

Interferons: Roles in Maternal Recognition

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การตั้งท้องเริ่มจากการขบวนการที่เอมบริโอส่งสัญญาณในรูปของสารเคมีไปแจ้งให้ร่างกายของแม่รับรู้ ขบวนการนี้เรียกว่า maternal recognition of pregnancy สัญญาณที่ตัวอ่อนส่งไปยังแม่ในระยะแรกไปทำหน้าที่ยับยั้งการฝ่อของคอร์ปัส ลูเตียม ซึ่งเป็นแหล่งผลิตฮอร์โมน โปรเจสเทอโรน interferon เป็นสารเคมีที่สร้างจากเซลล์ในระบบภูมิคุ้มกัน และมีบทบาทในการควบคุมการติดเชื้อไวรัส จากการศึกษาเอมบริโอในสัตว์เคี้ยวเอื้อง และ สุกร ได้มีการรายงานว่าในระยะก่อนการฝังตัว เอมบริโอในสัตว์เคี้ยวเอื้อง และ สุกร สามารถผลิต interferon ที่ผลิตจากเอมบริโอ ของสัตว์เคี้ยวเอื้องคือ interferon-tau และ interferon ที่ผลิตจากเอมบริโอของสุกรคือ interferon-gamma และ interferon-delta บทบาทของ interferon ในขบวนการ maternal recognition of pregnancy และบทบาทในส่วนอื่นของการตั้งท้องในนำมารวบรวมไว้ในบทความนี้

Early embryonic loss is a main problem in livestock industry. Survival of an embryo is dependent on optimal uterine environments provided and failure of an embryo to communicate to its mother means its death. In species which are economically important, the profit comes from fertility of the breeder which is reflected by ability to produce healthy offspring. Embryos have ability to signal their mothers for preparation for uterine environments which are essential for their survivals. The process of signaling made by the embryos to their mother for recognizing their presence is called maternal recognition of pregnancy.

Mechanism for the corpus luteum regression

Uterine microenvironments are controlled by endocrine system. After ovulation, the corpus luteum is formed. Granulosa cells and cells of the theca interna of the follicle become luteal cells. The luteal cells secrete progesterone (Sawyer, 1995) which is a key factor to keep uterus in a quiescent state that favors an attachment of an embryo to uterine wall by inhibiting contractility of uterine myometrium. (Batra, 1994). In pregnancy of ruminants, progesterone is mainly contributed from corpora lutea with minor secretions from binucleated trophoblasts of bovine placenta. (Ullmann and

Reimers, 1989). In ruminants, regression of luteal cells is mediated by pulsatile release of prostaglandinF2 alpha (PGF-2 α) by uterine endometrium (Huges *et al*, 1987, Tsai and Wiltbank, 1998). PGF-2 α exerts its leuteolytic effects on luteal cells through activating of endothelin-1, a vasoactive peptide produced by endothelial cells surrounding corpus luteum. Endothelin-1 inhibits progesterone in vitro secretion by luteal cells (Girsh *et al.*, 1996, Meidan R *et al*, 1999). Signals synthesized from trophoblast control maternal endocrine system by promoting progesterone secretion by luteal cells and inhibiting PGF-2 α synthesis from arachidonic acid by endometrium. The process is mediated by increasing prostaglandin endoperoxide H syntase which mediates PGF-2 α synthesis from arachidonic acid (Thatcher *et al.*, 1995).

Interferons

The interferons (IFNs) are generally known as antiviral cytokines, small molecules produced by cells of various kinds. The interferon family contains two types; Type I inteferons which include IFN-alpha (IFN- α), IFN-beta (IFN- β), IFN-omega (IFN- ω), IFN-delta (IFN- δ) and IFN-tau (IFN- τ) and type II interferon which has only one member IFN-gamma (IFN- γ). Productions of IFN both type I and II are induced by viral infection. The main production come from the cells of immune system. The IFNs limit the viral infection by their cytotoxicity and anitproliferative actions. The findings of Interferon productions by trophoblasts of swine and ruminant

lead to the increasing evidences of the roles of interferons in maternal recognition.

