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Stem Cells and Female Reproduction

Hongling Du, MD, PhD and **Hugh S. Taylor, MD**
Department of Obstetrics, Gynecology and Reproductive Sciences (HD), and Molecular Cellular and Developmental Biology (HST), Yale University, New Haven, Connecticut.

Abstract

Several recent findings in stem cell biology have resulted in new opportunities for the treatment of reproductive disease. Endometrial regeneration can be driven by bone marrow derived stem cells. This finding has potential implications for the treatment of uterine disorders. It also supports a new theory for the etiology of endometriosis. The ovaries have been shown to contain stem cells that form oocytes in adults and can be cultured in vitro to develop mature oocytes. Stem cells from the fetus have been demonstrated to lead to microchimerism in the mother and implicated in several maternal diseases. Additionally the placenta may be another source of hematopoietic stem cell. Finally endometrial derived stem cells have been demonstrated to differentiate into non-reproductive tissues. While 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.

Keywords

stem cell; reproduction; ovary; uterus

INTRODUCTION

Stem cells are defined as undifferentiated cells, capable of reproducing themselves (self-renewing) and differentiating into many different cell types, which can produce at least 1 type of highly differentiated descendant.[1] Many terms are used to define various stem cells with these characteristics. Totipotent stem cells have the potential to differentiate into all the cells and tissues that make up an embryo and that support the development of the fetus, eg, the zygote, or fertilized egg. Pluripotent stem cells have the potential to give rise to cells derived from all 3 germ layers, eg, embryonic stem cells. Multipotent stem cells have a capability of producing a limited range of differentiated cell lineages appropriate to their location, eg, somatic or adult stem cells. Unipotent stem cells are capable of differentiating along only 1 lineage, eg, epidermal stem cells. Embryonic stem (ES) cells are derived from the inner cell mass of the blastocysts. They were first isolated from mouse in 1981 and can be maintained in tissue culture under conditions where they can be propagated indefinitely as pluripotent ES cells.[2] In 1998, EC cells were isolated from human blastocysts; these cells have the developmental potential to form trophoblast and derivatives of all 3 germ layers in vitro.[3] Because of these characteristics of ES cells, research on ES 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 and determine their full potential.

Address correspondence to: Hugh S. Taylor, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University, PO Box 208063, 333 Cedar St, New Haven, CT 06520. Hugh.taylor@yale.edu.

ADULT STEM CELL PLASTICITY

Nearly all postnatal organs and tissues contain populations of stem cells, which have the capacity for renewal after damage or ageing. Because it was thought that adult stem cells have a limited potential for production of differentiated derivatives, the main difference between blastocyst-derived pluripotent stem cells and multipotent stem cells from adult organs is the number of types of differentiated cells that can be produced. In past several years, studies on adult stem cell plasticity have questioned the view. For example, neural stem cells can produce a variety of blood cell types including myeloid and lymphoid cells as well as early hematopoietic cells; cells derived from the dermis can differentiate into neurons, glia, smooth muscle cells and adipocytes.[4,5] Bone marrow (BM) is a mesodermal derived tissue consisting of a complex hemopoietic cellular component supported by a microenvironment composed of stromal cells embedded in a complex extracellular matrix. Bone marrow stem cells develop into hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). Hematopoietic stem cells are the best characterized stem cells. In the late 1990s, previously unknown properties of HBCs were identified; HSCs not only commit to their natural lineage, eg, erythrocytes, thrombocytes, and leukocytes, but also are able to differentiate into microglia, macroglia, and hepatocytes. [6–8] Several studies on MSCs determined that MSCs can differentiate into osteoblasts, chondrocytes, myoblasts, and adipocytes.[9–12] More recently, MSCs were unexpectedly determined to differentiate into cardiomyocytes, neural cells, and pneumocytes.[13–15] Based on these findings, it is now believed that some adult stem cells are not lineage restricted. They are able to differentiate into other cell types in new locations, in addition to their usual progeny in their organ of residence. After transplantation of BM or enriched HSCs, skeletal myoblasts, endothelium, cardiac myoblasts, renal parenchymal, hepatic and biliary duct epithelium, lung, gut and skin epithelia, and neuroectodermal cells of donor origin have been detected.[16–29] These studies show that BM 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 these multipotent cells.

