Mechanisms of Development 147 (2017) 17–27

Contents lists available at ScienceDirect

Mechanisms of Development

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

Cell adhesion molecules expression pattern indicates that somatic cells arbitrate gonadal sex of differentiating bipotential fetal mouse gonad

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ARTICLE INFO

Article history:
Received 8 May 2017
Available online 28 July 2017

Keywords:
Cell adhesion molecules
Sertoli cells
Interstitium
Germ cells
Testis
Ovary

ABSTRACT

Unlike other organ anlagens, the primordial gonad is sexually bipotential in all animals. In mouse, the bipotential gonad differentiates into testis or ovary depending on the genetic sex (XY or XX) of the fetus. During gonad development cells segregate, depending on genetic sex, into distinct compartments: testis cords and interstitium form in XY gonad, and germ cell cysts and stroma in XX gonad. However, our knowledge of mechanisms governing gonadal sex differentiation remains very vague. Because it is known that adhesion molecules (CAMs) play a key role in organogenesis, we suspected that diversified expression of CAMs should also play a crucial role in gonad development. Using microarray analysis we identified 129 CAMs and factors regulating cell adhesion during sexual differentiation of mouse gonad. To identify genes expressed differentially in three cell lines in XY and XX gonads: i) supporting (Sertoli or follicular cells), ii) interstitial or stromal cells, and iii) germ cells, we used transgenic mice expressing *EGFP* reporter gene and FACS cell sorting. Although a large number of CAMs expressed ubiquitously, expression of certain genes was cell line- and genetic sex-specific. The sets of CAMs differentially expressed in supporting versus interstitial/stromal cells may be responsible for segregation of these two cell lines during gonadal development. There was also a significant difference in CAMs expression pattern between XY supporting (Sertoli) and XX supporting (follicular) cells but not between XY and XX germ cells. This indicates that differential CAMs expression pattern in the somatic cells but not in the germ line arbitrates structural organization of gonadal anlagen into testis or ovary.

1. Introduction

The testes and ovaries arise from common precursors – genital ridges that are the clusters of mixed cells of different types. The specific testicular or ovarian structures develop during fetal life in the process of sexual differentiation of the gonad. In this process cells within developing gonads segregate and group in sex specific manner. In differentiating testes the cells form solid, elongated testis cords separated by interstitial cells (Fig. 1A,B). In differentiating ovaries the cells form germ cell cysts (that later break down into spherical follicles), which are embedded within the stromal cells. Thus, depending on the genetic sex, the bipotential gonad anlagen develop different cellular structures.

The earliest sign of gonad development is the transformation of coelomic monolayer epithelium into a cluster of somatic cells at the ventral surface of mesonephros. This process involves proliferation of coelomic epithelial cells and disintegration of the basement membrane in the sites of gonad formation. In the mouse fetus this process starts at 10.3 days *post coitum* (*dpc*) (Hu et al., 2013). The multilayered cluster of coelomic-epithelium derived cells is invaded by immigrating primordial germ cells (PGCs) leading to the formation of genital ridges. Such genital ridges are still bipotential and morphologically indistinguishable between two sexes. In XY gonads, the expression of *Sry* gene between 10.5 and 12.5 *dpc* along with other sex-determining genes, such as *Sox9*, triggers a cascade of genes expression that orchestrates a series of structural changes leading to the formation of the testis (Koopman et al., 1991; Hacker et al., 1995; Kim et al., 2006; reviewed by Piprek, 2009a). The first sign of testis differentiation is significant acceleration of somatic cell proliferation at the gonadal surface starting from 11.25 *dpc* (Schmahl et al., 2000; Schmahl and Capel, 2003). Subsequently,

