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Stem cells and reproduction

Hongling Du[a] and **Hugh S. Taylor**[a,b]

[a]Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, Connecticut, USA

[b]Molecular Cellular and Developmental Biology, Yale University, New Haven, Connecticut, USA

Abstract

Purpose of review—To review the latest developments in reproductive tract stem cell biology.

Recent findings—In 2004, two studies indicated that ovaries contain stem cells which form oocytes in adults and that can be cultured in vitro into mature oocytes. A live birth after orthotopic transplantation of cyropreserved ovarian tissue in a woman whose ovaries were damaged by chemotherapy demonstrates the clinical potential of these cells. In the same year, another study provided novel evidence of endometrial regeneration by stem cells in women who received bone marrow transplants. This finding has potential for the use in treatment of uterine disorders. It also supports a new theory for the cause of endometriosis, which may have its origin in ectopic transdifferentiation of stem cells. Several recent studies have demonstrated that fetal cells enter the maternal circulation and generate microchimerism in the mother. The uterus is a dynamic organ permeable to fetal stem cells, capable of transdifferentiation and an end organ in which bone marrow stem cells may differentiate. Finally stem cell transformation can be an underlying cause of ovarian cancer.

Summary—Whereas we are just beginning to understand stem cells, the potential implications of stem cells to reproductive biology and medicine are apparent.

Keywords

bone marrow; endometriosis; endometrium; oocyte; reproduction; stem cells

Introduction

Stem cells are defined as undifferentiated cells that are capable of reproducing themselves (self-renewal) and differentiating into many different cell types, which can produce at least one type of highly differentiated descendant. Embryonic stem cells are derived from the inner cell mass of the blastocysts. They were first isolated from mouse in 1981 and these cells have the developmental potential to form trophoblast and derivatives of all three germ layers *in vitro* [1,2]. Due to these characteristics of embryonic stem cells, research on embryonic stem cells raises the possibility of ‘designer’ tissue and organ engineering. However, ethical considerations question the instrumental use of embryos for the isolation of stem cells, even if those embryos are surplus to requirements for assisted reproduction and destined for destruction. One alternative is to explore the use of adult stem cells; however, their full potential remains to be determined.

Correspondence to Hugh S. Taylor, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University, P.O. Box 208063, 333 Cedar St, New Haven, CT 06520, USA, Tel: +1 203 785 4005; Hugh.taylor@yale.edu.

Nearly all postnatal organs and tissues contain populations of stem cells, which have the capacity for renewal after damage or ageing. In the past several years, studies on adult stem cell plasticity show that adult stem cells are able to differentiate into other cell types in new locations, in addition to their usual progeny in their organ of residence [3,4]. Bone marrow derived stem cells can differentiate into skeletal myoblasts, endothelium, cardiac myoblasts, renal parenchymal, hepatic and biliary duct epithelium, lung, gut and skin epithelia, and neuroectodermal cells [5]. These studies show that bone marrow-derived stem cells may be involved in the regeneration of damaged tissue. The concept of plasticity of stem cells also opens up the possibility of repairing an individual's failing organ by transplanting.

The adult stem cells are responsible for the growth, homeostasis and repair of many tissues. How can they balance self-renewal with differentiation, and make the proper lineage determination? In normal adult tissues, stem cells are ultimately controlled by the integration of intrinsic factors (such as nuclear transcription factors) and extrinsic factors (growth factors, cell–cell contact or external influences). In 1978, Schofield [6] proposed the stem cell niche hypothesis, which hypothesized that stem cells reside within fixed compartments, or niches. This physiological microenvironment, consisting of specialized cells, secretes signals and provides cell surface molecules to control the rate of stem cell proliferation, determine the fate of stem cell progeny, and protect stem cells from death. Mammalian stem cells niches have been described in the hematopoietic, neural, epidermal, and intestinal systems [7]. Recent work has revealed that the interactions between stem cells and their niches may be more dynamic than originally believed. For example, hematopoietic stem cells (HSCs) may occupy two anatomically and physiologically distinct niches, an osteoblast niche and a vascular niche, and shuttle between them [8,9]. The vascular niche might explain stem cell survival in extramedullary haematopoietic sites, such as the liver and spleen, in which HSCs exist throughout adulthood without osteoblasts.

