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Local action of cytokines and immune cells in communication between the conceptus and uterus during the critical period of early embryo development, attachment and implantation – Implications for embryo survival in cattle: A review

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ABSTRACT

Early embryo development, implantation and pregnancy involve a complex dialogue between the embryo and mother. In cattle this dialogue starts as early as days 3–4 when the embryo is still in the oviduct, and it continues to implantation. Immunological processes involving cytokines, mast cells and macrophages form an important part of this dialogue. Amongst the cytokines, interleukin-6 (Il-6) and leukemia inhibitory factor (LIF) are secreted by both the embryo and uterine endometrium and form part of an ongoing and reciprocating dialogue. Mast cells and macrophages populate the uterine endometrium during embryo development and are involved in achieving the correct balance between inflammatory and anti-inflammatory reactions at the uterus that are associated with embryo attachment and implantation. Embryo loss is the major cause of reproductive wastage in cattle, and livestock generally. A deeper understanding of immunological processes during early embryo development will help to achieve the next step change in the efficiency of natural and assisted breeding.

1. Introduction

In cattle, embryo loss between fertilization (zygote) and day 45 of gestation is the major cause of reproductive wastage [1–14]. Fertilization rates in cattle (beef and dairy) are in the order of 85–95%; however, 40–50% of embryos do not establish a pregnancy [11–13,15,16]. Most embryo loss occurs between days 0 and 7 (25–30%), days 8 and 14 (10–20%), and days 15 and 21 (5–10%) [8,17–19] (Fig. 1). The range in embryo losses from zygote to day 45 is partially explained by the greater loss in high-producing dairy cows compared with beef cows [19] and it can also be explained by differences in conditions between studies. Embryo losses for *in vitro* produced cattle embryos are in the order of 60–70% [16,20]. Whilst the contribution of embryo loss to reproductive wastage in cattle has been known for more than 40 years, little progress has been made in reducing the loss of embryos. The refinement of methods to produce and evaluate both *in vivo* and *in vitro* derived embryos has only marginally improved pregnancy rates in cattle [21–29].

High embryo loss is not unique to cattle and occurs in other important livestock including buffaloes [30], goats [31,32], pigs [33] and sheep [31]. The failure to make meaningful progress in improving embryo survival in livestock can be explained by insufficient knowledge regarding the cellular and molecular events during the pre-implantation period [34]. Recent reviews on conceptus development, attachment, and implantation have summarized the role of cell-cell adhesion molecules [11,35], interferon tau (IFN-τ) [12,35–40], kisspeptin [13] and exosomes/extracellular vesicles [41–49]. It is abundantly clear that ongoing communication between the conceptus and uterus is fundamental to implantation and pregnancy [34,38,50]. The success, or failure, of this communication occurs against a background of estrogen and progesterone priming [51–53]. The latter relies on a functional corpus luteum [54–56]. Priming by estrogen and progesterone prepares

