



Review

Interferon Tau and Its Immunobiological Role in Ruminant Reproduction

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Abstract. Interferon tau (IFN- τ) is an key cytokine in maintaining pregnancy in ruminants. It is produced by the ruminant conceptus around the time of implantation. IFN- τ belongs to the type I interferon family but, unlike the other members of this group, it is not virus inducible and its expression is temporal and restricted to the trophoblast cells of the ruminant conceptus. The main target of the paracrine action of this cytokine is the endometrium. It changes the prostaglandin metabolism and secretory function of the cells by upregulating the secretion of several proteins. It also presents immunomodulatory action towards leukocytes by changing their proliferative responses and cytokine production. This cytokine activity in reproductive biology and immunology has been intensively explored for the last ten years. It has been regarded as a potential tool in improving the performance and biotechnological processes in ruminant reproduction. Additionally, its high antiviral potency and low cytotoxicity in comparison with IFN- α has placed this cytokine in the group of possible therapeutics in human and animal medicine.

Key words: interferon tau; cytokine; ruminants; reproduction; pregnancy.

Introduction

The maintenance of the secretory activity of the corpus luteum after the time of physiological regression is one of the first legible signs of progressing pregnancy. During this time, ovarian progesterone secures the appropriate intrauterine environment for the developing embryo. On the other hand, in the cyclic ovaries of farm animals, luteolysis is under the control of the pulsatile output of prostaglandin $F_{2\alpha}$ (PGF $_{2\alpha}$), which is synthesized the mucous membrane of the uterus²⁵. Therefore, the inhibition of the pulsative release of this prostaglandin extends the lifespan of the corpus luteum and progesterone production.

Over 3 decades ago, MOOR and ROWSON²⁸ showed that intrauterine infusion of extracts of sheep embryos suppresses corpus luteum regression. Similarly, HELMER et al.^{16, 17} showed that bovine conceptus secretory proteins changed prostaglandin metabolism in bovine endometrial explants and exerted an antiluteolytic effect in cyclic cows. The factor responsible for this phenomenon was previously called “trophoblastin” but then became known as ovine trophoblast protein-1 in the ewe and as bovine trophoblast protein-1 in cattle⁵. At present this protein is recognized as the interferon tau (IFN- τ , τ -trophoblast)²⁷. This protein is responsible for maternal recognition of pregnancy in ruminants. On the other hand, some biological properties of IFN- τ are

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characteristic for the other members of type I interferons. This unique cytokine, which links the fields of developmental biology and reproductive immunology, is the subject of the current review.

Origin and Gene Structure

Evolutionary, IFN- τ is derived from group I interferons. The IFN- τ gene diverged from the IFN- ω genes about 24 million years ago, together with the radiation of the so-called true ruminants. It is most closely related to IFN- ω and less closely to IFN- α . Similarity in amino acid sequences of IFN- τ is equal to 40–45% compared with IFN- α and 70–80% compared with IFN- ω . There is a faint identity in the amino acid sequence shared between IFN- τ and IFN- β , and no homology with IFN- γ ³⁸.

The existence of IFN- τ is restricted to the following subfamiliae: *Bovidae* (cattle, antelopes, sheep and goats), *Cervidae* (deer), *Giraffidae* (giraffe) and *Tragulidae* (mouse deer), within the suborder *Ruminantia*. Genomic Southern blot gene distribution analyses for IFNT genes (encoding IFN- τ) did not confirm the presence of these genes in the hippopotamus, zebra, horse, lama, elephant, rabbit, human and dolphin³⁸. The IFNT and IFNW genes are localized on one chromosome: 8q15 in cattle and goats, 2p15 in sheep, and 3p15 in river buffalo²⁷. The genetic structure of IFN- τ is similar to type I of interferons. Like all other members of the type I IFNs, its genes lack introns. mRNA for the protein is about 1 kb in length and has an open reading frame consisting of 585 bp. The encoding precursor polypeptide has 195 amino acids, with the signal peptide built up of the first 23 amino acids. The mature IFN- τ polypeptide is 172 residues long, which is similar to IFN- ω . Both of these possess a six amino acid extension at their carboxyl ends when they are aligned with the IFN- α . The main differences in nucleotide structure between IFN- τ and IFN- ω are localized in the promoter region and 3' untranslated flanking sequence (130 bp downstream of the stop codon)^{20, 23, 36, 37}.