Germline stem cells in the postnatal ovary in mammal

Germline stem cells (GSCs) are the self-renewing population of germ cells that serve as the source for gametogenesis. GSCs in Drosophila females maintain oocyte production in adult ovaries [10]. However, it was believed that ovaries of some vertebrates, especially those of mammals, did not contain self-renewing stem cells in adults. A long-held dogma in ovarian biology in mammals is that females are born with a finite population of nongrowing primordial follicles; oocyte numbers decline throughout postnatal life, eventually leaving the ovaries devoid of germ cells [11,12]. In humans, the decline in oocytes numbers is accompanied by exhaustion of the follicle pool and menopause before the end of life [13].

In 2004, Johnson *et al.* [14] provided evidence to challenge this doctrine. They demonstrated the existence of proliferative GSCs that give rise to oocytes and follicle production in the postnatal period of mammalian ovary [14]. In these experiments, the numbers of healthy (nonatretic) and degenerating (atretic) follicles in ovaries of C57BL/6 mice were counted; the numbers of nonatretic quiescent (primordial) and early-growing (primary) prenatal follicles in single ovaries were higher than expected, and the rate of depletion in the immature ovary was less than anticipated. In the same year, Bukovsky *et al.* [15] also claimed to identify GSCs and formation of new primary follicles in adult human ovaries. This group showed that cytokeratin-positive mesenchymal cells in ovarian tunica albuginea differentiate into ovarian surface epithelium (OSE) cells by amesenchymal–epithelial transition.Germ cells can originate from surface epithelial cells which cover the tunica albuginea. The data also indicate that the pool of primary follicles in adult human ovaries may not represent a static, but rather a dynamic population of differentiating and regressing structures. These studies suggested the existence of proliferative germ cells that sustain oocyte and follicle production in the postnatal mammalian ovary, and indicate that oocytes

are continuously formed in the adult. However, subsequent work has not demonstrated offspring from donor-derived oocytes. The function of these 'oocytes' remains to be determined.

Origin of germ cells in adult ovary

The origin of oocytes (and primary follicles) in ovaries of adult mammalian females has been disputed for over 100 years. In the 19th century, Weismann's theory assumed that, before embryonic cells become committed along specific pathways, a set of germ cells is set aside, which are destined to give rise to the gametes. This theory was not questioned until the 1970s. In the early 2000s, evidence confirmed that functional mouse oocytes and sperm can be derived from mouse embryonic stem cells in culture [16–18]. Toyooka *et al.* [16] reported embryonic stem cells can form germ cells *in vitro*, and Geijsen *et al.* [17] found that injecting these cultured haploid male gametes into unfertilized egg led to embryo development to the early blastocyst stage. Hubner *et al.* [18] reported that mouse embryonic stem cells in culture can develop into oogonia that enter meiosis and recruit adjacent cells to form follicle-like structures and later developed into blastocysts.

More than 10 years ago, Bukovsky *et al.* [19] proposed that in adult human females, the OSE was a source of germ cells. As mentioned before, in 2005, this group demonstrated that new primary follicles differentiated from the OSE, which arises from cytokeratin-positive mesenchymal progenitor cells residing in the ovarian tunica albuginea. OSE cells in-vitro culture confirmed their in-vivo observations that in adult human ovaries, the OSE is a bipotent source of oocytes and granulosa cells [20]. In 2005, Johnson *et al.* [21] reported that mammalian oocytes originate from putative germ cells in bone marrow and are distributed through peripheral blood to the ovaries. Their data showed that bone marrow transplantation restores oocyte production in wild-type mice sterilized by chemotherapy, as well as in ataxia telangiectasia-mutated gene-deficient mice, which are otherwise incapable of making oocytes. Donor-derived oocytes are also observed in female mice following peripheral blood transplantation. It was suggested that bone marrow is a potential source of germ cells that could sustain oocyte production in adulthood. In 2007, the same group reported that bone marrow transplantation generates immature oocytes and rescues long-term fertility in a preclinical mouse model of chemotherapy-induced premature ovarian failure [22]. However, these studies are challenged by some. To test directly the physiological relevance of circulating cells for female fertility, Wagers' team established transplantation and parabiotic mouse models to assess the capacity of circulating bone marrow cells to generate ovulated oocytes, both in the steady state and after induced damage. Their studies showed no evidence that bone marrow cells, or any other normally circulating cells, contribute to the formation of mature, ovulated oocytes. Instead, cells that travelled to the ovary through the bloodstream exhibited properties characteristic of committed blood leukocytes [23]. So far, the origin of germ cells in female mammals is still an open issue. Controversy will be sure to stimulate further research on GSCs.

