

New insights into interferon- τ mediated luteal regulation during ruminant pregnancy

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Abstract

Main pregnancy failures in ruminants arise from two causes: failure of the embryo to attach, and early or late abortions, which are due to failure of the corpus luteum and luteal phase deficiency. Interferon- τ is a type I interferon mainly produced by the trophoctoderm of ruminants, which acts on all body tissues and organs by paracrine and endocrine actions during embryo attachment as a pregnancy recognition signal. Among them, interferon- τ inhibits the pulse release of prostaglandin $F_{2\alpha}$ in the endometrium through paracrine action, avoids luteolysis, protects luteal formation in pregnancy, and enables pregnancy to continue. Recent studies have shown that interferon- τ extends luteal lifespan through endocrine action; however, the specific mechanism is unclear. In this review, we provide new insights into a series of interferon- τ -regulated physiological changes that occur during the formation of the pregnant corpus luteum, covering its functional, structural, and immunological features.

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Introduction

The corpus luteum (CL) is a transient endocrine gland that typically regresses following the estrous cycle in non-pregnant animals, allowing the initiation of a new estrous cycle. However, during pregnancy, luteolysis is prevented through molecular mechanisms that maintain CL structural integrity and endocrine function. This results in the transformation of the cyclic CL into a pregnancy-sustaining CL, which secretes progesterone (P_4) to support pregnancy. The primary function of CL is to secrete P_4 , a hormone essential for the elongation of the conceptus, establishing early pregnancy, supporting embryo implantation, and maintaining pregnancy^[1,2]. Maintenance of luteal function is mainly dependent on its continuous P_4 synthesis and support from an abundant vascular system^[3]. The important causes of pregnancy failure in ruminants are failure of embryo attachment, early or late abortion due to the failure of CL formation, and luteal phase deficiency. The CL originates from follicles. Post ovulation, the CL is formed through luteinization, in which endometrial and granulosa cells differentiate into small and large luteal cells, respectively^[4]. In addition, the CL contains endothelial cells, fibroblasts, various immune cells, and blood cells^[5]; therefore, the process of CL formation is accompanied by a variety of physiological changes such as vascularization and inflammation. Before embryo implantation, P_4 induces the expression of abundant receptivity-related genes in the maternal uterus, ensuring the establishment of a receptivity window^[6]. This allows the blastocyst, which has undergone early development, to develop further into an elongated conceptus and engage in a series of conversations with the maternal uterus to induce maternal recognition of pregnancy (MRP)^[7,8].

Interferon- τ (IFNT) is a type I interferon unique to ruminants and is the only known pregnancy recognition signal in ruminants. IFNT is

produced by trophoctoderm cells and induces MRP via a paracrine action on the endometrium^[9]. In addition to inducing MRP, IFNT also inhibits the expression of the estrogen receptor (ESR1), and oxytocin receptor (OXTR) in the endometrium via paracrine signaling, thereby inhibiting the release of $PGF_{2\alpha}$ pulses and protecting the CL from degeneration^[10]. This is the conventional view that IFNT protects the CL from degeneration caused by the $PGF_{2\alpha}$ pulse. However, with a deeper understanding of the IFNT, its mode of action has been further explored. Researchers have detected IFNT signals in the uterine vein and the expression of ISGs, such as ISG15, IFI6, and MX1, in the CL, liver, and other peripheral tissues^[11,12]. Injecting IFNT through the uterine or jugular vein was found to block endogenous luteolysis and prolong the estrus cycle in sheep^[13–15]. This suggests that, in addition to inhibiting the $PGF_{2\alpha}$ pulse through intrauterine paracrine signaling, IFNT also plays a luteal protective role through endocrine secretion.

Although interest in luteolysis and functional maintenance studies in ruminants has grown rapidly, reviews on the biology of IFNT remain scarce. In this review, we discuss the latest advances in our understanding of the mechanisms underlying the effects of IFNT on luteal fate through paracrine and endocrine actions.

Paracrine actions of IFNT in regulating pregnant CL formation

In species where the CL persists throughout pregnancy, the $PGF_{2\alpha}$ pulse serves as a key regulator of luteolysis, and IFNT exerts a protective effect by paracrinely suppressing $PGF_{2\alpha}$ pulses, thereby facilitating the transition of the cyclic CL into pregnant CL. On the 6th day post-fertilization, the conceptus began to express IFNT mRNA. In the conceptuses of sheep and cattle, IFNT mRNA levels peaked on the 14th

and 20th days, respectively. At this time, the expression of OXTR in the endometrium has not yet been established, and high concentrations of IFNT prevent the PGF_{2 α} pulse from the endometrium by inhibiting the expression of ESR1 and OXTR (only OXTR was affected in cattle), thereby preventing CL from degradation and continuing pregnancy (Fig. 1). Recent studies have shown that the release of PGF_{2 α} pulses is regulated by a PGT-mediated mechanism^[16]. IFNT inhibits PGT-mediated PGF_{2 α} pulse release through the JAK/EGFR/ERK/EGFR1 signaling pathway, thereby protecting CL from degradation^[17,18]. In addition to inhibiting the PGF_{2 α} pulse, IFNT induces the production of prostaglandin E₂ (PGE₂) in the uterus and increases the expression of PGE receptors (EP₂ and EP₄). PGE₂ acts as a protective agent for the CL by extending its life and promoting P₄ secretion^[19–21]. Suppressing the expression of prostaglandin E synthase (PTGES) in uterine reinstates PGF_{2 α} pulses, triggering CL luteolysis^[22].

IFNT inhibited the pulsing release of PGF_{2 α} but did not inhibit the expression of cyclooxygenase 2 (COX-2), and the production of PGF_{2 α} ^[23]. It has been reported that IFNT can upregulate the activity of COX-2 in the uterus of early pregnant cattle and induce the synthesis of PGF_{2 α} through the IFNT/FOXO1/COX-2 axis^[23,24] (Fig. 1). This may explain the higher PGF_{2 α} base yield in pregnant ewes than in cyclic ewes^[25,26]. However, studies have shown that the release patterns and concentrations of PGF_{2 α} in pregnant sheep are not significantly different from those in non-pregnant sheep^[27]. This suggests that, in addition to paracrine action, there are other mechanisms or additional mechanisms that protect the CL from degeneration during luteolysis.

Endocrine actions of IFNT in regulating pregnant CL formation

Ruiz-Gonzalez et al. used a radioimmunoassay to detect IFNT in uterine venous blood^[28]. After being produced by the conceptus, IFNT reaches the CL via the utero ovarian plexus (paracrine) and systemic circulation and reaches peripheral tissues such as the liver through the systemic circulation to induce the expression of ISGs^[29–31]. In addition, the induced expression levels of ISGs in the periphery were closely related to the size of the conceptus and the amount of IFNT^[32]. These results indicated that IFNT acts on all tissues through endocrine secretion. Bott et al. investigated the endocrine effects of IFNT by injecting it into either the uterine or jugular vein of sheep; they discovered that it blocked endogenous luteolysis and extended the estrus cycle^[14,33]. Therefore, the

IFNT endocrine system may be another form of protecting pregnant CL formation during pregnancy, in addition to the paracrine manner. In this paper, we summarize relevant studies on endocrine-mediated luteum protection by IFNT.