The Promoter Region and Regulation of Expression

Recently, the structure of the IFN- τ promoter region has been subjected to very intense exploration. The species- and tissue-specific expression, the time-restricted production (only around implantation) and the lack of virus inducibility indicate a significant role for this structure in the distinct biological properties of this interferon.

In contrast to other type I interferons, where only about 150 bases upstream of the transcription start are highly conserved, which is probably connected with virus inducibility, the trophoblast IFN genes have a high degree of sequence conservation up to 400 bp²³.

The region responsible for virus-induced response (viral response elements – VRE) in IFN- τ is arranged differently from other type I interferons. The most characteristic sequence motif for this region is a repeating tetramer, GAAA, which is present in several locations up to base position –150. IFN- τ possesses only five GAAA sequences, but these sequences are not found clustered into regions characteristic for the virus-inducible interferons^{12, 23, 37}. It seems that this feature protects developing embryos from an accidental and earlier induction of transcription of that protein.

The constitutive production of IFN- τ is observed not only by trophoblast cells *in vivo*, but also *in vitro* by IVF-derived bovine blastocysts and trophoblastic vesicles^{18, 42}.

Several enhancer/silencer elements, to which transcription activator factors such as AP-1, the GATA-like sequence, or Ets-2 could bind in the promoter region of the IFN- τ gene, have been defined^{10, 51, 52}. IFN- τ secretion is probably also dependent on the expression of protooncogenes c-fos and -jun. XAVIER et al.⁴⁸ showed that c-fos mRNA expression and protein concentration decreased concomitantly with decreasing expression of mRNA and protein production of IFN- τ . On the other hand, expression of junB mRNA and protein synthesis increased before implantation. Despite very intensive research devoted to the mechanisms of regulation of IFN- τ production, the precise way of transcription activation still remains unexplained. Although the process of IFN- τ synthesis initiation is genetically programmed, the amount of its production may be influenced by the intrauterine environment. Human rGM-CSF and human rIL-3 increased IFN- τ production in *in vitro* cultures of 14- and 16-day ovine conceptus¹⁹. On the other hand, DE MORAES et al.²⁹ did not confirm the stimulatory influence of bovine rGM-CSF on IFN- τ synthesis in *in vitro*-derived bovine blastocysts or in trophoblast culture. Nevertheless, supernatants from a culture of bovine mononuclear cells, activated with a bacterial antigen, enhanced IFN- τ synthesis in *in vitro*-derived bovine embryos⁷.

Cytokines could promote IFN- τ production by a signal transduction pathway via protein kinase C¹⁹ and protooncogenes c-fos and c-junc^{27, 50}. But even though the IFN- τ gene contains an interferon response element, the lack of an interferon receptor on trophoblastic cells prevents an autocrine response to this cy-

tokine¹⁴. IFN- τ production is restricted to mononuclear trophoblast cells of the ruminant conceptus during the elongation stage, i.e. between 12/14 to 21 days in cattle and 12–18 days in the ewe and goat, and implantation rapidly ceases the production of this cytokine¹¹. Similarly to the initiation of transcription, the process of its termination also remains obscure, but so far the presence of silencer sequences have been identified, both in the conservative part and in parts situated beyond base –400, past the transcription start site^{13, 50, 51}.

The Protein and Its Receptor

IFN- τ is a protein whose molecular weight of the unglycosylated form, characteristic for sheep, is about 20 kDa. Bovine and caprine interferons are glycosylated and their molecular weight are about 20–22 kDa³⁷. Like other type I IFNs (except IFN- β), IFN- τ is the product of multiple genes in cattle and sheep. The occurrence of many genes and their alleles was revealed by cloning and genomic library techniques. The products of these genes differ among themselves in antilytic and antiviral activity^{8, 47}. They also exist in many isoforms and isoelectric variants of the protein³⁷. Such a way of encoding may probably serve for maintaining the massive production of the cytokine in the short time around implantation: the bovine conceptus produces approximately 100 μ g of IFN per day²⁶.

