The immunoregulatory disturbances in the pathogenesis of pre-eclampsia

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Abstract

Pre-eclampsia is one of the most common obstetric disorders that occurs in 5-10% of pregnant women. The signs and symptoms of this syndrome appear during the second or the third trimester of pregnancy. It manifests mainly as hypertension and proteinuria. This disorder is a leading cause of mortality and morbidity among not only mothers but also newborns. Although many researchers have carried out studies concerning pre-eclampsia, the etiology of the syndrome is still unknown. It was found that pre-eclampsia as a placenta disorder develops in two stages. During the first stage there is too shallow invasion of cytotrophoblast into spiral arteries. The second stage of the disease relies on the production of some substances from ischaemic placenta which can induce the damage of endothelium. There are some observations which suggest that the syndrome is an immunological disorder. For example, there is a protective effect of sperm exposure which can support an immunological etiology. There are also evidences that the length of sexual cohabitation before pregnancy is one of protective factors. It has been suggested that the cause of pre-eclampsia is an insufficient maternal tolerance to paternal antigens. It has been found out that pre-eclampsia is a “Th1 phenomenon” what means that in feto-maternal unit and in peripheral blood of pre-eclamptic women there is a predominance of Th1 response over Th2 immunity. Moreover, the deficiency of T regulatory cells has been observed in pre-eclampsia. There was also underlined that the alterations in the function of natural killer (NK) cells, macrophages and dendritic cells (DCs) play an important role in the development of pre-eclampsia.

Key words: cytokines, etiology, lymphocytes, pre-eclampsia

Introduction

Pre-eclampsia (PE) is a common obstetric syndrome manifesting with hypertension and proteinuria. It affects about 5-10% of pregnant women annually [50]. The signs and symptoms appear during the second or the third trimester of pregnancy. It is one of the cause of both maternal and fetal morbidity or even mortality. The only way to cure and prevent the consequences is to deliver a baby [1, 2]. The etiology of the syndrome is still unclear but it is well known that PE is a placental disorder that develops in two stages. It is composed of the inappropriate transformation of spiral arteries and the impaired cytotrophoblast differentiation that leads to too shallow invasion in the early period of pregnancy (8-18 weeks). Placental ischemia, the second stage of the disorder is a consequence of decreased blood flow to placenta [3-5]. Although two classes of PE have been described: maternal and placental, however most frequent type is the mix of both of them [10]. The syncytiurn is a placenta layer that is in contact with maternal blood. Hypoxia induces release of soluble factors like cytokines, eicosanoids, peroxides, the anti-angiogenic factors soluble fms-like tyrosine kinase (sFlt)-1 or endoglin [91-97]. All those factor are suppose to activate immune response and are responsible for clinical signs and symptoms.

Incidence

Preeclampsia mainly occurs during the first pregnancy. It may be because of fetal alloantigens which challenge the maternal immune response [11]. Furthermore, symptoms of PE occur more often in subsequent pregnancy with a different partner [8, 9]. Short interval between the first coitus and conception often leads to PE [13, 14]. Robillard et al. mentioned that pre-eclampsia appears in approximately 40% of couples with less than 4 months of cohabitation before conception, 25% of those with 5-8 months, 15% of those with 9-12 months and 5% of those of more than 12 months (and the same father in multigravidae). The observation also suggests a paternal-maternal interaction in the etiology of PE [53].

Those results might indicate the immunological etiology of PE. Moreover, it was underlined that the earlier exposure to sperm has protective effects. It was revealed that higher incidence of PE is among women conceiving by intrauterine insemination (IUI) with foreign donor than in women who had IUI with sexual partner [12].

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There are works on mice where it was found that seminal plasma is more important than sperm. It was proved that transforming growth factor-β (TGF-β) present in seminal plasma induce T regulatory cells (Treg) as well as pro-inflammatory cytokines such as IL-17. The exposition to paternal seminal fluid induces tolerance to paternal antigens [15, 16]. There are also papers in which is underlined that women with vascular diseases such as diabetes, obesity, thrombophilsia or chronic hypertension are predisposed to preeclampsia. It can be the result of inappropriate systemic endothelial activation [51, 52].