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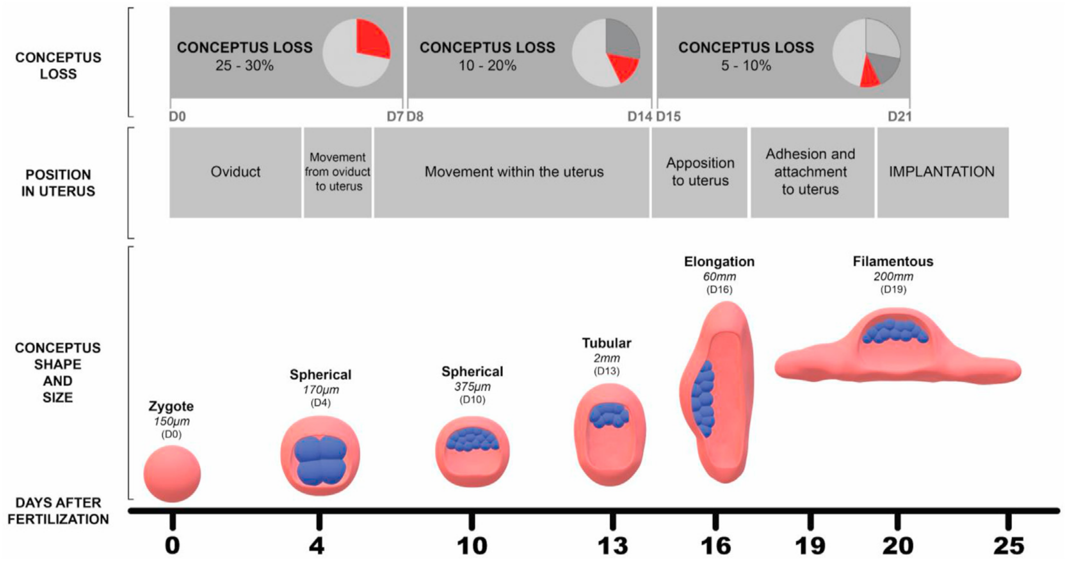

Fig. 1. Early embryonic development and embryo loss in cattle. The red in the pie charts in the upper panel represents the percentage embryo loss at different stages.

the uterus to respond to signals emanating from the conceptus, and it also enables the uterus to engage in crosstalk with reciprocal signals that impact the conceptus [56].

Communication between the developing conceptus and uterus is necessary for successful implantation and pregnancy in livestock [34,37,57–63]. In cattle, communication between the oviduct and embryo begins as early as day 3–4 when the conceptus is still in the oviduct [64]. The conceptus produces IFN-τ from days 3–4 of development [65,66] with increased production from days 7–8 [12]. IFN-τ is a Type I interferon (cytokine family) and it initiates a sequence of events at the uterus [12,67–69] and systemically [70] that are associated with the maternal recognition of pregnancy. The latter prevents rejection of the conceptus in a semi-allogeneic, quasi-allograft manner [farm animals, [71–74]; humans [75–78]]. It also facilitates attachment of the conceptus to the uterine endometrial epithelium to commence implantation [12,13]. Modulation of the maternal immune response to the conceptus is a particularly important component of the maternal recognition of pregnancy [65,66,72,79–87]. As noted by Khatib and Gross [10] the uterus has remarkable plasticity in gene function and signals from the conceptus can have a major impact on the expression of immune-related genes in the uterus. The degree of maternal immune modulation during implantation is likely to differ for species with invasive placentation (humans, rodents) [88,89] compared to species with less-invasive placentation (ruminants, pigs) [13,34,59,90–95]. Cattle are recognized as a 'late-implanting' species and the conceptus moves within the uterus and undergoes notable elongation during the pre-implantation period [96–100]. This contrasts to 'early-implanting' species such as humans and rodents. Elongation of the trophoblast in cattle ensures maximum contact with the endometrium, and specifically caruncles which form the diffuse placenta in cattle [101–106]. Hence, in cattle, communication between the conceptus and uterus occurs over an extended period before implantation and it can be assumed that this includes an immune dialogue. This could make the immunology of early embryo development and implantation in cattle particularly important.

It is apparent that immune-related processes before and during implantation are integral to the establishment of a pregnancy [89,107,108]. The present article provides an immunological perspective on conceptus-maternal communication and looks at the implications in cattle. The focus is on cytokines and immune cells within the oviduct and uterus during the critical period from fertilization to attachment of the trophoblast to the uterine epithelium. Cytokines and immune cells have been looked at separately in previous articles and it was considered useful to bring this field together in a single article. A goal of the present article is to build on other recent papers which have sought to raise awareness of the complexity of conceptus-maternal interaction during the pre-implantation period in cattle [11–13]. A deeper understanding of the molecular and cellular features of early embryonic development and implantation/placentation is needed before a step change can be made in the efficiency of natural and assisted breeding in cattle.

