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Placental and Pregnancy Stem Cells

Everyone Is, or Should Be, Interested in the Placenta

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The placenta is indeed a miraculous organ. Not only does it provide nutrition in the form of amino acids and glucose to the developing embryo and fetus in the form of amino acids and glucose, but it also acts as an organ of respiration providing oxygen and removing carbon dioxide. It is also an excretory organ. One of the most amazing things about the placenta is its role in stem cell physiology, a role which is only recently being studied and is presented in this issue of *Stem Cell Reviews*. The placenta may prove to be a noncontroversial source of hematapoetic stem cells (HSCs) and mesenchymal stem cells (MSCs) as well amniotic epitherial (AE) stem cells and endothelial progenitor cells.

Fetal stem cells enter the maternal circulation as early as 6 wk of gestation. In his article, Nguyen Huu reports on this phenomena in his article, and describes pregnancy-associated progenitor cells (PAPCs), which have been shown to home to areas of maternal tissue injury. By 37 wk, 100% of pregnant women have these progenitor cells in their maternal circulation. These authors suggest that patients consider banking these PAPCs. It certainly would make sense to collect and bank these cells from mothers who have male offspring with conditions amenable to stem cell therapies.

In mammals, the allantois forms the umbilical cord and the mesodermal components of the fetal placenta. Gastrulation occurs during the third week of gestation and the process establishes all three germ layers including the ectoderm, mesoderm, and the endoderm. Gastrulation begins on the surface of the epiblast and is responsible for the differentiation and specification of cell fate. As the embryo and the placenta develop, various stem cell entities become operative. As Miki and Strom report, the AE cells are derived from the epiblast during early embryonic life at approx 8 d after fertilization. The AE cells therefore are derived before gastrulation which occurs between days 15 and 17. Gastrulation marks a "tipping point" at which cell fate is determined. Because the amnion, and therefore the AE cells, differentiate from this epiblast, these retain their pluripotentency and these AE cells differentiate into cells of all three germ layers. Miki and Strom describe the unique characteristics of these amniotic epithelial cells and summarize the previous work regarding AE cells.

Weiss reports on the mesenchymal-like cells found in Wharton's jelly, also known as the matrix of the umbilical cord. These umbilical cord matrix (UCM) cells are multipotent and can differentiate into tissues of both the mesoderm and ectoderm. These primitive stem cells that have been trapped in the Wharton's jelly in early embryonic life are extracted postnatally with great ease. In early embryonic life, HSC precursors migrate from the aortic-gonadotropin-mesonephric region in the hind gut of the developing embryo, forming the fetal liver through the allantois. Migration then occurs from the fetal liver to bone marrow again through the primitive allantois/umbilical cord. These cells therefore are trapped at a very early embryological age and retain the properties of primitive stem cells.

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The umbilical vein and artery also yield stem cells. Park and Galper report on human umbilical vein endothelial cells (HUVECs), which offer new insights into the relationship between lipid metabolism and angiogenesis. HUVECs have "provided a critical role for an in vitro model for major breakthroughs in molecular medicine." The model helps to explain molecular trends in the pathophysiology of atherosclerosis and plaque formation and observes the control of angiogenesis and neovascularization in response to hypoxia and ischemia.

Breymann discusses umbilical cord cells as a source of cardiovascular tissue engineering and observes that the umbilical cord provides various types of stem cells, including umbilical cord blood stem cells and endothelial progenitor cells, and he recognizes that the umbilical cord derived cells are an attractive concept for regenerative medicine. Also in this issue, Curtis L. Cetrulo, Jr., introduces some unique experiments that utilize umbilical cord blood mesenchymal cells for regenerative medicine.

Hemapoetic stem cells (HSCs) found in umbilical cord blood have been used in more than 8000 transplants since the first reported case in 1989. Stem cells from the umbilical cord for transplantation may soon replace stem cells from any other source including bone marrow as the most attractive option for transplantation. Perlow provides an interesting perspective from an obstetrician's viewpoint and discusses the goal of the Stem Cell Act of 2005 to bank 150,000 cord blood samples. Hathspell and Ballen provide an extensive review of cord blood transplantation, including a review of the use of double cord blood transplants to overcome the limiting factor of low cell dosage in cord blood when compared to bone marrow or peripheral blood stem cells.

Umbilical cord cells have also been used to study other entities. Savarese et al. in their paper propose a novel means of using stem cells to investigate the *in utero* etiology of breast cancer. They provide references to their own and other studies that offer insight into the molecular signals that may affect breast stem cell proliferation and development. The recent finding that breast cancer stem cells exist and may have characteristics of normal breast stem cells supports the hypothesis that breast cancers arise from breast stem cells.

Theoharides describes cord blood stem cell physiology and reports on his long-term studies of mast cells from umbilical cord blood. He also describes cell array technology for fast output screening and for obtaining data from individual cells, a new and powerful tool.

Perhaps we should begin to think about saving all placentas and banking the cells collected from other tissues in the placenta including HUVECs, UCM cells, AE cells, mesenchymal cells collected from various tissues of the placenta, and HSCs from the umbilical cord blood. The cells obtained from the maternal circulation, PAPCs, could also be banked. All of these cells or various combinations of these cells may be used in the future to save lives and enhance the quality of life for many people. We might envision a time when a child is born and the placenta is saved and a "cocktail" of these elements might be used to treat hypoxic ischemic encephalopathy (HIE) in the newborn during the peripartum period for neuroregeneration. A combination of these cells may also be used to treat congenital heart disease in the newborn period.

In addition, a combination of these cells might be used to treat one or more of the 80 diseases that have responded to stem cell transplantation. Further, these cells also have the potential to treat degenerative diseases, including heart disease in the adult, orthopedic problems, endocrine disorders such as diabetes, and neurodegenerative diseases such as stroke, Alzheimer's disease, Parkinson's disease, and spinal cord injuries. The time has to come to focus on pregnancy and the placental cells for a noncontroversial source of primitive stem cells. Everyone is, or should be, interested in the placenta.