Actions of interferon tau during maternal recognition of pregnancy

Ações do interferon tau durante o reconhecimento materno da gestação

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Abstract

Maternal recognition of pregnancy in ruminants is a physiological process that requires an interaction between the conceptus and the mother in order to avoid luteal regression. Studies on 60's started to investigate the communication, and late on the 80's it was identified a Type I interferon called interferon tau. In the 90's the local action of interferon tau was described. It suppresses luteolytic pulses of prostaglandin F2 alpha inhibiting endometrial expression of estrogen and oxytocin receptors. Several studies presented the expression of interferon-stimulated genes on extrauterine tissues. After, the endocrine action of interferon tau was described. This study revealed a greater interferon bioactivity in the serum of uterine vein from pregnant ewes when compared to non-pregnant ewes. Following a series of experiments were preformed to better understand the endocrine action of interferon tau in several extrauteine tissues. This review presents the endocrine action of interferon tau during maternal recognition of pregnancy period in ruminants.

Keywords: IFNT, pregnancy, endocrine, paracrine, interferon-stimulated genes, ruminants.

Resumo

O reconhecimento materno da gestação em ruminantes é um processo fisiológico que requer a interação entre o concepto e a mãe com o obejetivo de evitar a regressão luteal. Estudos na década de 1960 começaram a investigar essa comunicação entre concepto e mãe, e durante a década de 1980 foi identificado um tipo I de interferon que foi denominado interferon tau. Nos anos 1990, foi descrita a ação local do interferon tau. Essa ação suprime os pulsos luteolíticos de prostaglandina F2 alfa inibindo a expressão endometrial dos receptors de estrógeno e ocitocina. Muitos estudos têm apresentado a expressão dos genes estimulados por interferons nos tecidos extrauterinos. Posteriormente, a ação endócrina do interferon tau também foi descrita. Este estudo revelou uma maior bioatividade de interferon no soro da veia uterina de ovelhas prenhes quando comparada com ovelhas não gestantes. Após, uma série de experimentos foram realizados para melhor compreender a ação endócrina do interferon tau em vários tecidos extrauterinos. Esta revisão destaca a ação endócrina do interferon tau durante o período de reconhecimento materno da gestação em ruminantes.

***Palavras-chave**: IFNT, gestação, endócrino, parácrino, genes estimulados por interferon, ruminantes.*

Introduction

Maternal recognition of pregnancy in ruminants is a multifactorial process and requires a crosstalk between the conceptus and the mother. This interaction is necessary for the establishment and maintenance of pregnancy. Interferon tau (IFN tau) is the pregnancy recognition signal in ruminants (Bazer et al., 2015). Classical maternal recognition of pregnancy period occurs between Days 12 and 26 with conceptus elongation and maximum production of IFNT (Farin et al., 1990b). IFNT acts via Type I interferon receptors (IFNAR1 and IFNAR2) activating JAK/STAT pathway (Binelli et al., 2001).

Early studies suggested that the embryo produces a factor responsible for signalling its presence to the mother and avoid luteolysis. Later, a cytokine secreted by the conceptus was identified as the major factor of pregnancy recognition (Godkin et al., 1984) and eventually named IFNT (Imakawa et al., 1987). Conceptus-derived IFNT acts on the uterus to avoid luteolytic pulses of prostaglandin F2 alpha (PGF) and consequently luteolysis (Spencer and Bazer, 1996). Further, *in vitro* and *in vivo* studies demonstrated that IFNT action was not restricted to the uterus, and it also acts on extrauterine tissues (Oliveira et al., 2008; Bott et al., 2010; Antoniazzi et al., 2013; Romero et al., 2015). These studies characterized an endocrine action of IFNT, believed to support a paracrine mechanism. IFN tau influence on the immune system was recently described (Shirasuna et al., 2011; Talukder et al., 2018).

Maternal recognition of pregnancy in ruminants is a process involving several tissues and systems. There are many factors and cytokines that participate on this mechanism, however it is evident IFNT is the major product secreted from the embryo during this period. The objective of this review is to present endocrine actions of IFNT during the maternal recognition of pregnancy on the corpus luteum.