IFNT induces the expression of ISGs in luteum

The JAK/STAT signaling pathway plays a crucial role in enabling IFNT to exert its downstream effects^[34], with genes encoding the STAT family, key transcription factors of this pathway, being strongly expressed in the CL during early pregnancy^[35]. After activating the JAK/STAT signaling pathway, IFNT promotes the expression of a large number of type I ISGs (MX1, ISG15, OAS1, and IRF3) (Fig. 2). These ISGs are key genes that are expressed significantly more in both the CL and uterus during early pregnancy than in cyclic subjects during the same period^[36,37]. Luteal cells (LCs), endothelial cells, and endometrial cells respond to IFNT^[38–40]. Therefore, the protective effects of IFNT on the luteus may be related to ISG expression. Indeed, the mRNA expression of ISG15 was detected in the CL, endometrium, and liver on both the same and opposite sides of the injection site after IFNT was administered to the uterine or jugular veins of sheep^[41]. Similarly, we detected the expression of ISG15 mRNA and protein in the CL of pregnant goats, and the expression level was highest on the 18th day of pregnancy, which was consistent with the secretion trend of IFNT (data not published). These results suggest that IFNT induces ISG expression in CL, and ISGs induction may be an important mediator by which IFNT promotes the transition from the cyclic CL to the pregnant CL in ruminants.

IFNT regulates the production and metabolism of PGs in CL

The prostaglandin (PG) auto-amplification pathway is present in the CL. PG biosynthesis in the CL selectively directs PGF_{2 α} during luteolysis and selectively directs PGE₂ during pregnancy^[22,42]. PGF_{2 α} significantly increased the expression of COX-2, PTGFS, and carbonyl reductase 1 (CBR1) and the synthesis of PGF_{2 α} in luteal cells via the NF κ B signaling pathway^[43,44]. Many reactions induced by PGF_{2 α} , such as decreased P₄ synthesis and increased endothelin-1 (EDN1) and cytokines, also increase PGF_{2 α} production in the CL^[45]. During pregnancy, endometrial PGE₂ is transported to ovaries, further inducing the synthesis of PGE₂ in the CL and activating the signaling of EP₂ and EP₄ in the CL while inhibiting the expression of PTGFR and playing a protective role in the CL^[42,46]. Thus, the regulation of PG production in the CL may contribute to the activation or amplification of physiological signals in the CL, thereby affecting its fate.

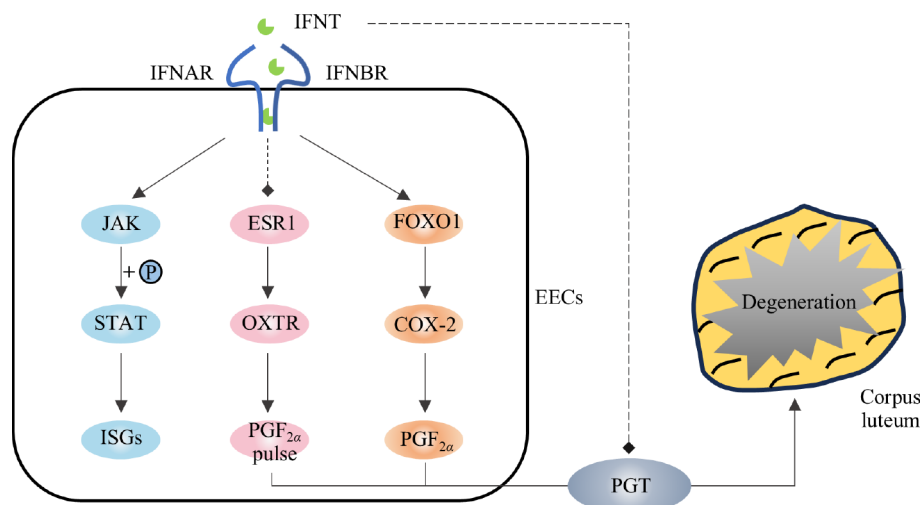


Fig. 1 Mechanism of IFNT protection of corpus luteum via paracrine. The solid arrows represent promotion, the dotted arrows represent inhibition. Blue represents the JAK/STAT pathway; orange represents the PGF_{2 α} synthesis pathway, and pink represents the PGF_{2 α} pulse release pathway.

Although the $\text{PGF}_{2\alpha}$ pulse induces luteolysis, the combination of the $\text{PGF}_{2\alpha}$ pulse and prostaglandin E_1 (a subtype of PGE) can rescue luteal function^[20], suggesting that PGE antagonizes the luteolytic effect of $\text{PGF}_{2\alpha}$, and PGE may be another important medium promoting the transition from cyclic CL to pregnant CL^[47]. PGE_2 has been widely recognized as a luteal protective hormone^[47], intrauterine infusions of IFNT and PTGES inhibitors can re-establish endometrial $\text{PGF}_{2\alpha}$ pulses to induce luteolysis, whereas simultaneous infusions of PGE_2 into the ovaries can salvage the CL^[22]. Additionally, PGE_2 stimulates P_4 secretion in the CL of cattle and sheep^[48–51]. Studies have shown that IFNT induces PGE_2 synthesis by stimulating PTGES expression without affecting PTGFS expression^[48–51], thereby enhancing the $\text{PGE}_2/\text{PGF}_{2\alpha}$ ratio to protect the CL^[23,52]. In addition, IFNT induces EP_2 expression (without affecting the EP_3)^[23,52]. EP_2 signaling activates the cAMP/PKA pathway, which regulates the expression of steroid synthase steroidogenic acute regulatory protein (StAR)^[53], which further regulates P_4 synthesis (Fig. 2). Therefore, the increased EP_2 expression enhances the conduction of the P_4 synthesis signal. However, EP_3 , another PGE receptor, mediates the downregulation of cAMP signaling, and its expression in the CL is inhibited by IFNT^[23].

In addition to the PG synthesis pathway, genes related to the prostaglandin response and metabolism are regulated by IFNT^[54] (Fig. 2). Compared to non-pregnant cattle, PTGFR and its inhibitor, prostaglandin F2 receptor negative regulator (PTGFRN), are negatively regulated in pregnant cattle^[54], indicating that IFNT inhibits the $\text{PGF}_{2\alpha}$ pathway and prevents CL degeneration stimulated by $\text{PGF}_{2\alpha}$. At the same time, IFNT induces the expression of the $\text{PGF}_{2\alpha}$ -degrading enzyme phosphoglycerate dehydrogenase (PGDH)^[54] and promotes the degradation of $\text{PGF}_{2\alpha}$ in the CL to reduce the concentration of $\text{PGF}_{2\alpha}$, thereby protecting the CL.

