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The interleukin-6 cytokine system in embryonic development, embryo-maternal interactions and cardiogenesis.

Abstract

Various biological systems originating in the embryo and the mother are involved in embryo development, embryo implantation, maintenance of pregnancy and the protection of the embryo against external influences, namely the immune, endocrine, and the endothelial system. Cytokines, a large group of soluble

proteins and peptides modulating cellular and extra cellular processes, enable the exchange of information between the systems.

Full text

EARLY EMBRYONIC DEVELOPMENT

A correctly developing preimplantation embryo is one prerequisite for successful implantation. Adjustment between the maternal immunological and endocrinological responses is considered to have potentially important influences on the production of cytokines and growth factors by early embryos. These cytokines may act in an autocrine fashion, similar to their pleiotropic effects on the immune system and other tissues, or may act on the endometrium, taking part in the maternal recognition of pregnancy.

IL-6 (reviewed in [6]) is known to be produced by cultured mouse blastocysts [7], by human oocytes as well as by one to eight-cell human embryos [8]. During the early phase of mouse development, IL-6 mRNA is differentially expressed and translated into a mature protein [9], indicating the involvement of IL-6 in the growth and differentiation of the preimplantation mouse embryo. In the human, IL-6 has been shown to be expressed in the blastocyst [10] and to be of trophoblastic origin [11, 12]. Other studies of IL-6 mRNA expression were performed on preimplantation embryos of farm animals [13]. By flushing out the uteri at different days of pregnancy during the elongation and attachment stage of embryonic development, IL-6 mRNA was demonstrated in elongating preimplantation conceptuses of pregnant pig, sheep and cattle [13].

One of the most notable activities of IL-6 cytokines, from an embryonic developmental point of view, is the coincidental expression of LIF in the murine uterine endometrial glands of pregnant mice with the onset of blastocyst implantation [14, 15], indicating its necessity for the implantation process. LIF promotes preimplantation development of mouse embryos *in vitro* [16]. In the early embryo, LIF mRNA has been found in murine morulae and blastocysts [7, 17, 18] and in bovine embryos derived *in vitro* or *in vivo* [19]. However, contradictory data exist about the LIF gene in human embryos. Transcripts for LIF could neither be detected in human blastocysts by Charnock-Jones and colleges [20] nor by Sharkey and co-workers [10], in any embryonic stage studied from the two-cell- to the blastocyst stage. In contrast to this, in a more recent study by Chen and

colleagues [21], the detection of LIF mRNA in human preimplantation embryos has been reported. Taken together, LIF may affect embryo development at stages before implantation in an autocrine or paracrine way. Suggestive of a paracrine coupling between embryonic cell types is the complementary expression pattern of LIF and its receptor. LIF mRNA has been detected in differentiated trophoectoderm of mouse blastocysts, but not in the pluripotential inner cell mass, whereas LIF receptor (LIF-R) mRNA is present in the inner cell mass but not in trophoectoderm [18]. This is in line with earlier results of Conquet and Brulet [17], which suggest that LIF synthesis takes place in the extraembryonic part of the mouse embryo, and has an effect on embryonic tissues during early development.

Further data showed, that LIF-R- and gp130 mRNA were expressed in the murine blastocysts stage, but not in 1- or 2 cell stage embryos [18]. However, in the human preimplantation embryo LIF-R mRNA was found in oocytes, in 2-, 4-, 8-, 10 cell stage embryos, in cavitating, expanded and hatched blastocysts; gp130 mRNA was present in oocytes, 4-cell stage and expanded blastocyst stage embryos [22]. Recent data by Chen and colleagues [21] confirmed the presence of LIF-R mRNA in human preimplantation embryos at various stages of development, whereas the IL-6 receptor (IL-6R), likewise IL-6, were preferentially transcribed in blastocysts [10]. Studies on farm animals demonstrated gp130 transcripts in bovine embryos [19] and LIF-R mRNA expression in early pig and cow embryos [19, 23]. In cattle, gp130 mRNA was detected from the morula to the hatched blastocyst, while no LIF-R transcripts were observed at the morula to blastocyst transition [19], indicating that in farm animals individual members of the IL-6 system do not have the same essential physiological role during preimplantation development as in the human. It becomes clear that transcription of LIF-R and gp130 takes place in the murine and bovine embryo in a stage specific manner and in the human embryo throughout preimplantation.

The data presented here show dynamic and stage-specific expression patterns, which are consistent with the regulatory role for cytokines, both in the maintenance of pluripotency in the early embryo, and in the development of the embryo-maternal dialogue.

