The physiological role of AMH

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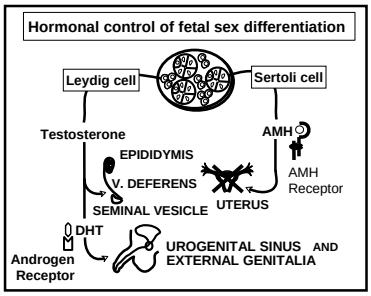
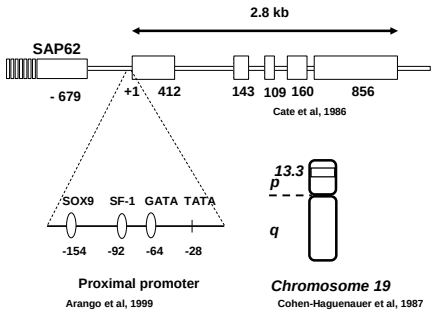


Anti-Müllerian hormone (AMH)
Müllerian Inhibiting Substance (MIS)



Cloned AMH genes

Mammals (eutherians)

Homo sapiens, chimpanzee, rhesus monkey

pig, cattle, mouse, rat, dog, iberian mole

Marsupials

Tammar wallaby, opossum, silver brushtail possum, platypus

Birds

Chicken, duck, japanese quail

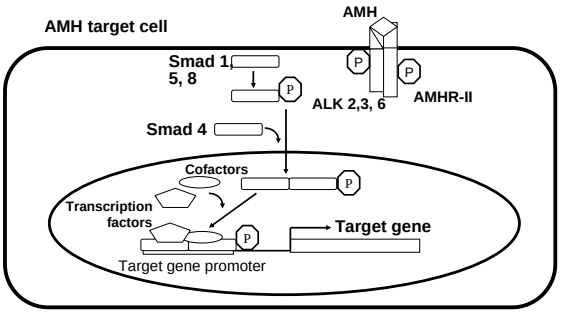
Reptiles

American alligator, red-eared slider turtle

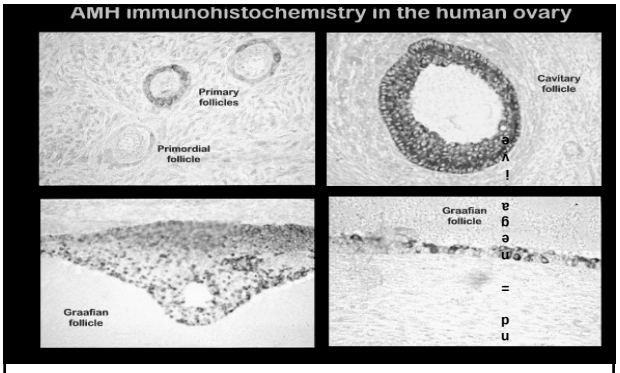
Fish

Japanese eel, japanese medaka, zebrafish, atlantic salmon, japanese ricefish, blue tiapia, european sea bass, japanese flounder

AMH signal transduction



15-day old rat fetus



AMH is expressed in granulosa cells of follicles recruited from the primordial follicle pool which have not been selected for dominance.

Methods for studying the AMH physiological role

Remove it

AMH

Block hormone action

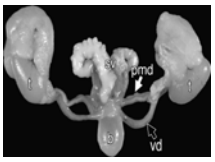
Add it

Blocking AMH expression or action in the male

AMH or AMHRII mutations : persistent Müllerian duct syndrome

Genetic inactivation of AMH, Wnt7 or elements of the AMH transduction cascade (receptors I and II and Smads)

Hernia, cryptorchidism
Fertility compromised



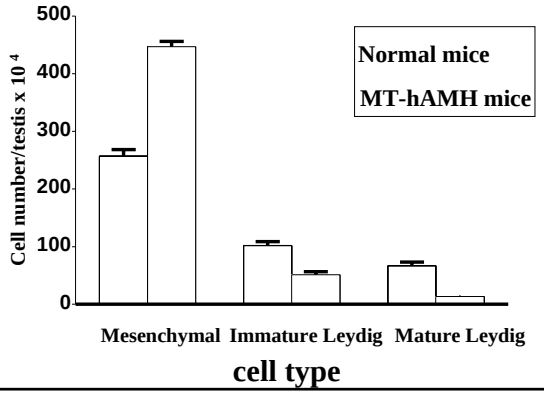
Mechanical infertility
Sperm OK

The MT-hAMH mouse

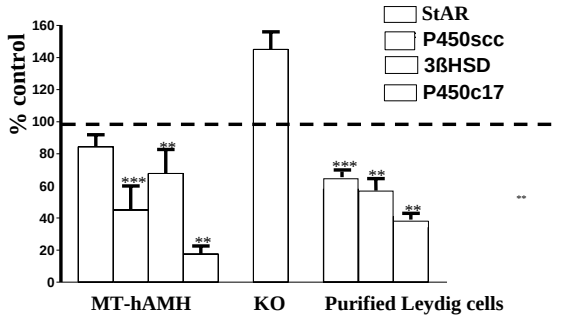
- **The AMH gene is placed under the control of the metallothionein promoter**
- **AMH is deregulated : in both sexes, it is chronically expressed in high amounts, ubiquitously and at all times.**