2. Biology of cytokines

The cytokines are a very large group of signaling molecules that comprise the following families: interleukins, interferons, chemokines, colony stimulating factors, mesenchymal growth factors, and tumor necrosis factors [109,110]. Cytokines are divided into functional classes that include lymphocyte growth factors, pro-and anti-inflammatory molecules, and cytokines that direct the immune response to antigens. Cytokines were initially thought to exclusively influence immune cells. For example, when first isolated, the cytokine interleukin-6 (IL-6) was shown to induce human B-cell differentiation and antibody production [111,112]. A second cytokine, leukemia inhibitory factor (LIF), was initially shown to induce macrophage differentiation in mouse leukaemic cells [113]. The cytokines IL-6 and LIF are specifically mentioned as these were subsequently shown to have important roles in reproduction [114–117]. The fundamental role of the cytokine IFN-τ in early embryonic development and implantation, which is noted above, has been extensively reviewed [12,40,54,68,84,118–123]. It could be argued that the cytokines IL-6 and LIF have lesser roles compared with IFN-τ; nevertheless, IL-6 and LIF are still highly important for normal embryonic development and pregnancy. Cytokines influence almost all cell types and are termed pleiotropic and a single cytokine can affect the activity of many different cells [109]. Cytokines have been considered as analogous to 'hormones'

[109]. However, an important distinction between classical hormones and cytokines is that whilst each hormone acts at specific target cells and tissues, cytokines act broadly at many different cells and tissues.

2.1. Interleukin-6 (IL-6) cytokine family

The interleukin-6 (IL-6) cytokine family, in particular, is involved in early embryonic development and implantation [115–117,124–127] (Fig. 2). The IL-6 family comprises IL-6, IL-11, IL-27, leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), cardiotrophin 1 (CT-1), cardiotrophin-like cytokine (CLC) and new neuropoietin (NPN) [128,129]. These cytokines are grouped as one family based on their common binding to the receptor gp130 which links the cytokines to the JAK/STAT3 intracellular signal transduction pathway [112,130–135]. A functional JAK/STAT3 pathway was shown to be necessary for development of the inner cell mass in bovine embryos [136–138] and for trophoblast implantation in women [139,140]. Interleukin-6 first binds to the membrane IL-6 receptor (IL-6R) which complexes with a homodimer of gp130 receptor which provides the intracellular signal transduction pathway [128,131,141]. For cells that do not have IL-6R, IL-6 can first bind to a solubilized form of IL-6R (IL-6SR), which then complexes with a homodimer of gp130 receptor [128,130,135]. The direct binding of IL-6 to cells with IL-6R is termed ‘IL-6 classic signaling’ and indirect binding through the IL-6SR is termed ‘IL-6 trans signaling’ [133]. The functional significance of IL-6 classic and trans signaling is that it is thought to explain how IL-6 can have both inflammatory and anti-inflammatory activities [133]. Leukemia inhibitory factor binds to a membrane LIF receptor (LIFR) which complexes with a heterodimer of gp130 receptor for intracellular signal transduction [130,131,133].

2.1.1. Leukemia inhibitory factor (LIF)

Leukemia inhibitory factor (LIF), first characterized in 1987 [113], has been described as the most pleiotropic of the IL-6 cytokine family [142]. In mice, *LIF* expression was shown in preimplantation blastocysts and the trophectoderm [143,144] (Fig. 2). *LIF* expression was also found in uterine endometrial glands on day 4 after mating in mice, immediately before the commencement of implantation [145]. It was subsequently demonstrated that female *LIF* knockout mice were fertile, but blastocysts failed to implant [146–148]. Disruption of the LIF receptor (LIFR) in mice was associated with abnormal development and perinatal death [149]. These findings in mice provided the first evidence that LIF has an essential role in early embryonic development and in the modulation of endometrial function during implantation and placentation [95,116,125,150–153]. Female mice lacking the IL-11 receptor also cannot support implantation [152,154].

