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IMMUNOMODULATORY PROPERTIES OF ANGIOGENIC FACTORS AND MYELOID SUPPRESSOR CELLS: A ROLE IN THE GESTATIONAL PROCESS

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The review presents data on the immunomodulatory role of angiogenic factors and myeloid suppressor cells. The mechanisms that play a key role in shaping the balance of proangiogenic and antiangiogenic factors, the role of endothelial growth factor (VEGF), placental growth factor (PlGF) and myeloid suppressor cells (MDSC, MS) in the development of gestational immunosuppression are shown. Data are presented on the molecular mechanisms of immunosuppression, the expression of check-point molecules that play a major role in the suppression of cellular immunity reactions. The role of tyrosine kinase receptors for proteins of the VEGF family - VEGF-1 (Flt-1), VEGFR-2 (KDR/Flk-1) in the regulation of immune responses has been characterized. Data are presented on the cross-regulatory interaction of angiogenic factors and myeloid suppressor cells and the immunomodulatory effect on cellular immunity responses. Disturbance of these mechanisms may be associated with the development of gestational complications, in particular preeclampsia. Based on the presented data, the possibility of evaluating VEGF and MS in pregnant women as prognostic biomarkers of preeclampsia is considered.

Keywords: vascular endothelial growth factor (VEGF), placental growth factor (PlGF), myeloid suppressor cells (MDSC), preeclampsia.

The process of formation of new vascular vessels plays an important role in many diseases and pathological conditions. the most intense neoangiogenesis occurs during embryonic development, pregnancy, and tissue repair [32].

Both activating and inhibiting angiogenic factors are involved in the regulation of angiogenesis [28]. Both during the tumor process and during pregnancy, a balance of proangiogenic and antiangiogenic factors is formed [9]. The formation of new organs is carried out due to two mechanisms - angiogenesis and vasculogenesis. Angiogenesis is the process of neovascularization from already inflammatory vessels, while vasculogenesis is the process of colon formation from cells - elevated angioblasts. During pregnancy, the processes of vasculogenesis and angiogenesis develop, including the key role of the growth of vascular endothelial inflammation (VEGF) [28].

Recent studies have expanded our understanding of the role of pro-angiogenic factors, in particular VEGF-A, in the regulation of immune responses. It is known that the cytotoxic activity of VEGF significantly increases the toxic activity of T cells, can increase the number of T cell regulators (Treg) and myeloid suppressor cells (MDSC), and also prevent the differentiation and activation of dendritic cells (DC) [10]. Basically, the VEGF family exerts its influence on T cell function through binding to type 2 receptors (VEGFR-2) [32], while the function of type 1 receptors (VEGFR-1) remains unclear. To identify a selective ligand for VEGFR-1 is placental growth factor (PlGF), also identified for a protein of the VEGF family, a study of the PlGF study to assess the role of VEGFR-1 signaling T-cells in the regulation of T-lymphocyte functions. At the same time, the revealed immunomodulatory properties make it possible to identify new manifestations of T-cell immunosuppression in conditions of neoangiogenesis [2].

Receptors for VEGF. Three types of tyrosine kinase receptors are known for the VEGF family - VEGF-1 (so-called Flt-1), VEGFR-2 (so-called KDR/Flk-1) and VEGFR-3 (Flt-4); and as a coreceptor of neuropilin-1 (NRP-1) and neuropilin-2 (NRP-2) bundles [9]. Neuropilins exhibit an extracellular part, a transmembrane segment, and a short (about 40 amino acid residues) intracellular domain that require enzymatic activity [9]. Also, NRP-1 and NRP-2 form complexes that are included in the composition and form in a cooperative mode [28]. Neuropilins, acting as co-receptors, increased VEGF affinity for VEGFRs [34].

Thus, the VEGF family stimulates the cellular response of binding to receptors with tyrosine kinase activity on the cell surface, and the products are activated due to their transphosphorylation [28]. Each VEGF receptor has an extracellular portion consisting of 7 immunoglobulin-like regions; an intracellular portion containing a tyrosine kinase domain; and one transmembrane region. As a result of alternative splicing, receptors can be membrane-bound and free.