Ovarian tissue transplantation

Ovarian transplantation has a long history, traced back 200 years. However, there was little progress until the middle of the 20th century. More recently Oktay and Karlikaya [24] have reported that ovulation occurred after laparoscopic transplantation of frozen-thawed ovarian tissue to the pelvic side wall in a 29-year-old patient who had undergone salpingo-oophorectomy. In 2004, the same group reported another case in which a four-cell embryo was obtained from 20 oocytes retrieved from tissue transplanted beneath the skin in a patient who had chemotherapy-induced menopause [25]. The same year, a live birth after ovarian tissue transplant was reported in a nonhuman primate [26]. Later in 2004, a successful

pregnancy and live birth after orthotopic transplantation of cryopreserved ovarian tissue was reported by Donnez *et al.* [27]. In that case, a patient whose ovaries were damaged by cancer chemotherapy received frozen-thawed ovarian tissue transplantation. These findings give new hope for fertility preservation, including immature oocyte retrieval, in-vitro maturation of oocytes, oocyte vitrification or embryo cryopreservation. However, one major concern over orthotopic auto-transplantation is the potential risk that the frozen-thawed ovarian cortex might harbor malignant cells. There is the potential that such cells could induce a recurrence of disease after re-implantation. Some studies have suggested that ovarian tissue transplantation in Hodgkin's disease is well tolerated [28,29]. However, Shaw and colleagues [30] reported that ovarian grafts from a lymphoma prone strain of mice could transfer lymphoma to recipient animals.

In 2005, Silber *et al.* [31] reported that a 24-year-old woman gave birth after a transplant of ovarian cortical tissue from her monozygotic twin sister. This patient had premature ovarian failure at the age of 14 years, whereas her sister had normal ovaries and three naturally conceived children. After unsuccessful egg-donation therapy, the sterile twin received a transplant of ovarian cortical tissue from her sister. About 1 year later, she delivered a healthy-appearing female infant. In 2007, Donnez *et al.* [32] reported another case of successful allograft of ovarian cortex between two genetically nonidentical sisters. In this case, the patient presented with beta-thalassemia major and underwent chemotherapy and total body irradiation before bone marrow transplantation (BMT) about 16 years ago. The treatment resulted in premature ovarian failure. After excision of ovarian cortical fragments from an HLA-compatible sister, these fragments were immediately sutured to the ovarian medulla of the patient. Restoration of ovarian function was achieved after six months. In 2007, Silber *et al.* [33] reported 10 more successful ovary transplants in monozygotic twins after premature ovarian failure in one twin; two healthy babies have been delivered, and another three pregnancies are ongoing. Ovarian tissue transplantation not only brings hope to cancer patients, but also to those with ovarian dysgenesis or premature ovarian failure.

Stem cells in the uterus

The uterine endometrium in mammals is one of the most dynamic human tissues and consists of a glandular epithelium and stroma that are completely renewed in each monthly menstrual cycle. Endometrial stem cells were thought to reside in the basalis layer and serve as a source of cells that differentiate to form the endometrium. Under systemic hormonal changes, such as the cyclic increase in the serum level of estradiol, stem cells migrate and give rise to a group of progenitor cells that become committed to specific types of differentiated cells, for example epithelial, stromal and vascular, within a certain microenvironment. These endogenous stem cells allow the rapid regeneration of the endometrium necessary to support pregnancy. There was no direct evidence to confirm this hypothesis until 2004. In that year, two studies from different labs provided evidence for the origin of this cyclic renewal [34,35]. A team led by Gargett demonstrated that human endometrium contains small populations of epithelial and stromal stem cells responsible for cyclical regeneration of endometrial glands and stroma and that these cells exhibited clonogenicity. The results showed that small numbers of epithelial (0.22%) and stromal cells (1.25%) initiated colonies in serum-containing medium and exhibit high proliferative potential [34]. In 2006, Gargett's team used label-retaining cell (LRC) approach to identify somatic stem/progenitor cells and their location. The results demonstrated the presence of both epithelial and stromal LRC in mouse endometrium, which suggests that these stem-like cells may be responsible for endometrial regeneration [36]. Later on, another group also demonstrated that the human endometrium contains a low number of cells with the characteristics of endometrial stromal stem/progenitor cells, which seem to belong to the family of the mesenchymal stem cells (MSCs) [37].

