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The Length of the Spermatogenic Cycle Is Conserved in Porcine and Ovine Testis Xenografts

WENXIAN ZENG*, GLEIDE F. AVELAR†, RAHUL RATHI*, LUIZ R. FRANCA† AND INA DOBRINSKI*

*From the * Center for Animal Transgenesis and Germ Cell Research, School of Veterinary Medicine, University of Pennsylvania, Kennett Square, Pennsylvania; and the † Laboratory of Cellular Biology, Department of Morphology, Institute of Biological Sciences, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil.*

Correspondence to: Dr Ina Dobrinski, Center for Animal Transgenesis and Germ Cell Research, 147 Myrin Building, New Bolton Center, University of Pennsylvania, 382 West St Rd, Kennett Square, PA 19348 (e-mail: dobrinsk{at}vet.upenn.edu).

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Abstract

Xenografting of immature mammalian testis tissue into mice can accelerate sperm production. To determine whether this shortened time to sperm production is because of reduced length of the spermatogenic cycle, we applied bromodeoxyuridine (BrdU) incorporation to analyze the spermatogenic cycle in porcine and ovine testis xenografts. Small testis fragments from newborn pigs and sheep were ectopically grafted into mice. Once complete spermatogenesis was present in grafted tissue, mice were injected with BrdU and grafts were recovered at different time points thereafter. In porcine grafts, the most advanced germ cells labeled 1 hour, 9 days, 12.3 days, and 18 days after BrdU injection were stage 1 preleptotene/leptotene primary spermatocytes, stage 1 pachytene primary spermatocytes, stage 5 newly-formed round spermatids, and late stage 2 elongating spermatids, respectively. In ovine grafts, the most advanced labeled germ cells at 1 hour, 11 days, and 22 days post-BrdU injection were stage 2 preleptotene/leptotene primary spermatocytes, late stage 1 pachytene primary spermatocytes, and stage 2 elongating spermatids, respectively. These results indicate that each spermatogenic cycle in porcine and ovine xenografts lasts approximately 9 and 11 days, respectively, which is similar to their durations in situ. Therefore, the length of the spermatogenic cycle is conserved in porcine and ovine testis

xenografts. This is consistent with earlier reports showing that the cycle length is inherent to the germ cell genotype. The shortened time to sperm production in xenografts therefore appears attributable to accelerated maturation of the testicular somatic compartments. Our results suggest that testis xenografts provide a useful model to study the timing of testicular maturation and spermatogenesis in different mammalian species.

Key words: Pig, sheep, graft, spermatogenesis, seminiferous epithelium cycle

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Spermatogenesis is a continuous, highly organized process by which spermatogonia proceed through mitotic and meiotic divisions and complex cytologic transformations resulting in the formation of sperm throughout the adult life of a male (Russell et al, 1990; Franca and Cardoso, 1998; Franca et al, 1999). At any given location in the seminiferous tubule, the onset of spermatogonial stem cell differentiation is cyclic and is followed by an orderly stepwise differentiation of progeny cells into mature sperm (Franca et al, 1998).

The sequence of events that occurs from the disappearance of a given cell association to its reappearance in a given area of the seminiferous epithelium constitutes the cycle of the seminiferous epithelium (Leblond and Clermont, 1952). The time interval required for 1 complete series of cell associations to appear at a given point within the seminiferous tubule is called the duration of the cycle of the seminiferous epithelium (Leblond and Clermont, 1952). The total duration of spermatogenesis takes about 4.5 cycles in mammals (Franca and Russell, 1998) and is under the control of germ cell genotype (Franca et al, 1998). The length of the spermatogenic cycle has been generally considered to be constant for a given species, although strain or breed differences have been reported for members of the same species (Russell et al, 1990; Franca and Russell, 1998). In pigs, each spermatogenic cycle lasts 8.6–9.0 days, and the total duration of spermatogenesis is around 40 days (Swierstra, 1968; Franca and Cardoso, 1998). In sheep, the length of the spermatogenic cycle and the total duration of spermatogenesis are 10.6 and 47–48 days, respectively (Ortavant, 1956; Cardoso and Queiroz, 1988).