Pathophysiology

Preeclampsia is the result of inappropriate invasion of trophoblast causing maladaptation of maternal spiral arteries, but it can also be diagnosed in hyperplacentation disorders such as hydatiform mole or multiple pregnancy. In PE poor villous development causes insufficiency of placenta. At that moment there is a fibrin deposition and thrombosis [54]. It leads to inadequate amount of blood flow to the fetus. The process of development of the disease was divided into two stages. Firstly trophoblast invasion is too shallow. This invasion into vessels stops only in the decidual parts of the spiral arteries [55, 56]. The second step in the development of PE is ischemia. Substances produced during deficiency of oxygen lead to endothelial dysfunction. At this stage apoptosis of trophoblast cells have been observed [57, 58].

Zhou et al. observed that cytotrophoblast do not strongly express α1β1 integrines that are receptors for collagen and laminins. However there is the expression of α5β1 integrins on cytotrophoblast cells. Cytotrophoblast also expresses α6β4 integrins. P-selectin is a member of the selectin family. It belongs to cell surface adhesion molecules. It is present on platelets and endothelial cells upon activation and plays pivotal roles in inflammatory reactions by supporting the recruitment and activation of circulating leucocytes. This molecule was detected in peripheral blood of preeclamptic patients. It is mainly released by platelets that are highly activated in this disorder [59-63].

Endoglin (Eng) is another highly expressed co-receptor on cellular membranes of the vascular endothelium and on the syncytiotrophoblast. It cooperates with transforming growth factor (TGF)-β1 and TGF-β3. It was described that it is involved in angiogenesis and the regulation of the vascular tone. In vitro, it was written that soluble Endoglin (sEng) plays a role as a negative regulator of angiogenesis by competitive interaction with TGF-β. Therefore it impairs capillary formation by endothelial cells. Moreover, the over-expression of the protein induces high blood pressure and increases vascular permeability on pregnant rat models. It is either worth to underline that the combined introduction of sEng and sflt-1 during animal pregnancy induced renal, placental and hepatic changes reminiscent to HELLP syndrome [64-66, 68, 69].

Immunological response in preeclampsia

During the physiological pregnancy many immunological changes are present. Wegemann et al. marked that there is a domination of T helper 2 (Th2) cells over Th1 cells in peripheral blood. It is called a Th2 phenomenon [6]. It was emphasized that spontaneous abortion is connected with Th1 type response [70, 71]. Based on many observations, the immunological theory of preeclampsia has been created. It was said that fetal (paternal) antigens are recognized by maternal organism that leads to the activation of the immune system. In PE there is higher response of Th1 cells. Moreover, it was underlined that there is also the activation of innate immune response [7].

It is well known that cytotrophoblast mainly produce IL-4. In that mechanism it can modulate progress of physiological pregnancy. When there is inadequate trophoblast invasion we may observe lower level of Th2 type cytokines [70, 71]. In the process of vascularisation or activation of NK cells another cytokines could be engaged. It was described that IL-11, IL-12, IL-13, IL-15, IL-16, IL-17, IL-18 play a role in the process of physiological implantation [71].

We found elevated expressions of Th-1 type cytokine IL-2 in peripheral blood T CD4⁺ cell and CD8⁺ lymphocytes of preeclamptic patients. Moreover, in preeclampsia higher expressions of IL-2 cytokine in T CD8⁺ than in CD4⁺ lymphocytes have been observed. It might suggest that the main source of IL-2 in preeclamptic patients are CD8⁺ lymphocytes. We also noticed higher expressions of IFN-γ in NK cells [79]. Other authors have similar results [81, 82]. It is well known that the function of IFN-γ enhance cytotoxic properties of T cells, NK cells and also it is able to activate macrophages and what is more important induce the expressions of proinflammatory cytokines [80].

T regulatory (Treg) cells and B-cells

The population of regulatory T cells is responsible for suppressing of inflammatory immune responses, and it is essential for preventing destructive immunity in all tis-
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...sues of the body. Their function is important in the places where the tolerance for dangerous foreign antigens is essential to a normal function. The cells have specific properties and are able to suppress responses to tissue-specific antigens and alloantigens. They play a pivotal role in tolerance for fetal foreign antigens [72, 73].

Maternal immune system has a specific tolerance to paternal antigens. It might be possible because of the function of T regulatory cells, that play a key role in a suppression of reactive cells [74, 75]. In pre-eclampsia, CD4+CD25\textsuperscript{high} T cells are significantly reduced in both peripheral blood and decidual tissue, in comparison with physiological pregnancy [77, 78]. Moreover, in miscarriage, lower levels of Treg cells might reduce immunosuppressive capability of immune system. What is interesting, both decidual and peripheral blood CD4+CD25\textsuperscript{high} T cells are fewer in the case of spontaneous abortion compared with induced abortions [77, 78].