Our laboratory found that bone marrow is an exogenous source of endometrial cells [35]. In a 2004 study, we provided evidence of endometrial regeneration in bone marrow transplant recipients who received marrow from a single-HLA antigen mismatched donor BMT for leukemia. Donor-derived endometrial epithelial cells and stromal cells were detected in endometrial samples of bone marrow recipients by RT-PCR and immunohistochemistry. These cells appeared histologically to be endometrial epithelial and stromal cells and also express appropriate markers of endometrial cell differentiation. Cyclic mobilization of bone marrow-derived stem cells may be a normal physiologic process. In 2007, our group also reported that after BMT, male donor-derived bone marrow cells were found in the uterine endometrium of female mice, and, although uncommonly (<0.01%), these cells can differentiate into epithelial cells [38]. Later, another study confirmed that bone marrow progenitor cells contribute to the uterine epithelium, and the population of cells may include CD45þ cells [39]. Further, in 2008, a new study showed that bone marrow-derived endothelial progenitors contribute to the formation of new blood vessels in the endometrium [40]. Last year, a group from Japan also reported that bone marrow-derived cells from human male donors can compose endometrial glands in female transplant recipients [41].

We also generated experimental endometriosis in a mouse model by ectopic endometrial implantation in the peritoneal cavity and detected LacZ expressing cells in the wild-type ectopic endometrium after BMT from LacZ transgenic mice [38]. The result showed that bone marrow-derived cells also contribute endometriosis. It was suggested that the repopulation of endometrium with bone marrow-derived stem cells may be important to normal endometrial physiology and also may help to explain the cellular basis for the high long-term failure of conservative alternatives to hysterectomy. The endometrium may regenerate after resection or ablation from a stem cell source outside of the uterus. Disorders of the uterine endometrium are common, leading to abnormal uterine bleeding, infertility, pregnancy complications, miscarriage, endometriosis and cancer. These findings have potential implications for the treatment of uterine disorders. Finally these data support a new theory for the cause of endometriosis, which may have its origin in ectopic transdifferentiation of stem cells.

In 2007 two studies determined the existence of a small population of multipotent stem cells in endometrium [42,43]. The Gargett lab collected human endometrial tissue from reproductive-aged women, and prepared human endometrial stromal cell cultures. Then endometrial stromal cells were incubated with adipogenic, osteogenic and myogenic differentiation induction media for 4 weeks. The results showed that a subset of endometrial stromal cells differentiate into cells of adipogenic, osteogenic, myogenic and chondrogenic cell lineages [42]. Wolff *et al.* [43] from our laboratory also collected endometrial tissue from reproductive-aged women and monolayer endometrial stromal cell (ESC), myometrial, fibroid, fallopian tube, and uterosacral ligament tissue cultures were generated. These cells were cultured in a defined chondrogenic media containing dexamethasone and transforming growth factor for 21 days and then were analyzed for markers of human articular cartilage, including sulfated glycosaminoglycans and type II collagen. Cultured endometrial derived stem cells (EDSCs) contain cells that can be differentiated into chondrocytes [43]. Finally, the Taylor group has recently reported that EDSCs can be differentiated into neurons which produce dopamione and have the potential to treat Parkinson's disease. Since endometrium can easily be obtained, it may represent a new potential source of pluripotent cells. Regenerative medicine holds tremendous potential to treat many forms of human disease. Endometrial biopsy could become an important source of stem cells for future cell-based therapies.

Placenta and stem cells

Over the last 30 years, colonization has been a long-accepted theory which proposes that the yolk sac was the sole source of hematopoiesis in the mammalian embryo. It was believed the embryonic yolk sac-derived HSCs colonized fetal liver to initiate definitive hematopoiesis and subsequently colonize bone marrow at the neonatal stages to support adult hematopoiesis. However, in the 1990s, accumulating evidence located hematopoiesis to another site in the aorta-gonad-mesonephros (AGM) of mouse embryos [44]. A 2003 study indicated that the placenta contains a high frequency of multipotential clonogenic progenitors including CFU-GMs, CFU-GEMMs, BFU-Es and HPP-CFCs [45]. The study results suggest that the placenta may function as a hematopoietic organ during development. In 2005, two studies simultaneously reported that HSCs activity can be detected in the mid-gestation placental labyrinth region [46,47]. The onset of HSC activity in the placenta coincides with that in the AGM region and the yolk sac. The HSC pool size in the placenta is 15-fold greater than in the AGM. The expansion of the HSC pool in the placenta occurs prior to and during the initial expansion of HSCs in the fetal liver. The size of the placental HSC pool diminished, whereas the HSC pool in the fetal liver continues to expand. These data suggest that placenta is another site contributing to the establishment of the mammalian definitive hematopoietic system. Further, in 2004, three groups also identified and isolated cells with MSC-like potency in human placenta [48–50]. In the last couple of years, the Huang group reported that placenta-derived multipotent cells can differentiate into hepatocyte-like cells, neuronal and glial cells when the cells cultured under appropriate conditions *in vitro* [51,52]. The placenta may be another source of multipotent stem cells.

