

LECTURE OUTLINE – PRIMARY SEX DETERMINATION

- Primary vs Secondary sex determination

Primary: differentiation of bipotential genital ridge into ovary or testis

Secondary: differentiation male and female sexual phenotypes (internal reproductive structures, and external genitalia).

Primary SD has to occur for secondary SD to happen

- Primary sex determination → **Genetic** (mammals, birds, snakes, amphibians) or **temperature** dependent (some reptiles (crocodiles), many turtles)
- History:
  - 515 BC: side of the womb → males on right, females on left (Parmenides)
  - 500-428 BC: side of the farther's testis (Anaxagoras)
  - 384-322 BC: goal semen is to produce males. High temps → male, cold temps → female (Aristotle)
  - 19<sup>th</sup> century: environmental factors (food) impose the sex on the fetus
  - 20<sup>th</sup> century: sex determined by sex chromosomes
    - Klinefelter XXY male and Turner XO female → Y chromosome maleness
- Genital ridge → bipotential gonad → ovary or testis
  - What directs bipotential gonad to develop as ovary or testis?
  - 1970's → H-Y antigen (Histocompatibility antigen)
    - discovered in 50's as male specific antigen that caused female mice to reject male skin.
    - Male specific antibodies detected in females with male skin rafts → serologically defined H-Y antigen

## SLIDE 1

Late 80's → Sxr mutant mice separated Tdy from H-Y

Sxra → XX males containing both Tdy AND H-Y antigen +

Sxrb → gene fusion of Zfy1 & 2 deletes H-Y locus, but leaves  
Tdy. Also XX males

1990 → discovery Tdy = SRY/Sry

XX mice transgenic for Sry → males

Sry → HMG domain

## SLIDE 2 & 3

- Insight using transgenic mice → genes required for establishment genital ridge
- Genetic control sex determination **SLIDE 4-8**
  - Sry, Sox9, Dax1 (transcription factors) → testis determination → AMH
  - Wnt4 → prevent steroidogenesis/vascular development
- Anatomy of fetal gonadal differentiation
  - Precursor somatic cells → Sertoli cells (coelomic epithelium) & Leydig cells
  - PGC's → oogonia (enter meiosis) & spermatogonia (enter mitotic arrest)

- Sry induces several pathways to initiate testis development: **SLIDE 9 & 13**
  - Pre-SCs proliferation
  - Sertoli cell differentiation → Leydig cell differentiation
  - Cell migration (vascular endothelial cells, peritubular myoid cells)
  - Development of testis specific vasculature → activin B

Sox9 upregulation!!
- Sry expression
  - Mouse 24 hours vs humans into adulthood
  - Expression pattern → center to poles

Expression alone required but not sufficient

  - XX Sox9 transgenic mice → male
  - XY(Sry-) Sox9 transgenic mice → fertile male
  - Dax1/Gata4/Fog2 mutant B6 XY mice → Sry+, Sox9- → ovaries
- Do PGCs play a role in GSD?
  - PGCs important for ovarian, NOT testicular development!

XX PGCs develop into spermatogonia in XY gonad

XY PGCs develop into oogonia in XX gonad

→ hypothesis: meiosis inhibiting substance secreted by XY gonad
- Recent work by Koopman and Page → role of Retinoic Acid **SLIDE 14**
  - XY gonads metabolize RA, thereby preventing PGC entering meiosis

## Intersex disorders

Musculinized genetic females (excess androgens)

Undermasculinized genetic males (defects androgen synthesis, resistance to androgens)

True hermaphrodites (testicular and ovarian tissue) → mostly XX

Free martins (cows and sheep): most frequent form of intersexuality in cattle →  
**projector slide**

= masculinized XX female calf born as twin of XY male

due to vascular connections between female and male fetuses

→ results in masculinization of female internal reproductive tract

male hormones and/or XY cells?

Humans → monozygotic twins of opposite sex (Wachtel et al., 2000)

Both were 46 XY

46 XY female → normal external genitalia + 1 undifferentiated gonad

46 XY male → 1 normal developed testis + 1 underdeveloped testis

both intact Sry

46XY,45X composition?

Mutation in downstream gene?

XX/XY chimeras

Tissue containing cells with different genotypes

XX-XY chimerae → Sertoli cells predominantly XY

True hermaphrodites: **SLIDE 15**

Ovotestes → concordant with Sry expression pattern

OT – OT, OT – T, OT – O, O – T

Within gonad: O-T-O, O-T-T, T-T-O

Complete gonadal sex reversal

XY females (~20% explained by Sry mutations) → streak gonads

XX males (~80% explained by Sry translocation)