The complex role of IL-6 in physiology and pathology

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Abstract

The study briefly reviews the biological role of IL-6 in various physiological and pathological situations. IL-6 participates in the broad spectrum of biological processes such as immune responses, oncogenesis, in pregnancy it enables the maintenance of the balance between immunoregulatory activity of the placenta, maternal immune system and fetal immune system, finally co-creating the phenomenon of the immune tolerance during pregnancy. The deregulation of IL-6 production and expression of IL-6 membrane and soluble receptors results in various pathologies such as immune mediated diseases, chronic inflammations, recurrent miscarriages, preeclampsia, preterm birth, malignant neoplasms including multiple myeloma, ovarian cancer and others. The biological activity of IL-6 is determined by the tumor microenvironment. The future understanding of the complex regulation of the biological activity of this cytokine might provide the new therapeutic strategies in various inflammatory and neoplastic diseases.

Key words: Immune tolerance, cancer microenvironment, IL-6

Introduction

Interleukin-6 (IL-6) is a pleiotropic cytokine with a wide range of biological activities in the immune regulation, hematopoiesis, inflammation, and oncogenesis [1-3]. IL-6 was shown to be produced by T-cells, B-cells, monocytes, fibroblasts, endothelial cells and several kinds of tumor cells. This cytokine has also a wide range of biological activities on various target cells. IL-6 is a differentiation factor for B-cells, T-cells and macrophages, differentiates the megakaryocytes to produce platelets and hematopoietic stem cells [4, 5]. IL-6 stimulates hepatocytes to produce acute phase proteins such as C-reactive protein (CRP), fibrinogen, α1-antitrypsin and serum amyloid A (SAA), and suppresses the production of albumin. IL-6 introduced in vivo induces leukocytosis fever. IL-6 is also a growth factor for mesangial cells, various tumor cells including lymphoma cells, multiple myeloma cells and Kaposi sarcoma cells [2, 3]. This cytokine plays an important role in the etiology of various pathological conditions as inflammatory, autoimmunity and malignant diseases [2].

The IL-6 receptor system consists of two functional membrane proteins: an 80 kDa ligand binding chain (IL-6R) and a 130kDa (known also as gp130) non-ligand binding chain acting as a signal transducing chain. Activation of gp130 activates members of Janus kinases (JAK) family, the signal transducers and activators of the transcription-3 (STAT3) pathway, and the CCAAT/ enhancer binding protein (C/EBP) pathway [6]. IL-6 can induce STAT1 with the balance STAT1 and STAT3 signals influenced by the microenvironment and costimulation by IFNγ and Toll-like receptor-4 (TLR4) ligands, which changes the balance towards STAT1 and inhibits STAT3 [7]. The distribution of IL-6R and gp130 among the cells is different, gp130 is identified in almost all cells, while IL-6R expression is observed in hepatocytes and leucocytes [8, 9]. The biological activity of IL-6 is determined also by the distribution of the soluble form of IL-6R (sIL6-R). This receptor forms a complex with IL-6 that binds cell surface gp130 to induce the response, the regulation of this process is named IL-6 trans-signaling [8]. IL-6 trans-signaling can be inhibited by a soluble form of gp130, by competing with membrane-bound gp130 for IL-6/IL-6R complexes [10, 11].

Overproduction of IL-6 is observed in various inflammatory diseases, such as rheumatoid arthritis where it...
is produced by synovial tissues of the joints, in Castelman’s disease with the symptoms of fever, lymph nodes enlargement, anemia, high levels of acute phase proteins. In such pathological conditions the high IL-6 levels were accompanied by high soluble IL-6R levels. In order to block the signal transducing for the treatment of these diseases, an antibody against the receptors, a humanized anti-IL-6R antibody was prepared (tocilizumab). The results of the treatment with tocilizumab in various immune mediated diseases including reactive arthritis, juvenile idiopathic arthritis, rheumatoid arthritis, Castelman’s disease were very promising and are under continuous investigations [2, 12].

**IL-6 and reproductive tract**

The IL-6 production remains also under hormonal influence, for example hormones including oestrogen and testosterone seem to inhibit the secretion of IL-6, and this has been proposed to be the reason of increased circulating IL-6 following menopause and andropause [13]. Moreover, IL-6 participates in the early pregnancy, from the peri-conceptual period. IL-6 is produced by luminal and glandular epithelial cells in the proliferative cycle phase with the strongest expression in the epithelium and the stroma in mid-secretory cycle phase at the time of implantation. The menstrual cycle-dependent expression of IL-6 suggests that this cytokine may play a role in changes in endometrium that prepare this tissue for implantation and menstrual shedding [14]. *In vitro* studies revealed that IL-6 can promote the preimplantation embryo development and increase blastocyst cell number [15]. IL-6 seems to control trophoblast/placenta cells invasiveness depending on the differentiation stage of pregnancy growth [16, 17]. IL-6 protein and mRNA are observed to be expressed in decidual tissue and placenta over the course of gestation [18]. IL-6 expression seems to participate in the process of angiogenesis and vascular remodeling in placenta through the induction of VEGF expression [19, 20]. IL-6 seems also to be involved in the induction and progress of the labor, however the mechanism regulating this process is not defined [21]. Steinborn et al. documented the growth of the number of fetal monocytes and IL-6 concentration in umbilical blood during the spontaneous beginning of the labor. It was not only observed in decidua and in amniotic fluids but also in the umbilical blood. The fetal monocytes and macrophages seem to be the source of IL-6 apart from amniotic membrane and decidua [22]. Interleukin-6 induces a concentration-related increase in prostaglandin production by amnion and decidual cells, upregulates production of PGE2 and PGF2α, the receptor of PDGFR in human amnion and decidual cells *in vitro* [23]. Moreover, IL-6 stimulates also the uterine contractility by stimulating the expression of oxytocin receptor [24]. As a key regulator of the immune response, IL-6 controls the progression of inflammation and differentiation of T cells. The alterations in IL-6 ligand, its receptors and the inhibitory sgp130 seem to be strongly related with various complications of pregnancy, including unexplained infertility, preeclampsia and preterm birth [21].

