Growth Factors and Cytokines in Periimplantation

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Understanding the molecular factors involved in embryonic implantation is critical to comprehending the mechanisms controlling reproduction. The field of growth factor and cytokines and their effects on reproduction is a rapidly growing new area of investigation. Successful implantation depends on appropriate interaction between blastocyst and endometrium. While the embryo is the driving force in initiation of inflammatory responses necessary for successful implantation, it is apparent that a bidirectional interaction between the maternal immune system and the embryo exists. This interaction is under control of paracrine cytokines secreted from trophoblast and endometrial cells. Thus, maternal endometrium recognized fetus as an allograft. However, control of growth and differentiation during mammalian embryogenesis regulated by growth factors from embryonic or maternal sources. Also, growth factors play a central role in cyclic mitosis, differentiation of endometrial cellular components, endometrial-trophoblast interactions, and early pregnancy maintenance.

At present, it has been known that EGF, TGF, PDGF, insulin, IGF-I, IGF-II, and FGF commonly regulate the mitosis of embryo and endometrial cellular componenets *in vitro*. Growth factors are typically proteins of molecular weight <30,000 which are synthesized and act within the local tissue environment as paracrine or autocrine hormones. They interact with specific, cell surface receptors which possess tyrosine kinase activity. This tyrosine kinase activity is considered to be the primary effector system in transmembrane signaling processes of most growth factor, and results in phosphorylation of intracellualr proteins which regulate pathways altering gene expression, cellular metabolism, and cellular division. In addition, there are some selectivity since differing cell types may recognize each growth factor with different relative sensitivity. Futhermore, this diversity may be originated from the action phase of each growth factor at cell cycle according to cell type. Study on expression of a number of growth factor ligand and receptors genes has been demonstrated mainly in mouse. Among the growth factors, EGF is one of the most biologically potent mitogen. Although the transcripts for EGF is not detected even at the blastocyst stage in preimplantation embryos, many researchers reported that EGF can stimulate growth and protein synthesis in preimplantation embryo through the EGF-R expressed from the early embryonic stage. In several experiment, we confirmed the effect of EGF on preimplantation development between mouse and bovine embryos. Also, it showed that EGF increases cell number of ICM and TE and of hatching rate of blastocyst. Receptors for EGF are abundant in placenta, especially on the microvillous plasma membranes in contact with the maternal circulation, and

on the basolateral membranes adjacent to the fetal circulation. This distribution implies an interaction between EGF and the syncytiotrophoblast, and studies with isolated trophoblasts and placental cultures have shown that EGF modulates trophoblast differentiation and function. Considering with above contents, it demonstrated that role of growth factors is very important on reproduction and that those effects on preimplantation embryo development continued for the implantation and fetal growth.

Cytokines participating at the implantation site include IL-3, IL-4, IL-6, IL-7, IL-8, IL-11, IL-12, GM-CSF, INF, TNF, and TGF. Cytokines are small regulatory peptides or glycoproteins with molecular weights ranging from 6,000 to 60,000, which are synthesized and secreted by activated immune and mesenchymal cells. They are known by various names either describing their function or derived from the interleukin nomenclature. Cytokines function as intercellular signals between various cells of the immune system. The majority of the immune responses are probably local, and hence cytokines act generally in a paracrine or autocrine manner rather than in an endocrine manner on distinct target cells. At the point of implantation, the endometrial stromal cells are decidualizing but not yet clearly decidua, the embryo is a few hundred undifferentiated cells, and the inflammatory and immune system cells can just now come into direct contact with the embryonic allograft. Implantation is under embryonic control, and maternal immunologic response is essential for normal implantation. Embryonic trophoblast is resistant to lysis by cytotoxic lymphocytes, antibody dependent complement mediated cytotoxicity and by natural killer cells secreted from maternal immune cells. These immunologic responses are mediated through immune cells and cytokines. Embryonic tolerance is induced by local suppressor activity and ensured by systemic changes in the immune system.

This lecture will focus on 1) growth factor and early embryonic development, and 2) function, biological activity and regulation of growth factors and cytokines in periimplantation.