THE ADULT STEM CELL NICHE

Stem cells are responsible for the growth, homeostasis, and repair of many tissues. How can stem cells balance self-renewal with differentiation? How can adult stem cells make the proper lineage determination? In normal adult tissues, stem cells are ultimately controlled by the integration of intrinsic factors (such as nuclear factors) and extrinsic factors (through growth factors, stroma, or external influences).[30] In 1978, Schofield proposed the stem cell niche hypothesis, which proposes that stem cells reside within fixed compartments or niches.[31] 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 daughters, and protect stem cells from death. In past decade, mammalian stems cells niches have been described in the germinal (testis), hematopoietic, neural, epidermal, and intestinal systems. [32–35] In the niches, integrins and extracellular matrix are believed to influence the survival and development of the committed cells. Numerous signaling molecules which orginate from supporting cells within the niche or from stem cells themselves have been implicated in the ability of the niche to control stem cells' fate. For example, β1 integrin receptor is required for maintenance of epidermal stem cells, and TGF β superfamily members instructively promote neural crest cell fates.[36,37] Wnts stimulate proliferation of HSCs and intestinal stem cells, Bone morphogenetic protein (BMPs) promote stem cells differentiation in hair follicle and epidermis.[38–41] Notch signaling promotes differentiation in neural crest stem cell and epidermal stem cells, but delays differentiation in cultured human hematopoietic cells.[42–44] Recent work has revealed that the interactions between stem cells and their niches may be more dynamic than

originally believed. For example, HSCs may occupy 2 anatomically and physiologically distinct niches, an osteoblast niche and a vascular niche, and shuttle between them.[45–47]

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. Germline stem cells exist in diverse forms in many organisms, ranging from Drosophila melanogaster to mammals.[48] Spermatogonial stem cells have been found in all metazoan species, which maintain spermatogenesis throughout the entire reproductive life of a male.[48–50] Germline stem cells in Drosophila females maintain oocyte production in adult ovaries.[51] However, it was believed that ovaries of some vertebrates, especially those of mammals, did not contain self-renewing stem cells in adults. In contrast to spermatogenesis, there was an apparent evolutionary disparity in the female. The formation of new primary follicles in adult ovaries is a controversial issue. 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.[52–57] In humans, the decline in oocytes number is accompanied by exhaustion of the follicle pool and menopause before the end of life.[58] In these organisms, primordial follicles (oocytes) are arrested in diplotene stage of meiosis I and are surrounded by a single, squamous layer of somatic cells.[54]

In 2004, Johnson et al 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.[59] In these experiment, 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. The results are consistent with past studies of follicle depletion in CBA/Ca mice.[56] Later Kerr et al demonstrated that following a marked depletion of follicles and oocytes during the first postnatal week, mean primordial follicle numbers per ovary did not decline significantly in the subsequent 13 weeks up to day 100 of age in the C57BL/6 strain of mice. The persistence of follicle numbers in the primordial follicle pool from day 7 to 100 and their recruitment into the population of growing follicles was accompanied by no significant decay in the total numbers of all healthy follicles over the same time period. Those data supports postnatal follicle renewal in postnatal and adult ovaries in C57BL/6 mice.[60] In 2004, Bukovsky et al also claimed to identify GSCs and formation of new primary follicles in adult human ovaries.[61] This group showed that cytokeratin (CK) positive mesenchymal cells in ovarian tunica albuginea (TA) differentiate into surface ovarian epithelium (OSE) cells by a mesenchymal-epithelial transition. Germ cells can originate from SE cells which cover the TA. 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.[62,63] 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 more than one hundred years. In 19th century, Weismann’s theory assumed that before embryonic cells become committed along specific pathways, a set of germ cells is set aside that are destined to give rise to the gametes. This theory was not