IFNT protects the function of P_4 synthesis

The main function of CL is to secrete P_4 . P_4 concentration affects the fate of the embryo. In early pregnancy of ruminants, the protective effect of IFNT on the CL is mainly achieved by inhibiting the release of $\text{PGF}_{2\alpha}$ pulses, inhibiting apoptosis, and maintaining vascular stability. IFNT

indirectly increases the secretion of P_4 *in vitro* by stimulating IL-8 expression and neutrophil migration in the CL but does not directly affect the secretion of P_4 ^[55]. During embryo attachment, the plasma P_4 concentration was not significantly different between pregnant and non-pregnant animals^[56], and the serum P_4 concentration was not significantly affected by the intravenous administration of IFNT in the jugular and uterine veins^[14,33]. Similarly, no changes in the expression of StAR, 3 β -hydroxysteroid dehydrogenase (3 β -HSD), cholesterol side-chain cleavage enzyme (P450scc), and peripheral benzodiazepine receptor (PBR) were found in the luteal transcriptome during IFNT secretion and non-IFNT secretion^[57], which are key enzymes in P_4 synthesis. In addition, there was no difference in nuclear receptor subfamily 5 group A member 1/2 (NR5A1/2) expression between pregnant and non-pregnant luteal transcriptomes, transcription factors that control steroid gene expression^[57,58], and their expression *in vitro* was not regulated by IFNT^[59]. Surprisingly, the treatment by Bott et al. of the CL with $\text{PGF}_{2\alpha}$ for 12 h resulted in decreased mRNA expressions of StAR, PBR, and 3 β -HSD regardless of subsequent IFNT treatment. The expressions of StAR and 3 β -HSD were also inhibited by IFNT alone^[14]. This may be a direct result of the endocrine action of IFNT since IFN- γ , one of a type I IFN, also reduces the activity of StAR and P450scc in various cells^[60,61].

Although IFNT could not stimulate further P_4 secretion from normal CL, it could salvage (more than twice) the dramatic decrease in P_4 concentration induced by $\text{PGF}_{2\alpha}$ ^[33]. Additionally, IFNT inhibited the expression of the vasoconstrictive peptide EDN1 in LCs, luteinized granular cells (LGCs), and luteal endothelial cells (LECs)^[38,39,54]. EDN1 is a negative regulator of CL function. EDN1 inhibits the secretion of P_4 by LCs through the endothelin type A receptor (ETR-A) and stimulates the secretion of $\text{PGF}_{2\alpha}$, disrupting CL function. The EDN1 signaling pathway is inhibited in the CL of pregnant cattle^[54].

In conclusion, IFNT protects CL function by negatively regulating genes that inhibit P_4 synthesis, stabilizing key enzyme expression for P_4 production, and maintaining P_4 secretion rather than increasing its synthesis. Importantly, other mechanisms may also contribute to the regulation of P_4 secretion in luteum cells.

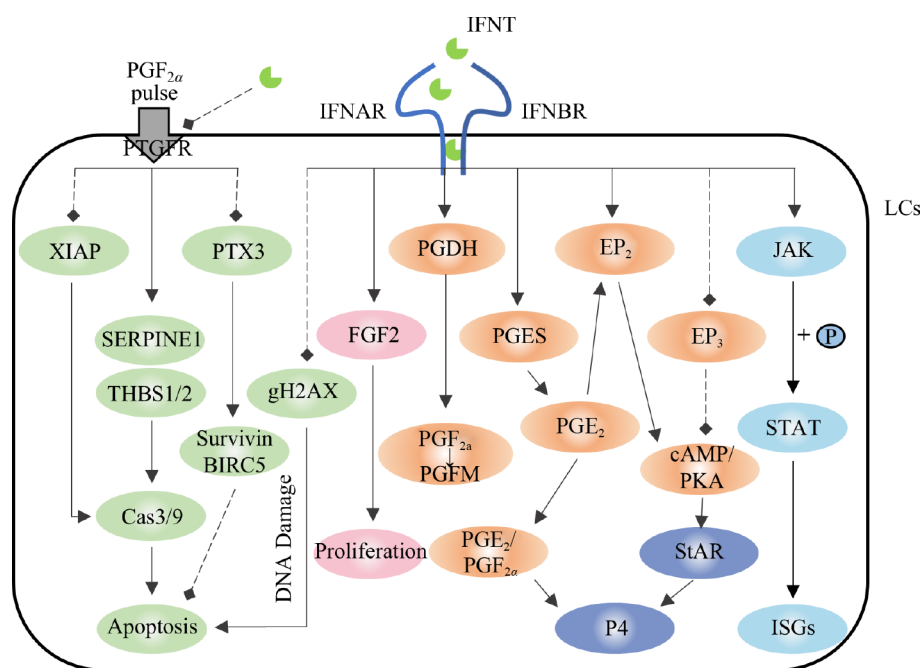


Fig. 2 Regulation of prostaglandin synthesis, progesterone synthesis, and apoptosis in the corpus luteum by IFNT. The solid arrows represent promotion, the dotted arrows represent inhibition. Light blue represents the JAK/STAT pathway, orange represents the prostaglandin synthesis and metabolism pathway, pink represents the cell proliferation pathway, green represents the apoptosis pathway, and dark blue represents the progesterone synthesis pathway.

IFNT maintains the vascular stability of CL

Maintenance of CL function relies on a rich vascular system^[62]. IFNT can stabilize the luteal vascular system, facilitating the acquisition of P_4 synthetic substrates and P_4 transport. The main genes involved in the positive regulation of luteal vascular stability in early pregnancy are VEGF and fibroblast growth factor 2 (FGF2), while the main negative regulatory factors are transforming growth factor beta-1 (TGFB1) and EDN1, both of which are regulated to varying degrees by IFNT (Fig. 3).

VEGF and FGF2 are involved in LC proliferation and angiogenesis^[63]. VEGF promotes the proliferation, migration, and branching of microvascular endothelial cells and enhances their permeability^[64]. FGF2 induces rapid phosphorylation of the proliferation-related signaling pathway (ERK/AKT/STAT1) and is a mitogen in luteal fibroblasts. VEGF and FGF2 expression are activated during luteal formation in pregnancy^[65]. During pregnancy in ruminants, IFNT secreted by the conceptus may induce the expression of VEGF and FGF2 to maintain vascular stability and protect the CL^[38]. *In vitro*, IFNT induces the expression of VEGFC and the proliferation of lymphoendothelial cells in lymphocytes and further induces the formation of capillaries^[66]. When VEGF and/or FGF2 were blocked with antibodies, the proliferation of endothelial cells was inhibited, the volume of the CL decreased, and P_4 decreased. Moreover, FGF2 blocking also increases the ANG2/ANG1 ratio, which disrupts vascular stability^[67,68]. TGFB1 and EDN1, critical luteolytic genes, are induced by $\text{PGF}_{2\alpha}$. TGFB1 is involved in the luteal degeneration pathway by promoting apoptosis and destroying capillary morphology^[69,70]. IFNT can inhibit the expression of TGFB1 and its receptors, TGFBR1 and TGFBR2, and shut down TGFB1 signal transduction in the CL during pregnancy^[39,54]. Consequently, the CL is maintained, and the pregnancy continues. The expression of EDN1 was also inhibited by IFNT^[39]. Additionally, IFNT stimulated the expression of other pro-angiogenic genes, such as FGF1, platelet-derived growth factor subunit B (PDGFB), and platelet-derived growth factor receptor alpha (PDGFAR); their expression levels were significantly higher in the CL of cows on the 18th day of pregnancy than in the cyclic CL during the same period^[38,57].

In conclusion, IFNT plays a crucial role in regulating vascular stability by universally stimulating or stabilizing the expression of key factors that promote vascular integrity while inhibiting genes associated with vasoconstriction and vascular destruction. This action protects the vascular structure of the CL.

IFNT protects LCs from apoptosis

Apoptosis is the main internal mechanism of luteolysis. IFNT has been widely demonstrated to be a survival factor for LCs and LECs, inhibiting apoptotic signals and enhancing the transduction of signaling pathways related to cell survival.