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Interferon tau

The discovery of interferon tau occurred late 70's (Bazer and Thatcher, 2017), even though its function is known since mid 60's (Moor and Rowson, 1966a). Originally, the protein was called trophoblastin (Martal et al., 1979). Another group called the protein as "Protein X", it was released from trophoblast cells and produced transiently from Days 13 to 21, these findings suggested a role in the maternal recognition of pregnancy in sheep (Godkin et al., 1982). The protein was renamed to ovine trophoblastic protein-1 (oTP-1) and by *in situ* hybridization and immunocytochemical analyses it was localized in mononuclear trophectoderm cells (Godkin et al., 1984). The oTP-1 was sequenced and suggested to be an interferon alpha (Imakawa et al., 1987), and later known as interferon tau (IFNT) (Bazer et al., 1992; Roberts et al., 1992), is the main protein secreted by trophoblast embryonic cells and responsible for the maternal recognition of pregnancy signal in ruminants (for review(Roberts et al., 2008). IFNT is a 17-20 kDa protein that evolved from IFN omega (IFNW) (Roberts et al., 1996; Roberts et al., 2008). The type I interferons group is composed by interferon alpha (IFNA) (Nagata et al., 1980), interferon beta (IFNB) (Taniguchi et al., 1980), interferon omega (IFNW) (Hauptmann and Swetly, 1985), interferon kappa (IFNK) (LaFleur et al., 2001) and IFNT in ruminants (Roberts et al., 1999).

IFNT signals using classical Type I interferon receptors 1 and 2 (IFNAR1 and IFNAR2) activating JAK-STAT signaling pathway (Binelli et al., 2001). IFNAR1 and IFNAR2 are expressed in the ovine uterus on Days 14-15 non-pregnant and pregnant ewes (Rosenfeld et al., 2002). IFNT can also signal via mitogen-activated protein kinase (MAPK) and phosphatidyl inositol 3-kinase (PI3K) (Platanias, 2005). IFNT acts to rescue the corpus luteum (CL) and maintain the pregnancy. However, IFNT is not stimulated by viral infection (Roberts et al., 2008) and transcriptional factors that control of IFNA and IFNB do not regulate IFNT expression (Leaman et al., 1994). The expression of IFNT gene is controlled by transcription factor ETS2 (Ezashi et al., 1998). Additionally, IFNT expression is also increased in the elongation phase by combinatory trophoblastic gene regulators DLX3, CDX2, GATA2/3 (for review:(Ezashi and Imakawa, 2017; Kim et al., 2018).

Interferon-stimulated genes

Interferons mediate innate immune response, and are the first line of defense to pathogens. This response triggers via JAK/STAT pathway a regulation of hundreds of interferon-stimulated genes (ISGs) (Binelli et al., 2001; Schneider et al., 2014). Particularly, IFNT increases expression of several ISGs in the uterus (Mirando et al., 1991; Rueda et al., 1993; Naivar et al., 1995), like interferon-stimulated gene 15 (*ISG15*), 2',5' oligoadenylate synthetase (*OAS*), myxovirus resistance 1 and 2 (*MX1* and *MX2*) (Mirando et al., 1991; Schmitt et al., 1993; Johnson et al., 2001). ISG15 is increased during early pregnancy in bovine endometrium (Austin et al., 1996) and also in extrauterine tissues, such as the CL (Oliveira et al., 2008; Bott et al., 2010; Romero et al., 2015). ISG15, first termed ubiquitin cross-reactive protein because of its cross-reactivity with antibody against ubiquitin (Austin et al., 1996) is up-regulated in mouse (Bebington et al., 1999; Austin et al., 2003) and human (Bebington et al., 1999) endometrium in response to pregnancy. ISG15 is induced as a Type I interferon response and becomes conjugated to intracellular proteins (Loeb and Haas, 1992) in a mechanism different to that described for ubiquitin (Narasimhan et al., 1996). The expression of *ISG15* mRNA (Hansen et al., 1997) and protein (Austin et al., 2004), follows the same IFNT temporal pattern during early pregnancy (Romero et al., 2015). *ISG15* mRNA is localized to glandular epithelium, stroma, and myometrium with less extension to luminal epithelium in the cow (Johnson et al., 1999a) and very restricted or even no localization in the ewe (Johnson et al., 1999b).