Liao et al. in their work found out that in peripheral blood of pre-eclamptic patients there are functional changes in comparison with healthy pregnant women. They notice significantly higher population of peripheral CD27+CD38\textsuperscript{+} memory B-cells as well as CD27+CD38\textsuperscript{+} plasma cell precursors. What is more they also noticed increased capacity to differentiate into cytokine-producing cells [98]. It was described that the production of Ig depends on CD4\textsuperscript{+} cells. Furthermore it was either published that Tregs are able to suppress T cells, and also B-cell response not suppressing Th response [100]. Therefore low level of Treg cells might be consequences of decrease of suppressive role to B-cell Ig production. It was either observed that in pre-eclamptic patients there is a higher level of memory T-cells, CD45RO-positive, whereas a level of CD45RA-naïve T-cells is decreased [99].

Apoptosis

Programmed cell death is an important immunoregulatory mechanism responsible for maintaining homeostasis in the immune system [83]. Activated lymphocytes are removed from the organism in the FAS/FASL-mediated programmed cell death. Fas antigen is present on the surface of activated lymphocytes, whereas non-active cells do not express this molecule [84]. It was observed that there is higher expression of Fas/APO-1 antigen on CD8\textsuperscript{+} cells in the peripheral blood of pre-eclamptic women in comparison with physiological pregnancy. In the same study the expression of this molecule on either CD4\textsuperscript{+} or NK cell was observed [85]. Furthermore there are studies where Fas ligand was found on the human cytotrophoblast [86, 87]. It was suggested that Fas ligand present on trophoblast protects fetus from cytotoxic maternal immune system cells. Hsu et al. noted lower expression of the ligand on trophoblast in pre-eclamptic women [87, 88]. As a conclusion it might be said that lower expression of Fas ligand affect on lymphocyte accumulation in women with pre-eclampsia.

IDO

The role of indoleamine 2,3-dioxygenase (IDO) in the regulation of the maternal immune system has been recently described. The enzyme is responsible for catabolism of tryptophan that ‘feeds’ lymphocytes. It promotes Treg cells, but when there is decreased level of the IDO immunological response is switched into pro-inflammatory state. In the mouse model, 6.5 days after conception, the injection of the IDO inhibitor caused the rejection of allogenic fetuses. However, the injection of the same inhibitor after following 6.5 days caused increase of blood pressure as well as proteinuria. Those results might indicate that early changes in the maternal immunological system induce abortion, whereas during the second part of pregnancy induce development of PE [17, 22-24].

Human leukocyte antigens in pre-eclampsia

It is well known that fetus is semi-allograft because half of its histocompatibility antigens becomes from the father. Although fetus is treated as a semi allograft it is not rejected by a maternal immune system. It is not only because of mechanical barrier, such as maternal-fetal interface. Trophoblast does not express the main histocompatibility antigens, however it express non-polymorphic HLA-G, HLA-E, HLA-F, and classic HLA-C molecules which is present on extravillous trophoblast. They protect trophoblast from the activation of decidual NK cells. Paternal HLA-C molecule is recognized by NK cells, that express killer immunoglobulin-like receptors (KIR) receptors for the molecule. We can distinguish the A and B type of KIR, through promote the production of proinflammatory cytokines (type B receptor) by uterine NK cells. Contrary ligation to KIR A type inhibit inflammatory process [17, 18, 21]. There are studies which state that the expression of HLA-G induces production...
of immunosuppressive cytokines such as IL-3, IL-1β, and reduce amount of TGF-β [19]. The expression of HLA-G antigens is reduced in the case of PE [20].

Autoimmunity and pre-eclampsia

It was described that pre-eclampsia is present more frequently in women with autoimmune disorders such as lupus erythematosus, antiphospholipid syndrome or diabetes mellitus. Furthermore, like in classical autoimmune diseases, majority of severe PE-E cases appears to result in more autoantibody abnormalities, and also more pathogenic IgG isotypes.

