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Involvement of the Interferon Tau Gene in Maternal Recognition of Gestation in Sheep

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ABSTRACT

Objective: To describe the involvement of the *interferon tau gene* in the maternal recognition of pregnancy in sheep.

Design/Methodology/Approach: A search and analysis of the scientific documents retrieved from the Web of Science and Scopus databases related to the functions of the interferon tau gene in the maternal recognition of pregnancy in sheep were conducted.

Results: The interferon tau gene (IFNτ) participates in maternal recognition of pregnancy to avoid possible rejection of the embryo, and supports the secretion of progesterone involved in preparing the endometrium for implantation; it also inhibits myometrial motility to maintain pregnancy. IFNτ stimulates the transcription of so-called interferon-stimulated genes (ISGs), which are the effectors of cell-autonomous antiviral defense. One of the representative members of ISGs is the interferon 15-stimulated gene (ISG15) which regulates endometrial receptivity at implantation, as well as survival, growth and development of the conceptus.

Study Limitations/Implications: Most embryonic losses occur between fertilization and maternal recognition of pregnancy. Understanding this issue is essential to understanding the possible causes of early pregnancy losses.

Findings/Conclusions: Considerable progress has been made in the discovery of how the IFNτ and ISG15 genes act in maternal recognition of gestation in sheep. However, some of the regulatory mechanisms involved remain poorly understood.

Keywords: IFNτ, ISG15, pregnancy, sheep.

Image by Roman Grac at Pixabay

INTRODUCTION

A large portion of embryo loss originates during the first few weeks post conception. Most embryonic losses occur between fertilization and maternal recognition of gestation (Lonergan *et al.*, 2016). Therefore, it is necessary to address this issue with research into the enigmas of embryo implantation (Miller *et al.*, 2012). Evolving molecular insights have been used to study the process of maternal recognition of gestation, along with the molecular aspects of endometrial-embryo interactions, embryo development and implantation (Zohni *et al.*, 2016). In ruminants, the establishment of adequate communication between the conceptus and the endometrium is essential for embryo implantation and subsequent successful placentation (Nakamura *et al.*, 2020). This process involves the protein known as interferon tau (IFNτ), initially called trophoblast protein or trophoblastin (Taverne & Noakes, 2019), which is produced by its homologous gene now known as interferon tau or also known as TP-1 gene (Ealy & Wooldridge, 2017). Some studies performed with ISG15 and IFNτ genes *in vivo* as well as *in vitro* have confirmed their importance in reproductive function in ruminants.

The IFNτ gene is involved in the maternal recognition of gestation to prevent possible rejection of the embryo and also supports progesterone secretion (D'Occhio *et al.*, 2020). IFNτ molecules bind to cell surface receptors and initiate signal transduction; this activates the transcription of so-called ISGs which are the effectors of cell autonomous antiviral defense. One of the representative and well-studied ISG members with specific antiviral activities is the ISG15 gene (Wang *et al.*, 2017). Given the critical importance of the process of maternal recognition of gestation, the objective of this review was to describe the implications of the interferon tau gene on maternal recognition of gestation in the ewe.

Maternal Recognition of Gestation and Implantation

Successful establishment of gestation involves ovulation of an oocyte, fertilization by a sperm and growth of the embryo in an environment conducive to normal development (Lonergan & Sanchez, 2020). In several domestic species, the corpus luteum (CL) is important in regulating the periodicity of the estrus cycle (Hennebold, 2018), because the establishment of gestation requires that progesterone concentrations remain elevated. This results in negative feedback in the hypothalamus and the anterior pituitary gland with inhibition of follicular development. In several species, the placenta subsequently replaces or supplements the luteal source of progesterone (Taverne & Noakes, 2019). The presence of a viable developing embryo prevents the CL from being destroyed (Pate, 2020) by the action of prostaglandin F2α and thus inhibits the return to estrus. This phenomenon was defined in 1969 as the "maternal recognition of gestation" (Short, 1969).

The developing embryo eventually undergoes a process called conceptus elongation, which is a short-lived phenomenon resulting from remodeling and cellular migration of the developing embryo. Conceptus elongation begins on days 12-13 in ewes and is associated with implantation and recognition of gestation (Kasimanickam & Kasimanickam, 2020). Around day 12, the embryo's trophoectoderm cells begin to secrete IFNτ, the gestation recognition factor that overrides the uterine luteolytic mechanism to ensure maintenance of a functional CL (Lonergan & Sanchez, 2020). Embryo implantation is a complex

succession of events involving the attachment, adhesion, and invasion of the blastocyst in the endometrium (Liu & Li, 2019). Understanding this issue is basic to understanding the possible causes of early gestational losses (Taverne & Noakes, 2019).