The duration of the spermatogenic cycle is typically determined from experiments in which [^{3}H]-thymidine incorporated at the last S-phase of spermatogenesis (preleptotene spermatocyte) is identified by autoradiography at a later time in the most advanced labeled cell type (Clermont, 1972; Franca et al, 1998). Recently, a nonradioactive labeling methodology using bromodeoxyuridine (BrdU) incorporation for the analysis of the spermatogenic cycle has been developed in rats (Rosiepen et al, 1994, 1995; Aslam et al, 1999) and macaques (Rosiepen et al, 1997; Weinbauer et al, 1998; Aslam et al, 1999).

Grafting of immature testis tissue into mouse hosts results in sperm production from different mammalian donor species (Honaramooz et al, 2002, 2004; Schlatt et al, 2002, 2003; Ohta and Wakayama, 2004; Snedaker et al, 2004). Xenografting of testis tissue can serve as a powerful system for the study of spermatogenesis and testicular maturation and provides a novel approach to obtaining sperm from immature male individuals. Live progeny were produced from sperm or round spermatids extracted from ectopic allografts of immature mouse testes or fetal male gonads by intracytoplasmic injection into mouse oocytes and subsequent embryo transfer (Schlatt et al, 2003; Ohta and Wakayama, 2004). Sperm isolated from xenografts of immature rhesus monkey testis also supported embryonic development in vitro (Honaramooz et al, 2004). The successful generation of fertile mouse offspring and monkey embryos indicated that the male germ cells recovered from xenografts are capable of supporting normal development.

Grafting of testis tissue from immature rhesus monkeys into host mice resulted in the acceleration of testicular maturation (Honaramooz et al, 2004). Mature sperm were produced from immature 13-month-old rhesus monkeys in as little as 7 months following xenografting into mice. Male monkeys from the same population typically do not reach puberty until about 3 years of age. Similarly, xenografting of testis tissue from neonatal pigs into a mouse host accelerated testicular maturation (Honaramooz et al, 2002). Additionally, when testis tissue from 1-week-old Suffolk rams was xenografted into mice, development in the mouse host accelerated the onset of sperm production by at least 2 months. At the time of xenografting, the donor tissue contained only immature Sertoli cells and gonocytes. By 3 months after transplantation, ovine testis xenografts had completed spermatogenesis and mature sperm were present. In contrast, in intact Suffolk rams, first testicular sperm appear after 5–6 months of age (Dobrinski et al, unpublished data). From these reports, it was not clear whether the shortened time to sperm production was due entirely to an accelerated maturation of the testicular somatic component or whether the length of the spermatogenic cycle was also affected. Therefore, the objective of this study was to determine, based on BrdU incorporation, whether the duration of the spermatogenic cycle is altered after xenografting of testis tissue into recipient mice.

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Testicular Tissue

The donor testes were obtained from routine castration of 1- to 2-week-old Yorkshire cross piglets and a 1-week-old Suffolk ram lamb. The testicular tissue was cut into small fragments, approximately 1 by 1 by 2 mm. The tissue fragments were placed into Dulbecco modified Eagle medium (Invitrogen Corporation, Grand Island, NY) prior to grafting.

Transplantation of Testicular Tissue Into Mice

The testicular tissue was transplanted into 6- to 8-week-old immunodeficient NCR Nude mice (Taconic, Germantown, NY). Xenografting was performed as described previously (Honaramooz et al, 2002). Briefly, recipient male mice were anesthetized and castrated, and 8 pieces of donor testis tissue fragments (from 3 donors in pigs and 1 donor in sheep) were grafted under the back skin of each mouse. Porcine testicular fragments were transplanted to 9 recipient mice, and ovine tissue to 5 mice. Animals were handled and treated in accordance with the University of Pennsylvania Institutional Animal Care and Use Committee.

