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DMRT1 turns on testicular differentiation during XX sex-reversal in the goat

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Background

In mammals, ovaries (XX) and testes (XY) differentiate from a common bipotential gonad. Testicular differentiation depends on the activation of *SRY* located on the Y chromosome. Numerous studies realized in the mouse demonstrated that *SRY* activates *SOX9* and the testis pathway. In females, the absence of *SRY* and the activation of several pro-ovarian genes (*ie. FOXL2, RSPO1, WNT4*) leads to ovarian differentiation.

• XX gonads lacking *FOXL2* differentiate into testes in the goat

In goats, the Polled Intersex Syndrome (PIS) mutation is a natural mutation responsible for hornlessness and female-to-male sex-reversal [1]. Using a zinc-finger nuclease technology, we demonstrated that the XX sex-reversal is due to *FOXL2* silencing in the differentiating XX *PIS*^{-/-} gonad. Thus, the XX gonads lacking *FOXL2* differentiate into testes instead of ovaries [2]. To highlight (i) the morphogenetic mechanisms occurring downstream of *FOXL2*, and (ii) its targets implicated in ovarian differentiation and anti-testis action, we performed RNA-sequencing at the onset of gonadal switch in the goat (36 dpc), using XY testes, XX ovaries and XX *PIS*^{-/-} intersex (IS) gonads (Fig.1).

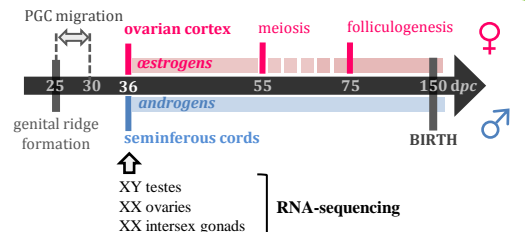


Fig.1 : Identification of *FOXL2* target genes by RNA-sequencing at 36dpc.

Results

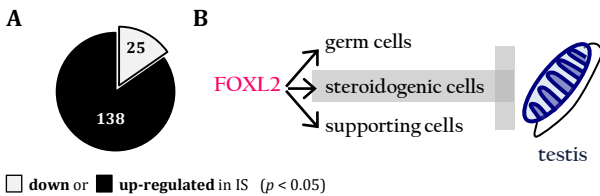


Fig. 2 : *FOXL2* is mainly an inhibitor of male pathway in XX gonads.

• *FOXL2* acts mainly as a repressor in the XX-developing ovary.

The RNA-sequencing results showed that 163 genes were deregulated in the IS gonads comparing to ovaries (Fig.2). 25 of them (15%) were down-regulated and may correspond to genes activated by *FOXL2*, whereas 138 genes were up-regulated and may correspond to genes inhibited by *FOXL2* (Fig. 2A). So *FOXL2* appeared to act mainly as a repressor in the developing ovary. Further analyses revealed that this repression impact all the cellular levels in XX gonads (Fig. 2B). For instance, *FOXL2* indirectly protect XX germ cells fate and permit them to enter meiosis by repressing *CYP26B1*. At the steroidogenic level, *FOXL2* avoids androgens synthesis by inhibiting *17βHSD3* and it promotes estrogens production as it directly activates *CYP19* [3]. At least, *FOXL2* prevents the expression of testes supporting cell-markers, such as *DMRT1*.

• Characterization of maleness progression : role of *DMRT1*.

Whereas neither *FOXL2* nor *SOX9* were expressed in the IS gonad at 36 dpc (Fig. 3A&B), *DMRT1* was already up-regulated. *SOX9* expression increases few days later [4], around 40 dpc. When we looked at maleness progression in XX *PIS*^{-/-} gonads (Fig. 4), we found that Sertoli-like cells (AMH and so *SOX9*-positive cells) first appeared at the center of the gonad, in *DMRT1*-expressing cells. Then at 45 dpc, AMH-staining and so Sertoli-like cells differentiation spread from the center to the cortex of the gonad. Taking together, these results strongly suggested that *DMRT1* is at the onset of maleness activation during sex-reversal in the goat.

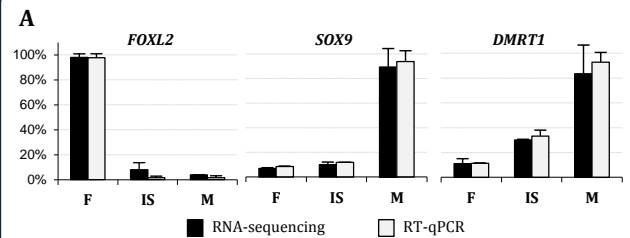


Fig. 3 : *DMRT1* is up-regulated before *SOX9* in XX gonads lacking *FOXL2*.

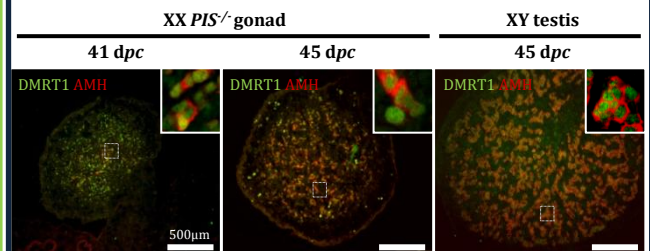
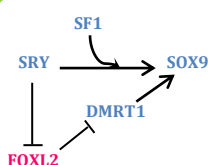


Fig. 4 : Sertoli-like cells differentiate from *DMRT1*-expressing cells in XX *PIS*^{-/-} gonads.

Conclusion and working model



In mice, *Foxl2* conditionnal knock-out leads to ovary-to-testis transdifferentiation at adulthood, starting with *Sox9* up-regulation then followed by *Dmrt1* expression [5]. In the goat, the absence of *FOXL2* in the XX-developing gonad leads to sex-reversal as soon as fetal life [1,2,4]. Our results showed that contrary to the mouse, the primary event of this sex-reversal is *DMRT1* up-regulation, followed by *SOX9* expression. This supports that, in the goat (i) *FOXL2* is a sex-determining gene, (ii) *FOXL2* antagonizes male pathway in the developing ovary, and (iii) *DMRT1* can be an activator of *SOX9* and the male pathway.

References :

- [1] Pailhoux et al., 2001, *Nat. Gen.*
- [2] Boulanger et al., 2014, *Curr. Biol.*
- [3] Pannetier et al., 2006, *J. Mol. Endo*
- [4] Pailhoux et al., 2002, *Dev Dyn.*
- [5] Ulhnhaut et al., 2009, *Cell*