Maternal recognition of pregnancy

Late 50's and early 60's a series of experiments in sheep recognized the conceptus or a secreted product from the conceptus was responsible for maternal recognition of pregnancy. Initially, one study suggested the embryonic mortality in sheep occurred in two peaks, one before and other after the attachment to the endometrium. Two or 5 embryos were transferred to normal or super ovulated ewes and progesterone was assessed on recipients on Day 15 of pregnancy. Super ovulated ewes had greater concentration of progesterone, however the embryo mortality was higher on ewes that received 5 embryos. It was concluded embryo mortality could not have been due to a reduced concentration of progesterone (Moore et al., 1960). The same group identified the lifespan of the CL is affected by the uterus, and that there is a local interdependence among the uterus, the embryo and the CL (Moor and Rowson, 1966b). The embryo development was followed by Day 14 of pregnancy, and it was suggested the rapid phase of elongation on Days 12-14 may have a relationship to corpus luteum maintenance (Rowson and Moor, 1966a). Later it was observed embryos should be transferred to recipients with synchronous days (Rowson and Moor, 1966b), and the conceptus must be present in the uterus by Days 12 or 13 of the cycle for a successful pregnancy following embryo transfer (Rowson and Moor, 1967). In the 70's there was identified IFNT as the major product from the embryo (previous section). Pregnancy recognition in ruminants occurs when the embryo secretes interferon tau (Farin et al., 1990a; Gray et al., 2002) to extend CL lifespan (Knickerbocker et al., 1986).

Maternal recognition of pregnancy period where bovine conceptus secretes IFNT to signal its presence within the uterus occurs between Days 12 to 26 of pregnancy (Farin et al., 1990b). However, recent researches have

shown that bovine conceptus signals to the mother previously to this period. Bovine oviduct epithelial cells (BOECs) stimulate *in vitro* bovine embryos on Day 4 to produce IFNT, which then acts on immune cells to promote anti-inflamatory response in the oviduct. However, in this period the IFNT was not able to stimulate ISGs expression in BOECs (Talukder et al., 2018). Studies report that the endometrial preparation to embryonic receptivity can occur as early as Day 4 due to increase concentration steroid hormones concentration from large follicles (Mesquita et al., 2015). Moreover, on Day 7 after artificial insemination, embryo dependents factors already are able to modulate ISGs, prostaglandins biosynthesis, water channels and solutes transport pathways in the endometrium at uterotubal junction of the uterine horn ipsilateral to the CL (Sponchiado et al., 2017), demonstrating that IFNT secretion may occur before of the classic maternal recognition period of pregnancy.

IFNT is a major product of ovine and bovine conceptus before attachment and its main function is to prevent return to cyclicity (Roberts et al., 2008). IFNT acts in a paracrine manner to prevent luteolytic pulses of PGF (Spencer and Bazer, 1996) and more recently it has been reported an endocrine action of IFNT on the CL (Oliveira et al., 2008) and an autocrine role of IFNT on the ovine trophectoderm, which suggest that IFNT acts as an factor to regulate trophectoderm cell proliferation (Wang et al., 2013). Based in this, IFNT-derived from conceptus has an important biological role for successful pregnancy during maternal recognition period of pregnancy.

Paracrine action of Interferon tau

Initial studies reveal that estrogen receptor (ER) and progesterone receptor (PR) gene expression are regulated in a tissue and cell specific manner along the estrous cycle and early pregnancy (Spencer and Bazer, 1995). IFNT is secreted from conceptus in the uterine lumen and acts on the endometrial luminal epithelium (Roberts et al., 1989) by JAK/STAT signaling pathway. When this pathway is active, transcription factor ISGF3 suppresses transcription of estrogen receptor (ESR1) and oxytocin receptor (OXTR) genes (Spencer and Bazer, 1996) but not progesterone receptor (Spencer et al., 1995). This suppression causes inhibition of PGF synthesis by the endometrium and consequently inhibits luteolysis (Spencer et al., 2007; Dorniak et al., 2011). Through JAK/STAT signaling pathway, tyrosine kinases phosphorylate STAT proteins forming multimeric complexes that act as transcription factors and regulate ISGs expression. Among the multimeric complexes formed is the ISGF3, which binds to interferons stimulate responsive regions (ISRE), starting ISGs synthesis (Hansen et al., 1999).

