Ectodermal β-catenin is an essential modulator of mouse external genitalia formation: New mouse model for the human congenital anomaly "hypospadias"

Graduate School of Pharmaceutical Sciences, Department of Organ Formation

Ahmad Reza F. Mazahery

β-catenin is a molecule belonging to the armadillo family of proteins that is a crucial core-component of cellular adherens junctions (AJ), and a component of the canonical Wnt-signaling pathway. This study attempted to analyze the functional significance of ectodermal-derived β-catenin during the development of the mouse genital tubercle (GT), a mammalian anlage of the external genitalia. For this purpose the conditional loss of function mouse mutant *Wnt7a-cre;β-cat$^{f/f}$* was utilized. Loss of ectodermal β-catenin leads to the formation of urethral cleft during preputial uprising. Although expression of E-cadherin was retained in the GT ectoderm of mutants probably through Plakoglobin compensatory expression, ectodermal expression of other crucial AJ components such as α–catenin and F-actin in the cell-cell boarder were distinctly reduced. Further, the study also shows that β-catenin is necessary for the expression of its transcriptional downstream target Lef-1 which was localized in the basal layer of the preputial ectoderm, excluding the midventral region, at E15.5. Such specialized region was observed to poses prominent cytoplasmic β-catenin expression at this stage. Coincidentally, mitotically active cells were also mostly found in such ectodermal layer. In mutant GTs, cell proliferation in the preputial ectoderm was significantly decreased. This

suggests that β-catenin may be required to regulate ectodermal cell proliferation, possibly through Lef-1 expression. Thus, β-catenin is shown to perform dual function, initially as an adhesion molecule and later on as a possible transcription factor,