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Immuno tolerance of conceptus through feto-maternal interaction in ruminants: A review

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Abstract
This review focuses on innate immunological event modulated by conceptus signalling during early pregnancy in ruminants. All mammals must have proper connection between the growing conceptus and the endometrium of the mother in order to achieve and maintain pregnancy. Ruminant interferon-tau (IFN-) plays an important role in the detection of pregnancy, which entails more than only blocking $PGF_{2}\alpha$ luteolytic pulses to preserve corpus luteum activity. However, the process of conceptus elongation after blastocyst hatching and before implantation is fully controlled by the mother and is necessary to make sure that the developing conceptus secretes enough interferon-tau (IFNT) to block the mechanisms that cause Luteolysis. The production of type I and type II IFNs by trophoblasts during the peri-implantation stage of pregnancy in most mammals is a characteristic that stimulates expression of a variety of IFN-stimulate genes (ISGs). IFN- thus controls the innate immune system and prevents conceptus rejection by paracrine and endocrine effects. Therefore, this review will address various types of immunological reaction occur during feto-maternal interaction and how the interferon-tau act and prevent early embryonic rejection of conceptus from mother.

Keywords: Interferon-tau, Luteolysis, pregnancy and bovines

Introduction
The endometrial epithelium is point of contact between maternal tissue and embryo with in uterus. To protect the pregnancy in animals, it is necessary to develop a tightly coordinated cellular and molecular contact between the capable embryo and the receptive endometrium. Disturbances in this intricate process cause early embryonic losses, which in turn cause subfertility. Cattle are particularly important because 40% of embryonic losses within first three weeks of pregnancy. (Diskin *et al*., 2012, 2016) [6-7].

In all animals, proper communication between the growing conceptus and the maternal endometrium is required for the creation and maintenance of pregnancy. Depending on the species, many mechanisms exist for maternal recognition of pregnancy (Geisert & Bazer, 2015) [10]. The hatched blastocyst in ruminants undergoes significant morphological changes during the preimplantation period, changing from a spherical to an ovoid, tubular and finally filamentous shaped structure due to rapidly proliferating conceptus trophectoderm cells Maddox-Hyttell *et al*. 2003; Fléchon, *et al*., 2007) [16, 9].

In cattle, this crucial elongation phase begins between 12 and 14 Days. Through endometrial secretions that make up the uterine lumen fluid or histotroph the uterine endometrium plays a critical role in promoting the elongation process (Spencer & Hansen, 2015) [22]. The success of pregnancy depends on the spatial and temporal alterations in the endometrial transcriptome and histotroph composition that are required to create uterine receptivity for implantation.

The progesterone production in cattle induces both temporal and spatial (cell-specific) changes in the endometrial transcriptome necessary to establish uterine receptivity. These changes include downregulation of the nuclear progesterone receptor (PGR) in the luminal and then glandular epithelium, which allows expression of genes and secretion of their protein products, as well as active transport of others (Hafez, 2007) [12]. The trophoblast must be implanted in the luminal endometrial epithelium of mammals in order for implantation to be successful. This procedure is thought to involve conceptus trophoblast adhering and invading the uterine luminal epithelium (Rice and Chard, 1998) [17].

Feto-maternal relationship
The ability to create an antibody response and an immunological T-cell driven response, as

demonstrated by allograft rejection, is pretty well developed at birth. Antibody levels, with the exception of IgG, are low in the absence of an intrauterine infection. The transmission of antibodies, antigens and cells from the mother to the foetus and infant via the placenta and breast milk, respectively, is critical in the conceptus immune development (Hafez, 2007) [12].