Behringer et al, Nature, 1990

Effect of AMH on Leydig cell differentiation

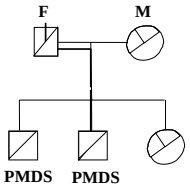


Effect of AMH on expression of Leydig cell steroidogenic enzyme mRNAS



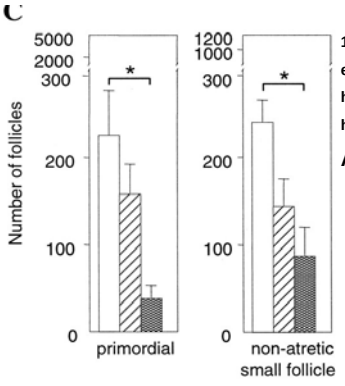
Inactivation of AMH cascade in females

Transmission of mutations in KP family



Arg406->Gln, 9th exon AMH-RII gene

1 bp deletion, 5th exon AMH-RII gene

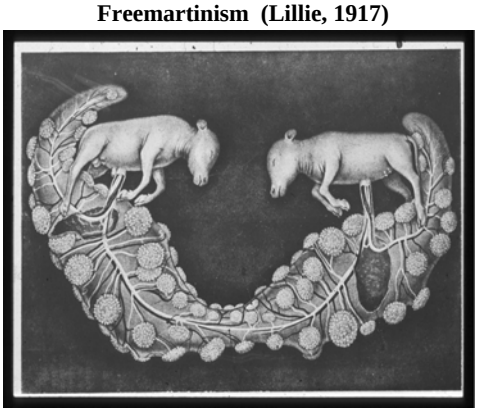


13-month old mice either wild-type, hemizygous or homozygous

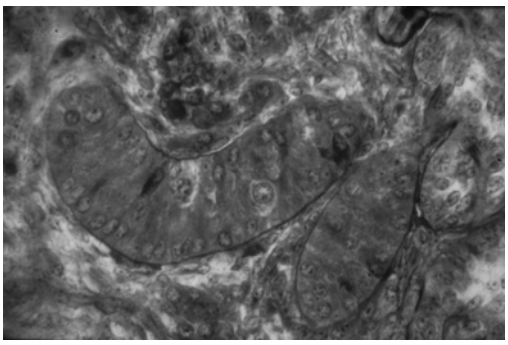
AMH-null mice

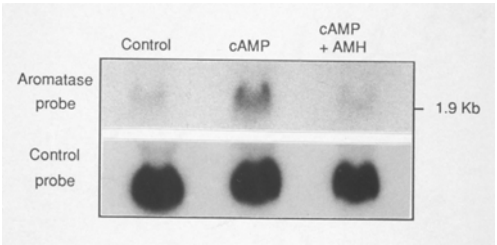
Durlinger, A. L. L. et al. Endocrinology 1999;140:5789-5796

Freemartinism (Lillie, 1917)



Seminiferous tube in a freemartin ovary





AMH inhibits aromatase expression elicited in fetal rat ovaries by cyclic AMP

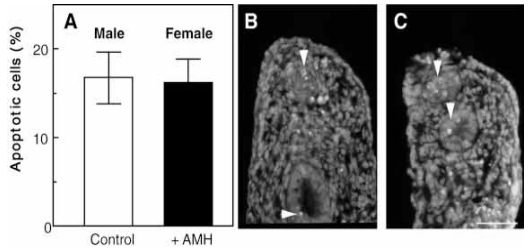
Physiological role of AMH

- Regression of fetal Müllerian ducts

No regression of Müllerian ducts in males without AMH

Regression of Müllerian ducts in freemartins and in MT-hAMH mice

Effects of AMH in vitro upon Müllerian duct apoptosis in the rat.



Molecular mechanisms of hormone-mediated Müllerian duct regression: involvement of ß-catenin
Allard et al. Development, 2000

Effect of AMH on testes

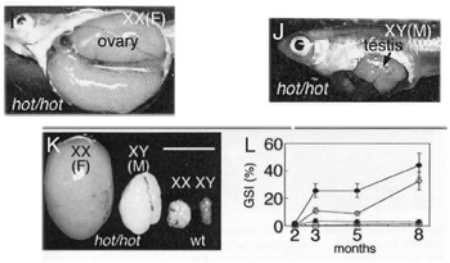
- Post-natal inhibition of Leydig cell differentiation and steroidogenesis
- Decrease of testosterone serum level

Effect of AMH on ovaries

- Stunting, germ cell destruction in fetuses
- Rare development of seminiferous tubules
- Inhibition of aromatase transcription

- Inhibition of recruitment into growing pool
- Inhibition of follicle growth
- Decrease of FSH sensitivity
- Antiproliferative effect on reproductive organs

Mutation hotei in medaka AMH receptor
(Morinaga et al, 2007)



Ovaries : unrestrained follicle growth
Testes : sex reversal (50%) and premature meiosis

AMH workers

- **Identification : Pr A Jost**
- **Purification : Picard and Josso**
- **Cloning : Cate and Donahoe**
- **Receptor cloning : Baarends, di Clemente and Cate**
- **Granulosa cell expression : Bernard Vigier**
- **Role on Leydig cells : Chrystèle Racine**
- **Role in the ovary : Durlinger, Visser, Themmen**
- **Transgenic mice : Richard Behringer**
- **Anti-proliferation : Maheswaran, Donahoe**