XIAP plays a key anti-apoptotic role by chelating caspase9 and caspase3 to inhibit their activities. On day 18, XIAP expression in the pregnant CL of cattle was significantly higher than that in the non-pregnant CL, which may be the result of the endocrine effect of IFNT occurring on the 18th day of pregnancy. Basavaraja et al. confirmed this finding^[38]. Treatment of LCs with IFNT significantly induced protein expression of XIAP, and continuous intravenous injection of 200 μg IFNT on days 7 and 10 of sheep's estrus cycle could significantly induce XIAP expression in CL and prolong the luteal lifespan to more than 32 d^[33]. Additionally, IFNT increased the viability of LECs in a STAT-independent manner^[39].

Serpin family E member 1 (SERPINE1), thrombospondin 1 (THBS1), THBS2, and TGFB1 are widely studied luteolytic factors. SERPINE1 is a natural proapoptotic gene expressed as PAI-1, which inhibits cell adhesion and angiogenesis^[69]. SERPINE1 expression was significantly increased in the CL of cattle treated with $\text{PGF}_{2\alpha}$ for 12 h^[69,71]. THBS1 and THBS2 are endogenous anti-angiogenic molecules that are widely expressed in degraded CL. Inhibiting the expression of FGF2 and XIAP causes THBS1 and THBS2 to activate the caspase-3 pathway, exerting strong proapoptotic activity^[72,73]. A feedforward cycle exists between THBS1, TGFB1, and SERPINE1, whose gene products promote apoptosis and matrix remodeling, ultimately leading to luteolysis^[69] (Fig. 2). Therefore, all three are inhibited during MRP. As an MRP signal, IFNT reduces the stimulation of $\text{PGF}_{2\alpha}$ on THBS1 and SERPINE1, thereby reversing the negative effects of THBS1, THBS2, SERPINE1, and TGFB1 on LGC activity and reducing the numbers of apoptotic and dead cells^[39]. Additionally, IFNT rescues the apoptosis in LGCs mediated by THBS1^[38]. These positive effects of IFNT may be achieved by inhibiting the expression of THBS1 and THBS2 and by enhancing the activity of FGF2. Since THBS1 and THBS2 chelate FGF2 to impair its biological activity, inhibiting them may release more biologically active FGF2, thereby increasing overall FGF2 levels^[72].

In addition to the above genes, apoptosis-related factors, such as Bcl-2 and pentraxin 3 (PTX3), are also regulated by IFNT (Fig. 2). The

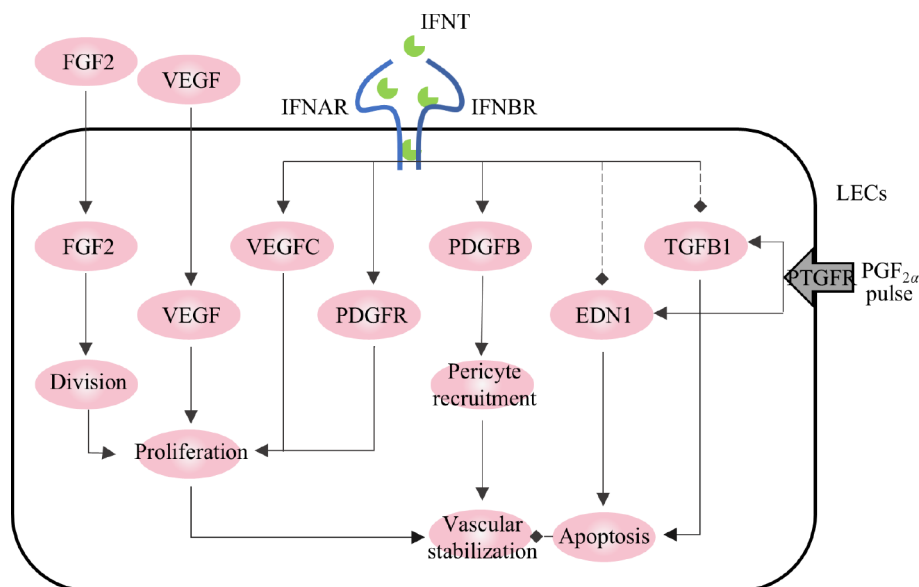


Fig. 3 Regulation of vascular stability in corpus luteum by IFNT. The solid arrows represent promotion, the dotted arrows represent inhibition.

Bcl-2 family of proteins is involved in the regulation of various apoptotic pathways. According to a previous report, the expression of the survival genes BCL2L1, Bcl-xL, AKT, MCL1, and PARP in the LC of ewes was upregulated by endocrine delivery of IFNT^[33,35], which was inhibited by PGF_{2 α} during the luteolytic period. PTX3 is a polysaccharide protein that is highly expressed in the CL during early pregnancy and is negatively correlated with THBS1. Deletion of endogenous PTX3 can lead to cell death. IFNT induces the expression of PTX3 in LGCs, LECs, and luteum sections and upregulates the expression of the anti-apoptotic proteins BIRC5 and survivin, thereby protecting cells from apoptosis^[74]. Additionally, IFNT inhibited the expression of PTGFR and histone 2AX (gH2AX), in which gH2AX is a marker of DNA damage that is closely related to apoptosis^[75].

In conclusion, the role of IFNT in protecting LCs from apoptosis has been widely validated. However, the underlying mechanism requires further exploration.

IFNT regulates inflammatory response during the formation of pregnant CL

Immune cells and cytokines are important regulators of steroid hormone production and vascular function in the CL. When the state of the CL changes, immune cells are recruited to produce and secrete various cytokines that regulate their function and organizational structure^[76]. Zhao et al. identified a variety of immune cells in the CL, such as macrophages, neutrophils, and eosinophils, and indicated that these immune cells accumulate and support angiogenesis and P₄ production during CL development^[77]. During luteolysis, PGF_{2 α} stimulates the production of inflammatory cytokines and chemokines and accelerates CL decomposition by enhancing the inflammatory response^[77]. IFNT can act as an immune modulator during pregnancy and participate in regulating the activation and recruitment of immune cells, thereby calibrating defense, inducing an anti-inflammatory state, preventing autoimmunity, and preventing CL injury^[41,78,79].

The proliferating T cells in the functional CL are mainly gamma-delta T cells ($\gamma\delta$ + T cells), and the CL exerts an immunosuppressive effect on the proliferation of $\gamma\delta$ + T cells in the CL through the production of IL-10^[80]. Studies have shown that the expression level of IL-10 in the transcripts of the uterine flushing fluid of pregnant cattle is

upregulated, and IFNT-blocking antibodies inhibit this change^[81], indicating that IFNT may induce the expression of IL-10. In addition, the expression of CX3C chemokine ligand 1 (CX3CL1) and TFPI2 is stimulated by IFNT in the CL and is highly expressed in the CL during pregnancy. CX3CL1 acts as an adhesion molecule that regulates the interactions between LCs and immune cells^[82]. TFPI2 is an MMP inhibitor that may maintain the stability of the extracellular matrix (ECM) components of the CL by interfering with MMP signaling in pregnant CL^[83].

We described how FGF2 and VEGF are induced by IFNT and thus regulate angiogenesis in the CL. Beyond their pro-angiogenic roles, FGF2 and VEGF act as chemoattractants for polymorphonuclear neutrophils (PMNs). In synergy with IL-8, these recruited PMNs further enhance vascular and lymphatic angiogenesis within CL, thereby supporting its structural formation and functional development^[84]. PMN also promotes immune transfer and facilitates communication between the CL and other organs. During early pregnancy in cattle, IFNT regulates the reconstruction of the luteal lymphatic system via the VEGFC/VEGFD-VEGFR3 system^[66] and enhances neutrophil function and numbers in the CL by promoting IL-6 and IL-8 secretion^[85]. This upregulation of IL-8 and neutrophils by IFNT contributes to sustained P₄ production during MRP^[55] (Fig. 4).

