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REVIEW ARTICLE

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Cytokines in Obstetricsand Gynaecology

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Introduction

Cytokines are low molecular weight extracellular signaling proteins secreted by immune and inflammatory cell populations, as well as growth factors, oncogenes, chemokines, and other soluble factors, which affect growth, differentiation, and viability of cells. Cytokines may be divided into six groups: interleukins, colony-stimulating factors, interferons, tumor necrosis factor, growth factors, and chemokines.

Each cytokine binds to a specific cell-surface receptor. Subsequent cascades of intracellular signaling then alter cell functions. This may include the upregulation and/or down-regulation of several genes and their transcription factors, in turn resulting in the production of other cytokines, an increase in the number of surface receptors for other molecules, or the suppression of their own effect by feedback inhibition.

Many cytokines can share similar functions. Cytokines are also pleiotropic (acting on many different cell types). A given cell type may express receptors for more than one cytokine, and many different tissues can express receptors for the same cytokine. Generally, the effect of cytokines is paracrine i.e. the action is restricted to the cells in their close proximity. However, they may also act in autocrine (the cytokine acts on the cell that secretes it), or an endocrine manner (the cytokine diffuses to distant regions of the body through blood or plasma to affect different tissues.)

Cytokines, originally known as immuno-regulatory proteins, may affect the neuro-endocrine events of reproduction, ovarian/testis function, endometrium, the developing embryo, placenta and parturition. Cytokines can modulate and mediate the actions of hormones at their target cells and, in the opposite way, hormones may regulate the production and action of cytokines at three different levels: cytokine secretion, cytokine receptor expression and cellular responses. Cytokines may also function in an endocrine manner affecting distant targets. As many of the cyclic changes that occur in the ovary and endometrium during the normal menstrual cycle are similar to those associated with the inflammatory and regenerative processes, it is likely that cytokines are involved in these reactions. Furthermore, cytokines secreted by endometrial white blood cells may influence embryo development and trophoblast growth and may play a fundamental role in the mechanisms of immunological reproductive failure. Cytokines have been implicated in the mechanisms responsible for the onset of parturition [1].

Cytokines in ovulation

Cytokines are produced locally in the ovulatory follicle, and the role of these factors in the different components of the ovulation process: follicle rupture and remodelling, leukocyte infiltration, angiogenesis, ovarian steroidogenesis and oocyte maturation. Transcripts for about 16 different cytokines common to normal and tumor bearing ovaries have been identified.

During follicular development, cytokines assist granulosa cell growth while inhibiting their differentiation. During the LH peak, several cytokines are released. Cytokines and chemokines presumably promote migration of monocytes and granulocytes to ovaries [1]. They also stimulate secretion of ovulation-associated substances such as prostaglandins, which are essential for the breakdown of the follicular wall and for the release of the oocyte. The role of cytokines in ovulation is underlined by the ability of both IL-1ß and TNF-alpha to induce ovulation in perfused rat[2] and rabbit ovaries and by the effect of IL-1ß on oocyte maturation. Cytokines may also participate in the vascular proliferation associated with corpus luteum formation, and they promote cellular

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differentiation resulting in steroid synthesis. Impaired local production of cytokines, therefore, may be involved in luteal phase defects, a condition characterized by insufficient progesterone production and infertility. The mutual interaction between gonadotrophins, steroid hormones and ovarian cytokines is an additional example of the close relationship between the neuro-endocrine and the immune systems. Better definition of the role of cytokines in the ovulation process and in the formation and maintenance of the corpus luteum should provide new clues to the understanding of the immunological mechanisms leading to infertility.

The correlation found between plasma cytokines activities and severity of Ovarian Hyper Stimulation Syndrome (OHSS) suggest that cytokines may also be involved in the pathogenesis of this complication of ovulation induction and may serve as a means of monitoring the syndrome during acute phase and throughout convalescence. IL-1, IL-6, IL-8 and TNF-? are found to be elevated in subjects developing severe OHSS after induction of ovulation for in-vitro fertilization. Il-6 is a mediator of the acute phase response to injury; a systemic reaction characterized by leucocytosis, increased vascular permeability and increased synthesis of acute phase proteins by the liver. IL-8 is a chemoattractant cytokine and a potent angiogenic agent.