In pre-eclampsia there were found antibodies which are able to activate angiotensin AT-1 receptor [89, 90]. During physiological pregnancy lower levels of this receptor were noticed. That fact might confirm autoimmunological theory of pre-eclampsia. Pathological symptoms might be the result of circulating autoantibodies which activate AT1 receptor. The antibodies activate AT1 receptors present on human trophoblast cells, what increases the synthesis and secretion of plasmin activator inhibitor-1 (PAI-1). PAI-1 takes part in invasion of trophoblast by inhibiting the urokinase-type plasminogen activator, decrease the conversion of plasminogen to plasmin and therefore it is responsible for shallow invasion of trophoblast [31, 32].

It was found that the antiphospholipid and anti-angiotensin II type I receptor (AT-1) antibodies increase the risk of PE [25-27]. Moreover it was found that Th17 cells that are activated in PE promotes secretion of those antibodies [28]. It was either observed that pregnant women who have those antibodies more frequently develop intrauterine growth retardation [29, 30]. Antiphospholipid antibodies fixed to cell membranes and antigens present on endothelial cells induce placental infarction. Wallukat et al. observed that those antibodies are present in all pregnant women with PE, therefore they concluded that antiphospholipid antibodies play a key role in the pathogenesis of this disorder [31, 32]. On the other hand, Leanos-Miranda et al. suggested that angiotensin II type I receptor (AT1R-AA) cannot be treated as a factor involved in the pathogenesis of preeclampsia [101]. However blocking this receptor by losartan decrease vessels construction, inducing low blood pressure in pre-eclamptic women [102]. Moreover, a positive correlation between severity of pre-eclampsia and the level of the receptor in the peripheral blood has been observed [103].

Role of dendritic cells in pre-eclampsia

Dendritic cells (DCs) are antigen presenting cells that play a pivotal role in inducing immunity or contrary inhibiting immune reactivity. They stimulate immunological response by regulating T cells. In the thymus DCs eliminate autoreactive T cells [41]. Two main populations of dendritic cells, myeloid and lymphoid DCs have been described. Myeloid DCs express BDCA-2 antigen and they are CD11c+/CD123+. They are responsible for inducing Th1 cell differentiation, whereas lymphoid DCs are CD11c-/CD123++ and they induce Th2 cell differentiation [36, 37]. There is also known the third population of dendritic cells, marked as CD11c+/CD123−, that is less differentiated DC population [38-40]. Myeloid DCs are described as CD4+, Lin−, CD11cbright, CD123dim, CD45RO− and CD2+. They express myeloid markers (CD13, CD33) as well as Fc receptors (CD32, CD64, Fc eRI). Myeloid dendritic cells (DC-1) express BDCA-1 (CD1c) antigen which is characteristic of peripheral blood DC-1 cells. Plasmacytoid (lymphoid) DCs (DC-2) have been found in human peripheral blood and lymphoid tissue. Peripheral blood DC-2 cells have a specific BDCA-2 marker. Phenotyping of BDCA-2 dendritic cells in peripheral blood characterizes these cells as being CD4+, Lin−, CD11c+, CD123bright, CD45RA−, CD2+. After appropriate activation, DC-2 cells induce T-cell differentiation into Th2 cells [47-49]. The growth factors for myeloid DCs are GM-CSF, IL-4, TNF-α but TNF-α seems to be the most important. It is able to both to stimulate production of IL-12 in CD1c+ cells and mature myeloid DCs. The role of IL-12 is also important in pathogenesis of PE. It is produced by APCs and is responsible for differentiation of Th0 into Th1 cells [43, 44]. Myeloid DCs also produce IL-18. Interleukin-12 (IL-12) up-regulates IL-18 receptor alpha (Ra) expression and synergistically with IL-18 elevates levels of IFNγ and intensify Th1 response [46]. As it was mentioned above, lymphoid DCs induce differentiation of Th0 into Th2 cells. In pre-eclampsia decreased levels of BDCA-2+ lymphoid dendritic cells and elevated ratio of CD1c+ : BDCA-2+ dendritic cells have been observed [99]. It was underlined that lower levels of peripheral blood BDCA-2+ cells and elevated ratio of CD1c+ : BDCA-2+ cells can promote increased Th1 response, that is present in patients with pre-eclampsia [99].

It was underlined that lower level of BDCA-2 and higher CD1+: BDCA-2 cell ratio is connected with increased Th-1 type response, that is present in women with PE [42].
Conclusion

The etiology of pre-eclampsia is still not clear, but the latest data put a new light on pathomechanism of this disorder. It was confirmed that immunological changes play a pivotal role in the etiology. Hopefully, in the near future there would be known markers that could predict development of this disease and what is more important could prevent it.

References


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