questioned until the 1970s. In 1977, studies of mouse embryos, in which genetically marked cells were introduced to the 4- and 8-cell stage blastomere, have shown that such cells can either become germ cells or somatic cells.[64] Therefore it is believed that no specific germ cell commitment exists prior to implantation. During the 1990s, evidence was presented that egg and sperm cells (gametes) of the mouse differentiate from somatic linage and cellular differentiation of grafted embryonic cells does not depend on where the grafts were taken, but where they have been placed.[65,66] In the early 2000s, evidence confirmed that functional mouse oocytes and sperm can be derived from mouse ES cells in culture.[67–69] Toyooka et al[67] reported ES cells can form germ cells in vitro, and Geijsen et al[68] found that injecting these cultured haploid male gametes into unfertilized egg led to embryo development to the early blastocyst stage. Hubner et al reported that mouse ES 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 proposed that in adult human females, the OSE was a source of germ cells.[70] As mentioned before, in 2004, this group demonstrated that new primary follicles differentiated from the OSE, which arises from cytokeratin-positive mesenchymal progenitor cells residing in the ovarian TA. Later they demonstrated that the both oocytes and granulosa cells differentiate in cultures derived from adult human ovaries.[71] Cells were scrapped from the surface of human ovaries, obtained at the time of hysterectomy/bilateral salpingo-oophorectomy. In the presence or absence of estrogenic stimuli, cells were cultured for 5 to 6 days. Without stimulus, the OSE cells differentiated into small cells of granulosa phenotype, and epithelial, neural, and mesenchymal type cells. In contrast, stimulated OSE cells differentiated directly into large cells of the oocyte phenotype. Such cells exhibited germinal vesicle breakdown, expulsion of the polar body, and surface expression of zona pellucida proteins. These studies on OSE cells in vitro confirmed their in vivo observations that in adult human ovaries, the OSE is a bipotent source of oocytes and granulosa cells. Additionally, based on accumulated data, germ cells may also be derived from BM. Germline markers, such as Oct4, Mvh, Dazl, Stella, and Fragilis are expressed in BM cells which are isolated from adult female mice.[72–76] In addition, female-germ-cell-specific homeobox gene Nobox was detected in BM cells of adult female mice, which is critical for directing expression of Oct4 and Gdf9 in primordial oocytes as well as for folliculogenesis.[77–79] In 2005, Johnson et al reported that mammalian oocytes originate from putative germ cells in BM and are distributed through peripheral blood to the ovaries.[80] Their data confirmed that germline markers were expressed in BM cells. Further, BM 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 BM is a potential source of germ cells that could sustain oocyte production in adulthood. In 2007, the same group reporetd that BM transplantation generates immature oocytes and rescues long-term fertility in a preclinical mouse model of chemotherapy-induced premature ovarian failure.[62] However, these reports have been challenged. 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 BM cells to generate ovulated oocytes, both in the steady state and after induced damage. Their studies showed no evidence that BM 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.[63] Recently, the Tilly group has published a paper repeating the parabiosis experiments reported by Eggan and coworkers with a germline-specific enhanced green fluorescent proteins (EGFP)-expressing transgenic line (ΔPE-*Oct4* or TgOG2) for oocyte tracking. In their hands, the EGFP-positive immature oocytes are easily detected in the ovaries of adult wild-type female partners within 4 weeks

after joining to adult TgOG2 females.[81] 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