Collection of Grafts and Histologic Evaluation

The mice carrying porcine testicular tissue received an intraperitoneal injection of BrdU at 100 mg/kg at 7 months after grafting. Mice were sacrificed 1 hour (2 mice), 9 days (3 mice), 12.3 days (2 mice), and 18 days (2 mice) after BrdU injection by CO_2 inhalation. The host mice with ovine testicular tissue received an intraperitoneal injection of BrdU at 100 mg/kg at 6 months after grafting, and were sacrificed 1 hour (1 mouse), 11 days (2 mice), and 22 days (2 mice) after BrdU injection. Analysis time points were chosen based on the reported length of the spermatogenic cycle in pigs and sheep (approximately 9 and 11 days, respectively). Xenografts were collected and fixed overnight in 4% paraformaldehyde. The weight of the seminal vesicles in host mice was recorded as evidence of bioactive testosterone production by xenografts. The harvested xenografts were embedded in paraffin wax and cut into sections. Sections were stained with hematoxylin and eosin. The slides were coded and the percentage of seminiferous tubule cross-sections with complete spermatogenesis was counted in each graft.

Immunostaining for BrdU

Immunohistochemical staining of cells in S-phase was performed as previously described (Schlatt et al, 2003). Briefly, after deparaffinizing and rehydrating, the slides were incubated in 1 M HCl for 8 minutes at 70 °C in a hybridization oven. After washing in distilled water and Tris-buffered saline (TBS; 10 mM Tris, 150 mM NaCl, pH 7.6), the slides were incubated in 0.1% trypsin (Type II; Sigma Chemical Co, St Louis, Mo) in TBS for 15 minutes at room temperature. Nonspecific staining was blocked by incubation with 5% goat serum for porcine xenografts, or horse serum for ovine xenografts, in TBS for 20 minutes at room temperature. A monoclonal mouse anti-BrdU antibody (DakoCytomation Denmark, Glostrup, Denmark; 1:30 dilution with TBS plus 0.1% bovine serum albumin [BSA]) was added for 1 hour at 37 °C. The slides from porcine xenografts were incubated with secondary goat anti-mouse immunoglobulin G (IgG) linked to horseradish peroxidase (Jackson ImmunoResearch Laboratories, Inc, West Grove, Pa; 1:100 diluted with phosphate-buffered saline plus 1% BSA) for 60 minutes at room temperature. A donkey anti-mouse IgG linked to horseradish peroxidase (Jackson ImmunoResearch) was applied for ovine xenografts. The label was visualized using a Vector DAB kit (Vector Laboratories, Inc, Burlingame, Calif). The reaction was stopped by washing in distilled water. Slides were counterstained with hematoxylin, dehydrated, and mounted.

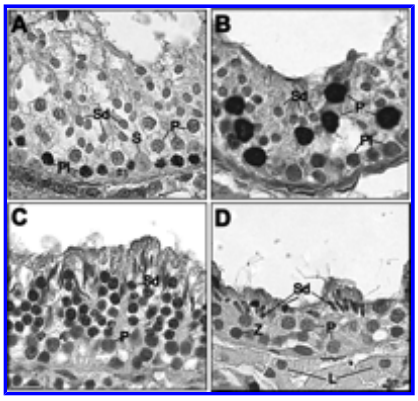

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Figure 1. Most advanced germ cells labeled after bromodeoxyuridine (BrdU) injection in pigs. One hour after BrdU injection, the labeled cells were stage 1 preleptotene/leptotene primary spermatocytes **(A)**. Nine days, 12.3 days, and 18 days after BrdU injection the labeled spermatogenic cells were stage 1 pachytene primary spermatocytes **(B)**, stage 5 newly-formed round spermatids **(C)**, and late stage 2 elongating spermatids **(D)**, respectively. Pl indicates preleptotene/leptotene primary spermatocytes; Z, zygotene spermatocytes; P, pachytene spermatocytes; Sd, spermatids; S, Sertoli cell; and L, Leydig cells. Scale bar = 15 µm.