Besides all IFNT paracrine action blocking luteolytic PGF pulses, it also induces expression of ISGs that may have a biological function during maternal recognition and establishment of pregnancy (Hansen et al., 1999). *Isg15*$^{-/-}$ mice females had an increase in embryo mortality when compared with *Isg15*$^{+/+}$, besides impaired early decidualization, vascular development, and formation of the labyrinth (Henkes et al., 2015), demonstrating the importance of ISG15 gene expression to pregnancy successful.

Endocrine action of interferon tau

Since the identification of IFNT as the major product from the embryo responsible for signal to the mother its presence, some studies have been completed to test the hypothesis that exogenous administration of IFNT would increase conception and pregnancy rates. An experiment using recombinant bovine (rb) IFNA determined the effects of two injections per day of 2mg of rbIFNA from Days 12 to 16. The IFNA-infused ewes presented longer interestrous interval and greater embryonic survival (Nephew et al., 1990), suggesting rbIFNA administration for 3 to 5 days improves pregnancy rates in sheep (Martinod et al., 1991; Schalue-Francis et al., 1991).

Initially, IFNT was not believed to leave the uterus, and consequently act on a paracrine manner. One study tried to quantify IFNT in systemic fluids was not successful (Kazemi et al., 1988). However, some studies revealed ISGs expression in PBMC in sheep (Yankey et al., 2001) and cattle (Han et al., 2006). One hypothesis is that IFNT could leave the uterus through the lymphatic system. Iliac and submandibular lymph nodes mRNA expression for *ISG15* were tested and there were no differences between non-pregnant and pregnant ewes (Antoniazzi and Hansen, personal communication). Another study evaluated antiviral activity in the uterine vein serum on Day 15 of estrous cycle or pregnancy ewes and found out uterine vein blood presents greater antiviral activity on Day 15 pregnant ewes. Also in this same study, it was found the presence of *ISG15* mRNA and protein in the CL (Oliveira et al., 2008). However, this antiviral activity in uterine vein blood and the induction of *ISG15* in the CL could be induced by any Type I interferon. To determine whether the antiviral activity was caused by IFNT or not, an antiviral assay was performed using antibody against IFNT. Pre-adsorbed samples with antibody against IFNT presented no antiviral activity. This study concluded the antiviral activity in the uterine vein blood on Day 15 pregnant ewes was mediated by IFNT (Bott et al., 2010). Following, a very elegant model was proposed to study endocrine action of IFNT. Mini osmotic pumps were surgically inserted into the uterine vein upstream to the ovarian artery plexus. They were loaded to continuously infuse IFNT into the uterine vein for 24h, 72h and 7 days (Bott et al., 2010; Antoniazzi et al., 2013). Ewes infused of IFNT from Days 10 to 17 of estrous cycle did not presented estrus by Day 32, whereas the control group infused of BSA returned to estrous by Day 19. This studied concluded infusion of IFNT in the blood (endocrine delivery) blocked luteolysis (Bott et al., 2010). A series of experiments using this infusion model were used to test the hypothesis that endocrine IFNT could protect the CL from luteolysis. The first experiment infused IFNT (200ug) for 24h on Day 10 of estrous cycle in sheep. After 12h of infusion ewes received a PGF

challenge. IFNT-infused ewes that were challenged with PGF presented a decline in serum concentration of progesterone which augment rapidly, whereas in BSA-infused ewes PGF challenge induced luteolysis (Bott et al., 2010). Similarly, an infusion of IFNT (200ug) for 72h on Day 10 of estrous cycle, challenged with PGF on Day 11 protected the CL against induced luteolysis. When the concentration of infused IFNT was reduced to 20ug per day for 72h, the CL remained protected (Antoniazzi et al., 2013). These studies concluded endocrine IFNT reaches and protects the CL against natural and induced luteolysis. Besides the CL, pregnancy (Romero et al., 2015) and infusion of IFNT (Bott et al., 2010; Antoniazzi et al., 2013) induce ISG15 on the liver and uterine vein. The mechanism explaining exactly how IFNT leaves the uterus is not clear. One hypothesis is the steroid hormones of pregnancy and conceptus-derived factors influence the junctional complexes in the ovine endometrium (Satterfield et al., 2007), thus allowing IFNT to leave the uterus. One recent study revealed that conceptus-derived exossomes are found in the uterine flushing could influence endometrial response (Nakamura et al., 2016). For this reason, IFNT could use exossome trafficking system.