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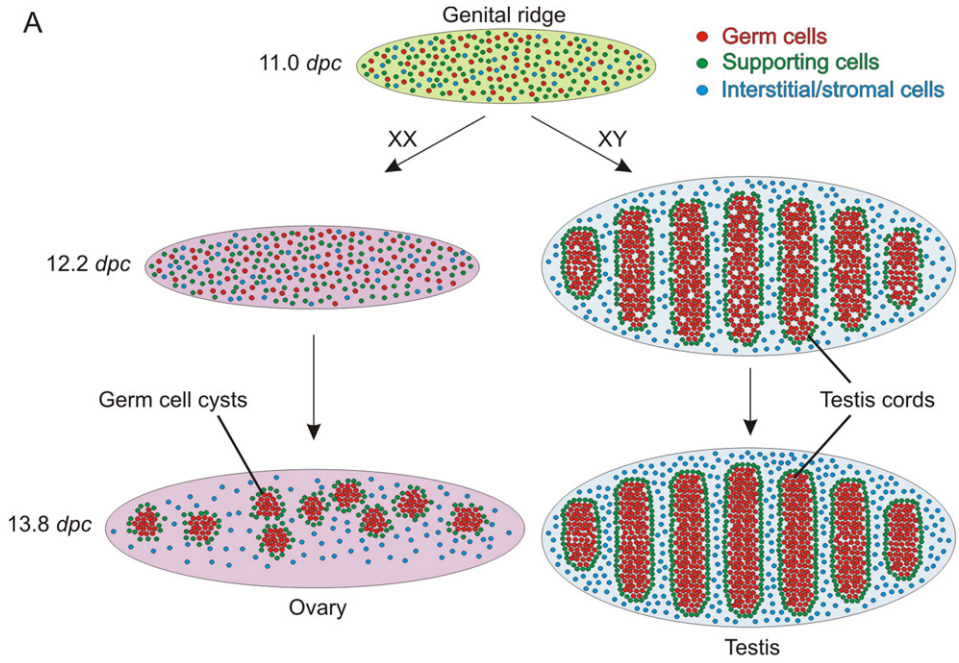
http://dx.doi.org/10.1016/j.mod.2017.07.001
0925-4773/



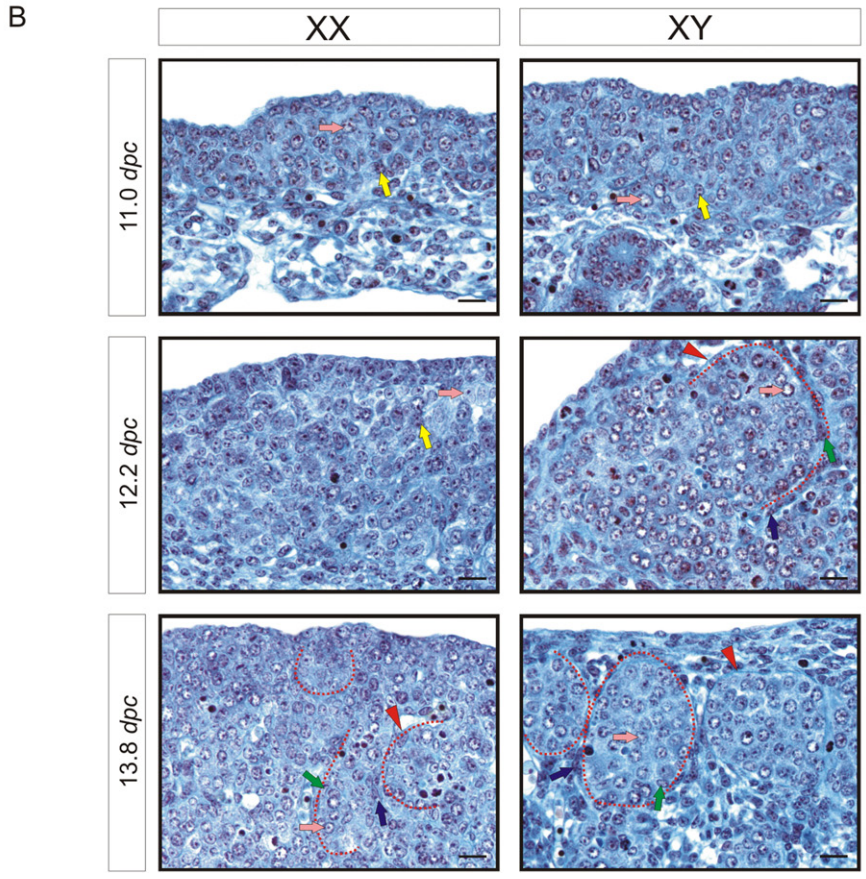


Fig. 1. Sexual differentiation of mouse gonads. A. Scheme of sexual differentiation of gonads in the mouse between 11.0 and 13.8 *dpc*. B. Histological sections through gonads during the sexual differentiation. At 11.0 *dpc* the gonads are sexually undifferentiated and the somatic (yellow arrow) and germ cells (pink arrow) are evenly mixed, distributed within the undifferentiated gonads. At 12.2 *dpc* a sexual differentiation is discernible; in the XY gonads, cell accumulation begins, and cord like structures emerge (germ cells enclosed by the pre-Sertoli cells – green arrow); interstitium begins to be visible (blue arrow) as streams of cells between forming cords; basal laminae form around the cords (red arrowhead); whereas the cells in the XX gonads are still evenly distributed. At 13.8 *dpc* clear testis cords are visible in the XY gonads, whereas in XX only small groups of accumulating cells (ovarian cysts) are present, and stromal cells (blue arrow) locate between the cysts. Scale bar 20 μm.