EARLY EMBRYO-MATERNAL COMMUNICATION

Implantation is dependent on the complex interactions between the developing blastocyst and the receptive endometrium. A remarkable number of data showed that soluble growth factors of maternal origin have direct effects on the early embryonic development, establishing the bi-directional maternal-embryonic communication.

The follicular fluid provides the surroundings in which the oocyte matures, and by which fertilization and early embryonic development is affected. IL-6 [24, 25], IL-11 [26, 25] and LIF [27] are present in human follicular fluid. Considerably higher IL-6 levels were found in follicular fluid as compared to serum, IL-11 was absent in serum but present in follicular fluid, in either case supporting the notion of intrafollicular production of these two cytokines. Concerning the amount of LIF in follicular fluid, it was shown to peak around ovulation [28]. LIF mRNA and LIF protein are expressed by granulosa and stromal cells which suggests a role for LIF in oogenesis and early embryogenesis in humans.

Numerous studies have been performed *in vitro* to determine the concentrations of cytokines either released from the human embryo itself or from maternally-derived cells. IL-6 activity was found in conditioned medium from oocytes and one to eight-cell embryos. Hence, IL-6 seemed to be present at all stages from the oocyte to the early cleaving embryo [8]. In a more recent study, IL-6, but not IL-6R, could be detected in embryonic culture medium. Levels of IL-6 were significantly higher in medium from the first 24 hour period than from the second 48 hour culture period [29]. In contrast, IL-6 levels remained undetectable in 24 hour embryo culture-conditioned medium in a different study by Baranao and coworkers [30]. Thus, the significance of IL-6 in the regulation of human embryonic development remains unclear. After all, apart from the embryo, non-embryonic cells such as granulosa, cumulus and sperm cells may also contribute to the IL-6 release into the medium.

Regarding the maternal response to early embryonic development, uterine stromal and uterine epithelial cells were looked at to determine their ability to secrete IL-6. IL-6 belongs to a group of epithelial cell-derived cytokines in the preimplantation uterus [31]. Vero cells, an African green monkey epithelial cell line, have been reported to synthesize IL-6 [32-34]. Human endometrial stromal cells also secrete IL-6 [35], but in our opinion its influence on human embryonic development is not yet fully understood. IL-6 levels were not predictive of a

successful embryo transfer outcome as measured in supernatants of preimplantation embryos co-cultured with a feeder layer of Vero cells [34].

There are considerable data regarding the function of LIF in reproduction [36]. LIF is of particular interest because its expression by the uterine epithelium appears to be mandatory for murine blastocyst implantation. Glandular LIF was found in normal pregnant mouse uteri at day 4.5 of gestation [37, 38]. Maternally-derived LIF was detected as mRNA or protein in the uterus of various species (mink [39], rabbit [40]; pig [41], human [20], mouse [14]). LIF is required for embryo attachment and for uterine decidualization [42]. One mechanism of LIF action in the implantation process could be by directly modulating trophoblast differentiation. Starting from the cytotrophoblast (stem cell of the placenta), the pathways of trophoblast differentiation lead to the development of three differentiated forms of trophoblasts in the human: villous syncytiotrophoblast, junctional anchoring trophoblast and invasive trophoblast [43]. *In vitro* culture studies of human cytotrophoblasts demonstrated biochemical changes characteristic of cytotrophoblast differentiation towards the anchoring junctional phenotype [43].

Since maternal LIF is essential for embryo implantation in mice it may also be the case in humans [44]. Among different members of the IL-6 system investigated (OSM, CNTF, LIF, LIF-R, gp130), LIF was the only one expressed in the endometrium of women with proven fertility [45]. Abnormal expression of LIF or IL-6 in the human endometrium has been suggested to play a role in implantation failure or might be a possible reason for unexplained sterility [44, 46, 47]. IL-6 is weakly expressed in the epithelial endometrium. Unlike IL-6R and gp130, demonstrating no cyclic variability, IL-6 reached peak values during the phase of the menstrual cycle, which is coincidental with the "implantation window" [48].

Animal studies showed, that IL-6 is present in porcine uterine secretions throughout the oestrous cycle and prior to conceptus attachment [41]. Gp130 is present in luminal epithelium of the rabbit uterus, reaching highest values shortly before the time of implantation [40]. In mice, IL-11 signalling at the endometrial implantation site seems to be necessary for decidualization [49], whereas in the human, IL-11 has only been detected in various reproductive tract fluids ([25]: human oviductal fluid, follicular fluid, amniotic fluid, seminal plasma).