In addition, IFNT regulates the state of immune cells and the secretion of cytokines. Macrophages are necessary for maintaining luteal function; however, they are also recruited in large numbers during the early stages of luteolysis^[86]. In addition to macrophages, immune cells that are highly recruited during luteolysis include CD4⁺ and CD8⁺ T cells^[87]. PGF_{2 α} stimulates the proliferation of these immune cells, while P₄ inhibits them^[88]. The secreted inflammatory factors (tumor necrosis factor- α (TNFA), IL-1 β , and IFN- γ) and chemokines (CCL2) from these cells contribute to luteolysis^[89]. Upon the initiation of luteolysis, there is further recruitment of macrophages and T lymphocytes. Macrophages secrete TNFA and other pro-inflammatory cytokines to promote inflammation and immune reactions, thereby enhancing the luteolysis cascade. TNFA is a pro-inflammatory factor secreted mainly by macrophages and strongly expressed during luteolysis^[90,91]. IFNT inhibits the activation of pro-inflammatory M1 macrophages *in vitro*

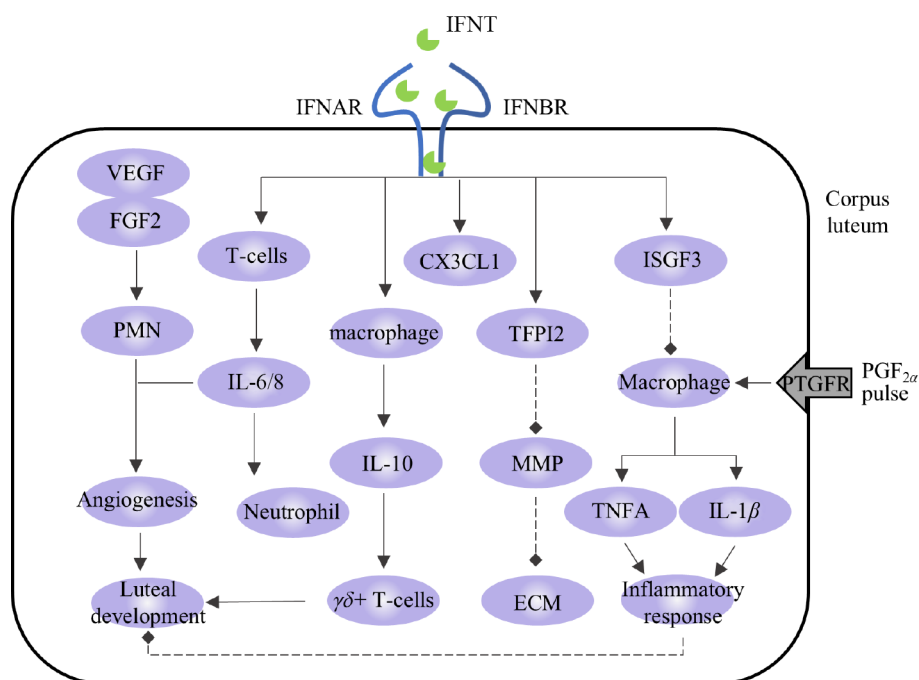


Fig. 4 Regulation of immunological events in corpus luteum by IFNT. The solid arrows represent promotion, the dotted arrows represent inhibition.

by controlling the activation of the ISGF3 complex and STAT3 pathway. It also inhibits the secretion of TNFA, thus playing a role in inhibiting inflammation^[53,92], which is consistent with the downregulation of the TNFA enrichment pathway in the CL of pregnant cattle^[54]. IL-1 β is a classical proinflammatory factor. When the CL is stimulated by the PGF_{2 α} pulse or its function is inhibited by other pathways, the expression level of IL-1 β increases^[93,94], while IFNT can downregulate the secretion of IL-1 β and inhibit the inflammatory response^[52,95] (Fig. 4). Beyond the factors described above, the expressions of peroxisome proliferator-activated receptor gamma (PPAR- γ), C-X-C motif chemokine ligand 10 (CXCL10), and arginase 1 (ARG1), which are involved in the regulation of inflammatory responses, were also regulated by IFNT to varying degrees^[85,96].

Conclusions

In summary, we have comprehensively elucidated the intrinsic mechanisms by which IFNT regulates the formation of the pregnant CL through modulation of apoptosis, immune responses, vascular stabilization, and other key processes. This study establishes a theoretical foundation for fully unraveling the mechanisms underlying CL formation in ruminants and improving their pregnancy rates. Future research should focus on further investigating IFNT-mediated regulatory mechanisms while developing targeted pharmaceuticals or therapeutic strategies to safeguard CL formation, thereby enhancing reproductive efficiency and economic outcomes.

Ethical statements

Not applicable.

Author contributions

The authors confirm their contributions to the paper as follows: manuscript conception: Shang C, Liu H; manuscript edition: Shang C, Liu H, Li Z; manuscript revision: Lin P, Jin Y, Wang A; figure preparation: Zhang R, Niu H, Liu S, Mou Y. All authors reviewed and approved the final version of the manuscript.