In 2004, a successful live birth after orthotopic transplantation of cryopreserved ovarian tissue in a woman whose ovaries were damaged by cancer chemotherapy demonstrates the clinical potential.[82] Radiotherapy, high-dose chemotherapy and bone marrow transplantation (BMT) have resulted in an increased number of long-term cancer survivors. Because the ovaries and germ cells are very sensitive to cytotoxic treatment, especially to alkylating agents and radiation, ovarian failure and infertility are common side effect after cancer treatment.[83] For young female cancer survivors, there are several potential treatments which were tried to avoid prematurely sterility. The methods for preserving fertility include oocyte cryopreservation, embryo cryopreservation, and cryopreservation of ovarian cortical tissue. Although mature oocytes can be successfully cryopreserved in the mouse, the success rate of human oocyte cryopreservation is still limited.[84–89] The cryopreservation of embryos is a well-established technique, however it has limited application in cancer patients. Obviously, it is not suitable for prepubertal children or patients without a partner who do not wish to use donor sperm. Cryopreservation of ovarian tissue has several potential advantages over both oocyte and embryo freezing.

Ovarian transplantation has a long history, traced back to middle of 19th century[90]; however, there was little progress until the middle of 20th century. Since the development of freezing methods in the 1950s, investigators started to report successful cryopreservation and transplantation of ovarian tissue in mammals, such as mice and sheep.[91–94] More recently Oktay and colleagues 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.[95] In 2004, the same group reported another case in which a 4-cell embryo was obtained from 20 oocytes retrieved from tissue transplanted beneath the skin in patient who had chemotherapy-induced menopause.[96] The same year, a live birth after ovarian tissue transplant was reported in a non-human primate.[97] Later in 2004, a successful pregnancy and live birth after orthotopic transplantation of cryopreserved ovarian tissue was reported by Dr Donnez.[82] In that case, the patient whose ovaries were damaged by cancer chemotherapy received frozen-thawed ovarian tissue transplantation. The vaginal echography and laparoscopy revealed a follicular structure 5 months after surgery. The vaginal ultrasonography and hormone measurements indicated recovery of regular ovulatory cycles. From 5 to 9 months, the patient had menstrual bleeding and the development of a follicle and corpus luteum every cycle. Eleven months after transplantation, human chorionic gonadotrophin concentration and ultrasound confirmed a viable fetus. In sum, immature oocyte or ovarian cortex retrieval, in vitro maturation of oocytes, with optional oocyte or embryo cryopreservation are all developing techniques. All of these strategies give new hope for fertility preservation. 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 which could induce a recurrence of disease after re-implantation. Some studies have suggested that ovarian tissue transplantation in Hodgkin's disease is safe.[92,98,99] However Shaw and colleagues reported that ovarian grafts from AKR mice could transfer lymphoma to recipient animals.[100] In addition, although ovarian tissue cryopreservation has been quite successful (>70% survival of primordial follicles after freezing and thawing),[101] we still do not know how much follicular loss occurs in this procedure.

In 2005, Silber et al reported that a 24-year-old woman gave birth after a transplant of ovarian cortical tissue from her monozygotic twin sister.[102] This patient had premature

ovarian failure at the age of 14 years, whereas her sister had normal ovaries and 3 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 reported another case of sucessful allograft of ovarian cortex between 2 genetically non-identical sisters.[103] Approximately 16 years ago, the patient aged 20 presented with beta-thalassemia major and underwent chemotherapy and total body irradiation before BMT. The treatment resulted in premature ovarian failure. After excision of ovarian cortical fragments from an human leukocyte antigen (HLA)-compatible sister, these fragments were immediately sutured to the ovarian medulla of the patient. Restoration of ovarian function was achieved after 6 months. In 2007, Silber et al reporeted 10 more sucessful ovary transplants in monozygotic twins after premature ovarian failure in 1 twin; 2 healthy babies have been delivered, and another 3 pregnancies are ongoing.[104] 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. More than 10 years ago, it was proposed that cyclic endometrial renewal depends on a small pool of tissue-specific multipotent stem cells.[105] 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, eg, 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, 2 reports from different labs provided evidence for the origin of this cyclic renewal.[106,107] 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.[106] 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.[108] 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 MSCs.[109]

Our laboratory found that BM is an exogenous source of endometrial cells.[107] In a 2004 report, we provided evidence of endometrial regeneration in BMT 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 BM recipients by reverse transcription polymerase chain reaction (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 BM-derived stem cells may be a normal physiologic process.