Role of Progesterone (P4) in Maternal Recognition of Gestation

Progesterone (P4) is secreted by the CL and placenta (Schumacher *et al.*, 2014), and it is necessary for the establishment, maintenance and success of gestation (Wilson & Mesiano, 2020). In the ewe it has two important functions: controlling the release of gonadotropin-releasing hormone (GnRH; Bartlewski *et al.*, 2017) and maintaining gestation (Keller *et al.*, 2019), because it is involved in preparing the endometrium for embryo implantation and it inhibits myometrial motility to maintain gestation (Mondal *et al.*, 2017).

P4 along with interferon tau are essential for maintening gestation (Reynolds *et al.*, 2014) and P4 blocks the proliferative effect of estrogen and induces the expression of genes that admit for the endometrium to accept embryo attachment (Halasz & Szekeres-Bartho, 2013). High concentrations of P4 in maternal recognition of gestation have been associated with conceptus elongation and increased production of interferon tau, resulting in high gestation rates (Lonergan & Forde, 2014). And low P4 concentrations are associated with lower fertility, reduced conceptus growth and elongation, decreased IFNτ production and lower gestation rates (Lonergan & Sanchez, 2020).

Interferons

Interferons (IFNs) are widely expressed cytokines with antiviral properties (Gonzalez-Navajas *et al.*, 2012). Mammalian IFNs are classified into Type I, Type II and Type III (Bayer *et al.*, 2016). Type I IFNs are a group of highly related proteins that include interferons alpha (IFNα), beta (IFNβ), delta (IFNδ), epsilon (IFNε), tau (IFNτ) and omega (IFNΩ) (Dembic, 2015). Type II IFNs are represented by a single member, referred to as IFN gamma (IFNγ); and the type III class of IFNs contains three members that are known as IFN lambda (IFNλ1, also known as IL-29), IFNλ2 (also known as IL-28A) and IFNλ3 (also known as IL-28B) (González-Navajas *et al.*, 2012). IFNs are elements of the immune system and serve as a response to pathogens, have a key role in reducing pathogen replication and regulating immune responses (Snell *et al.*, 2017).

Interferon Tau (IFNτ) and its Involvement in Gestation Recognition

Moor (1968) conducted research in ewes in which he demonstrated that the conceptus produces a protein. This protein is now known as interferon tau and is produced by its homologous gene IFNτ or also known as TP-1. The IFNτ gene interacts with uterine cells to direct the establishment and maintenance of gestation (Ealy & Wooldridge, 2017). After 1979, purification of IFNτ revealed its anti-luteolytic activity to prevent CL regression in sheep (Bazer & Thatcher, 2017). Originally, it was called ovine trophoblast protein (oTP-1) or trophoblastin. This substance has been shown to be a type I interferon, classified as ovine interferon tau (oIFNτ); (Taverne & Noakes, 2019). IFNτ is transiently produced by the ovine trophoectoderm, with expression being highest in the uterine epithelium between days 13 and 14 of the estrus cycle in ewes

(Bazer & Thatcher, 2017). Secretion of ovine IFNτ by the trophectoderm begins on day 10 and increases to peak concentrations between days 13 and 16; it then ceases to be secreted after day 21 of gestation (Fuller *et al.*, 2019). The main effect of IFNτ on maternal recognition of gestation is to alter the dynamics of PGF2α secretion in the early stage (Taverne & Noakes, 2019).

IFN$_\tau$ silences the transcription of receptors to estradiol type 1 (ER1) and, therefore, the expression of oxytocin receptors (ROX) that depend on ER1 receptors in the cells of the epithelial lumen and superficial glandular epithelial cells of the uterus to prevent the process of the endometrial luteolytic mechanism that requires pulsatile release of oxytocin-induced prostaglandins (Fleming *et al.*, 2006). Presently, it is known that IFNτ serves as a vital mediator of early signaling between the developing embryo and the uterine endometrium in ruminants (Bazer *et al.*, 2018). Progesterone and IFNτ operate mutually to induce expression of genes critical for conceptus development and implantation and in uterine glandular epithelial and stromal cells to induce expression of interferon-stimulated genes (ISG) such as: Interferon-induced myxovirus resistance protein (Mx1 and Mx2); Interferon-stimulated gene 15 (ISG15); 2'-5'-oligoadenylate synthetase 1 (OAS1); S-adenosyl methionine-containing radical domain 2 (RSAD2); Signal transducer and activator of transcription 1 (STAT1) and 2 (STAT2); Interferon regulatory factor 1 (IRF1) and 9 (IRF9; Bazer & Thatcher, 2017). Figure 1 shows the mechanism of action of IFNτ.