IFN- τ , similarly to other type I interferons, binds specific receptor belonging to the class II cytokine receptors. As in humans, in the cow and ewe, it consists of two subunits, IFNAR1 and IFNAR2. It was shown that the estrus cycle and early pregnancy have no influence on the mRNA synthesis for both subunits of the receptor in sheep endometrium¹⁴. The same author demonstrated, as mentioned before, a lack of expression of this receptor in the day 15 conceptus. However, despite the fact that they use the same type of the receptor, there are some important differences in activity between IFN- τ and other members of the type I interferons. IFN- τ shows a high antiviral activity in comparison with human IFN- α and sheep interferon induced by synthetic polynucleotides polyI: polyC³⁶. It is also characterized by high antiproliferative activity towards PHA- and ConA-stimulated ovine lymphocytes^{2, 35}. However, in contrast to IFN- α , trophoblast interferons are less cytotoxic. Comparative studies revealed a high homology in amino acid sequence for both IFN- τ receptor subunits in cattle and in ovine (92% identity for IFNAR1 and 88% identity for IFNAR2), but in comparison with human receptor subunits, the degree of

identity was only 67 and 68% for IFNAR1 in cattle and sheep, respectively, and under 60% for IFNAR2 in both species. These differences in receptor structure have no influence on the antiviral activity of human IFN- α and ovine IFN- τ tested on the Madin-Darby bovine kidney (MDBK) cell line¹⁴. Nevertheless, both interferons have different avidity for the receptor. Human IFN- α has a higher avidity for the receptor on MDBK cells than ovine IFN- τ ⁴³. This phenomenon is probably responsible for the higher cytotoxicity of IFN- α , but the mechanism underlying the process is not known. It is possible that both types of interferons differentially recognize the receptor. According to PONTZER et al.³³, antibodies against the C-terminal peptide of IFN- τ inhibit receptor binding of both IFN- τ and IFN- α , whereas antibodies against the N-terminal peptide only inhibit binding of IFN- τ .

These observations indicate that the differential cytotoxicity of IFN- α and IFN- τ may be connected with different receptor recognition by the N termini of these proteins.

High antiviral potency and low cytotoxicity turned attention to IFN- τ as a therapeutic agent in retrovirus infection and autoimmune diseases in humans and animals^{30, 34}. Unfortunately, it seems that not all IFN- τ subtypes show the same broad cross-species reactivity, and there are marked differences in antiviral activity and proliferation inhibition among different forms of ovine recombinant IFN- τ ^{1, 44}.

The signal transduction pathway, evoked by IFN- τ receptor binding, involves activation of JAK/STAT proteins in bovine endometrial cells. IFN- τ stimulates tyrosine phosphorylation, homo- and heterodimer formation of STAT proteins, their nuclear translocation and DNA-binding and also synthesis of interferon-regulatory factor (IRF)-1^{6, 27, 39, 41}. The involvement of the JAK/STAT pathway in the response to IFN- τ stimulation remains to be elucidated. Nevertheless, many proteins in the uterus are stimulated by this cytokine^{21, 22, 31, 39, 40}. Some of them (Mx protein, 2'5'-oligoadenylate synthetase and IRF) are typical for the antiviral response and their role is so far unknown. However, they may not be "useless" during the time around implantation. For example, OTT et al.³¹ suggested that Mx protein, which possesses GTPase activity, may be involved in the calcium metabolism of endometrial cells. IFN- τ is also a potent activator of GM-CSF secretion in bovine endometrial cells and peripheral blood leukocytes. Leukocytes stimulated with trophoblastic IFN produced 1000 times more GM-CSF than endometrial cells¹⁰. According to WEGMANN et al.⁴⁶, GM-CSF is an immunotrophic factor responsible for the undisturbed