In pigs, *LIF* and *LIFR* expression in the uterine endometrium fluctuated during the estrous cycle with expression elevated during late diestrus [155]. *LIF* and *LIFR* expression by pig endometrium was also elevated at days 11–12 of embryonic development [156]. Levels of LIF protein in the uterus of sows were elevated at days 7–13 of the estrous cycle and at day 12 of gestation [157]. In sheep, the highest *LIF* expression by the endometrium was observed at days 16–20 of gestation [158] and LIF protein was found in day 17 sheep blastocysts [158]. These studies in pigs and sheep provided strong evidence that LIF is involved in conceptus-endometrium communication in livestock. The addition of human LIF (hLIF) to cultured sheep embryos increased blastocyst hatching *in vitro* and the pregnancy rate after embryo transfer [159]. Similarly, in cattle, hLIF increased blastocyst development and the capacity of embryos to tolerate cryopreservation [160,161]. In addition to cattle and humans, the inclusion of LIF in IVF culture media was reported to be beneficial to embryo development in mice, goats, pigs and sheep [162].

2.1.2. Interleukin-6 (IL-6)

As noted, interleukin-6 (IL-6) was initially described as a T-cell soluble product that induced B-cells to produce IgG antibodies [163,164]. IL-6 was first named B-cell stimulatory factor-2 [111,112] and later recognized as IL-6 based on its broader actions beyond

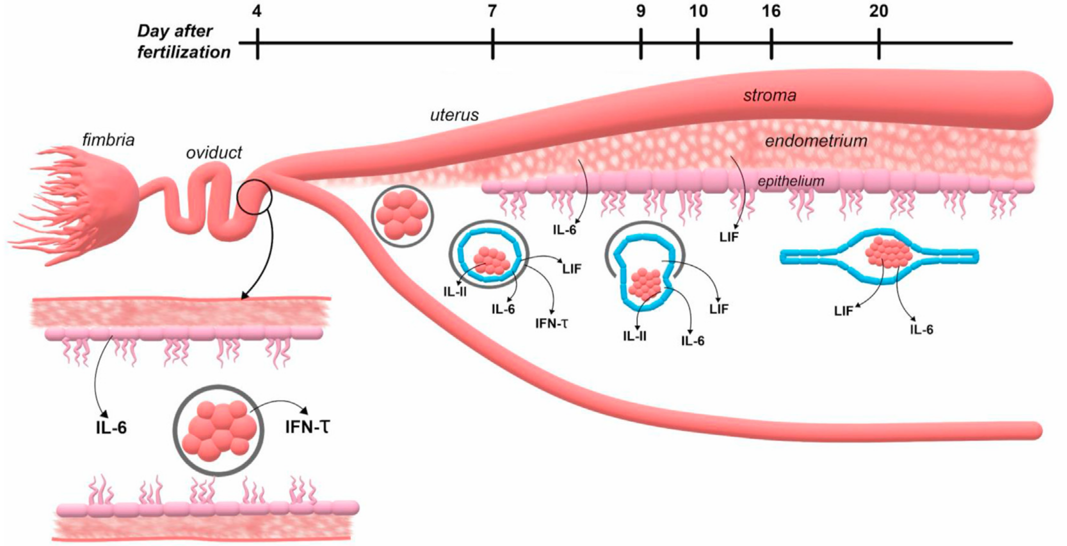

Fig. 2. Schematic representation of cytokine communication between the conceptus and uterus during early embryonic development, attachment, and implantation, in mammals. The timeline used is for cattle. The oviduct initiates crosstalk by secreting IL-6 which, in part, stimulates the early embryo to release IFN-τ. As the conceptus grows and develops to form the trophoblast it additionally secretes IL-6, IL-11 and LIF. During this period the uterine epithelium and endometrium release IL-6 and LIF. Attachment of the trophoblast to the uterine epithelium relies on a balance of pro-inflammatory and anti-inflammatory activity within the uterus. This balance is provided by the relative amounts of IFN-τ and IL-11 (anti-inflammatory) and IL-6 and LIF (pro-inflammatory). The diagram draws on published information [5,99,100,117,172]. INF-τ, interferon-tau; IL-6, interleukin-6; IL-11, interleukin-11; LIF, leukemia inhibitory factor.