**Cancer microenvironment**

In cancer, similarly to immune mediated diseases the significance of IL-6 seems to be very complex. Ovarian cancer represents the second most common women reproductive tract cancer, following uterine cancer, causes more deaths per year than any other female reproductive tract cancer. This cancer is also characterized by the recurrent course and developing of the resistance to the chemotherapy. The recurrent course of the disease is related with the biological adaptation of cancer cells and results from the ability of cancer cells to survive by local dissemination and the implantation to the peritoneal serosa. This results from the genetic instability of the cells and development of the resistance to chemotherapy and apoptosis. The auto/paracrine system of growth factors secretion might also play an important role in this process. Ovarian cancer develops from the cells that physiologically are responsible for the secretion of cytokines and growth factors. This secretion is controlled by the hypothalamo-hypophyseal axis. Human ovarian surface epithelial cells as well as granular cells secrete IL-6 [25]. Also, IL-6 was reported to play an important role in renal cancer expansion. As it was mentioned above, the primary role of IL-6 is related with hematopoiesis, maturation of lymphocytes, the secretion of acute phase proteins as well as immunity (by factors determining antigens presentation and differentiation of B lymphocytes). Physiologically IL-6 regulates the growth of B lymphocytes and is the main factor inducing the production of acute phase proteins by hepatocytes (like C-reactive protein-CRP). CRP augments the immune response by activating the alternative complement activation, potentiates the phagocytosis, prevents autoimmunization. IL-1 is strongly involved in the processes of activation of T lymphocytes. IL-6 and IL-1 are important factors in the maturation and differentiation of hematopoietic cells, IL-6 together with GMCSF and IL-3 induces the pluripotent stem cell differentiation into
Physiologically IL-6 regulates the growth of B lymphocytes. Recently, it was shown in ovarian cancer significantly correlated with the amount of peritoneal cancer, however, it appeared that CRP was statistically worsening the prognosis of the disease [34]. In ovarian example, in renal cancer the level of CRP is the marker potential marker for the course of ovarian cancer. For and CRP is very strong and the level of CRP reflects IL-6 malignant neoplasms [31]. The correlation between IL-6 with ovarian cancer than in patients with digestive tract cancer, it is also higher in peritoneal fluid from patients with ovarian cyst is significantly lower than in ovarian cancer. Thus, IL-6 was demonstrated to have a tumor-promoting activity. Recently, it was shown in ovarian cancer that IL-6 enhances tumor cell survival and increases resistance to chemotherapy through JAK/STAT signaling pathway in tumor cells [36] and IL-6 receptor trans-signaling on tumor endothelial cells [37]. Moreover, Nilsson et al. demonstrated that IL-6 play an important pro-angiogenic role in ovarian cancer [38]. IL-6 was also shown to inhibit the generation of CD4+ Treg cells by suppressing TGF-β-induced Foxp3 expression [39, 40]. It was also documented that IL-6 together with TGF-β, induced Th17 cell differentiation from naïve T cell, this process was negatively regulated by IFN-γ and IL-27 or IL-2 [2, 41]. Arylhydrocarbon receptor (Ahr) was specifically induced in naïve T cells under Th17 polarizing conditions (TGF-β, IL-6) and participated in the differentiation of Th17 cells [2, 41, 42]. It was also observed that Th17 positive regulation was controlled by STAT3, while negative regulation was controlled by STAT1 and STAT5. Moreover, Ahr was demonstrated to negatively regulate lipopolysaccharide (LPS)-induced inflammatory responses in macrophages [41, 42], it was suggested that Ahr which is under IL-6 control, might regulate the immune responses and inflammation through the regulation of T cells and macrophages [2, 41, 42]. Finally, IL-6 was shown to belong to a malignant cell autocrine cytokine network in ovarian cancer cells [42]. Coward et al. investigated the use of Siltuximab in human ovarian cancer. Siltuximab is a monoclonal, chimeric anti-IL-6 antibody. Siltuximab neutralized the negative IL-6 activity in ovarian cancer (production of inflammatory cytokines, angiogenesis of the tumor, infiltration of macrophages), however the response rate was 5.6% [43]. Siltuximab has been already investigated in Castelman’s disease, where the response rate reached 52%, while in prostate cancer it was only 3.2% [43].

**Summarization**

In conclusion, IL-6 participates in the broad spectrum of biological processes such as immune responses, oncogenesis, in pregnancy it enables the maintenance of the balance between immunoregulatory activity of the placenta, maternal immune system and fetal immune system, finally co-creating the phenomenon of the immune tolerance during pregnancy. The deregulation of IL-6 production and expression of IL-6 membrane and soluble receptors results in various pathologies such as immune mediated diseases, chronic inflammations, recurrent miscarriages, preeclampsia, preterm birth, malignant neoplasms including multiple myeloma, ovarian cancer and others. The biological activity of IL-6 is determined by the tumor microenvironment. The future un-
derstanding of the complex regulation of the biological activity of this cytokine might provide the new therapeutic strategies in various inflammatory and neoplastic diseases.

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References
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