In addition to the paracrine effects of IFNτ secreted by the trophectoderm, ISGs have been found to be expressed in cellular components of the CL (Bazer & Thatcher, 2017). The endocrine action of IFNτ has an impact on the CL to induce resistance to prostaglandin F2α in its cells (Antoniazzi *et al.*, 2013). It jointly enhances ISG15 expression in luteal cells (Oliveira *et al.*, 2008) and alters immune cell functions within the CL to maintain its function and gestation (Shirasuna *et al.*, 2015).

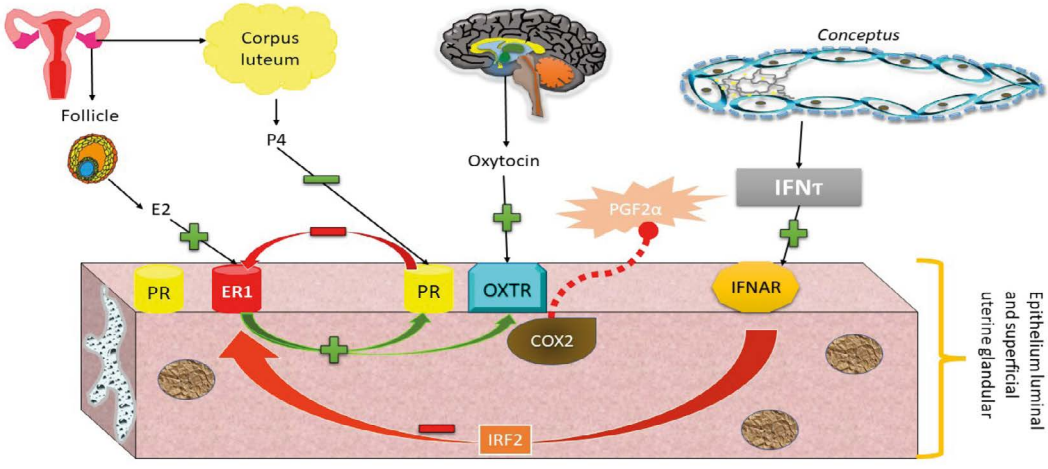

Figure 1. Mechanism of action of interferon tau (IFNτ). PR: progesterone receptor; ER1: estrogen receptor 1; OXTR: oxytocin receptor; IFNAR: interferon alfa receptor; PGF2α: prostaglandin F2 alfa; E2: estradiol; P4: progesterone; COX2: cyclooxygenase 2 or prostaglandin-endoperoxide synthase 2; IRF2: interferon regulatory factor 2.

Interferon-Stimulated Genes in Maternal Recognition of Gestation

IFNτ also stimulates ISGs in glandular epithelium and endometrial stromal cells. Also, in peripheral tissues such as the CL and liver (Antoniazzi *et al.*, 2013). Many ISGs have been hypothesized to play roles in implantation, placentation and conceptus development (Won, 2008). Some of the ISGs expressed in the ovine endometrium are shown below in Figure 2: *MX1*, *MX2*, *ISG15*, *OAS1* and *RSAD2*, *STAT1*, *STAT2* and *IRF*.

Interferon-Stimulated Gene 15 (ISG15)

ISG15 is expressed in the ruminant uterus in response to IFNτ (Joyce *et al.*, 2005). ISG15 was first identified in mouse tumor cells in which expression was regulated by a type I IFN (Farrell *et al.*, 1979). Subsequently, Blomstrom *et al.* (1986) purified and characterized the 15kDa protein. The polypeptide was named ISG15 (Joyce *et al.*, 2005). Austin *et al.* (2003) were the first to link it to the initiation of the gestation process by identifying the ISG15 protein secreted by the endometrium. ISG15 is a critical uterine response for the progressive processes of implantation and placentation, it was the first ubiquitin-like modifier (UBL) discovered and is stimulated with type I interferons and virus infections (Won, 2008). This ISG15 gene is synthesized in many cell types and secreted from monocytes and lymphocytes (Abidi & Xirodimas, 2015), and it induces the synthesis and secretion of IFNγ from lymphocyte B cells, implying that the role of ISG15 is like a cytokine that modulates the immune response (Kurz *et al.*, 2005). Although the biological activities of ISG15 have not yet been fully elucidated, it is clear that the ISG15 gene modulates diverse cellular and physiological functions.