just regulating B-cells [163–165]. Among the wider actions of IL-6 are its pro- and anti-inflammatory properties [133,166,167]. The control of inflammation requires a transition from innate immunity (acute, nonspecific immune response) to acquired immunity (specific, with antibodies to an antigen) [168]. IL-6 can participate in the switch from innate to active immunity by controlling leukocyte recruitment, activation and apoptosis [168]. The action of IL-6 in regulating inflammation is particularly relevant to changes at the uterus in conjunction with trophoblast attachment and implantation [89,169]. The bioavailability of IL-6 in early gestation is finely balanced in order to ensure that uterine inflammation is a precisely controlled and time-bound event [169]. The source of IL-6 during early gestation includes the uterine endometrium and uterine macrophages [170,171].

In pigs, *IL-6* receptor (*IL-6R*) and *gp130* receptor expression was increased in both uterine endometrium and the conceptus from day 12 of gestation [171]. *IL-6* expression by the endometrium did not differ between control sows and sows at day 12 of gestation but was greater in sows from day 30 of gestation [171]. In other studies *IL-6* expression was found to occur in day 11–17 pig conceptuses that were transitioning from a spherical to filamentous stage [156,172]. *IL-6* expression was also demonstrated in elongating conceptuses in sheep and cattle [172]. In a study in cows that utilized abattoir-sourced tissue, *IL-6* expression by the endometrium did not differ during the estrous cycle [173]. Further studies on *IL-6* expression are needed in cattle to clearly define the biology of IL-6 in early gestation. The present consensus would be that IL-6 communication between the trophoblast and uterine epithelium/endometrium is a necessary process during attachment and implantation [140,174].

The action of IL-6 during early embryonic development has also been studied *in vitro*. The inclusion of IL-6 in mouse embryo culture increased the number of blastocyst cells and the size of the inner cell mass (ICM) and, also increased blastocyst hatching [175]. Similarly, IL-6 enhanced the number of ICM cells in cattle embryos [138–137] and facilitated the development of pig parthenogenetic embryos [176].

3. Immune cells

3.1. Mast cells

Immune cells that have been shown to have an important role during implantation and placentation include mast cells and macrophages. Mast cells originate from progenitor cells (CD34$^+$/c-kit$^+$ cells) in bone marrow and are transported in blood to become localized in mucosal and epithelial tissues [177–181]. Tissue-localized mast cells mature under the local control of cytokines and growth factors [178,179,182]. Mast cells are primarily involved in innate and acquired immune immunity, and inflammation [183,184]. Inflammatory mediators in mast cells, which are stored in numerous cytoplasmic granules, include histamine and cytokines which have been implicated in implantation [123,181,183,185–189].

Interleukin-6 was shown to increase cytokine production by human mast cells by sensitizing the mast cell receptor FcϵRI to stimulation by IgE antibody from B cells [135,190]. Cytokines produced by human mast cells include IL-6 [191,192]. As noted, IL-6 is a pro-inflammatory cytokine and mast cells are thought to participate in the precisely controlled, and time-bound, inflammation that is associated with implantation and placentation [94,193–197]. An early study in rats and mice questioned whether mast cells had a role in implantation in murid rodents, as compared with humans [198]. It was subsequently reported that the number of mast cells in the uterine endometrium in rats increased at day 5 of gestation (implantation) which led to the suggestion that mast cells facilitated implantation [199,200]. Mast cells are localized in the uterine endometrium in cattle [201,202] and humans [203] and are considered to have a role in implantation. In cattle, mast cells in the endometrium are modulated by estradiol and progesterone [204] and increase during the peri-implantation phase [202]. Estradiol and progesterone also influence mast cell number and maturation in mice [205] and rats [206].