The expression of ISGs in extrauterine tissues and cells was identified by several studies (Han et al., 2006; Oliveira et al., 2008; Bott et al., 2010; Pugliesi et al., 2014; Romero et al., 2015). Luteal cells culture treated with IFNT did not increase progesterone secretion. However, these luteal cells treated with IL8 increase the progesterone production. IFNT stimulate neutrophils and IL8, which are associated with increase in the progesterone concentration during maternal recognition period in cows (Shirasuna et al., 2015). Polymorphonuclear granulocytes (PMNs), present a greater ISGs expression than peripheral blood mononuclear leukocytes (PBMCs) in pregnant cows on Day 5 following AI (Shirasuna et al., 2012). Also, ISGs expression was greater on Day 14 PMNs of pregnant cows (Kizaki et al., 2013). Therefore, bovine PMNs immune cells population is more sensible the embryo/conceptus presence during maternal recognition period (Shirasuna et al., 2012).

ISG15 and *MX1* mRNA expression were increased in liver biopsies from Day 18 Holstein pregnant heifers when compared to non-pregnant at the same period (Meyerholz et al., 2016). The relation between ISGs expression variation and liver function in bovine is unclear and more studies are necessary to understand the biologic role of regulation ISGs signaling pathways in others tissues from pregnancy dairy heifers (Meyerholz et al., 2016). Pregnant lactating Holstein cows had greater ISGs expression in cervical and vaginal mucosal membranes than non-pregnant cows on Days 17 to 18 after AI. This data suggests IFNT secreted from conceptus leaves the uterus and stimulates ISGs expression in cervical and vaginal tissue, which can be pregnancy-associated phenomenon (Kunii et al., 2018). Therefore, more studies are necessary to understand how endocrine actions of IFNT and ISGs expression can to maintain CL lifespan and consequently pregnancy successful.

In vitro models to study endocrine interferon tau signaling

A model to study mechanisms of luteolysis and luteal survival was established, luteal cells were isolated in small, large and mixed luteal cells (Fitz et al., 1982). This model was used later to verify IFNT action directly on the CL (Oliveira et al., 2008; Antoniazzi et al., 2013). Small, large and mixed luteal cells culture were treated in a dose-dependent concentration of IFNT to evaluate *ISG15* mRNA expression. All cells types had no detectable *ISG15* expression following 0ng/mL of IFNT, and ISG15 was expressed in all concentrations of IFNT, however, large luteal cells are more sensitive to lower concentration of IFNT (Antoniazzi et al., 2013). Based on the elegant model of IFNT continuous infusion into the uterine vein (Bott et al., 2010; Antoniazzi et al., 2013), we propose an *in vitro* model to study endocrine action of interferon tau (Bridi et al., 2018). Since CL is the most important gland to produce progesterone, and consequently maintain the pregnancy, the model uses luteal cell culture treated with IFNT. The source of IFNT is conditioned medium from parthenogenetic activated (PA) embryos. Luteal cells were treated with IFNA and conditioned medium in a dose-dependent manner and they do not express *ISG15* mRNA in the control group. IFNA and conditioned medium from PA embryos had similar *ISG15* mRNA expression patterns. The concentration of progesterone in the medium from luteal cells culture did not differ along the period and different treatments, the antiviral assay in the conditioned medium presented activity similar to IFNA. This study concluded luteal cells in culture respond to Type I interferons and to conditioned medium from PA embryos, IFNs do not influence concentration of progesterone in luteal cell culture, and both IFNA and conditioned medium induce *ISG15* mRNA expression in luteal cell culture (Bridi et al., 2018).

Conclusion

The paracrine mechanism of IFNT signaling on the maternal recognition of pregnancy is well characterized and described. The endocrine action of IFNT has been proposed recently and studies are building up concepts and theories, however there are many mechanisms and pathways to be understood. Our group has been focused on *in vitro* models to study IFNT signaling on different extrauterine tissues.

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Disclosure

The authors have no conflict of interests.

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