In summary, it is suggested that autocrine or paracrine acting cytokines of the IL-6 system play an essential role in maternal-embryonic communication.

LATE EMBRYONIC AND CARDIAC DEVE LOPMENT

Cytokines of the IL-6 system have been demonstrated to affect the growth, differentiation, and function of various cell types, beside those of the immune system (reviewed in [50]). Current knowledge concerning the influence of cytokines on late embryonic development is based on the application of transgenic technology and the generation of knockout mice which provide an ideal technique to elucidate the role of individual members of the IL-6 system.

Knockout mice for IL-6, LIF, or CNTF have been generated, but their phenotypes show much less severe defects than would be anticipated from the widespread effects of these cytokines [37, 51, 52]. This probably reflects the shared use of common gp130 signalling pathways by other gp130-dependent cytokines [53]. In fact, IL-6-deficient mice develop normally [52]. LIF-deficient females are fertile, but display failure in blastocyst implantation and development. However, after transfer into a surrogate mother the blastocysts are viable, implant and develop to term [37], whereas the inactivation of the LIF-R gene results in placental, skeletal, neural and metabolic defects followed by pe-rinatal death [54].

Mice lacking a functional CNTF gene, that has been proposed to take part in the development, survival, and maintenance of neurons and glia in the peripheral and central nervous system, had no defect in the number of motor neurons during embryonic and early postnatal development. But with increasing age the motor neurons degenerated [51]. In mice deficient in both the LIF and CNTF gene, degenerative changes in motor neurons were more extensive and appeared earlier [55].

A previously unrecognised role for IL-11 signalling in implantation has been demonstrated in female mice lacking the IL-11 receptor [56], which are infertile because of defective decidualization.

Embryos with a deficiency in the common IL-6 cytokine signal transducer gp130, exhibit severe ventricular hypoplasia and die between 12.5 *post coitum* and term [57] suggesting a role for gp130-mediated signalling pathways in the development of the ventricular myocardium and haematopoiesis during

embryogenesis. In contrast, ventricular-specific null mutant mice do survive and have normal cardiac structure and function [58].

Multiple animal data showed that the tissue expression of the IL-6 system is fairly ubiquitous, as transcripts and proteins have been found in a variety of different organs of the developing and adult organism [59-63]. Expression studies on members of the IL-6 cytokine system during late embryogenesis are scarce. Northern blot analysis revealed gp130 transcripts in mouse embryos as early as day 6 of pregnancy, with peak values on day 8 followed by a gradual decline thereafter during the remaining embryogenesis [61]. However, IL-6R transcripts were observed first in 8 day-old embryos, reaching a peak on day 10 and gradually declining until day 14. The finding that gp130 mRNA was present in embryos in which IL-6R was absent suggests that gp130 signalling can be compensated for by other gp130-stimulatory cytokines of the IL-6 system. In addition, gp130 appears to affect late embryogenesis by transducing the IL-6 signal *via* the IL-6 receptor as demonstrated by the concomitant expression of gp130 and IL-6R mRNA.

Little is known about the mechanisms underlying the developmental changes occurring during cardiogenesis and maturation of the heart, as the first functional organ in the developing embryo. Cytokines of the IL-6 family are discussed as possible regulators of embryonic heart development [64]. But contrary to our expectations, IL-6, LIF, or CNTF null-mutant mice express no obvious cardiac phenotype. This is in line with results of Hirota and co-workers [58], for gp130-ventricular-specific null mutant mice, which demonstrated that gp130 is not necessary for cardiac growth during normal development. Furthermore, none of these cytokines have been shown to be highly and preferentially expressed in the heart during cardiogenesis.

Recently, two investigations have been performed to detect gp130-mediated cytokines in hearts of murine embryos. As revealed by RT-PCR, LIF mRNA is expressed in hearts from 12, 14, 16 day old embryos, neonatal and adult mice [65]. As demonstrated by immunohistochemistry, CT-1 expression predominates in the primitive heart tube at day 8.5 *post coitum*, while other tissues display background levels of expression [63]. Until day 10.5, the heart tube remains the main tissue expressing CT-1. As the embryo develops, CT-1 protein expression can be detected in other tissues as well [63]. The preferential heart-restricted expression of CT-1 protein during an early stage of

cardiac development, and the detection of LIF mRNA during a later stage of cardiac development indicate that both cytokines are candidates for regulating embryonic heart development.

The discrepancy between the finding of Hirota and coworkers [58], that gp130 is not mandatory for cardiac development, and the potency of the gp130-mediated cytokines CT-1 and LIF as regulators of cardiogenesis reflects, that as well as gp130, other signal transducers might be responsible for heart development.