3.2. Macrophages

Macrophages are leukocytes that express the receptor CD14$^+$ [207,208]. Tissue-localized macrophages originate from fetal stem cells and from blood monocytes [209–213]. Tissue macrophages form a distributed phagocyte cellular system [212] and they also regulate local innate immunity [213]. Macrophages additionally have an important local trophic role through the secretion of cytokines and growth factors [214]. In the uterus, macrophages are localized in the endometrium, in close apposition to epithelial cells, and participate in trophoblast-maternal communication and in remodeling of the uterus in preparation for implantation [215–219].

Macrophages can specialize to have an inflammatory or anti-inflammatory action as a result of differential cytokine secretion profiles [220]. The shift from an inflammatory to anti-inflammatory action of macrophages during the peri-implantation phase is partly directed by CD4$^+$ regulatory T cells (Tregs) recruited to the uterus during early gestation [221]. Evidence for Tregs-macrophage cooperativity during implantation has come mainly from studies in humans and rodents [89,222]. Regulatory T cells can also directly regulate uterine inflammation and promote maternal immune tolerance, independent of CD14$^+$ macrophages [89,223]. The regulation of inflammation involves a divergence of Tregs to the Th1-type (produce pro-inflammatory cytokines) or Th2-type (produce anti-inflammatory cytokines). IL-6 can influence the differentiation of naïve CD4$^+$ Tregs into Th1-type (IL-6 inhibitory) or Th2-type (IL-6 stimulatory) [170,224,225]. Aberrant Tregs functionality in early gestation is associated with recurrent pregnancy failure in women [89]. The administration of Tregs at day 0 of gestation to mice prone to abortion increased uterine mast cells and angiogenesis, and reduced fetal mortality [226]. In sheep, hepatic *IL-6* expression was decreased at days 13 and 16 of gestation and it was suggested that changes in liver Tregs is part of the systemic maternal immune response to the conceptus in sheep [227]. Recent evidence in cattle and other ruminants suggests that changes in Th1 and Th2 cells in blood during early gestation are also part of the systemic immune response to the conceptus [70,73]. Natural killer cells (NK cells) are additionally recruited to the uterus in early gestation and infiltrate the decidua during the peri-implantation phase along with Tregs [228–232].

In cattle, there were notable increases in the number of CD14$^+$ macrophage cells and dendritic cells in the endometrium at days 7–13 of gestation [233,234]. CD14$^+$ macrophages were reported to also be present in the endometrium in cows at later stages of gestation [235]. Unlike humans and rodents, there was no evidence of CD4$^+$ regulatory T (Treg) cell activity in early gestation cattle, and it was suggested that macrophage-derived cytokines represented the predominant maternal immune mechanism in cattle [233]. In an earlier study in cattle, neither CD14$^+$ macrophages nor CD4$^+$ T lymphocytes in endometrium showed any change at day 16 of gestation [236]. It therefore remains unclear whether CD4$^+$ cells in endometrium undergo notable changes during the estrous cycle in cattle [81,237]. Natural killer (NK) cells have also been shown to participate in immune mechanisms associated with conceptus-maternal communication in cattle [238]. As a precautionary note, the bulk of information on the involvement of immune cells including macrophages, Tregs and NK cells in implantation has been obtained mainly from studies in humans and rodents that have invasive hemachorial placentation [196,239]. Further comparative studies are needed to establish the role of these immune cells in livestock that have non-invasive synepitheliochorial placentation (ruminants, pigs) [108,240]. In addition to actions at the uterus, macrophages were reported to also influence the structure and function of the corpus luteum in cattle [240–242] and mice [243].