Interferon-tau

IFN- τ is trophoblast-specific IFN found only ruminant embryos. It contains 172 amino acid and belongs to type I IFN. Like other type I interferon the IFN- τ showed in vitro antiviral activity (Peris *et al*, 1998). This molecule is formerly known as bovine trophoblast protein-1 (TP-1). It is initially secreted by bovine embryos during pre-implantation period between day 13 -25 of gestation and the peak of secretion is between day 14-16 of gestation. The secretion of IFN- τ is not dependent on growth rate of blastocysts (Kubisch Larson and Roberts, 1998) nor its transcription was induced by viral infection (Cross and Roberts, 1991). Its promoter is activated by protein kinase C (PKC) pathway in the presence of Granulocyte -macrophage- colony stimulating factor (Imakawa K *et al.*, 1997). The induction of IFN- τ production is restricted to the trophoblast cells of day 12-20. Several growth factors are identified in promoting IFN- τ synthesis. These include Leukemia Inhibitory Factor (LIF), GM-CSF, Interleukin(IL)-3 (Martal *et al.*, 1998). These growth factors are produced by endometrium and are showed to be crucial for implantation process (Paria *et al.*, 2002). It suggests that maternal-embryo cross-talk does occur during early pregnancy before the circulatory connection is established and this communication may help establish the pregnancy.

How IFN- τ rescues the CL?

To prevent the regression of corpus luteum and thereby maintain the progesterone levels, the ruminant embryos release Interferon- τ , an antiluteolytic substance which is produced by trophoblasts. IFN- τ directly regulates production of PGE2 and PGF-2 α . Addition of IFN- τ into bovine endometrial cell cultures resulted in increased PGE2 and PGF2- α production in both uterine epithelial cells and stromal cells but preferentially to PGE2 production and thereby caused increase in PGE2: PGF-2 α ratio (Asselin, Bazer and Forteir, 1997). An increase in PGE2 production was showed to be mediated by cyclooxygenase-2 (COX-2) when stimulation of PGE2 production by uterine epithelial cells and stromal cells was blocked by a specific COX-2 inhibitor (Asselin, Lacroix, Fronteir, 1997). In addition, increase in endometrial 9-keto-prostaglandin E(2) reductase may result in changing prostaglandin production from PGF-2 α to PGE2 (Asselin and Frontier, 2000). IFN- τ also attenuates endometrium responses to oxytocin which stimulates pulsatile secretions of PGF-2 α from endometrium (Thatcher, Meyer and Danet-Desnoyers, 1995) by down-regulating the expression of oxytocin receptors on endometrial cells.

Trophoblast-derived IFNs in swine embryos

Interferon gamma (IFN- γ) and interferon delta (IFN- δ) are trophoblast-derived IFN found in swine conceptuses between day 12 and 20 of gestation. The major IFN is IFN- γ whereas the minor

one is IFN- δ . IFN- γ is protein of 149 amino acid and mainly produced by activated T lymphocytes and Natural killer cells. IFN- δ the novel member of Type I IFNs is found in the trophoctoderm in the pre-implantation embryos of swine. their expressions and secretion by trophoblast are found uniquely in swine embryos. It contains antiviral activity as other members of type I IFN. The prevention of its binding to pig kidney cells with IFN- α suggests that its share type I receptor with porcine IFN- α (Lefevre *et al.*, 1998)

Possible roles of trophoblastic IFNs during porcine pregnancy

In pigs, estrogen is thought to play a role in preventing the luteolysis. Estrogen produced in high amount from trophoblasts as the embryo begin to elongate (Roberts *et al.*, 1996) has been shown to a solely antiluteolytic factor for porcine pregnancy. Two interferons IFN- γ and IFN- δ are also produced swine trophoblast cells. The presence of these two IFNs would account for antiluteolysis. However this statement are argued by the evidence of estrous females in which the uterine administration of porcine IFN- γ and IFN- δ was not able to prevent the regression of the CL (Cenci and LA Bonnardiere, 2002) . The production of the IFNs found in pre-implantation embryos, suggests that they may be a signal to maternal endometrium in preparation for implantation. The roles of IFN- γ in the preparation of implantation may indirectly involve in the activation of adhesion molecules on

human endometrium (Thomson *et al.*, 1999). It suggests that IFN- γ may mediate the process of cell adhesion and attachment of embryos to uterine epithelial cell surface. However, this action of IFN- γ on trophoblast cells and uterine endometrium of pigs has not been investigated.

The use of IFNs in reproduction improvement

The finding of IFN molecules by trophoblast cells of ruminant and swine embryos in early pregnancy expands the knowledge of IFN biology. The attempt to use these molecules as the indicators for pregnancy diagnosis has not been successful due to the trace amount of the molecules in uterine flushing and the absence of these molecules in maternal circulation. The production of recombinant IFN and establishment of trophoblastic cell lines may lead to the therapeutic aspect of these molecules in promoting pregnancy.

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