Cytokines in early pregnancy

There is arelease of biologically active molecules, including cytokines, at and around the implantation site. It is believed that thesecytokines may play an important role in the successful establishmentof the pregnancy [3-7]. There are two distinctive cytokine profiles, leading to their classification as Th1 and Th2. The differences in cytokines produced by these cells lead to differences in immune function. Th1-type cytokines, especially IFN-? and TNF-?, have been demonstrated to impair embryo development and trophoblast growth in vitro, and to mediate abortion in mice. The cytokines IFN-ã and TNF-á are involved in apoptosis of trophoblast cells and can also inhibit outgrowth. On the other hand, the Th2-type cytokines, IL-4 and IL-10, are found in the decidua during normal murine pregnancy. It has been suggested that a predominantly Th1 response at the maternal-fetal interface is associated with fetal loss, while a predominantly Th2 response is associated with fetal survival. The human endometrium and decidua contain CD4 and CD56 lymphocytes, which have the potential to secrete cytokines. Lymphocyte activation by the trophoblast or other antigens leading to the release of Th1- or Th2-type cytokines may be involved in the mechanisms underlying pregnancy loss and success, respectively. There appears to be a strong basis for the suggestion that normal successful pregnancy is brought about by a strong Th2 response, whereas Th1 response is antagonistic to pregnancy [8-10]. Women with unexplained recurrent spontaneous abortion (RSA) normally produced low levels of Interleukin-4.

Cytokines in parturition

The mechanisms of the onset of labour (term or preterm) involve mainly three physiological processes:

1. Remodeling of the cervix allowing it to soften and dilate
2. Initiation of uterine myometrial contractions, and
3. Disruption of membrane integrity leading to weakening and rupture

The main factors involved in cervical ripening are invasion of leukocytes, remodeling of extracellular matrix and proteolytic enzyme activity. There is an influx of leukocytes, mainly neutrophils, into the cervix leading to increased production of Il-6, IL-8, IL-1 B and TNF- á result in cervical softening and dilatation. IL-1B increases the production of MMP-1, MMP-3 and MMP-9 and down –regulates TIMP, which also favors cervical ripening mechanisms.

Prostaglandin increases myometrial activity and intra-uterine tissues produce increased amounts prior to the onset of labour and PGDH concentrations fall during labour. IL-1B and TNF- ? have been shown to decrease the expression of PGDH. Cytokines such as IL-2 and IL-6 act directly on the decidual stromal cells and increase myometrial contractility.

Rupture of the membranes is an essential part of normal parturition. Weakening of the membranes over the internal cervical os occurs with thinning and subsequent rupture. MMP degrade the collagen extra cellular matrix and lead to rupture of the membranes. During labour, the production of IL-6, IL-8 IL-1B and TNF- ? by the fetal membranes is increased. Increased activity of these also results in weakening of the membranes and rupture.

Cytokines play an active role in the connective tissue remodelling during the ripening process. This is supported by results from studies in other species [11-13]. Earlier studies demonstrating an increase of inflammatory cells, including granulocytes, in human cervix during the ripening process, further support this theory [14, 15]. Cytokines of particular interest in this context are IL-8, IL-6 and G-CSF, since IL-8 is an important chemo-attractant for neutrophils, whereas IL-6and G-CSF both interfere with and stimulate proliferation and activation of the neutrophilic cell line [16, 17].

In an extensive remodelling process such as cervical ripening, a potential role of proteoglycans must not be

neglected. These macromolecules are known to regulate many different cell interactions such as cell migration, cell adhesion and signal transduction in the extracellular matrix.[18] Heparin sulphate proteoglycan, i.e. syndecan glypicans and perlecan, carries multiple binding sites for cytokines[19] like IL-8 and may therefore contribute to a local accumulation of the cytokine as well as protecting it from rapid degradation. In concert with this, an interaction between cytokines and proteoglycans may be important for the regulation of cervical connective tissue reconstruction at term [20]. Cytokines also induce hyaluronic acid production by human cervical fibroblasts, which may promote cervical ripening [21].

Cytokines in prematurity

Prematurity has multiple causes. There is a growing body of evidence supporting the association between silent intrauterine infection and preterm birth. Bacterial products may activate macrophages ubiquitous present in the decidua, placenta and fetal membranes. These cells after activation secrete a large variety of mediators including TNF-? and IL-1. Besides these cytokines IL-2, IL-3, IL-4, IL-6, IL-8, IL-10, epidermal growth factor, GSF and TGF-beta have been identified in intrauterine tissues and in the amniotic fluid. The majority of these substances (TNF-?, IL-1, IL-2, IL-3, IL-6) can stimulate the prostaglandin-biosynthesis by intrauterine tissues (amnion, chorion, decidua), some of them have anti-inflammatory effects (IL-10, transforming growth factor alpha). These effects are mediated by receptors on the target cells; specific receptor antagonists (for example for IL-1) were found in high concentrations in amniotic fluid during normal pregnancy. This cytokine network is in a sensitive balance and probably associated with an uncomplicated course of pregnancy. Systemic or localized infections as well as tissue injury initiate the induction of the prostaglandin synthesis cascade thus leading to pregnancy loss via augmented cytokine secretion. Furthermore, cytokines may be involved in the regulation of preterm and term cervical ripening. The changes in mechanical properties of the cervix are associated with a reduction of collagen content and alterations in the glycosaminoglycan pattern within the cervical extracellular matrix. IL-1 can stimulate the synthesis of collagenases, and IL-8 may play an important role in the regulation of the invasion of neutrophilic granulocytes into the cervical stroma with subsequent degranulation and release of proteases. The cytokine-stimulated collagenase production in the fetal membranes is responsible for the reduction of their tensile strength and may be associated with rupture of the membranes. The cytokine network seems to be a sensitive regulation system. Disturbances of its balance by environmental (e. g. infection) or intrauterine influences (e. g. extension by the fetus) may lead to termination of pregnancy [22].