4. Uterine and conceptus transcriptome and proteome

Transcriptomics and proteomics are broad fields and outside the scope of the present review. These fields are nevertheless relevant when building a broader understanding of early gestation and a general overview is therefore provided. Details can be found in the papers cited. The complexity of immune mechanisms in early embryo development and implantation led, in part, to studies on the transcriptomes of the uterus and conceptus in early gestation in cattle [98,234,244–261] and other ungulates [262]. Changes in endometrial CD14$^+$ gene expression in early gestation were reported in several studies in cattle [233,235,236,238]. Also in cattle, endometrial gene expression differed between low and high fertility heifers and cows [8,246,263–266]. There were also differences in gene expression by endometrium exposed to age-matched bovine conceptuses that differed in size [267] and bovine conceptuses that differed in size at day 15 of gestation themselves differed in gene expression [268]. Gene expression differed for caruncular and intercaruncular endometrium in heifers and cows [269]. The proteome of uterine fluid and endometrium around the time of implantation has provided further information on conceptus-maternal communication in cattle [248,249,270,271]. Transcriptome and proteome studies typically identify a relatively large number of differentially expressed genes/proteins and it can be uncertain whether the transcriptome demonstrates correlation as opposed to causality [10]. Notwithstanding, the transcriptome can be used to inform the design of knockout and knockin studies that test the role of a specific gene and sets of genes. The next phase of gene manipulation studies will no doubt be accelerated by the availability of the CRISPR-Cas9 gene editing platform in livestock [272–278]. The use of *in vitro* culture of endometrial and oviductal explants and conceptuses to study the transcriptome and proteome can add to information on conceptus-oviductal and conceptus-endometrium communication in cattle [65,279–286].

5. Seminal plasma, sperm and uterine immunoregulation

The contribution of seminal plasma and/or sperm to the uterine inflammatory response at mating has been recognized for about 60 years in cattle [287–289]. There is renewed interest in this area in line with attempts to increase the efficiency of assisted breeding in cattle [290–292]. In mice, the composition of the seminal plasma includes cytokines (e.g. IL-6) which are thought to influence the recruitment of CD45$^+$ leukocytes to the uterus and their incorporation into the epithelium [293,294]. Bull seminal plasma also contains cytokines (IL-6, IL-10) which could be presumed to have an immunoregulatory function in the uterus [295]. In one study, day 7 *in vitro* blastocysts transferred to crossbred beef heifers that had been mated to a vasectomized bull at estrus produced a longer conceptus at day 14 (7 days after transfer) compared with blastocysts transferred to unmated heifers [296]. It was concluded that exposure to seminal plasma at mating induces a uterine environment that is supportive of embryo development in cattle [296]. In different studies, bovine seminal plasma both increased [297] and decreased [298] *IL-6* expression by endometrial explants [299].

Bovine seminal plasma and sperm increased the expression of both inflammatory (*IL-6, IL-8*) and anti-inflammatory (*IL-10*) cytokines by endometrial and oviductal epithelial cells in culture [300–303]. Seminal plasma was additionally reported to decrease the general viability of bovine endometrial epithelial cells in culture [304]. In other *in vivo* studies, the expression of *IL-6* and *IL-8* in the uterus and oviduct did not differ between crossbred beef heifers 24 h after mating by entire and vasectomized bulls [305], and the intrauterine infusion of seminal plasma at the time of AI did not increase the pregnancy rate in lactating Holstein cows [306]. It can be concluded from the above studies that further research is needed to establish the immunoregulatory role of seminal plasma and/or sperm during early embryo development and implantation in cattle.