Stem cell transfer from the fetus

The presence of fetal cells in maternal circulation has now been confirmed by many investigators [53•]. Several studies reported that microchimeric cells of fetal origin have been identified in the peripheral blood of patients with the autoimmune disease systemic sclerosis (SSc) [54]. However, it has not been determined if these cells are integrally involved in the pathogenesis of SSc, or if fetal microchimeric cells are just a marker of inflammation. Increased numbers of microchimeric fetal cells have been identified in some diseases of pregnancy, for example preterm labor, preeclampsia and aneuploidy [55]. However, there is speculation that the increased number of fetal microchimeric cells in the maternal circulation is a reflection of the abnormalities within the structure of the placenta, and not directly related to the disease process. In 2001, a team led by Bianchi discovered that male cells were seen in thyroid sections in women, presumably from their sons [56]. They reported that male cells were seen individually or in clusters in all thyroid disease from which biopsies were examined; they were not restricted to inflammatory thyroid diseases. In one patient with a progressively enlarging goiter, they noted fully differentiated male thyroid follicles closely attached to and indistinguishable from the rest of the thyroid. Later on, this team reported that XY+ microchimeric cells in maternal tissue, acquired most likely through pregnancy, express leukocyte, hepatocyte and epithelial markers [57]. The results suggest that pregnancy may result in the physiologic acquisition of a fetal cell population with the capacity for multilineage differentiation. The study also showed that hepatocytes of fetal stem cell origin were identified in liver tissue of one woman with liver injury and another woman following hepatic transplantation. In other studies, rats that had been bred to GFP males sustained directed injury to the liver and kidney of postpartum females. They found that fetal cells were engrafted into the bone marrow with resulting detection of these cells in the peripheral blood of the rats [58]. This study also demonstrated that the engrafted GFP-positive fetal cells gave rise to hepatocytes in the liver and tubular epithelial cells in the kidney. The GFP-positive cells were not found in the organs of the rats that were not injured. These findings suggest that in a state in which the tissue injury is chronic, fetal cell

microchimerism may be established more frequently, or more easily and also suggests that microchimeric cells are involved in tissue repair.

In 2008, two groups reported interesting studies describing the contribution of fetal stem cells to cancer. One group investigated microchimeric fetal cells clustered at sites of tissue injury in the lung decades after known male pregnancy; male cells were identified in lung/thymus tissue from all women with sons. The male cells in the lung were clustered in tumors rather than in surrounding healthy tissues. These male presumed-fetal cells were identified in pathological postreproductive tissues, in which they were more likely to be located in diseased tissues at several-fold higher frequency than normal tissues. It is suggested that fetal cells are present at sites of tissue injury and may be stem cells, either recruited from marrow or having proliferated locally [59]. Since breast carcinomas associated with pregnancy display a high frequency of inflammatory types, multifocal lesions and lymph node metastasis, another group from France questioned whether fetal stem cells are involved in this disease process. They analyzed women presenting with carcinomas who were pregnant with male fetuses. The results showed that the presence of fetal cells in pregnancy-associated breast carcinoma is a frequent phenomenon. These cells were predominantly part of the tumor stroma and could contribute to the poorer profile of these carcinomas [60•].

Cancer stem cells in reproductive tract

Cancer stem cells (CSCs) are defined as a rare cell population in cancer with indefinite potential for self-renewal, and they are proposed to be the cancer-initiating cells responsible for tumorigenesis and contribute to cancer resistance. Alteration of self-renewal pathways seems to be an important mechanism underlying CSC formation.