Theories to Survival of Foetal Allograft during Pregnancy

It includes Immunosuppression-The placental and maternal tissue produces molecules that prevent generation of maternal antibody conceptus lymphocyte. Blocking Antibody-Maternal system produces anti-fetal antibody that do not fix complement and which mask fetal antigens. Reduced Antigenicity- MHC antigen are not express on region of trophoblast in contact with the mother to prevent activation of maternal anti-fetal MHC lymphocyte. Fas Ligand-t is type II membrane protein, it is part of TNF receptor family and is found on lymphocyte Trophoblast and endometrium express fas ligand to induce apoptosis in activated maternal T cell. The trophoblast and endometrium express fas ligand to induced programme cell death in activated maternal T cell. Temporary tolerance-The number of maternal T cell against T cell against fetal MHC antigen decreases during pregnancy to causes temporary tolerance to fetal MHC antigens-could be related to action of fas. T_H1-T_H2 Shift-During pregnancy antibody response are favored instead of cell-mediated immunity because of preferred activation of T_H1 helper T cell over T_H2 helper T cell. Immunotrophosism: trophoblast growth and hormone secretion is stimulated by maternal lymphocyte that secrete growth factors for trophoblast (Hafez, 2007) [12].

Maternal Recognition of pregnancy

The term maternal recognition of pregnancy is coined by Roger Short in 1969 and it defined as physiological process by which the conceptus indicates its presence to the maternal system and extends the duration of the ovarian CL is known as maternal recognition of pregnancy. In ruminants, progesterone from corpus luteum stimulates preimplantation blastocyst growth and conceptus elongation (Lonergan, 2011) [15]. The blastocyst begins to secrete trophoblastic protein belong to a class of glycoprotein known as interferons. The production of Type I and Type II IFN by trophectoderm, which induces expression of classical ISG in the uterus, is a typical feature of the periimplantation stage of pregnancy in domestic animals, rodents, and primates (Bazer *et al.*, 2009a & Johnson *et al*., 2009) [2, 13]. In sheep and cow it known as Ovine interferon-tau (oIFN- τ) and Bovine interferon-tau (bIFN-τ). In ruminants, the elongating conceptus releases IFNT is the pregnancy recognition signal that acts on the endometrium to hinder development of the luteolytic mechanism (Spencer *et al*., 2007 & Bazer *et al*., 2010) [20]. The IFNT inhibits transcription of the oestrogen receptor (ESR1) gene in sheep and the oxytocin receptor (OXTR) gene in both sheep and cattle, specifically in the endometrial LE and sGE. The absence of OXTR in the endometrium limits the release of luteolytic PGF2 pulses, extending the longevity of the CL and progesterone production. Interferons possess lack of viral inducibility, expression is restricted to the embryonic trophectoderm and high-level synthesis is sustained over several days and then terminates (Roberts *et al*., 2008) [18].

