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Review

Colony Stimulating Factors 1, 2, 3 and early pregnancy steps: from bench to bedside

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ABSTRACT

Reproductive immunology applies general immunology principles to specialised targets, reproduction and development. The involvement of colony-stimulating factors (CSFs) in reproduction illustrates this. The CSF family includes CSF-1 or macrophage CSF (M-CSF), CSF-2 or granulocyte macrophage CSF (GM-CSF), and CSF-3 or granulocyte CSF (G-CSF). Each member has a specific localisation and timed expression in the reproductive tract with specific functions involving them in ovulation, embryo implantation, placentation and further embryonic development. They are used in reproductive medicine, either as biomarkers of oocyte quality and competence (follicular G-CSF), or to supplement embryo culture media with human recombinant GM-CSF, or they are used as an innovative therapy by using human recombinant G-CSF for infertile patients. Given fundamental considerations on CSFs and their strong implication in reproduction, this review aimed to detail the current knowledge for each member of the family to improve our understanding of their implication in the maternal–foetal cytokinic dialogue and in possibly preventing reproductive disorders.

1. Introduction

The colony-stimulating factor (CSF) family includes: CSF-1 or macrophage colony-stimulating factor (M-CSF), CSF-2 or granulocyte macrophage colony-stimulating factor (GM-CSF), and CSF-3 or granulocyte colony-stimulating factor (G-CSF). CSFs are 18- to 70-kDa labile glycoproteins and act through specific membrane receptors, via JAK-STAT signalling pathways in an endocrine, paracrine or autocrine model (Metcalf, 2010).

These cytokines have been studied since the mid-1960s and were named after their action on the proliferation and differentiation of leucocytes. Their involvement in reproduction was raised from early 1970s, when it was demonstrated, in the mouse and human, that placental media could stimulate haematopoietic cell multiplication (Burgess et al., 1977). Next, higher levels of CSFs were described in the murine pregnant uterus. CSF-2/GM-CSF was then demonstrated by Athanassakis et al. (1987) and Wegmann et al. (1989) to be a growth factor for the placenta, whereas a key role for CSF-1/M-CSF was demonstrated during the same period by Pollard's group (1991). Messenger expression and protein production for these three cytokines and their receptors were further

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identified in the reproductive tract, especially in the ovary and at the maternal–foetal interface. Variations in CSF concentrations, under different reproductive conditions, are also described in serum and follicular fluid, suggesting the use of CSFs as possible predictive biomarkers in reproductive medicine.

In this review we detail what is now known with regard to reproduction for each member and describe the experiments that allowed their immunotrophic, anti-apoptotic and immunomodulatory actions during the early stages of pregnancy to be highlighted.

During the past five years, these cytokines played a large part in innovative therapies in reproductive medicine, particularly for two of them: CSF-2/GM-CSF and CSF-3/G-CSF. We will review their utilisation as biomarkers, their supplementation in embryo culture media to enhance the embryo quality, or their supplementation in different cases of reproductive failure such as dysfunctional ovulation, repeated pregnancy loss and embryo implantation failure.

2. Localisation of CSFs in the reproductive tract

2.1. Ovary: granulosa and follicular fluid

Ovarian CSFs are mostly studied in humans. Each CSF and its receptor are localised in the granulosa at protein and mRNA levels. Concentrations are higher in the follicular fluid than in the serum. Of all of them, follicular CSF-3/G-CSF seems to raise more interest in fundamental research and medical applications (Yanagi et al., 2002; Salmassi et al., 2004).

2.2. Maternal–foetal interface

Colony-stimulating factor activity was traced as early as 1980 in human placenta-conditioned medium and in the 1990s it was found in the human placenta, decidua and endometrium (Croy et al., 1991).

At the maternal–foetal interface, the presence of CSF-1/M-CSF was assessed quantitatively and, while serum levels were enhanced two-fold during pregnancy, the uterine concentration was enhanced 1000-fold, strongly suggesting an important role in gestation (Kauma et al., 1991). This observation was completed in mice by the localisation and temporal expression of the cytokine in endometrium and decidua, coupled with the expression of its receptor in the trophoblast (Arceci et al., 1989; Croy et al., 1991).

At the same time, a direct trophic role was demonstrated for CSF-2/GM-CSF and raised the concept of immunotrophism (Chaouat et al., 1983). The proof of immunotrophism came with the further demonstration that activated T cells secreted soluble factors, including CSF-2/GM-CSF, which acted as growth factors for the placenta (Athanassakis et al., 1987). Probably because of its promoting effects on embryo implantation and embryonic growth in murine abortive models (Wegmann et al., 1989; Chaouat et al., 1990), CSF-2/GM-CSF has been the most frequently studied CSF family member at the maternal–foetal interface. Production of CSF-2/GM-CSF and its receptor was first localised by Robertson et al. (2000) and Kanzaki et al. (1991) in the murine trophoblast and reproductive tract. CSF-2/GM-CSF secretion by uterine epithelial cells was interestingly demonstrated to be maintained in a variety of lymphocyte-deficient mice, establishing the secretion of an immune mediator by non-immune cells in the reproductive tract. Production of CSF-2/GM-CSF and its receptor was also confirmed in the human female reproductive tract (Giacomini et al., 1995). The membrane receptor was identified on endometrial immune cells such as macrophages, granulocytes and dendritic cells (Robertson et al., 2000). Endometrial CSF-2/GM-CSF production was shown to be regulated by oestrogen, progesterone and TGF beta 1.

In approximately the same period, the presence of CSF-3/G-CSF and its receptors in the reproductive tract was also established: in the placenta and the decidua (Saito et al., 1994). In mice, the cytokine and its receptor are shown to be expressed in spongiotrophoblasts and placental labyrinths, as well as in decidua basalis and endometrial epithelium. Likewise, they were detected in human cytotrophoblasts and syncytiotrophoblasts on the placental side, and also on the maternal side, in decidual stromal cells, endometrial glands and epithelium, in addition to local natural killer cells (NKs).

2.3. Seminal plasma

All three CSFs are detected in human seminal fluid at low concentrations, but their interest appears higher in mammalian study models without a cervical barrier such as the mouse or pig, where seminal CSF-3/G-CSF might modulate local cell-mediated immunity and seminal TGF beta 1 appears to be a major regulator of endometrial CSF-2/GM-CSF (Robertson et al., 2006).

3. Functions of CSFs in reproduction

3.1. Ovulation

In mice, Pollard's team took advantage of the total absence of CSF-1/M-CSF described in a macrophage-deficient osteopetrotic mouse model (op−/−) and demonstrated that pregnancy was impaired in such females (1991). Later on, they showed that females had extended oestrus cycles and poor ovulation rates. Interestingly, the systemic administration of CSF-1/M-CSF restored a variety of defects due to the op−/− mutation, but did not restore normal fertility, proving the importance of the synthesis of other CSF members. Studies using a CSF-1/M-CSF transgene showed that transgene expression did indeed correct all the reproductive defects, in addition to allowing more precise evaluation of the site of production (Ryan et al., 2001). In other species, the presence of CSFs in the ovary at the time of ovulation has been traced: in rodents, the cow, the buffalo, the horse, the dog and the hen.

In humans, CSF-1/M-CSF, CSF-3/G-CSF and limited CSF-2/GM-CSF were all found first in the supernatants of cultured ovarian epithelium cells (Ziltener et al., 1993).

Later on, cyclic serum changes, including a peri-ovulatory peak, higher serum concentration after ovarian hyper-stimulation (Salmassi et al., 2004) and higher follicular concentrations (Yanagi et al., 2002), suggested that