The VEGFR-2 receptor binds VEGF-A with high affinity and can also bind VEGF-C and VEGF-D [32]. It mediates the main properties of VEGF-A - acti-

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vation of angiogenesis and an increase in endothelial permeability; moreover, when bound to this receptor, the immunomodulatory activity of VEGF A is realized, which manifests itself in inhibition of the function of T-lymphocytes [34]. It is known that VEGFR-1 binds VEGF-A, VEGF-B, and PIGF, but its role in the implementation is insufficient (it is believed that it modulates VEGFR-2 signals) [28]. Another function of VEGFR-1 is solved as an "empty" receptor, isolating the VEGF protein from the VEGFR-2 receptor (which is especially important during angiogenesis during the development of the fetal volume). It has recently been shown that activation of VEGFR-1 upon binding to PlGF on immune cells can modulate the functions of the latter [8].

Immunomodulatory functions of VEGF family factors. The angiogenic role of all of the above factors is well known, and to a lesser extent, the immunomodulatory properties of VEGF-A and PIGF. In addition to stimulating neoangiogenesis, vascular endothelial growth factor has an immunosuppressive function, which manifests itself in the ability to suppress the functions of T-lymphocytes, differentiation and activation of dendritic cells (DCs), as well as stimulate an increase in the number of T-regulatory cells (Tregs) and myeloid suppressor cells (MDSCs) [33 34].

VEGF-VEGR interaction leads to activation of MAPK (mitogen-activated protein kinase, mitogen-activated protein kinase) and PI3K-Akt (PI3K–Akt signaling pathways, Akt signaling pathway) signaling pathways both in human CD4+ T cells and in endothelial cells [6]. It has been shown that activated T cells are characterized by increased expression of VEGFR-2 [34]. In addition to the direct immunomodulatory effects of VEGF A, it has been shown to have an indirect effect on T cells through combination with cyclooxygenase, activating FasL (Fas ligand). [34]. Apoptotic signaling occurs when the membrane form of FasL binds to Fas receptors that are expressed on the membrane of another cell.

It has been shown that VEGF-A, produced in the tumor microenvironment, enhances the expression of inhibitory check-point molecules, including PD-1 (Programmed cell death 1; CD279), CTLA-4 (cytotoxicT-lymphocyte-associated protein 4; CD152), TIM- 3 (T-cell immunoglobulin and mucin domain 3) and LAG-3 (Lymphocyte-activation gene 3), which are involved in the deletion of CD8+ T cells. Thus, VEGF A significantly reduces the cytotoxic activity of T cells [23].

An increase in VEGF production leads to the generation of Tregs, which have suppressor properties and can help reduce the number of effector T cells and suppress their proliferation [34]. Various types of Tregs are known to be involved in negative regulation of the immune response, including CD4+CD25+FOXP3+, CD8+CD25+FOXP3+, CD4+CD25+CD127 cells. At the same time, VEGFR 2 is selectively expressed by FOXP3high Tregs, which indicates the involvement of VEGFR-2 in the induction of the suppressor activity of regulatory cells [12].

Factors of the VEGF family suppress the maturation of dendritic cells, which are antigen-presenting cells and act as mediators between the innate and adaptive immune systems [14]. Immature DCs express relatively low levels of the surface MHC IMHC II (major histocompatibility complex) and costimulatory molecules such as CD80 and CD86 [34]. Mature DCs are characterized by an increased ability to process antigens [14]. Activated DCs differ from quiescent mature DCs in the expression of higher levels of MHC and co-stimulatory molecules and in the production of cytokines. In this case, maturation and activation can occur simultaneously [14]. Thus, factors that prevent differentiation, maturation, and activation of DCs can lead to the formation of tolerogenic DCs. According to research, VEGF A may be one such factor. Thus, it has been shown that an elevated level of VEGF A is associated with the presence of immature DC in the peripheral blood of cancer patients [34]. Probably, binding of VEGF to VEGFR blocks the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), which leads to inhibition of DC maturation.