Analysis of the Seminiferous Tubules

The stained testis grafts from the species investigated were analyzed using an Olympus BX-60 (Olympus, Tokyo, Japan). All 8 stages of the spermatogenic cycle, characterized according to the tubular morphology system (Berndtson, 1977; Franca and Russell, 1998), were analyzed in order to identify the most advanced germ cells labeled in each time period considered after BrdU injection. For both species, all seminiferous tubules containing full spermatogenesis were analyzed.

Results

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Histology

Most testicular xenografts (86% for porcine tissue, 78% for ovine tissue) were recovered from the host mice. There was a marked increase in the size of the recovered grafts, typically to about 5 mm in diameter. At the time of grafting, the testicular tissue consisted of primitive seminiferous cords

containing only immature Sertoli cells and gonocytes. Histologic analysis of the recovered xenografts showed 51.8% (range: 7%–98%, n = 2040 tubules) of seminiferous tubules from porcine grafts and 64.4% (range: 2%–92%, n = 2903 tubules) of seminiferous tubules from ovine grafts with complete spermatogenesis (sperm with tails present in seminiferous tubules). The other tubules showed dilated lumen with 0–3 layers of germ cells near the basement membrane of the seminiferous epithelium. The weight of the seminal vesicles as an indicator for production of bioactive testosterone from xenografts was restored to precastration values (200–400 mg) in recipient mice.

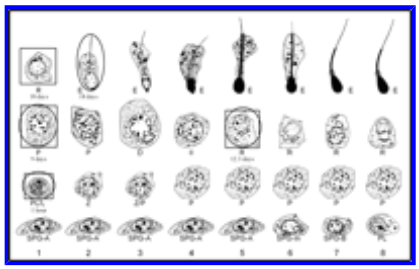

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Figure 2. Diagram showing the most advanced germ cell type labeled at the 8 stages of the seminiferous epithelium cycle in pig testis grafts at different time periods (1 hour, 9 days, 12.3 days, and 18 days) following bromodeoxyuridine (BrdU) injections. The Arabic numerals at the bottom of the figure indicate the 8 stages of the spermatogenic cycle, characterized according to the tubular morphology system. The square indicates the stage where labeled germ cells would be located according to the literature (Swierstra, 1968; França and Cardoso, 1998). The circle indicates the most advanced labeled germ cells at 1 hour, 9 days, 12.3 days, and 18 days after BrdU injection, suggesting that each spermatogenic cycle lasts about 9 days in porcine testis grafts. SPG-A indicates type A spermatogonia; SPG-B, type B spermatogonia; SPG-In, intermediate spermatogonia; Pl, preleptotene spermatocytes; L, leptotene; Z, zygotene; P, pachytene; D, diplotene; II, secondary spermatocytes; R, round spermatids; and E, elongate spermatids.

Spermatogenic Cycle

In pigs, the most advanced germ cells labeled 1 hour after BrdU injection were stage 1 preleptotene/leptotene primary spermatocytes (Figure 1A). At 9, 12.3, and 18 days after injection, the most advanced labeled germ cells were stage 1 pachytene primary spermatocytes (Figure 1B), stage 5 newly-formed round spermatids (Figure 1C), and late stage 2 elongating spermatids (Figure 1D), respectively. These observations indicate that each spermatogenic cycle in porcine xenografts is a little shorter than 9.0 days (Figure 2). No effect of donor on the parameters analyzed was noted. In ovine grafts, the most advanced labeled germ cells at 1 hour, 11 days, and 22 days were stage 2 preleptotene/leptotene primary spermatocytes (Figure 3A), stage 1 pachytene primary spermatocytes (Figure 3B), and stage 2 elongating spermatids (Figure 3C), respectively. These results indicate that each spermatogenic cycle in ovine testis xenografts is a little shorter than 11 days (Figure 4).