Data availability

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Lonergan P, Forde N. 2015. The role of progesterone in maternal recognition of pregnancy in domestic ruminants. *Advances in Anatomy, Embryology, and Cell Biology* 216:87–104
2. Wiltbank MC, Souza AH, Carvalho PD, Cunha AP, Giordano JO, et al. 2014. Physiological and practical effects of progesterone on reproduction in dairy cattle. *Animal* 8(Suppl 1):70–81
3. Woad KJ, Robinson RS. 2016. Luteal angiogenesis and its control. *Theriogenology* 86:221–28
4. Hansel W, Alila HW, Dowd JP, Milvae RA. 1991. Differential origin and control mechanisms in small and large bovine luteal cells. *Journal of Reproduction and Fertility Supplement* 43:77–89
5. Channing CP. 1969. Steroidogenesis and morphology of human ovarian cell types in tissue culture. *Journal of Endocrinology* 45:297–308
6. Feng R, Qin X, Li Q, Olugbenga Adeniran S, Huang F, et al. 2022. Progesterone regulates inflammation and receptivity of cells via the NF- κ B and LIF/STAT3 pathways. *Theriogenology* 186:50–59
7. Lonergan P, Sánchez JM. 2020. Symposium review: Progesterone effects on early embryo development in cattle. *Journal of Dairy Science* 103:8698–707
8. Rabaglino MB, Sánchez JM, Mc Donald M, Crowe MA, O'Callaghan E, et al. 2023. Transfer of bovine embryos into a uterus primed with high progesterone concentrations positively impacts fetal development at 42 days of gestation. *Theriogenology* 200:25–32
9. Roberts RM. 2007. Interferon-tau, a type 1 interferon involved in maternal recognition of pregnancy. *Cytokine & Growth Factor Reviews* 18:403–8
10. Fleming JGW, Spencer TE, Safe SH, Bazer FW. 2006. Estrogen regulates transcription of the ovine oxytocin receptor gene through GC-rich SP1 promoter elements. *Endocrinology* 147:899–911
11. Zhang L, Xue J, Wang Q, Lv W, Mi H, et al. 2018. Changes in expression of ISG15, progesterone receptor and progesterone-induced blocking factor in ovine Thymus during early pregnancy. *Theriogenology* 121:153–59
12. Yang L, Wang XL, Wan PC, Zhang LY, Wu Y, et al. 2010. Up-regulation of expression of interferon-stimulated gene 15 in the bovine corpus luteum during early pregnancy. *Journal of Dairy Science* 93:1000–11
13. Guzeloglu A, Bishop JV, Van Campen H, Plewes MR, Gonzalez-Berrios CL, et al. 2024. Interferon-tau infusion into the ovine corpus luteum delays luteolysis. *Biology of Reproduction* 111:667–77
14. Bott RC, Ashley RL, Henkes LE, Antoniazzi AQ, Bruemmer JE, et al. 2010. Uterine vein infusion of interferon tau (IFNT) extends luteal life span in ewes. *Biology of Reproduction* 82:725–35
15. Madureira G, Mion B, Van Winters B, Peñagaricano F, Li J, et al. 2024. Endometrial responsiveness to interferon-tau and its association with subsequent reproductive performance in dairy heifers. *Journal of Dairy Science* 107:7371–91
16. Lee J, McCracken JA, Banu SK, Rodriguez R, Nithy TK, et al. 2010. Transport of prostaglandin F_{2 α} pulses from the uterus to the ovary at the time of luteolysis in ruminants is regulated by prostaglandin transporter-mediated mechanisms. *Endocrinology* 151:3326–35
17. Banu SK, Lee J, Stephen SD, Nithy TK, Arosh JA. 2010. Interferon tau regulates PGF_{2 α} release from the ovine endometrial epithelial cells via activation of novel JAK/EGFR/ERK/EGR-1 pathways. *Molecular Endocrinology* 24:2315–30
18. Lee J, Stanley JA, McCracken JA, Banu SK, Arosh JA. 2014. Intrauterine coadministration of ERK1/2 inhibitor U0126 inhibits interferon TAU action in the endometrium and restores luteolytic PGF_{2 α} pulses in sheep. *Biology of Reproduction* 91:46
19. Krishnaswamy N, Chapdelaine P, Tremblay JP, Fortier MA. 2009. Development and characterization of a Simian virus 40 immortalized bovine endometrial stromal cell line. *Endocrinology* 150:485–91
20. Ochoa JC, Peñagaricano F, Baez GM, Melo LF, Motta JCL, et al. 2018. Mechanisms for rescue of corpus luteum during pregnancy: gene expression in bovine corpus luteum following intrauterine pulses of prostaglandins E₁ and F_{2 α} . *Biology of Reproduction* 98:465–79
21. Piotrowska-Tomala KK, Jonczyk AW, Szóstek-Mioduchowska AZ, Żebrowska E, Ferreira-Dias G, et al. 2022. The effects of prostaglandin E₂ treatment on the secretory function of mare corpus luteum depends on the site of application: an *in vivo* study. *Frontiers in Veterinary Science* 8:753796
22. Arosh JA, Banu SK, McCracken JA. 2016. Novel concepts on the role of prostaglandins on luteal maintenance and maternal recognition and establishment of pregnancy in ruminants. *Journal of Dairy Science* 99:5926–40
23. Arosh JA, Banu SK, Kimmins S, Chapdelaine P, MacLaren LA, et al. 2004. Effect of interferon- τ on prostaglandin biosynthesis, transport, and signaling at the time of maternal recognition of pregnancy in cattle: evidence of polycrine actions of prostaglandin E₂. *Endocrinology* 145:5280–93
24. Bu LG, Wang B, Li TY, Sun Y, Kong LL, et al. 2023. An IFNT/FOXO1/PTGS2 axis regulates prostaglandin F_{2 α} synthesis in goat uterus during early pregnancy. *Journal of Dairy Science* 106:8060–71
25. Dorniak P, Bazer FW, Spencer TE. 2013. Physiology and Endocrinology Symposium: biological role of interferon tau in endometrial function and conceptus elongation. *Journal of Animal Science* 91:1627–38

