

 DEVELOPMENT

AR signalling and sexual development

Newly published data have demonstrated that androgen exposure and androgen receptor (AR) signalling *in utero* influence sexual differentiation of the urethra and movement of the sinus ridge, which are important processes in the formation of the vaginal opening. This new insight increases our understanding of the mechanisms involved in disorders of sexual development such as congenital adrenal hyperplasia.

In mice, the morphogenic events that result in the sexually dimorphic urogenital system, such as urethral lengthening and sinus ridge positioning, were initiated by embryonal day 16.5. Administration of methyltestosterone to pregnant mice during embryonal days 14.6–16.5 and 16.5–18.5 but not during days 12.5–14.5 resulted in aberrant vaginal and vulval development in female offspring. Mice exposed to excess androgen levels between embryonal days 14.5 and 16.5 had masculinization of the sinus-ridge position and urethral length on day 17.5. However, acute androgen exposure, given as a single dose on embryonal day 16.5 did not disrupt vaginal development.

Methyltestosterone was observed to directly affect the sinus ridge, acting via AR signalling. In male mice, conditional deletion of *Ar* in the urogenital sinus epithelium did not affect the sinus-ridge position, but conditional *Ar* deletion in urogenital sinus mesenchyme caused the relative position of the sinus ridge to distally shift and the urethra failed to elongate by embryonal day 17.5, suggesting that mesenchymal AR expression is sufficient for masculinization of the urethra.

Mosaic analysis of androgen-treated female embryos revealed a significant positive correlation between the number of AR-positive mesenchymal cells in direct contact with the basement membrane and the position of the sinus ridge.

These data indicate that AR signalling in the mesenchyme of the sinus ridge determines the position of the sinus ridge, providing new insight into how AR signalling influences prenatal sexual differentiation.

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ORIGINAL ARTICLE Larkins, C. E. *et al.* Spatiotemporal dynamics of androgen signaling underlie sexual differentiation and congenital malformations of the urethra and vagina. *Proc. Natl Acad. Sci. USA* <http://dx.doi.org/10.1073/pnas.1610471113> (2016)