In 2007, our group also reported that after BMT, male donor-derived BM cells were found in the uterine endometrium of female mice, and, although uncommonly (<0.01%), these cells can differentiate into epithelial cells.[110] They also generated experimental

endometriosis in a mouse model by ectopic endometrial implantation in the peritoneal cavity and deceted LacZ expressing cells in the wild-type ectopic endometrium after BMT from LacZ transgenic mice. The result showed that BM-derived cells also contribute endometriosis. It was suggested that the repopulation of endometrium with BM-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. Later, another report confirmed that BM progenitor cells contribute to the uterine epithelium, and the population of cells may include CD45+ cells.[111] Furthermore, in 2008, a new report showed that BM-derived endothelial progenitors contribute to the formation of new blood vessels in the endometrium.[112] 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 etiology of endometriosis, which may have its origin in ectopic transdifferentiation of stem cells.

In 2007, 2 reports determined the existence of a small population of multipotent stem cells in endometrium.[113,114] 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.[113] Wolff et al 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 (CM) containing dexamethasone and transforming growth factor for 21days and then were analyzed for markers of human articular cartilage, including sulfated glycosaminoglycans and type II collagen. Cultured endometrial derived stem cells (EDSC) can be differentiated into chondrocytes.[114] Other reproductive tissues did not contain these multipotent stem cells. Finally, we have recently reported that EDSC can be differentiated into neurons which produce dopamione and have the potential to treat Parkinson’s disease. Because 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.

THE 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 BM at the neonatal stages to support adult hematopoiesis.[115] However, in the 1990s, accumulating evidence located hematopoiesis to another site in the aorta-gonad-mesonephros (AGM) of mouse embryos.[116–118] A 2003 study indicated that the placenta contains a high frequency of multipotential clonogenic progenitors including Colony-forming units, granulocytes, macrophages (CFU-GMs), Colonyforming units, granulocytes, erythrocytes, monocytes, macrophages (CFU-GEMMs), Burst-forming units, erythroid (BFU-Es), and High-proliferation-potential colonyforming cells (HPP-CFCs).[119] The study results suggest that the placenta may function as a hematopoietic organ during development. In 2005, 2 articles simultaneously reported that HSCs activity can be detected in the mid-gestation placental labyrinth region.[120,121] The onset of HSC activity in the placenta coincides with that in the AGM region and the yolk sac. The HSC pool size in

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 while 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, 3 groups also identified and isloated cells with MSC-like potency in human placenta.[122–125] In last 2 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.[126,127] The placenta may be another source of multipotent stem cells.

STEM CELL TRANSFER FROM THE FETUS

The presence of fetal cells in maternal circulation and tissues has now been confirmed by many investigators.[128–132] Fetal cells enter the maternal circulation during all pregnancies, and also persist in the maternal blood and other tissues for decades, thus creating a state of physiologic microchimerism in the parous woman. The fetal cells are detected as CD34+ and CD38+ cells, which represent progenitor cells.[132,133] Fetal trophoblast cells, HSCs, and MSCs have all been detected in pregnant women.[134–137] The observation of feto-maternal cell trafficing and maternal organ chimeras raised an important question: what is the role of fetal stem cells in the pregnant woman? In the 1990s, 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).[138–140] However, it has not been determined whether these cells are integrally involved in the pathogenesis of SSc, or whether fetal microchimeric cells are just a marker of inflammation. Increased numbers of microchimeric fetal cells have been identified in some diseases of pregnancy, eg, preterm labor, preeclampsia, and aneuploidy.[140–143] 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.[144] 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 1 patient with a progressively enlarging goiter, they noted fully differentiated male thyroid follicles closely attached to and indistinguishable from the rest of the thyroid. In 2004, this team reported that XY+ microchimeric cells in maternal tissue, acquired most likely through pregnancy, express leukocyte, hepatocyte, and epithelial markers.[145] 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 1 woman with liver injury and another woman following hepatic transplantation. In other studies, rats that had been bred to green fluorescent proteins (GFP) males sustained directed injury to the liver and kidney of postpartum females. They found that fetal cells were engrafted into the BM, with resulting detection of these cells in the peripheral blood of the rats.[146] 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 fetal cells in the liver were found to express albumin confirming that they were hepatocytes. Furthermore, they observed fetal cells expressing GFP in the cytoplasm of cells in the tubular basement membrane. The GFP-positive cells were not found in the organs of the rats that were not injured. These findings suggest that in a state where the tissue injury is chronic, fetal cell microchimerism may be established more frequently or more easily and also suggest that microchimeric cells are involved in tissue repair.

