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CYTOKINES IN VERTEBRATE REPRODUCTION

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***Abstract.*—Mechanisms determining survival and growth of the semi-allogeneic fetus in the maternal uterus are still not completely defined. Studies in mammals have shown that soluble substances with autocrine/paracrine action (cytokines) have a central role in the maternal-fetal immunotolerance, thus, contributing to the expansion of fetal tissues in the maternal uterus. We report here about a methodological approach based on analysis of cytokines in reproductive tissues of vertebrates using different reproductive strategies, i.e., placental and aplacental viviparity and oviparity. Most of the studies focused on Interleukin-1 (IL-1), an evolutionarily conserved cytokine with many roles in mammalian reproduction, particularly in uterine receptivity and blastocyst implantation. The presence of IL-1, mainly IL-1β and of its functional membrane receptor IL-1 receptor type I (IL-1R tI) in reproductive tissues of oviparous and viviparous species, suggests that this cytokine is a fundamental mediator of maternal-fetal immunotolerance.**

Key Words.—amphibians; cytokines; elasmobranch fishes; maternal-fetal immunotolerance; oviparity; squamate reptiles; viviparity

VIVIPARITY: AN IMMUNOLOGICAL CHALLENGE

Viviparity is a reproductive strategy usually attributed to mammals. However it is also present in other vertebrates such as squamate reptiles, amphibians, and elasmobranch fishes. Though viviparity is considered a great advantage for nutrition and protection of the embryo, it involves prolonged exposure of the semi-allogeneic fetal tissues to the maternal immune system (Medawar 1953). This is a great risk for the embryo that could be rejected and thus not reach complete maturation. Therefore, viviparity required the development of immunological mechanisms to allow the survival and growth of the fetus in the maternal tissues (Medawar 1953).

Many studies in the last few decades have identified biochemical, molecular, and cellular factors involved in these immunological mechanisms. Although none of them alone provides a complete explanation, together they shed light on the processes that prevent fetal rejection. The proposed mechanisms include (a) the placenta as a barrier separating fetal and maternal blood; (b) the lack of trophoblastic expression of classical major histocompatibility complex (MHC) class I antigens and the expression of HLAG (Kovats et al. 1990); (c) the immunologically privileged nature of the uterus due to the increase in NK cells at implantation (King and Loke 1991); (d) the local release of immunoregulatory peptides or glycopeptides (cytokines) with autocrine/paracrine action at the maternal-fetal interface (Saito 2000).

In this paper we will focus on cytokines and summarize the concepts that make these substances critical mediators of maternal-fetal immunotolerance. We will report on the methodological approaches and animal models that have contributed much to our understanding of the role of cytokines in reproduction. Among the methods used, we will emphasize the evolutionary approach based on the presence of cytokines in non-mammalian vertebrates with different reproductive strategies.

CYTOKINES AT THE MATERNAL-FETAL INTERFACE

Cytokines are proteins or glycoproteins of molecular weight < 100 kDa produced by different cell types, which act as autocrine/paracrine signals by binding to specific membrane receptors (Vilcek and Le 1994). Cytokines are involved in a variety of biological effects including inflammation, immunosuppression, cell differentiation, and cell apoptosis. Therefore, their presence at the maternal-fetal interface may modulate the maternal immune response and contribute to the expansion of fetal tissues in the maternal uterus (Saito 2001; Paria et al. 2002; Schäfer-Somi 2003). In the last two decades, a great number of cytokines have been shown at the maternal-fetal interface, mainly in humans and mice (Moffett and Loke 2006; Chaouat et al. 2007). These include Interferons (IFNs), Interleukins (ILs), Leukemia inhibitory factor (LIF), Tumor necrosis factors (TNFs), Transforming growth factors (TGFs), Colony

TABLE 1. Main cytokines in mammalian reproduction.

Cytokines	Species	References
IFN-α/β/γ	Human	Paulesu et al. 1991
IFN-τ	Ovine	Imakawa et al. 1987
IFN γ	Porcine	Lefevre et al. 1990
LIF	Murine/Human	Stewart et al. 1992; Charnock-Jones et al. 1994
IL-1	Human	Simon et al. 1997
IL-4, 5, 10	Murine	Wegmann et al. 1993
IL-6	Human	Tabibzadeh et al. 1995
IL-11, 12, 13, 15	Murine/Human	Zourbas et al. 2001; Chegini et al. 2002
GM-CSF	Human	Jokhi et al. 1994
CSF-1	Murine	Pollard et al. 1991; Pollard 1997
TNF-α	Murine	Toder et al. 2003
TGF-α/β	Human/Murine	Graham et al. 1992; Das et al. 1997a
VEGF	Rabbit	Das et al. 1997b

stimulating factors (CSFs), Vascular endothelial growth factors (VEGFs), and others (Table 1).