conceptus development and maintenance of pregnancy. The above-mentioned findings indicate a probably important role of leukocytes in early pregnancy in ruminants. However, the subpopulation of peripheral blood leukocytes is markedly different from the repertoire of leukocytes in the endometrium. Therefore, the response of uterine leukocytes on IFN- τ may be different. Although IFN- τ does not change the CD4, CD14 and CD21 lymphocyte distribution in bovine endometrium²⁴, it stimulates production of granulocyte chemotactic protein-2 in bovine and monocyte chemotactic protein-1 and -2 in ovine endometrium^{4, 40}. These chemokines may modulate the traffic and activity of leukocytes in the uterus and/or on the periphery.

Ubiquitin cross reactive protein (UCRP), also known as IFN-stimulated gene product 17 (ISG17), is another protein released in the bovine and ovine uterus in response to IFN- τ ^{15, 21}. This 17 kDa protein reacts with antibody against ubiquitin, and the gene of bovine ISG17 is similar to its human counterpart, ISG15³². IRF-1 is probably a direct activator of bUCRP secretion. The role of the presence of this protein in the uterus around implantation time is highly speculative, but its immunoregulatory activity and involvement in the processes of proteasomal degradation of the proteins responsible for prostaglandin synthesis cannot be ruled out.

Maintenance of Pregnancy in Ruminants

The crucial event in the maintenance of pregnancy in ruminants is the inhibition of the pulsatile release of PGF_{2 α} , which in these animals is locally synthesized in the uterus.

In the cyclic ewe the PGF_{2 α} release is preceded by an increase of estrogen receptor expression followed by the upregulation of the oxytocin receptor. Oxytocin, in turn, (via its receptor) is responsible for the synthesis of cyclooxygenase-2 (COX-2) involved in prostaglandin production³. On the other hand, in cyclic cattle the moderate rise of the oxytocin receptor is not dependent on the expression of the estrogen receptor.

IFN- τ , produced by the ovine conceptus, inhibits estrogen and, subsequently, oxytocin receptor gene expression. This is probably the basic mechanism responsible for pregnancy recognition in the ewe²⁵. In cattle, however, only a slight decrease in oxytocin receptor mRNA expression in the endometrium on the 16th day of pregnancy is observed²⁵.

There is good evidence that in cows IFN- τ inhibits PGF_{2 α} secretion independently from the oxytocin re-

ceptor^{25, 49, 35}. PRU et al.³⁵ showed that bovine rIFN- τ considerably diminished phorbol ester-induced COX-2 gene expression in the culture of bovine endometrial cells. However, the signal transduction pathway induced by phorbol ester resulted in COX-2 expression, and secretion of PGF was not disturbed. Thus, it was concluded that IFN- τ may directly influence the promoter activity of the COX-2 gene, probably via IFN response elements.

According to a concept of Prof. VOISIN⁴⁵, presented during the 3rd Congress of the European Society for Reproduction and Developmental Immunology, reproductive and developmental immunology should be perceived as an older child of the marriage of Immunology with Reproduction, blessed by Development. In this context, IFN- τ ought to be considered as an ideal particle which supports this concept. Firstly, we may place it in the family of cytokines (paracrine action, specific IFN-receptor recognition, JAK/STAT signal transduction pathway induction) belonging to type I IFN (antiviral potency, intronless gene structure, IRF-1 induction): these features correspond to the immunological counterpart of the marriage. Secondly, IFN- τ may be designated as a reproductive hormone (regulation of estrogen and oxytocin receptor expression, modulating prostaglandin production): properties characteristic of the reproductive counterpart. Thirdly, this IFN is produced by the developing embryo in the restricted time-frame around implantation, which indicates its transient control of the developing embryo. For all these reasons this cytokine is recognized as a potent tool in limiting early embryo mortality²⁶ and increasing reproductive performance in ruminants. Its immunomodulatory properties, cross-species activity and low cytotoxicity may prove very useful in human and animal medicine.

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