Differentiation 91 (2016) 78–89

Contents lists available at ScienceDirect

Differentiation

journal homepage: www.elsevier.com/locate/diff

Review article

Investigation of sexual dimorphisms through mouse models and hormone/hormone-disruptor treatments

Lerrie Ann Ipulan [a,1], Dennis Raga [a,1], Kentaro Suzuki [a], Aki Murashima [a], Daisuke Matsumaru [a], Gerald Cunha [b], Gen Yamada [a,*]

[a] Department of Developmental Genetics, Institute of Advanced Medicine, Wakayama Medical University (WMU), Wakayama, Japan
[b] Department of Urology, School of Medicine, University of California San Francisco, San Francisco, CA, USA

ARTICLE INFO

Article history:
Received 8 November 2015
Accepted 11 November 2015
Available online 2 December 2015

Keywords:
Reproductive tissue
Sexual dimorphism
Mouse Cre lines
Hormone
Hormone disruption
Androgen
Perineum
External genitalia

ABSTRACT

Sexual dimorphism in mouse reproductive tissues is observable in adult, post-natal, and embryonic stages. The development of sexually dimorphic tissues starts with an ambisexual structure. It is followed by sex-specific organogenesis as guided by different signaling pathways that occur from late embryonic stages. The measurement of the anogenital distance (AGD), and the observation of the external genitalia are practical ways to distinguish male and female pups at birth and thereafter. Careful observation of the morphological or histological features and the molecular signatures of the external genitalia and perineum enable identification of sex or feminization/masculinization of embryos. Aberrations in hormone signaling via castration or treatment with hormones or hormone disruptors result in dysmorphogenesis of reproductive tissues. Several hormone disruptors have been used to modulate different aspects of hormone action through competitive inhibition and exogenous hormone treatment. Concomitantly, the vast advancement of conditional mutant mouse analysis leads to the frequent utilization of Cre recombination technology in the study of reproductive/urogenital tissue development. Mouse Cre-lines that are tissue-specific and cell-specific are also effective tools in identifying the molecular mechanisms during sexually dimorphic development. Cre-lines applicable to different cell populations in the prostate, seminal vesicles, testis and ovaries, and mammary glands are currently being utilized. In the external genitalia and perineum, Cre lines that examine the signaling pathways of cells of endodermal, ectodermal, and mesenchymal origin reveal the roles of these tissues in the development of the external genitalia. The interaction of hormones and growth factors can be examined further through a variety of techniques available for researchers. Such cumulative information about various technologies is summarized.

Contents

* Corresponding author at: Department of Developmental Genetics, Institute of Advanced Medicine, Wakayama Medical University (WMU), Wakayama, Japan.
E-mail addresses: genyama77@yahoo.co.jp, transg8@wakayama-med.ac.jp (G. Yamada).
[1] Equal contributing author.

http://dx.doi.org/10.1016/j.diff.2015.11.001
Join the International Society for Differentiation (www.isdifferentiation.org)
0301-4681/

1. Introduction

The reproductive system is essential for the continuity of species. The differences and the complimentary nature of male and female reproductive systems provide optimal fertility, ensure reproduction, and facilitate the continuous caring for the offspring. The female reproductive system is composed of ovaries, oviducts, uterus, cervix and vagina. Other sexual characteristics include mammary glands and fat deposition in the torso. The male reproductive system is composed of testes, epididymes, vas deferens, urethra, seminal vesicles, prostate gland, bulbourethral glands, and penis.

The study of reproductive tract tissues requires a multidisciplinary approach. The morphological changes and effects of hormone balance on developing male and female reproductive tracts distinguish them from other organ systems. Disruptions in hormone signaling affect both the morphology and subsequent adult physiological functions of reproductive tract tissues. As such, factors related with stage-dependent perturbations, tissue-specificity, and proper mouse models in the development of such tissues must be considered.