6. Summary

The term 'embryokines' has been used to describe the mix of chemokines, cytokines and growth factors that are secreted by the oviduct and uterus during early embryo development and implantation [307–309]. 'Embryokines' is only partly correct as factors produced by the uterus impact both the conceptus and the uterus itself. Cytokines have a particularly fundamental role in regulating the balance of pro-inflammatory and anti-inflammatory actions that prepare the uterus for implantation. This review has

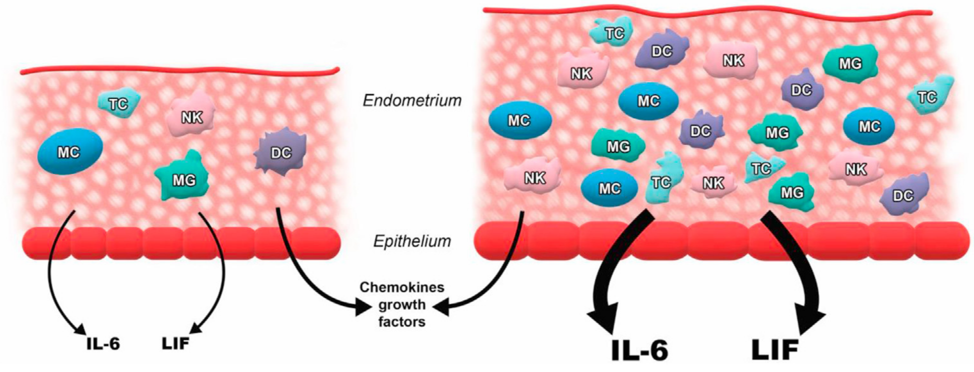

Fig. 3. Schematic depiction of changes from a non-pregnant uterus (left) to early gestation uterus (right). The changes include an increase in size of the uterine epithelium and endometrium and the infiltration of mast cells (MC), macrophages (MG), natural killer cells (NK), dendritic cells (DC) and regulatory T cells (Tregs, TC). A further change is increased production of interleukin-6 (IL-6) and leukemia inhibitory factor (LIF). The depiction is a mosaic of information obtained for different species and is not meant to represent any single species.

highlighted IL-6 and LIF but, as evident in the papers cited, there are clearly other cytokines and different factors that determine the course of early embryo development and implantation. 'Embryokines' are partially produced by mast cells, macrophages and natural killer cells that populate the uterine endometrium in early gestation (Fig. 3). The immunology of pregnancy is complex and differs for invasive hemachorial placentation and non-invasive synepitheliochorial placentation. Cattle are recognized as 'late-implanting' which means that for around three weeks the conceptus could be considered vulnerable before it attaches to the uterus and establishes a pregnancy. A deeper understanding of the immunology of the pre-implantation period in cattle is therefore required. It could be argued that the lack of information in this field is a major reason for the failure to make any meaningful progress in reducing early embryo loss in cattle, both in natural mating and assisted breeding.

7. Conclusions

The transfer of *in vitro* produced cattle embryos to the oviduct of sheep for a transient period increases embryo quality, particularly with respect to survival after cryopreservation, and results in a higher pregnancy rate after transfer to recipients [281,310,311]. This is clear evidence that factors in the female reproductive tract support early embryonic development. The present paper has highlighted the cytokines IL-6 and LIF but there are many other factors involved. In cattle, the embryo enters the uterus at days 4–5 of gestation and the uterus secretes cytokines and other factors that impact the conceptus and prepare the uterine endometrium for implantation. Differences among cows (beef and dairy) in uterine ability to support early embryo development and implantation [19,312,313] could be partly due to differences in conceptus-maternal immune communication. The *in vitro* production of embryos will continue to increase rapidly in cattle given the global demand for animal source protein, and the need to balance adaptation with efficiency of production in cattle. The next step change in assisted breeding in cattle will depend on a deeper understanding of conditions within the reproductive tract that optimize the survival of embryos, and which facilitate implantation and the establishment of pregnancy. This paper has argued that the immunology of early embryo development and implantation is one area that needs to be better understood in cattle. It is conceivable that a deeper understanding of the immunology of embryo development could lead to treatments that induce an immunological environment that is favorable to embryo survival and pregnancy in cattle.

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