Hypothesis

Immune cells contribute to systemic cross-talk between the embryo and mother during early pregnancy in cooperation with the endocrine system

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In early pregnancy, human chorionic gonadotropin (HCG) stimulates the corpus luteum to produce progesterone that in turn maintains human embryo implantation in the uterus. This inevitable communication through blood circulation can be called 'systemic cross-talk between the embryo and mother'. Despite considerable evidence suggesting that the human corpus luteum cannot be maintained by HCG alone, no other responsible soluble factors have been proposed. We found that peripheral blood mononuclear cells (PBMC) derived from pregnant women promoted progesterone production by human luteal cells and propose that both hormones and immune cells participate in this systemic cross-talk. This systemic cross-talk by immune cells is believed to operate in embryo implantation. Splenocytes derived from pregnant mice promoted endometrial differentiation and embryo implantation in vivo. Human PBMC derived from women early in pregnancy promoted invasion of murine embryos in vitro. In addition, recombinant HCG increased the effects of human PBMC on murine embryo invasion. Human chorionic gonadotropin also increased chemokine production by human PBMC through a lectin–glycan interaction, which is a primitive pathway in the immune system. Furthermore, chemokines were shown to induce human trophoblast invasion. These findings suggest that the immune system positively contributes to systemic cross-talk between the embryo and mother in cooperation with the endocrine system. (Reprod Med Biol 2006; 5: 19–29)

Key words: corpus luteum, cross-talk, embryo implantation, endometrial differentiation, trophoblast invasion.

ENDOCRINOLOGICAL REGULATION OF SYSTEMIC CROSS-TALK BETWEEN THE MOTHER AND EMBRYO

In mammals, embryo implantation in the uterus is an essential phenomenon to maintain the species. The hypothalamic–pituitary–ovarian axis of the neuroendocrine system induces cyclic production of estrogen and progesterone from the follicles and corpus luteum (CL) in the ovary. These ovarian sex steroid hormones elicit endometrial differentiation that facilitates embryo implantation. Endometrial epithelial cells should accept the normally developing embryo, but must reject non-fertilized oocytes or foreign organisms such as bacteria. When the human female does not receive embryonal signals, menstruation occurs. Human chorionic gonadotropin (HCG), a hormone secreted from trophoblasts, is considered to play a central role in maintaining embryo implantation. Through blood circulation, HCG reaches the maternal ovary and stimulates the CL to produce progesterone, which is in turn transferred to the uterus to maintain embryo implantation in early pregnancy. This communication through blood circulation is an inevitable process for human embryo implantation and can be called 'systemic cross-talk between the embryo and mother'. It has been proposed that direct cross-talk between the developing embryo and maternal tissues while the embryo travels through the fallopian tubes and becomes implanted in the endometrium plays an important role in successful embryo implantation. This local interaction can be called 'local cross-talk between the embryo and mother' and it has currently being extensively explored by various investigators.1,2

Although it has been widely accepted that HCG mainly functions as a mediator for systemic interaction, few findings show the precise mechanism of HCG on human CL function around embryo implantation. In
human CL derived from the mid-luteal phase, immunoreactive luteinizing hormone (LH)/HCG receptor was highly expressed on both large and small luteal cells. This high expression of immunoreactive LH/HCG receptor is rapidly decreased in the regressing CL in the late luteal phase. In contrast, the expression of LH/HCG receptor was maintained in the CL in pregnancy. However, its expression intensity is not as high as that in CL in the mid-luteal phase and its expression on small luteal cells had almost disappeared. These decreasing expression profiles of LH/HCG receptor in CL in pregnancy are compatible with previous histological results from autoradiography and mRNA. These profiles also support the results of binding assay using human CL homogenates, which showed that $^{125}$I-HCG binding capacity was very low in the CL in pregnancy. These findings suggest that some factor(s) other than HCG must be involved in the functional regulation of the human CL in pregnancy.

In addition, accumulating evidence suggests that systemic cross-talk between the embryo and mother through blood circulation cannot be maintained by HCG alone. For example, in 7 weeks of gestation more than 15 ng/mL of serum progesterone is estimated to be produced by the CL in pregnancy, and the removal of the CL during this period led to an abrupt reduction in serum progesterone. However, HCG alone cannot induce progesterone secretion from the normal CL for more than a few weeks. In addition, HCG-induced relaxin production in the menstrual CL cannot be maintained beyond a few weeks by HCG stimulation alone. Although relaxin and progesterone production by the CL in pregnancy continues until delivery and human CL is considered to remain functional during the term of pregnancy, how CL function is regulated during that time is unknown. Furthermore, progesterone production is low in ectopic pregnancy despite comparable immunoreactive HCG levels to those in normal pregnancy, and the lower serum steroid level in women with ectopic pregnancy cannot be explained by altered HCG bioactivity. Furthermore, delayed implantation and subsequent successful delivery were reported in a patient undergoing in vitro fertilization therapy where CL function was maintained for a few weeks despite a lack of serum HCG elevation. Thus, investigators speculate that the synthesis of a factor other than HCG produced by the embryo or endometrium in response to implantation may be necessary to control CL function.

Chorionic gonadotropin among mammals is observed only in primates and a few equine species. In rodents, prolactins derived from decidua and placenta are well known to regulate the function of CL in pregnancy and contribute to systemic cross-talk between the embryo and mother. In ruminants, interferon-τ was identified as a trophoblast-producing hormone that stimulated the CL in pregnancy. However, in humans there are no biologically active soluble factors other than HCG that have been proposed as candidates to mediate this essential communication. Consequently, the endocrine system cannot fully explain the mechanism for systemic cross-talk in human pregnancy and it remains a mystery.

**IMMUNOLOGICAL REGULATION OF CORPUS LUTEUM FUNCTION THROUGH SYSTEMIC CROSS-TALK BETWEEN THE MOTHER AND EMBRYO**

Two decades ago, Wegmann proposed the immunotrophic hypothesis that the immune system contributes to the establishment and maintenance of pregnancy, showing evidence that T cells promote placental growth and prevent spontaneous abortion. Later, T-helper cell 2 (Th-2) cytokine interleukin-10 (IL-10) was shown to rescue abortion-induced mice, suggesting that successful allopregnancy is a Th-2 phenomenon. Recently, numerous studies support that cytokine and growth factor networks at implantation sites play an important role in promoting adequate relationships among trophoblast, decidinal immune cell and placental cells including natural killer (NK) cells, and in regulating materno-fetal immunotolerance, placentation and vascularization. Thus, it has been widely accepted that the immune system is deeply involved in ‘local cross-talk between the mother and embryo’. In this review, we reconsider the possible role of the immune system in ‘systemic cross-talk’, presenting evidence that immune cells may positively participate in systemic communication.

To clarify the mechanism of systemic cross-talk between the embryo and mother, we investigated the expression profiles of various molecules on human luteal cells, which may be concerned with regulating the function or differentiation of the CL. Using available and newly produced monoclonal antibodies, we found that human luteal cells in the CL express several cell adhesion molecules such as integrins and related molecules. Among these, the cell adhesion molecules for T-lymphocytes were also demonstrated to be expressed on the cell surfaces of luteal cells in the CL in pregnancy, suggesting physiological interaction between luteal cells and peripheral lymphocytes during early pregnancy.