In 2008, 2 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, where 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.[147] Because 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.[148]

Although the functional contribution of these fetal-derived cells remains to be determined, the possibility that newly implanted or persistent fetal stem cells may promote tissue regeneration in maternal disease states is novel and exciting.

CANCER STEM CELLS IN THE REPRODUCTIVE TRACT

As early as 1983, Mackillop presented a simple stem cell model of human tumor growth based on the observation that not all cells within a tumor can maintain tumor growth; instead, most cancers consist of heterogeneous cell populations similar to the hierarchical tree of stem cell lineages.[149] In 2001, it was hypothesized that similar signaling pathways may regulate self-renewal in all stem cells. Tumors may originate from the transformation of normal stem cells, and cancer cells may include cancer stem cells (CSCs).[150] Cancer stem cells 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 CSCs formation. It is known that the signaling pathways required for normal stem cell self-renewal are also involved in cancer development, such as *HOX* genes, Wnt, Sonic Hedgehog, and Notch signaling pathways.[151–165]

The best known and most comparable pairs of somatic and CSCs are HSCs and leukemic stem cells (LSCs).[166–169] Human LSCs are strikingly similar to normal HSCs, with respect to their ability for self-renewal,cell-surface markers, and differentiation capacities.[170,171] Colinear and differential expression of *HOX* genes is required for the proper development of hematopoietic cells. Two murine studies demonstrating that purified hematopoietic progenitors engineered to overexpress the *HOX* gene regulators MLL-AF9 or MLL-GAS7 can be transformed into LSCs.[172,173] Dysregulation of *HOX* gene activity may be a central mechanism underlying the self-renewal capacity of LSCs. Recently, CSCs have been positively identified and successfully isolated from a large number of cancers.[174–181] 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. The *Hoxa9, Hoxa10*, and *Hoxa11* genes are related to differentiation of the müllerian ducts into the fallopian tubes, uterus, and cervix.[182,183] *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 müllerian-like

differentiation of these cancers.[184] 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. As described above, a group of OSE cells in the adult ovary is a source of germ cells. Is it possible that *HOX* genes expressed in this group of OSE cells may play a role in cells differentiation and lineage determination in ovarian cancer, and may even identify CSCs.

Stem cell transformation may be the underlying mechanism leading to ovarian cancer.[185] 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 (SP) cells. This in turn has led to the finding that SP cells exhibit many stem cell—like properties.[186–190] In 2006, a group claimed to identify and characterize stem cell—like subpopulation of ovarian cancer cells from 2 distinct genetically engineered mouse ovarian cancer cell lines.[191] This study identified a rare population of verapamil-sensitive SP cells in mouse ovarian cancer cell lines that have clonogenic properties in vitro and forms tumors in vivo. In contrast, non-SP 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 SP and non-SP fractions. Only the SP fraction was tumorigenic. And this rare subset of cells are capable of initiating tumor formation in NOD/SCID mice.[192] Later another study reported that expression of the adult stem cell marker Musashi-1 was increased in endometriosis and endometrial carcinoma.[193] Musashi-1 is an RNA-binding protein associated with maintenance and asymmetric cell division of neural stem cells.[194] 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 likely 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. Stems cells can be the underlying cause of 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.

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