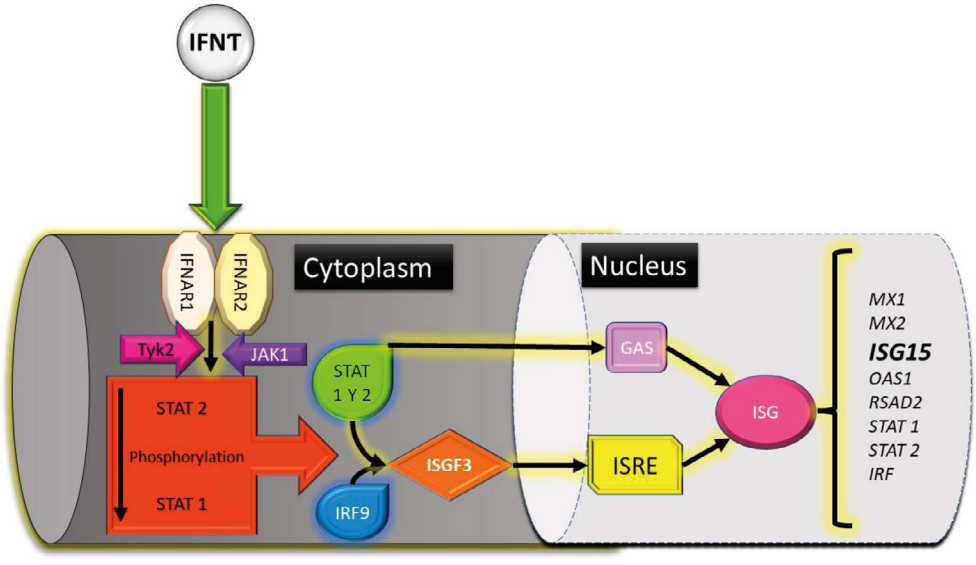

Figure 2. Signaling pathways for interferon *tau* in the ovine endometrial epithelium. IFNτ: Interferon tau; IFNAR1 and -2: interferon alfa receptor 1 and 2; activation of Janus kinase (JAK) members Tyk2 and JAK1; STAT1 and 2: signal transducer and activator of transcription 1 and 2; IRF9: interferon regulatory factor 9; ISGF3: interferon-stimulated gene factor 3; interferon-stimulated response element (ISRE); GAS: interferon gamma-activated site; ISG: interferon-stimulated genes; Mx: Mixovirus resistance 1 and 2; OAS1: 2ŧ-5ŧ-oligoadenylate synthetase 1; *RSAD2*: Radical S-adenosyl methionine domain-containing protein 2; *ISG15*: interferon-stimulated gene 15; IRF: interferon regulatory factor.

Effect of the ISG15 Gene on Embryonic Development in Sheep

The induction of ISG15 in response to IFNτ (Dzimianski *et al*., 2019) is mediated by an intracellular transduction signal system involving type I IFN receptors STAT1, STAT2 and IRF (Morales & Lenschow, 2013). It is presumed that ISG15 regulates endometrial receptivity in implantation, survival, growth and development of the conceptus (embryo and associated extraembryonic membranes; Johnson *et al*., 1999). There is a significant increase in ISG15 gene expression in the ovine uterus at 15 days of gestation (Guo *et al*., 2020). Expression of this gene has been found in parts of the stroma along the utero-placental interface in gestation. In addition, results from some studies demonstrate that ISG15-conjugated protein levels increase and then decrease during gestation (Alak *et al*., 2020), which indicates that it is a biologically active molecule that responds to IFNτ signaling from the conceptus and which temporarily targets proteins for regulation and modification associated with the gestation process (Jain *et al*., 2012). Endometrial ISG15 is not simply a consequence of an antiviral state induced by high levels of IFNτ in the lumen of ruminants at gestational recognition, but is a uterine response to conceptus processes; development, implantation and placentation (Joyce *et al*., 2005).

CONCLUSIONS

The IFNτ gene acts via paracrine in the endometrium and endocrine in the CL to exert its anti-luteolytic effects; this triggers progesterone production to be maintained and maternal recognition of gestation to occur. High concentrations of P4 in maternal recognition of gestation have been associated with lengthening of the conceptus and an increase in IFNτ production and higher gestation rates. IFNτ induces positive regulation of several ISG genes including the ISG15 gene, which is involved in maternal immunoregulation and other functions in early gestation in the ewe, such as regulation of endometrial receptivity during implantation.

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