CONCLUSION

Cytokines of the IL-6 system are important secretory components of the early embryo. As this review has demonstrated, they have been localized in various stages of early and late embryonic development, during which a complex cascade of the IL-6 system network has to be regulated to result in successful implantation (summarized in Table 2). The production of knockout animals has provided a powerful tool with which to understand the developmental function of this regulatory system. Studies on LIF- and IL-11-deficient mice demonstrate that both cytokines may contribute to the embryo-maternal dialogue during the implantation process. In addition, from the data presented we can hypothesize, that CT-1 and LIF are emerging as potent regulators of embryonic heart development. However, further studies such as a more systematic investigation of the temporal and spatial expression of individual members of the IL-6 system *in vivo* are required before the full range of physiological functions of these cytokines in embryonic development can be established.

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Figures

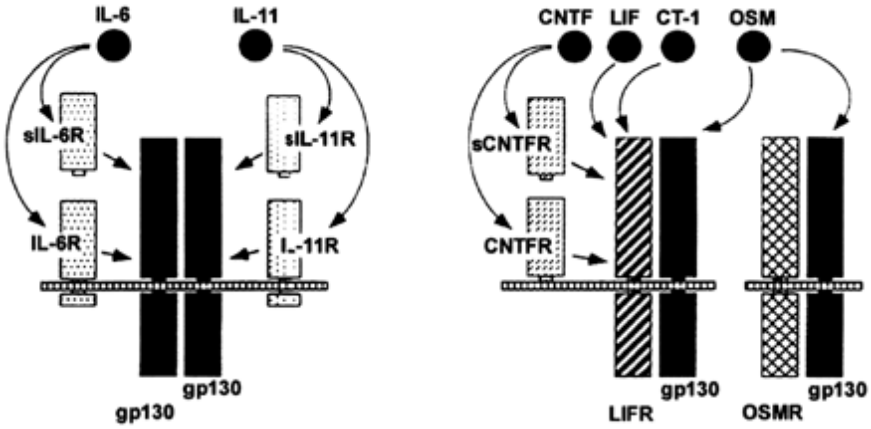


Figure 1

The IL-6 cytokine system.

Receptor complexes associated with gp130. IL-6 binds to IL-6 receptor (IL-6R). The IL-6/IL-6R binding complex then forms a homodimer with gp130. The gp130 homodimer is also utilized in the IL-11/IL-11R complex. LIF binds with low affinity to LIF receptor (LIFR) forming a heterodimer with gp130. Formation of the LIFR/gp130 heterodimer is further induced by the CNTF/CNTFR complex and is also utilized for CT-1 binding. OSM exceptionally binds to gp130 and signals through either LIFR/gp130 or OSMR/gp130 complex. IL-6R, IL-11R, and CNTFR are not necessarily anchored to the membrane. Their soluble forms (sIL-6R, sIL-11R, sCNTFR) can bind corresponding ligands and signal through gp130 [50].

Table 1
Biological effects of the IL-6 family [50]

	IL-6	LIF	CT-1	OSM	IL-11	CNTF
Stem cell pluripotency	No	Yes	Yes	Yes	No	Yes
Cardiac hypertrophy	No	Yes	Yes	Yes	Yes	?
Acute phase protein	Yes	Yes	Yes	Yes	Yes	Yes
Macrophages	Yes	Yes	Yes	Yes	No	No
Myeloma cells	Yes	Yes	n.r.	Yes	Yes	Yes
Haematopoiesis	Yes	Yes	n.r.	Yes	Yes	n.r.
Thrombopoiesis	Yes	Yes	n.r.	Yes	Yes	n.r.
Osteoclast	No	Yes	n.r.	Yes	Yes	n.r.

? = data not conclusive; n.r. = not reported.

Table 2
Summary of the significance of the IL-6 system in embryonic and cardiac development

	IL-6	IL-6 R	LIF	LIF-R	CT-1	OSM	IL-11	IL-11R	CNTF	gp130
Early embryo	Yes	n.r.	Yes	Yes	n.r.	n.r	n.r.	n.r.	n.r.	Yes
Embryo-maternal dialogue	Yes	?	Yes	No	n.r.	No	Yes	n.r.	No	Yes
Late embryo	No	Yes	Yes	Yes	Yes	n.r	Yes	n.r.	Yes	?
Cardiac development	No	n.r.	?	n.r.	Yes	n.r.	n.r.	n.r.	No	?

? = data not conclusive; n.r. = not reported.

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IL-10, recombinant, rat, cytokines.

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