Vascular endothelial growth factor can recruit monocytes to the tumor and promote the generation of tumor-associated macrophages (MAOs), which are characterized by low antigen-presenting ability, reduced cytotoxic function and high production of IL-10, TGF-β and prostaglandins. Most MAOs are type 2 (M2) macrophages with tolerogenic activity, which promote tumor progression and metastasis [34].

The immunomodulatory properties of PlGF have been studied to a lesser extent. Nevertheless, this angiogenic factor, when bound to VEGFR1, has been shown to be able to suppress the differentiation of dendritic cells and induce a tolerogenic DC phenotype by inhibiting their Th1-stimulating activity [3, 24]. Our studies have shown that the activation of T-lymphocytes is accompanied by a pronounced increase in VEGFR1 expression. When PlGF binds to VEGFR1, T cell proliferation is inhibited, affecting both CD4 and CD8 T cells [2]. In addition, the addition of PlGF to T cells activated through the T cell receptor enhances the expression of VEGFR1 and VEGFR2 [8].

Myeloid suppressor cells. In recent years, new data have emerged that expand our understanding of the role of VEGF as an immunoregulatory factor. Thus, according to studies, VEGF is able to induce the generation of myeloid derived suppressor cells (MDSC) (MS), which have a pronounced suppressor activity [5, 29].

Myeloid suppressors are bone marrow cells of myeloid origin, which are formed from hematopoietic precursors, accumulate in the bone marrow and then enter the peripheral blood, lymph nodes, and other organs of the immune system [16]. Initially, MS represent a heterogeneous population of immature myeloid cells with a pronounced suppressor activity. Subsequently, MC accumulate in peripheral lymphoid organs and are able to differentiate into mature myeloid cells - macrophages, dendritic cells, granulocytes. Currently, 3 populations of MS have been characterized in humans: monocytic (M-MDSC), granulocytic (PMN-MDSC or G-MDSC), and early MS (e-MDSC) [6]. All types of MS are registered in the peripheral circulation: CD11b+CD14+HLA-DR−/loCD15− M-MDSC; CD11b+CD14−CD15+ PMN-MDSC and Lin− HLA-DR−CD33+ e-MDSC [13]. A number of authors consider MS as a key population of regulatory cells capable of controlling the immune response [29], including during the development of inflammation, trauma, autoimmune and oncological diseases, as well as during pregnancy [5, 18, 19, 26, 25].

The regulatory role of MS is due to the expression of a number of not only surface suppressor molecules - CD73, ADAM17, PD-L1, galectin-9 (Gal-9), but also intracellular markers such as arginase 1 (Arg 1), iNO-synthase (iNOS) , indolamine-2,3-dioxygenase (IDO) [15, 7]. Expression of a large number of suppressor molecules on MC, which bind to the corresponding receptors on cells, leads to suppression of the immune response and the formation of immunosuppression and death of T-lymphocytes. One of these mechanisms is the activation of inhibitory check-point molecules, in particular, the interaction of PD-L1 with the death receptor, PD-1 (Programmed Cell Death 1), which is present on all T cells [7]. The interaction of Gal-9 with the TIM-

3 receptor, which is expressed on the surface of CD4 and CD8 lymphocytes, leads to suppression of T-cell activity and MC generation [30].

Metabolic disorders and deficiency of arginine and tryptophan, due to increased production of Arg 1 and activation of IDO, can lead not only to the suppression of T-lymphocyte proliferation, but also to the suppression of macrophages and dendritic cells [22]. The ability of MC to produce suppressor cytokines (IL- 10, TGF-β1), which, together with the expression of a number of suppressor molecules, enhances their regulatory activity [19].

The presented data indicate the regulatory properties of VEGF and MC, which is manifested by the suppression of the functions of effector cells and the activation of lymphocytes with suppressor properties.

The role of VEGF and MS in the development of gestational complications. The processes of angio- and vasculogenesis and the formation of immunological tolerance are necessary conditions for successful placentation and the development of pregnancy. The development of late gestational complications is largely due to impaired endothelial function, which leads to the development of preeclampsia (PE). Preeclampsia is a multisystem pathological condition that develops after 20 weeks of pregnancy, is characterized by the appearance of symptoms of arterial hypertension, proteinuria, and still remains one of the five main causes of maternal death [1, 20].