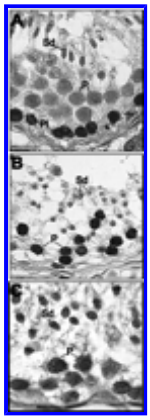

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Figure 3. Most advanced germ cells labeled after bromodeoxyuridine (BrdU) injection in sheep. One hour after BrdU injection, the labeled cells were stage 2 preleptotene/leptotene primary spermatocytes **(A)**. Eleven days and 22 days after injection the labeled cells were stage 1 pachytene primary spermatocytes **(B)** and stage 2 elongating spermatids **(C)**, respectively. Pl indicates preleptotene/leptotene primary spermatocytes; P, pachytene spermatocytes; Sd, spermatids; and S, Sertoli cell. Scale bars = 15 μm (A and B) and 10 μm (C).

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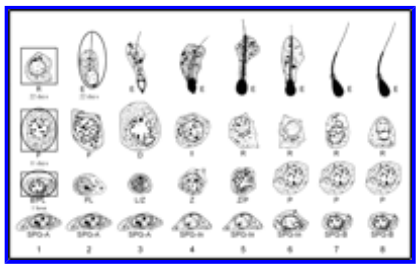

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Figure 4. Diagram showing the most advanced germ cell type labeled at the 8 stages of seminiferous epithelium cycle in sheep testis graft, at different time periods (1 hour, 11 days, and 22 days) following bromodeoxyuridine (BrdU) injections. The Arabic numerals at the bottom of the figure indicate the 8 stages of the spermatogenic cycle characterized according to the tubular morphology system. The circle indicates the most advanced labeled germ cells at 1 hour, 11 days, and 22 days after BrdU injection, suggesting that each spermatogenic cycle in ovine testis grafts lasts approximately 11 days. The square indicates the stage where the labeled germ cells would be located according to the literature (Ortavant, 1956; Cardoso and Queiroz, 1988). SPG-A indicates type A spermatogonia; SPG-B, type B spermatogonia; SPG-In, intermediate spermatogonia; Pl, preleptotene spermatocytes; L, leptotene; Z, zygotene; P, pachytene; D, diplotene; II, secondary spermatocytes; R, round spermatids; and E, elongate spermatids.

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When immature testis tissue is grafted ectopically into a castrated male mouse host, testicular maturation and spermatogenesis occur with the support of the host's endocrine system. Initial exposure to elevated levels of FSH in the castrated host stimulates Sertoli cell proliferation, and LH secretion from the mouse pituitary supports Leydig cell maturation and subsequent androgen production. Production of bioactive testosterone by grafts results in restoration of the weight of the seminal vesicles in the mouse host to those of an intact male mouse and has been documented to occur in xenografts from a variety of species (Honaramooz et al, 2002, 2004; Schlatt et al, 2002, 2003; Snedaker et al, 2004). We demonstrated previously that a functional endocrine feedback loop becomes established between the graft tissue and the mouse hypothalamic-pituitary axis (Schlatt et al, 2003) such that FSH levels decrease to precastration levels. Differentiation of testis tissue in the mouse host from testicular cords containing only gonocytes and immature Sertoli cells at the time of grafting results in complete spermatogenesis in a variety of donor species (Honaramooz et al, 2002, 2004; Schlatt et al, 2002, 2003; Snedaker et al, 2004), and fertilization-competent sperm can be harvested from allografts and xenografts (Honaramooz et al, 2002, 2004; Schlatt et al, 2002, 2003). However, it was noted that time to sperm production was shorter than in the donor species in xenografts from pigs, sheep, and nonhuman primates (Honaramooz et al, 2002, 2004; Dobrinski et al, unpublished data). Conversely, accelerated testicular maturation was not reported in xenografts from cats or cattle; however, onset of sperm production was not critically compared to the donor animals in those studies (Oatley et al, 2004, 2005; Snedaker et al, 2004). In the reports of accelerated sperm production in the testis xenografts of pigs, sheep, and monkeys, only the total time required to the first appearance of mature testicular sperm was compared to the donor species. It therefore became important to determine whether the kinetics of spermatogenesis were affected in testis xenografts or whether the shortened time to appearance of sperm was because of accelerated time to "puberty" in the endocrine environment of the castrated adult mouse host. In the present study, complete spermatogenesis occurred in xenografts from neonatal porcine and ovine testes examined 6–7 months after grafting in more than half of the seminiferous tubule cross-

sections, which is consistent with previous reports (Honaramooz et al, 2002; Dobrinski et al, unpublished data). Although spermatogenesis can occur with efficiency comparable to that in the donor species (Honaramooz et al, 2002) heterogeneity of tubular development has been observed in all species studied to date (Honaramooz et al, 2002, 2004; Schlatt et al, 2002, 2003; Snedaker et al, 2004).