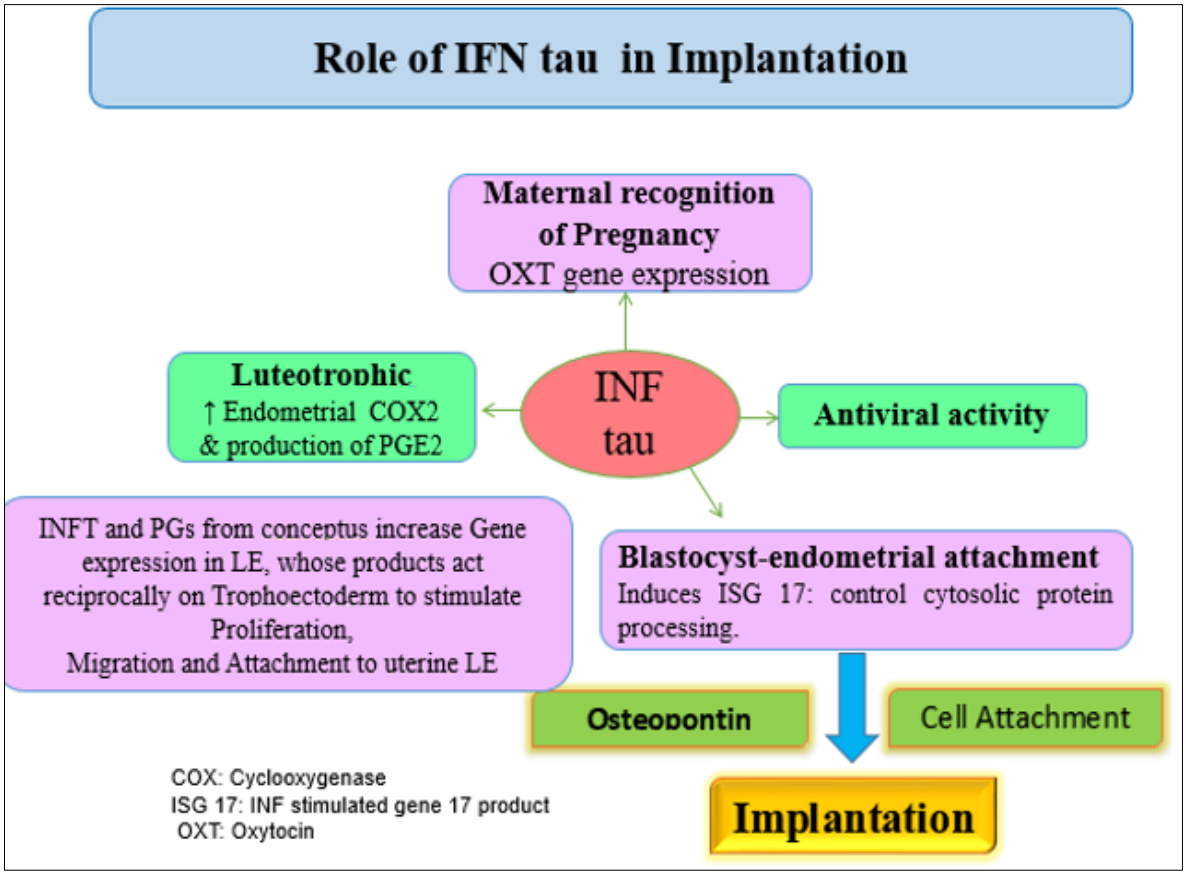

Fig 1: Schematic illustrating the role of interferons tau represent absence of OXTR gene expression in the endometrium prevents the release of luteolytic pulses of PGF2α, thereby sustaining lifespan of the CL and progesterone production. Interferons act as luteotrophic and increase endometrial COX2 and production of PGE2.

Mechanism of Apposition

The apical surface of uterine epithelium is covered by thick glycocalyx that diminishes as time of conceptus attachment approaches. One transmembrane glycoprotein termed Muc-1 is abundant during non-receptive phase of pregnancy and could serve as an antiadhesive factor (Burghardt *et al*., 2009) [5]. The abundance of Muc-1 on uterine LE/sGE is reduced during the peri-implantation period (mouse, pig, and sheep) or at sites of blastocyst attachment (human and rabbit) due to activation of cell surface proteases and loss of expression of progesterone receptors (PGR) in uterine LE/sGE. Loss of MUC1 unmasks adhesion and attachment molecules on uterine LE/sGE to permit initial apposition and stable adhesive interactions between maternal ECM and stromal cells in species in which implantation involves invasion beyond LE/sGE. The stable adhesions with integrins expressed on trophectoderm and uterine LE and their ECM ligands are required for implantation through their roles in adhesion, migration, invasion, cytoskeletal organization and bidirectional signaling (Johnson *et al*., 2003, Brayman *et al*., 2004) [13, 14].