26. Ulbrich SE, Schulke K, Groebner AE, Reichenbach HD, Angioni C, et al. 2009. Quantitative characterization of prostaglandins in the uterus of early pregnant cattle. *Reproduction* 138:371–82
27. Lewis GS, Jenkins PE, Fogwell RL, Inskeep EK. 1978. Concentrations of prostaglandins E_2 and $F_{2\alpha}$ and their relationship to luteal function in early pregnant ewes. *Journal of Animal Science* 47:1314–23
28. Ruiz-González I, Xu J, Wang X, Burghardt RC, Dunlap KA, et al. 2015. Exosomes, endogenous retroviruses and toll-like receptors: pregnancy recognition in ewes. *Reproduction* 149:281–91
29. Mathew DJ, Peterson KD, Senn LK, Oliver MA, Ealy AD. 2022. Ruminant conceptus-maternal interactions: interferon-tau and beyond. *Journal of Animal Science* 100:skac123
30. Ruhmann B, Giller K, Hankele AK, Ulbrich SE, Schmicke M. 2017. Interferon- τ induced gene expression in bovine hepatocytes during early pregnancy. *Theriogenology* 104:198–204
31. Feltrin IR, Melo GD, Freitas PP, Morelli KG, Binelli M, et al. 2025. Conceptus signaling markers in immune cells enhance pregnancy prediction in beef cattle. *Scientific Reports* 15:17548
32. Hansen TR, Sinedino LDP, Spencer TE. 2017. Paracrine and endocrine actions of interferon tau (IFNT). *Reproduction* 154:F45–F59
33. Antoniazzi AQ, Webb BT, Romero JJ, Ashley RL, Smirnova NP, et al. 2013. Endocrine delivery of interferon tau protects the corpus luteum from prostaglandin F_2 alpha-induced luteolysis in ewes. *Biology of Reproduction* 88:144
34. Liu H, Wang C, Li Z, Shang C, Zhang X, et al. 2021. Transcriptomic analysis of STAT1/3 in the goat endometrium during embryo implantation. *Frontiers in Veterinary Science* 8:757759
35. Hughes CHK, Mezera MA, Wiltbank MC, Pate JL. 2022. Insights from two independent transcriptomic studies of the bovine corpus luteum during pregnancy. *Journal of Animal Science* 100:skac115
36. Binelli M, Subramaniam P, Diaz T, Johnson GA, Hansen TR, et al. 2001. Bovine interferon- τ stimulates the Janus kinase-signal transducer and activator of transcription pathway in bovine endometrial epithelial cells. *Biology of Reproduction* 64:654–65
37. Kim MS, Min KS, Imakawa K. 2013. Regulation of interferon-stimulated gene (ISG)12, ISG15, and MX1 and MX2 by conceptus interferons (IFNTs) in bovine uterine epithelial cells. *Asian-Australasian Journal of Animal Sciences* 26:795–803
38. Basavaraja R, Madusanka ST, Drum JN, Shrestha K, Farberov S, et al. 2019. Interferon-tau exerts direct prosurvival and antiapoptotic actions in luteinized bovine granulosa cells. *Scientific Reports* 9:14682
39. Basavaraja R, Przygodzka E, Pawlinski B, Gajewski Z, Kaczmarek MM, et al. 2017. Interferon-tau promotes luteal endothelial cell survival and inhibits specific luteolytic genes in bovine corpus luteum. *Reproduction* 154:559–68
40. Chen Y, Antoniou E, Liu Z, Hearne LB, Roberts RM. 2007. A microarray analysis for genes regulated by interferon-tau in ovine luminal epithelial cells. *Reproduction* 134:123–35
41. Hansen TR, Henkes LK, Ashley RL, Bott RC, Antoniazzi AQ, et al. 2010. Endocrine actions of interferon-tau in ruminants. *Society of Reproduction and Fertility Supplement* 67:325–40
42. Lee J, McCracken JA, Stanley JA, Nithy TK, Banu SK, et al. 2012. Intraluteal prostaglandin biosynthesis and signaling are selectively directed towards $PGF_{2\alpha}$ during luteolysis but towards PGE_2 during the establishment of pregnancy in sheep. *Biology of Reproduction* 87:97
43. Kumagai A, Yoshioka S, Sakumoto R, Okuda K. 2014. Auto-amplification system for prostaglandin $F_{2\alpha}$ in bovine corpus luteum. *Molecular Reproduction and Development* 81:646–54
44. Taniguchi K, Matsuoka A, Kizuka F, Lee L, Tamura I, et al. 2010. Prostaglandin $F_{2\alpha}$ (PGF $_{2\alpha}$) stimulates PTGS2 expression and $PGF_{2\alpha}$ synthesis through NF κ B activation via reactive oxygen species in the corpus luteum of pseudopregnant rats. *Reproduction* 140:885–92
45. Wiltbank MC, Ottobre JS. 2003. Regulation of intraluteal production of prostaglandins. *Reproductive Biology and Endocrinology* 1:91
46. Weems YS, Bridges PJ, Jeoung M, Arreguin-Arevalo JA, Nett TM, et al. 2012. *In vivo* intra-luteal implants of prostaglandin (PG) E_1 or E_2 (PGE_1 , PGE_2) prevent luteolysis in cows. II: mRNA for $PGF_{2\alpha}$, EP1, EP2, EP3 (A-D), EP3A, EP3B, EP3C, EP3D, and EP4 prostanoid receptors in luteal tissue. *Prostaglandins & Other Lipid Mediators* 97:60–65
47. Ginther OJ. 2024. Uteroovarian pathway for embryo-empowered maintenance of the corpus luteum in farm animals. *Theriogenology* 216:103–10
48. Fitz TA, Mock EJ, Mayan MH, Niswender GD. 1984. Interactions of prostaglandins with subpopulations of ovine luteal cells. II. Inhibitory effects of $PGF_{2\alpha}$ and protection by PGE_2 . *Prostaglandins* 28:127–38
49. Kim L, Weems YS, Bridges PJ, LeaMaster BR, Ching L, et al. 2001. Effects of indomethacin, luteinizing hormone (LH), prostaglandin E_2 (PGE_2), trilostane, mifepristone, ethamoxytriphetol (MER-25) on secretion of prostaglandin E (PGE), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and progesterone by ovine corpora lutea of pregnancy or the estrous cycle. *Prostaglandins & Other Lipid Mediators* 63:189–203
50. Weems YS, Bridges PJ, LeaMaster BR, Sasser RG, Ching L, et al. 2001. Effect of the aromatase inhibitor CGS-16949A on pregnancy and secretion of progesterone, estradiol-17 β , prostaglandins E and $F_{2\alpha}$ (PGE ; $PGF_{2\alpha}$) and pregnancy specific protein B (PSPB) in 90-day ovariectomized pregnant ewes. *Prostaglandins & Other Lipid Mediators* 66:77–88
51. Weems Y S, Bridges P J, Sasser R G, Ching L, LeaMaster B R, et al. 2002. Effect of mifepristone on pregnancy, pregnancy-specific protein B (PSPB), progesterone, estradiol-17 β , prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and prostaglandin E (PGE) in ovariectomized 90-day pregnant ewes. *Prostaglandins & Other Lipid Mediators* 70:195–208
52. Rashid MB, Marey MA, Fukuda K, Haneda S, Kusama K, et al. 2022. Intrauterine infusion of low levels of interferon-tau on day-8 post-estrus stimulates the bovine endometrium to secrete apolipoprotein-A1: a possible implication for early embryo tolerance. *American Journal of Reproductive Immunology* 88:e13592
53. Rizk-Rabin M, Chaoui-Ibadioune S, Vaczavlik A, Ribes C, Polak M, et al. 2020. Link between steroidogenesis, the cell cycle, and PKA in adrenocortical tumor cells. *Molecular and Cellular Endocrinology* 500:110636
54. Basavaraja R, Drum JN, Sapuleni J, Bibi L, Friedlander G, et al. 2021. Downregulated luteolytic pathways in the transcriptome of early pregnancy bovine corpus luteum are mimicked by interferon-tau *in vitro*. *BMC Genomics* 22:452
55. Shirasuna K, Matsumoto H, Matsuyama S, Kimura K, Bollwein H, et al. 2015. Possible role of interferon tau on the bovine corpus luteum and neutrophils during the early pregnancy. *Reproduction* 150:217–25
56. Magata F, Shirasuna K, Strüve K, Herzog K, Shimizu T, et al. 2012. Gene expressions in the persistent corpus luteum of postpartum dairy cows: distinct profiles from the corpora lutea of the estrous cycle and pregnancy. *Journal of Reproduction and Development* 58:445–52
57. Mezera MA, Li W, Wiltbank MC. 2021. Pregnancy-induced changes in the transcriptome of the bovine corpus luteum during and after embryonic interferon-tau secretion. *Biology of Reproduction* 105:148–63
58. Taniguchi H, Komiyama J, Viger RS, Okuda K. 2009. The expression of the nuclear receptors NR5A1 and NR5A2 and transcription factor GATA6 correlates with steroidogenic gene expression in the bovine corpus luteum. *Molecular Reproduction and Development* 76:873–80
59. Hughes CK, Rogus A, Inskeep EK, Pate JL. 2021. NR5A2 and potential regulatory miRNAs in the bovine CL during early pregnancy. *Reproduction* 161:173–82
60. Herrmann M, Scholmerich J, Straub RH. 2002. Influence of cytokines and growth factors on distinct steroidogenic enzymes *in vitro*: a short tabular data collection. *Annals of the New York Academy of Sciences* 966:166–86
61. Lin T, Hu J, Wang D, Stocco DM. 1998. Interferon-gamma inhibits the steroidogenic acute regulatory protein messenger ribonucleic acid expression and protein levels in primary cultures of rat Leydig cells. *Endocrinology* 139:2217–22
62. Guo M, Yang L, Zhao X, Yan P, Zhu M, et al. 2022. Microcystin-LR inhibits early pregnancy by impairing the vascular network of luteum: Involvement of the MEK/ERK/SP1/VEGFR2 axis. *Food and Chemical Toxicology* 170:113454
63. Robinson RS, Hammond AJ, Mann GE, Hunter MG. 2008. A novel physiological culture system that mimics luteal angiogenesis. *Reproduction* 135:405–13
64. Kwiatkowski SC, Guerrero PA, Hirota S, Chen Z, Morales JE, et al. 2017. Neuropilin-1 modulates TGF β signaling to drive glioblastoma growth and recurrence after anti-angiogenic therapy. *PLoS One* 12:e0185065
65. Romero JJ, Antoniazzi AQ, Smirnova NP, Webb BT, Yu F, et al. 2013. Pregnancy-associated genes contribute to antiluteolytic mechanisms in ovine corpus luteum. *Physiological Genomics* 45:1095–108