Spermatogenesis describes the process of cell proliferation and differentiation from a spermatogonial stem cell to the release of the sperm produced from it. Before one spermatogenic series is completed, others occur in the same place in the tubule, and as a consequence, the germinal cells are arranged in several cellular layers, each one representing a different cell generation (Bustosobregon et al, 1975). The particular association of germinal cells is a stage of the spermatogenic cycle, and the stages are sequential. In the pig, the spermatogenic cycle in the seminiferous epithelium can be divided into 8 stages (Swierstra, 1968; Franca and Cardoso, 1998; Garcia-Gil et al, 2002). By studying incorporation of BrdU into dividing cells in all seminiferous tubules of porcine and ovine testis grafts, we established that the length of the seminiferous cycle was consistent with that expected for the donor species, that is, 8.6–9.0 days for porcine testis tissue and 10.6 days for ovine testis tissue (Ortavant, 1956; Swierstra, 1968; Cardoso and Queiroz, 1988; Franca and Cardoso, 1998; Franca et al, 2005). It can therefore be ruled out that shortened time to sperm production in xenografts is because of an accelerated cell cycle in spermatogenic cells. This study of spermatogenesis in the xenograft system thereby supports the assumption that the timing of the spermatogenic cycle is inherent to a given mammalian species (Russell et al, 1990; Franca and Russell, 1998), is controlled by the germ cell genotype (Franca et al, 1998), and is not altered by exposure to the gonadotropic hormone environment of a different species. The main reason for the acceleration in testicular development in testis xenografts is probably the change of the endocrine environment. When testis tissue from species showing a long prepubertal period of hypothalamic-pituitary quiescence is transplanted into mice, the testis xenografts are immediately exposed to a fully active hypothalamic-pituitary axis and therefore to the stimulation of gonadotropins. As a result, the time to puberty appears to be accelerated in the xenografts. It appears, though, that the time through puberty is unchanged, because rodent xenografts developed much faster than primate xenografts (Schlatt et al, 2002, 2003). This indicates that the acceleration is mainly because of the fact that the quiescent period of the hypothalamic-pituitary-gonadal axis is shorted in testis xenografts. This observation is important for several reasons. Faithful representation of the spermatogenic cycle in xenografts will allow the use of the xenograft system to study underlying mechanisms controlling the kinetics of spermatogenesis. It also lends support to the validity of testis xenografts as being representative of functional testis tissue in the donor species. This is an important prerequisite for using xenografts to study and manipulate spermatogenesis in different species, especially those species in which experimentation is logistically or ethically difficult, such as primates or rare or endangered species. Finally, it now appears likely that the shortened time to sperm production observed in xenografts is caused primarily by accelerated maturation of the testicular somatic compartment supporting germ cell proliferation and differentiation. This in turn opens the way for studying what factors support this accelerated maturation of testis xenografts without affecting the spermatogenic cycle. Once these factors have been identified, it could be investigated whether they will be beneficial to accelerate time to sperm production in the donor species itself. Early sperm production in nonhuman primates in a research setting could result in significant economic savings. In summary, the present study demonstrated that the timing of the spermatogenic cycle is conserved in testis tissue xenografts from pigs and sheep, supporting the notion that testis xenografting is a representative model of spermatogenesis in the donor species.

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Footnotes

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R. Parapanov, S. Nussle, and P. Vogel
Cycle Length of Spermatogenesis in Shrews (Mammalia: Soricidae) with High and Low Metabolic Rates and Different Mating Systems
Biol Reprod, May 1, 2007; 76(5): 833 - 840.
[Abstract] [Full Text] [PDF]