Important studies have established a hierarchy of cytokines secreted at the maternal-fetal interface. Wegmann et al. (1993) first proposed that a prevalence of Th2 cytokines (IL-4, IL-5, IL-10), i.e., those produced by Th2 lymphocytes whose immunity is of the humoral type, rather than Th1 cytokines (IFNγ, IL-2) whose immunity is of the cytotoxic type, is crucial for the success of pregnancy. Albeit the Th1/Th2 paradigm has been the foundation of studies on cytokines at the maternal-fetal interface, it is currently recognised that Th2 cytokines are mainly responsible for the maintenance of pregnancy while Th1 cytokines mainly contribute to the earliest and latest stages of pregnancy characterized by transient local inflammatory reaction (i.e., blastocyst implantation and labor; Chaouat et al. 2007). Yet, although still considered valid, the simple Th1/Th2 cytokines dichotomy now appears too simplistic (Chaouat et al. 2007). In recent years the balance between anti-inflammatory/pro-inflammatory cytokines appears overlapping to that of Th1/Th2. In fact, anti-inflammatory cytokines, such as IL-11 and IL-13, seem to be of prime importance in maintaining pregnancy, and a prevalence of inflammation-associated cytokines (IL-1, IL-12, IL-15) have been demonstrated during implantation and labor (Simón et al. 1997; Zourbas et al. 2001; Piccinni 2005).

Therefore, reproductive processes are based on a complex network of cytokines that can evolve with changes in the cytokine type or concentration. All these molecules work in concert or in sequence, first one or a group and then another or another group. Moreover, cytokines have unique properties including *pleiotropism*: a single cytokine has multiple target cells and produces different responses; *redundancy*: different cytokines act on the same cell type and produce the same responses; and *synergism* or *mutual antagonism*: different cytokines potentiate or inhibit each other's actions. This complex network of cytokines at the maternal-fetal interface makes it difficult to determine the crucial role of single cytokines in specific reproductive events.

METHODOLOGICAL APPROACHES

Most *in vivo* studies have been conducted on mice after administration of cytokines or after ablation or modification of specific genes. For obvious reasons, studies in humans have mainly been performed on tissues or on isolated cells either exposed to exogenous cytokines or treated with specific cytokine inhibitors. Thanks to the complex interaction between cytokines, a new balance is established after removal or addition of one of the cytokines with no apparent consequences. This is true for all the cytokines at the materno-fetal interface with two exceptions: LIF and IL-11 (Stewart et al. 1992; Robb et al. 1998; White et al. 2004). LIF knock-out mice and animals lacking the IL-11 receptor are infertile owing to complete implantation failure and defective decidualization (Stewart et al. 1992; Robb et al. 1998). In humans, the biological roles of LIF and IL-11 are still unknown and data are sometimes contrasting, as in the case of intrauterine LIF in fertile and infertile women (Hambartsolumian 1998; Tsai et al. 2000; Ledee-Bataille et al. 2002).

We think that analysis of cytokines in the whole organs preserving tissue homeostasis could help identifying the real situation. In this context, a physiological approach, performed in the last 15 years (Paulesu et al. 2005, 2008), is based on evolutionary studies in vertebrates using similar or different reproductive strategies including, viviparity, with or without formation of placental structures, and oviparity, with or without egg retention. In all these reproductive strategies, maternal reproductive tissues have to deal with paternal-derived antigens on sperm, fertilized eggs, and embryo. Therefore, there can be cytokine-mediated molecular mechanisms to prevent rejection of the embryo by the mother.

TABLE 2. IL-1 system in reproductive tissues of non-mammalian vertebrates.

Vertebrate class	Species	Tissues expressing IL-1	References
Fishes	*Mustelus canis*	Yolk sac placenta; uterine tissues during gestation.	Cateni et al. 2003
Amphibians	*Salamandra lanzai*	Uterine tissues during gestation.	Jantra et al. 2007
	Triturus carnifex	Oviductal tissues during reproductive season.	Jantra et al. 2007
Reptiles	*Chalcides chalcides*	Chorioallantoic placenta; uterine tissues during gestation.	Paulesu et al. 1995
	Lacerta vivipara	Uterine tissues during gestation, in both viviparity and egg retention, in oviparity.	Paulesu et al. 2005

NON-MAMMALIAN VERTEBRATES: A MODEL FOR THE STUDY OF MATERNAL-FETAL IMMUNOTOLERANCE

Among non-mammalian vertebrates, studies on cytokines in reproduction have been performed in fishes, amphibians, and squamate reptiles (Table 2). In particular, placental viviparity has been investigated in elasmobranch fishes, specifically in the viviparous *Mustelus canis* (Cateni et al. 2003) and in squamate reptiles, namely, the Three-toed Skink *Chalcides chalcides* and the lizard *Lacerta vivipara* (Paulesu et al. 1995; Paulesu et al. 2005b). Aplacental viviparity has been studied in the viviparous amphibian, *Salamandra lanzai* (Jantra et al. 2007) while oviparity has been investigated in oviparous specimens of *L. vivipara* and in the oviparous amphibian *Triturus carnifex* (Paulesu et al. 2005b; Jantra et al. 2007; Table 2).