66. Nitta A, Shirasuna K, Haneda S, Matsui M, Shimizu T, et al. 2011. Possible involvement of IFNT in lymphangiogenesis in the corpus luteum during the maternal recognition period in the cow. *Reproduction* 142:879–92
67. Ernst H, Konturek PC, Hahn EG, Stosiek HP, Brzozowski T, et al. 2001. Effect of local injection with basic fibroblast growth factor (BFGF) and neutralizing antibody to BFGF on gastric ulcer healing, gastric secretion, angiogenesis and gastric blood flow. *Journal of Physiology and Pharmacology* 52:377–90
68. Fraser HM, Dickson SE, Lunn SF, Wulff C, Morris KD, et al. 2000. Suppression of luteal angiogenesis in the primate after neutralization of vascular endothelial growth factor. *Endocrinology* 141:995–1000
69. Farberov S, Meidan R. 2016. Thrombospondin-1 affects bovine luteal function via transforming growth factor-beta1-dependent and independent actions. *Biology of Reproduction* 94:25
70. Maroni D, Davis JS. 2011. TGF β 1 disrupts the angiogenic potential of microvascular endothelial cells of the corpus luteum. *Journal of Cell Science* 124:2501–10
71. Dau AMP, da Rosa PR, dos Santos J, Ferst J, de Macedo M, et al. 2022. The influence of prorenin/(pro)renin receptor on progesterone secretion by the bovine corpus luteum. *Animal Reproduction Science* 241:106985
72. Farberov S, Meidan R. 2014. Functions and transcriptional regulation of thrombospondins and their interrelationship with fibroblast growth factor-2 in bovine luteal cells. *Biology of Reproduction* 91:58
73. Rusnati M, Borsotti P, Moroni E, Foglieni C, Chiodelli P, et al. 2019. The calcium-binding type III repeats domain of thrombospondin-2 binds to fibroblast growth factor 2 (FGF2). *Angiogenesis* 22:133–44
74. Basavaraja R, Madusanka ST, Shrestha K, Przygodzka E, Kaczmarek MM, et al. 2020. Pentraxin-3 mediates pro-survival actions of interferon tau in bovine luteinized granulosa cells. *Reproduction* 160:603–12
75. Rogakou EP, Nieves-Neira W, Boon C, Pommier Y, Bonner WM. 2000. Initiation of DNA fragmentation during apoptosis induces phosphorylation of H2AX histone at serine 139. *Journal of Biological Chemistry* 275:9390–95
76. Walusimbi SS, Pate JL. 2013. Physiology and Endocrinology Symposium: role of immune cells in the corpus luteum. *Journal of Animal Science* 91:1650–59
77. Zhao JH, Zheng ST, Lin FP, Wang ZC. 2022. Effects of immune cells on luteal development and regression in the mammalian ovary. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao Acta Academiae Medicinae Sinicae* 44:504–9
78. Rocha CC, da Silveira JC, Forde N, Binelli M, Pugliesi G. 2021. Conceptus-modulated innate immune function during early pregnancy in ruminants: a review. *Animal Reproduction* 18:e20200048
79. Feng X, Yang C, Wang T, Zhang J, Zhou H, et al. 2025. IFN- τ maintains immune tolerance by promoting M2 macrophage polarization via modulation of bta-miR-30b-5p in early uterine pregnancy in dairy cows. *Cells* 14:87
80. Walusimbi SS, Pate JL. 2014. Luteal cells from functional and regressing bovine corpora lutea differentially alter the function of gamma delta T cells. *Biology of Reproduction* 90:140
81. Rashid MB, Talukder AK, Kusama K, Haneda S, Takedomi T, et al. 2018. Evidence that interferon-tau secreted from day-7 embryo *in vivo* generates anti-inflammatory immune response in the bovine uterus. *Biochemical and Biophysical Research Communications* 500:879–84
82. Nakano M, Fujii T, Hashimoto M, Yukawa N, Yoshifuji H, et al. 2012. Type I interferon induces CX3CL1 (fractalkine) and CCL5 (RANTES) production in human pulmonary vascular endothelial cells. *Clinical and Experimental Immunology* 170:94–100
83. Herman MP, Sukhova GK, Kiesel W, Foster D, Kehry MR, et al. 2001. Tissue factor pathway inhibitor-2 is a novel inhibitor of matrix metalloproteinases with implications for atherosclerosis. *The Journal of Clinical Investigation* 107:1117–26
84. Miyamoto A, Shirasuna K, Haneda S, Shimizu T, Matsui M. 2014. Cell Biology Symposium: perspectives: possible roles of polymorphonuclear neutrophils in angiogenesis and lymphangiogenesis in the corpus luteum during development and early pregnancy in ruminants. *Journal of Animal Science* 92:1834–39
85. Tanikawa N, Seno K, Kawahara-Miki R, Kimura K, Matsuyama S, et al. 2017. Interferon tau regulates cytokine production and cellular function in human trophoblast cell line. *Journal of Interferon & Cytokine Research* 37:456–66
86. Care AS, Diener KR, Jasper MJ, Brown HM, Ingman WV, et al. 2013. Macrophages regulate corpus luteum development during embryo implantation in mice. *The Journal of Clinical Investigation* 123:3472–87
87. Poole DH, Pate JL. 2012. Luteal microenvironment directs resident T lymphocyte function in cows. *Biology of Reproduction* 86:29
88. Cannon MJ, Pate JL. 2003. The role of major histocompatibility complex molecules in luteal function. *Reproductive Biology and Endocrinology* 1:93
89. Townson DH, Liptak AR. 2003. Chemokines in the corpus luteum: implications of leukocyte chemotaxis. *Reproductive Biology and Endocrinology* 1:94
90. Kapoor K, Singh O, Pathak D. 2020. Immunoexpression of cytokine tumour necrosis factor- α suggesting its role in formation and regression of corpus luteum in Indian buffalo. *Reproduction in Domestic Animals* 55:1393–403
91. Galvão AM, Ferreira-Dias G, Skarzynski DJ. 2013. Cytokines and angiogenesis in the corpus luteum. *Mediators of Inflammation* 2013:420186
92. Zelová H, Hošek J. 2013. TNF- α signalling and inflammation: interactions between old acquaintances. *Inflammation Research* 62:641–51
93. Atli MO, Bender RW, Mehta V, Bastos MR, Luo W, et al. 2012. Patterns of gene expression in the bovine corpus luteum following repeated intrauterine infusions of low doses of prostaglandin F2alpha. *Biology of Reproduction* 86:130
94. Lüttgenau J, Herzog K, Strüve K, Latter S, Boos A, et al. 2016. LPS-mediated effects and spatio-temporal expression of TLR2 and TLR4 in the bovine corpus luteum. *Reproduction* 151:391–99
95. Hara K, Shirasuna K, Usui F, Karasawa T, Mizushima Y, et al. 2014. Interferon-tau attenuates uptake of nanoparticles and secretion of interleukin-1 β in macrophages. *PLoS One* 9:e113974
96. Fiorenza MF, Amaral CDS, da Anunciação ARA, Portela VVM, Marey MA, et al. 2021. Possible impact of neutrophils on immune responses during early pregnancy in ruminants. *Animal Reproduction* 18:e20210048



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