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The Rabbit as Experimental Model for Studying the Function of Genes Using the New Genome Editing Technologies: The Example of *AROMATASE* ^{-/-} Rabbits

Geneviève Jolivet, Laurent Boulanger, Erwana Harscoët, Nathalie Daniel-Carlier, Nathalie Daniel, Eric Pailhoux

UMR BDR, INRA, ENVA, Université Paris Saclay, 78350, Jouy en Josas, France

AROMATASE is the cytochrome enzyme responsible for the synthesis of oestrogens in vertebrates. In adults, *AROMATASE* gene is expressed mainly in gonads but also in adipose tissue, bone, muscular tissue and brain. In most mammals (but not in mice) there is a peak of expression of the aromatase gene only in the foetal XX gonad when sexual differentiation starts up. Our goal was to elucidate the role of this early peak of *AROMATASE* expression. This question is particularly relevant since, in some mammals, the *FOXL2* gene, which is a major determinant of ovarian differentiation, is an activator of transcription of the *AROMATASE* gene.

We thus produced genetically edited rabbits by using a TALEN specifically targeting the translation start site of the *AROMATASE* gene. Three lines of mutant rabbits were derived from 6 founders, with deletions from 339 to 829 bp length surrounding the position of the translation start site.

The phenotype of animals was similar in the three lines. Heterozygous rabbits (*ARO*^{+/-}) presented a normal phenotype. Homozygous (*ARO*^{-/-}) XY animals developed as males and were fertile; (*ARO*^{-/-}) XX animals developed as females but were totally infertile. Gonads of XX *ARO*^{-/-} foetuses developed as ovaries, but were significantly smaller than those of normal rabbits. In adults, the size of the genital tract of XX *ARO*^{-/-} was extremely reduced. The histological and immunohistological analyses showed that from foetal life, the number of germ cells was drastically reduced. Interestingly, germ cells engaged meiosis as in normal animals and all classes of follicles were visible from primordial to large antral follicles. However, the number of follicles from all types was extremely low. Primordial follicles were almost absent few months after birth indicating the loss of follicular reserve. Moreover, ovulation did not occur.

Finally, this work shows that the foetal surge of oestrogens in the rabbit gonad of the XX foetus is responsible for the high number of germ cells and that later on oestrogens are mandatory for ovulation. However, oestrogens are essential neither for differentiation of the foetal gonad as an ovary, nor for meiosis or differentiation of follicles.