The best known and most comparable pairs of somatic and CSCs are HSCs and leukemic stem cells (LSCs) [61,62]. Recently CSCs have been positively identified and successfully isolated from a large number of cancers [63]. Ovarian cancer is an extremely aggressive disease. The cellular mechanisms underlying the increasing aggressiveness associated with ovarian cancer progression are poorly understood. Although epithelial ovarian cancers (EOCs) have been thought to arise from the simple epithelium lining the ovarian surface or inclusion cysts, the major subtypes of EOCs show morphologic features that resemble those of the müllerian duct-derived epithelia of the reproductive tract. HOX genes, which normally regulate müllerian duct differentiation, are not expressed in normal OSE, but are expressed in different EOC subtypes according to the pattern of mullerian-like differentiation of these cancers [64–66]. Ectopic expression of Hoxa9 in tumorigenic mouse OSE cells gave rise to papillary tumors resembling serous EOCs. In contrast, Hoxa10 and Hoxa11 induced morphogenesis of endometrioid-like and mucinous-like EOCs, respectively. Hoxa7 showed no lineage specificity, but promoted the abilities of Hoxa9, Hoxa10, and Hoxa11 to induce differentiation along their respective pathways. Although those findings indicate roles for Hoxa7 and Abd-B-like HOX genes in aberrant differentiation, their roles in OSE transformation have yet to be defined.

Stem cell transformation may be the underlying mechanism leading to ovarian cancer [67]. The study showed that a single tumorigenic clone was isolated among a mixed population of cells derived from the ascites of a patient with advanced ovarian cancer. During the course of the study, another clone underwent spontaneous transformation in culture, providing a model of disease progression. Both the transformed clones possess stem cell-like characteristics and differentiate to grow in an anchorage-independent manner *in vitro* as spheroids, although further maturation and tissue-specific differentiation was arrested. Significantly, tumors established from these clones in animal models are similar to those in the human disease in their histopathology and cell architecture. Furthermore, the

tumorigenic clones, even on serial transplantation, continue to establish tumors, thereby confirming their identity as tumor stem cells. These findings suggest that stem cell transformation can be the underlying cause of ovarian cancer and continuing stochastic events of stem and progenitor cell transformation define the increasing aggression that is characteristically associated with the disease.

Many types of stem cells use a multidrug resistance (MDR) pump to rid themselves of chemicals, including nuclear dyes. This property facilitates fluorescence-activated cell sorting of those rare cells capable of nuclear dye exclusion, which have been termed side-population cells. This in turn has led to the finding that side-population cells exhibit many stem cell-like properties [68,69]. In 2006, a group claimed to identify and characterize a stem cell-like subpopulation of ovarian cancer cells from two distinct genetically engineered mouse ovarian cancer cell lines [70]. This study identified a rare population of verapamil-sensitive side-population cells in mouse ovarian cancer cell lines that have clonogenic properties *in vitro* and form tumors *in vivo*. In contrast, non-side-population cells derived from the same cancer cell lines do not exhibit clonogenic or tumor-forming properties. Similarly a 2008 study identified an endometrial cancer (EnCa) stem cell population; in that study the investigators tested relative tumor formation activity of the side-population and non-side-population fractions. Only the side-population fraction was tumorigenic. And this rare subset of cells is capable of initiating tumor formation in NOD/SCID mice [71]. Later on, another study reported that expression of the adult stem cell marker Musashi-1 was increased in endometriosis and endometrial carcinoma [72]. Musashi-1 is aRNA-binding protein associated with maintenance and asymmetric cell division of neural stem cells. These results are consistent with the hypothesis that EnCa contain a subpopulation of tumor-initiating cells with stem-like properties, and support the concept of a stem cell origin of endometriosis and endometrial carcinoma.

Conclusion

We are just beginning to understand stem cells, and many key questions remain. The potential advantages of stem cells in reproductive biology and medicine are apparent. Stem cells may play an important role in normal uterine and ovarian physiology. They likely are involved in the response of these tissues to injury and disease. The potential for these processes to be exploited for medical treatment is of great promise. Additionally, stem cells likely play a role in pathology of the reproductive tract. Stem cells give rise to cancers and endometriosis. A better understanding of stem cell biology may prove helpful in the treatment of these conditions. Finally the fetus, placenta and even the endometrium are all sources of stem cells. Endometrial-derived stem cells may provide an immunologically matched source of multipotent stem cells for tissue engineering and regenerative medicine.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 256).

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