Non-infected preterm cervical ripening is an inflammatory process, just as cervical ripening at term with cytokines as important mediators [23]. The anti-inflammatory actions of IL-10 and IL-4 oppose the pro-inflammatory cytokine actions leading to a decreased likelihood of spontaneous preterm labor, Preterm birth and preterm pre-labour rupture of membranes. IL-4 induces increased production of the IL-1 receptor antagonist IL-1RA, which leads to decreased prostaglandin production.

The therapeutic potential of cytokines

IL-1 receptor antagonist has been shown to reduce IL-1 induced prostaglandin production by the fetal membranes. Similarly, IL-4 has been shown to have an inhibitory effect on prostaglandin production by decreasing PGHS production in the amnion. The use of anti-inflammatory cytokines to manipulate the physiologically protective mechanisms or defenses may turn out to be the most effective method of preventing the onset of spontaneous preterm labor.

Cytokines in placental vascular disease

There have been reports of cytokine production and release and activation of the suppressor of cytokine signaling family by endothelial cells in response to fetal plasma in placental vascular disease. The role of all members of the suppressor of cytokine signaling family in this process must be investigated further. The fact that both the agonist (cytokines) and the antagonist (suppressor of cytokine signaling-2) are produced points to a significant role of endothelial cells in this disease [24].

Researchers found an association between variants in cytokine genes and preeclampsia. Preeclampsia is a systemic inflammatory condition characterized by high blood pressure and excess protein in the urine, and is a leading cause of maternal and neonatal problems. Levels of plasma proinflammatory cytokines (such as tumor necrosis factor and interleukin) are higher in women with preeclampsia than in pregnant women with normal blood pressure. An exaggerated inflammatory response to pregnancy may occur among genetically susceptible women, such as those who carry cytokine gene variants that are known to up-regulate cytokine production [25].

Cytokine genotyping may prove to be an effective tool to screen for preeclampsia risk early in a woman's pregnancy.

Cytokines in endometriosis

Peritoneal fluid in women with endometriosis contains an

increased number of activated macrophages that secrete a variety of cytokines, including IL-6, IL-8, vascular endothelial growth factor, and TNF-? . Cytokines may be involved in the control of implantation and the growth of endometrial cells outside the uterus. In addition, several cytokines have been implicated in or directly associated with angiogenic activity in endometriosis. There could be a relationship between the levels of cytokines in the peritoneal fluid of patients with endometriosis and the status of the lesions in such patients. Peritoneal endometriosis can be classified as having red, black, or white lesions. Red lesions are known to be an active form of early endometriosis, because vascularization and mitotic activity are shown to be most prominent in these lesions. It has been noted that the peritoneal fluid levels of TNF-? and IL-8 are significantly higher in patients with endometriosis, and they correlate with the size and number of active lesions. In addition, TNF-? and IL-8 stimulate the growth of ectopic endometrial stromal cells. These cytokines with angiogenic activity may therefore have significant roles in the pathogenesis of endometriosis [26-28]. Cytokines in ovarian tumors

Cytokines may also be involved in tumor growth. There are at least two ways in which cytokines can aid the growth of tumor cells. (1) They can enhance tumor growth directly by functioning as growth factors, promoting metastasis by increasing cell adhesiveness and/or enhancing tumor angiogenesis. (2) Cytokines can also be powerful modulators of the immune system, enhancing tumor growth by blocking cell-mediated mechanisms for identifying and destroying the tumor. The cytokines presumed to be involved in ovarian cancer are IL-1, IL-2, IL-6, IL-8, IL-10, IL-2, TGF, GM-CSF, M-CSF and TNF-? .

Cytokines in the treatment of ovarian cancer

Cytokines have been used for treating ovarian cancer patients basically in two ways: (1) to treat or prevent the myelosuppressive effects of chemotherapy and (2) directly to treat the disease itself. Cytokines have proved to be very useful in ameliorating the effects of bone marrow suppression caused by chemotherapy.

Also, gene therapy approaches involving tumor cells expressing introduced cytokine genes may, some day, provide active tumor vaccines.

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