The formation of the placenta during pregnancy and the accompanying changes affecting the mother's cardiovascular system are a highly regulated sequence of events. Normal maturation and development of placental tissue is necessary to provide the developing fetus with nutrients and oxygen. Violation of angiogenesis in the placenta determines incomplete remodeling of the uterine spiral arteries and, as a result, insufficient perfusion of the placenta and an imbalance in the production of angiogenic and antiangiogenic factors by trophoblast cells, which ultimately can lead to intrauterine growth retardation or PE [1, 4, 20]. Ischemia and hypoxia resulting from impaired trophoblast invasion lead to increased production of pro-inflammatory cytokines in the placenta. The state of hypoxia triggers a cascade of reactions, in which a group of transcription factors is activated: HIF 1 α and HIF 2 α (hypoxia-induced factors - 1-alpha, 2-alpha), which trigger the synthesis of angiogenesis stimulators, in particular, the VEGF factor [6, 4, 31].

Available data suggest that placental ischemia, which develops as a result of endothelial dysfunction with subsequent release of placental anti-angiogenic factors into the bloodstream, is of decisive importance in the development of PE. Currently, the possibility of using VEGF, PlGF, endoglin (sEng), and inhibin as biomarkers of timely prediction of the development of PE is being considered [1, 21]. The key molecules regulating early changes in placental vessels are VEGF A, PlGF, as well as Flt 1 (VEGFR-1) and KDR (VEGFR-2) receptors. Both VEGF and PlGF circulate at high concentrations during pregnancy, and their reduction can lead to poor vascularization and impaired vascular development during trophoblast invasion [6, 27]. It is known that the level of sFlt-1 increases in the blood of patients with PE [10]. According to experimental data, sFlt-1, obtained from chorionic villi in women with PE, induced an antiangiogenic state, which was leveled by the blockade of sFlt 1. When sFlt-1 was administered to pregnant rats, characteristic signs of PE appeared: hypertension, glomerular endotheliosis, and proteinuria [17]. Another anti-angiogenic factor secreted by the placenta that is elevated in women with PE is soluble endoglin (Eng). An increase in sEng concentration is observed in the blood sera of women with PE [6]. The exact role of these molecules during pregnancy and placentation is unclear, but it is suggested that Eng, via TGF-β, may play a role in the development of PE [6].

Thus, a significant decrease in the production of angiogenic factors - PlGF, VEGF, as well as an increase in the production of antiangiogenic factors - sEng and sFlt-1, are associated with the pathogenesis of PE [6]. Indeed, blocking VEGF by VEGF antagonists in cancer patients with monoclonal antibodies (bevacizumab, ranibizumab, and aflibercept) can lead to the development of a condition very similar to the development of PE - severe hypertension and proteinuria, as well as to an eclamptic pattern similar to leukoencephalopathy [17].

In recent years, data have appeared on the involvement of MS in the induction of physiological immunosuppression during pregnancy [18, 26]. However, data on the content of MS during pregnancy and their significance in the gestational process are presented by a few works. Thus, an increase in the number of MC in the peripheral blood in pregnant women compared with non-pregnant women and a decrease in MC in women with a threatened miscarriage were found [11]. An increase in the proportion of MS also occurs at the local level in the area of the fetoplacental complex. Placental MS shifts the T-cell response towards the Th2 type, suppressing the proliferation of the Th1 type. In this case, the overexpression of Arg1 and NOS2 (nitric oxide synthase), as well as the production of ROS (tyrosine kinase receptor) and IDO can serve as the mechanism of T cell suppression [15]. VEGF, the level of which also increases during pregnancy, can act as an inducer of MC generation [8].

Thus, the immunomodulatory activity of angiogenic factors and myeloid suppressor cells plays a significant role in the induction and maintenance of physiological tolerance to fetal antigens, and disturbance of their functions can be considered as a prognostic factor in the development of gestational complications.

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