This review aims to present technical information for the investigation of male and female reproductive tracts such as observable sexual dimorphisms, timeline of development, and appropriate mouse Cre lines for conditional mutagenesis (with particular focus on external genitalia and perineum formation). Information about different hormone and hormone-disruptors is also discussed together with technical tips in utilizing such chemicals and their interpretation.

2. Sexual dimorphism in mouse reproductive tissues

The development of reproductive tissues starts with bipotential primordial organ formation. It is followed by a sexually dimorphic developmental stage, which is governed by molecular pathways leading to morphologically different male and female structures. Fig. 1 summarizes the timeline of the bipotential stage, the stage of molecular sexual differences, and the stage of observable morphological dimorphism of reproductive tract organs. The onset of molecular sexual differences refers to the stage wherein differences in signaling or gene expression in such tissues can be detected, which is clearly a moving target subject to continued improvement in analytical techniques. Some detailed histological differences and cellular differentiation may occur concomitant with molecular sexual differences or shortly thereafter. Morphological dimorphism is defined as a stage wherein structural differences are apparent.

The ovary and the testis, which originate from the genital ridge, are the first structures to undergo molecular sexual differentiation (Koopman et al., 1991; Wilhelm and Koopman, 2006). The testes then secrete hormones (androgens, anti-Mullerian hormone) that

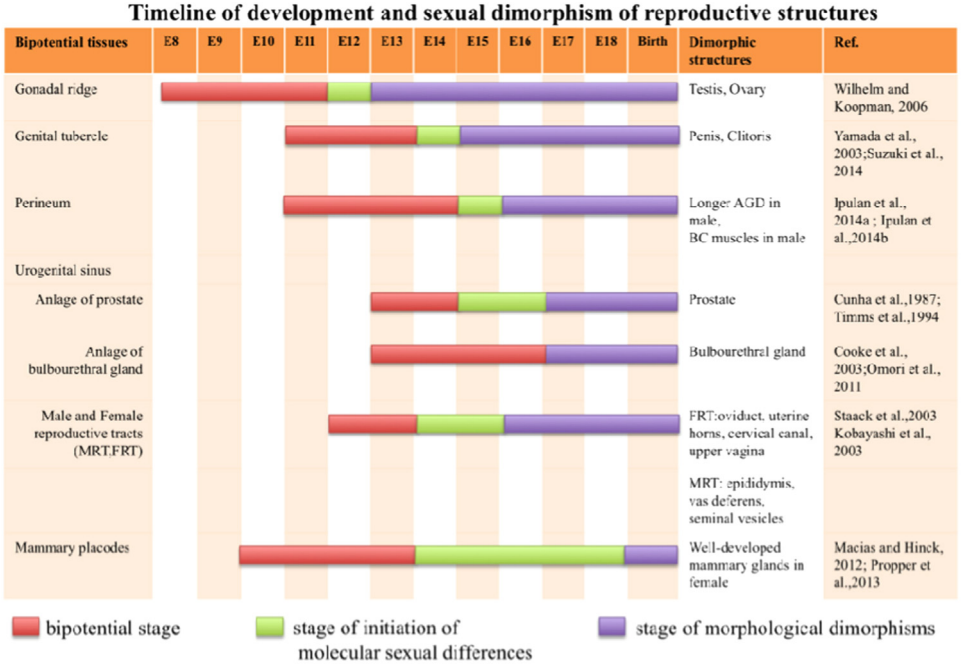

Fig. 1. Timeline of development and sexual dimorphisms of reproductive structures. This figure summarizes the approximate timepoints in the development of reproductive structures, which are divided into (i) the bipotential stage, the phase of ambisexual organ formation; (ii) the stage of initiation of molecular sexual differences, the phase of observed differences in signaling pathways/gene expression patterns with subtle histological differences; and (iii) the stage of morphological sexual dimorphisms. (AGD – anogenital distance, BC – bulbocavernosus).