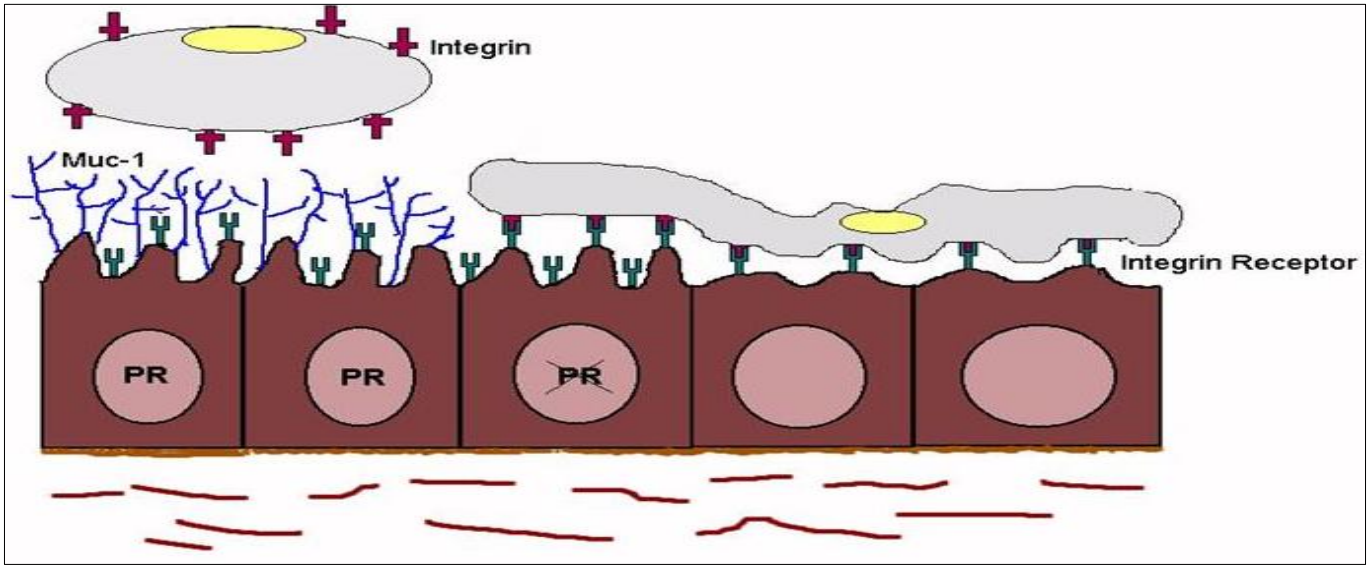

Fig 2: This schematic illustration represent conceptus cannot attach to the uterine epithelial surface until the large glycoprotein called Muc-1 has been removed. The Muc-1 losses its effect on endometrium when the progesterone receptor is downregulates. The loss of Muc-1 from endometrial epithelium they permit contact of integrin with their receptors which brings conceptus close with uterine surface

Implantation

The establishment of communication of Conceptus with the mother this process is initiated by union of two genetically distinct cells of the individuals. It is preceded by a close interaction of embryonic trophoblast and endometrial epithelial cells **(**Barker *et al*., 1993) [1]. Implantation in domestic ruminants are non-invasive (sheep, cattle and goats) and takes place at the blastocyst stage (Spencer *et al*., 2007a,2008) [20, 21]. The blastocyst develops from the preceding morula stage embryo as the result of compaction and contains a blastocoele. The morula (16–32 cells) stage embryo enters the uterus from the oviduct on day 4 after mating. The hatched blastocyst position in uterine horn-centrally which ipsilateral to CL Conceptus elongation (Day 13), By day 18 - blastocyst extended into contralateral horn elongation is critical for INF tau production Histotroph secreted from endometrial LE and GE, nourishes developing blastocysts and initiate the implantation by Muc-1 losses its effect on endometrium when the progesterone receptor is downregulates. The loss of Muc-1 from endometrial epithelium they permit contact of integrin with their receptors which brings conceptus close with uterine surface epithelium.

Conclusion

The opportunities for future research should focus on the effects of interferons and prostaglandin on additional endometrial cell types, including as immune cells, and their possible roles in the immunobiology of early pregnancy. The uterine secretions plays important role in ruminant implantation by nourishing the growing embryo. Progesterone dependent Immuno modulation and low expression of fetal MHC class I proteins plays a mediatory role in fetal allograft tolerance.

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