Studies on cytokines in species different from mammals focused on Interleukin-1 (IL-1), an evolutionarily conserved cytokine with many roles in mammalian reproduction (Simón et al. 1997). IL-1 is in fact one of the pro-inflammatory cytokines mainly involved in the earlier and later stages of pregnancy (Dinarello 1997; Krüssel et al. 2003; Romero et al. 2007). Numerous reports from *in vitro* and *in vivo* studies have shown that the action of IL-1 is fundamental for uterine receptivity and blastocyst implantation (Simón et al. 1994; Simón et al. 1998). Nonetheless, mice lacking the most important components of IL-1 system, IL-1β, or IL-1 RtI have been shown to breed normally (Abbondanzo et al. 1996; Horai et al. 1998). These data further support that the action of single cytokines is expressed in the interplay with the other cytokines and that a cytokine deficiency may result in an alternative pathway. Studies on IL-1 in fishes, amphibians, and reptiles have been possible because of the highly conservative properties of IL-1 components(i.e., IL-1 β and its functional membrane receptor, IL-1R tI). In particular, cloning of IL-1β has been performed in mammals, birds, amphibians, and fishes reflecting the well known phylogenetic relationships within vertebrates (reviewed in Bird et al. 2002; Huising et al. 2004). The IL-1 signaling system is also evolutionarily conserved and contains a highly conserved region in its cytoplasmic domain. Homologous regions have been found in a receptor-like protein of the Drosophila fruit fly, called Toll and in the Toll-like receptors, present in mammals and other vertebrates including amphibians, fishes, and birds (Luo and Zheng 2000; Fallon et al. 2001; Medzhitov et al. 1997; Du et al. 2000; Roach et al. 2005; Purcell et al. 2006; Ishii et al. 2007). The conserved region of the IL-1R/TLR superfamily has been termed a Toll/IL-1R domain.

Studies in non-mammalian vertebrates have shown that IL-1 components, mainly IL-1β and IL-1 RtI, are expressed in the placenta of elasmobranch fishes (Cateni et al. 2003) and in that of squamates reptiles, including the highly specialized chorioallantoic placenta of *C. chalcides* (Paulesu et al. 1995) and the very simple one of *L. vivipara* (Paulesu et al. 2005b). Similarly to mammals, evidence of IL-1 cytokine and receptor was shown in the uterine tissues as well as in the extraembryonic membranes (the yolk sac) in fishes and in the chorioallantois in squamates. Interestingly, IL-1 system components were also shown in the female reproductive tissues of the aplacental viviparous amphibian *S. lanzai.* Similarly, the IL-1 system was present in the oviparous *T. carnifex* (Jantra et al. 2007) and in the oviparous specimens of *L. vivipara* (Paulesu et al. 2005b).

The presence of IL-1 and its specific membrane receptor in reproductive tissues of non-mammalian vertebrates using different reproductive strategies, placental and aplacental viviparity, and oviparity, led us to speculate that oviparous as well as viviparous females are adapted to tolerate the semi-allogeneic embryo by making numerous changes in their reproductive tissues, including the secretion of immunoregulatory molecules, namely, cytokines. In fact, in oviparity as in viviparity, the egg is fertilized inside the female body and paternal-derived antigen-bearing cells such as sperm, fertilized eggs, and developing embryo, are in contact with female reproductive tissues. In this context, the local

presence of cytokines appears to be crucial for preventing maternal immunological attack versus these cells and therefore allowing the reproductive success.

CAN VERTEBRATE STUDIES BE USEFUL FOR HUMAN REPRODUCTION?

Vertebrates with different reproductive strategies appear to be a good physiological model for the study of cytokines in maternal-fetal immunotolerance. In fact, the presence of cytokines in oviparous as well as in viviparous species suggests the importance of these molecules in the immunological mechanisms allowing the tolerance of paternal-derived antigens in female reproductive tissues. These mechanisms seem to be highly conserved from fishes to mammals. Understanding molecular events underlying maternal-fetal immunotolerance might be useful to develop new strategies for the treatment of infertility, new contraceptives, new therapeutic interventions to prevent miscarriage or other pregnancy disorders, and new strategies to improve reproductive technologies.

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Erratum: Technical changes were made to the text which did not alter the meaning of any parts of the manuscript.