−;Spry2−/− male genital tubercles revealed that the epithelial lining of the urethra remained externalized. Closure defects in Spry1−/−;Spry2−/− male mice were associated with significantly reduced levels of apoptosis in the epithelium. Microarray analysis of Spry1−/−;Spry2−/− male genital tubercles at E13.5 revealed a number of genes with significantly altered levels of expression, which we are currently investigating in more detail. In summary, our data show that Sprouty genes play a critical role in formation of the tubular urethra in the external genitalia and that deletion of Sprouty genes results in hypospadias.

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Hippo-signaling pathway is an evolutionally conserved tumor suppression pathway that firstly identified in Drosophila. While it has been found to be dysregulated in a variety of human cancers and cancer cell lines, the underlying mechanism is still unclear. Although the Drosophila hippo pathway shows a linear scheme, the mammalian one (Mst/Ww45-Lats/Mob1-YAP/TAZ) seems to have more branches from each component, and function differentially in different organs. Our lab is specifically investigating the hippo pathway in mouse liver since we found that liver is very sensitive to its dysregulation. By using (albumin-) Cre/loxP system, we successfully generated conditional knockout mice with liver specific deletion of mst1/2, Ww45 and lats1/2 individually. The phenotypes of these mutant livers are quite different in terms of the liver/body weight ratio, tumor initiation, oval cell (liver stem cell) expansion and the mouse lifespan. Though all of them develop tumor-like nodules, the lats deletion has the most severe phenotype, the mst is less, and the Ww45 is mild. Microarray analysis indicates that these three hippo components share common targets but the majority are different, indicating they may have individual function besides forming a linear kinase cascade in the hippo pathway. Further evidence is that yap/taz deletion in lats mutant liver can only partially rescue its phenotype. It will be interesting to find out other lats target, which might play important roles in liver homeostasis.

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