INVITED REVIEW

THE CRITICAL ROLE OF TH17 CELLS, TREG CELLS AND CO-STIMULATORY MOLECULES IN THE DEVELOPMENT OF PRE-ECLAMPSIA*

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Abstract
There are suggestions in the literature that pre-eclampsia has an immunological basis, in which there is a failure of the immune system to recognize fetal alloantigens. It seems that abnormal activation of the inflammatory response may play a role in the etiopathogenesis of pre-eclampsia. Many authors have found a number of changes in the immune system which might have contributed to its development. Recent data suggest that pre-eclampsia is a Th17/Treg imbalance with a predominance of Th17 immunity.

Key words: co-stimulatory molecules; dendritic cells; pre-eclampsia; Th17 cells; Treg cells

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INTRODUCTION

Pre-eclampsia is a syndrome known as "the disease of the theories" because of many theoretical proposals which aim to explain the etiology of this disorder. There are numerous suggestions that the syndrome has an immunological basis. According to the immunological theory, there is a failure in the maternal immune system to recognize fetal alloantigens (1, 2).

The possible immunological etiology of pre-eclampsia has been suggested by clinical and epidemiological observations. The syndrome occurs more often during first pregnancy and subsequent pregnancy with a different partner (3, 4). Furthermore, there is a higher risk of the occurrence of pre-eclampsia in the group of women with autoimmune disorders, such as systemic lupus erythematosus and antiphospholipid syndrome. Moreover, there are pathophysiological similarities of pre-eclampsia to other immunologically mediated diseases, such as hemolytic uremic syndrome and thrombocytopenic thrombotic purpura (1, 2).

It has been observed that there is a protective effect of sperm exposure: the duration of sexual cohabitation before conception is inversely related to the risk of pre-eclampsia (3). There are also epidemiological data on a higher incidence of pre-eclampsia in women conceiving by intrauterine insemination with donor sperm compared with intrauterine insemination with partner sperm (4). Koelman et al. established that oral sex is correlated with a diminished occurrence of pre-eclampsia (5).

TH1/TH2 IMBALANCE IN PRE-ECLAMPSIA

It seems that abnormal activation of the immune system may play a role in the etiology of pre-eclampsia. Many authors have found a number of changes in the adaptive immune system which may contribute to the development of pre-eclampsia (6-8). Recent data suggest that pre-eclampsia is a T helper 1/T helper 2 immunity disorder with predominance of Th1 type immunity (6-8). Furthermore, there is an evidence regarding the activation of the innate immune system in pre-eclampsia (9). It has been shown that normal third trimester pregnancy is characterized by the activation of peripheral blood leukocytes, which is further increased in pre-eclampsia (9).

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During normal pregnancy, many changes in the maternal immunological state take place. According to Wegmann's hypothesis, a successful pregnancy is a Th2 phenomemon (10). Observations in pregnant mice demonstrated Th1/Th2 immunity alterations with a shift to predominant Th2 type immunity (11). On the other hand, predominant Th1 type immunity was correlated with spontaneous abortions in mice (12), and similar observations were made in humans (12). Several other authors observed Th1/Th2 immunity alterations with a shift to predominant Th2-type immunity during normal human pregnancy (13, 14). It is not yet known what factors can influence the Th2 predominance in normal pregnancy. It has been demonstrated that interleukin (IL)-4 rather than other Th1 or Th2 cytokines is produced by cytotrophoblast cells. These findings suggest that, in human pregnancy, placental cytotrophoblast cells can modulate a Th2 bias (13, 14).

Saito et al. estimated the numbers of Th0, Th1, Th2 cells and Th1/Th2 lymphocyte ratio in the group of pre-eclamptic patients and during normal human pregnancy. They analyzed both CD4 surface marker and intracellular expressions of IL-4 and interferon-γ (IFN-γ) to calculate Th0, Th1 and Th2 cell ratios. In normal pregnancy, the percentage of Th1 cells was significantly lower in the third trimester and the ratios of Th1/Th2 were significantly lower in the second and third trimesters than in nonpregnant subjects. In contrast, the percentage of Th1 cells and the ratios of Th1/Th2 in preeclampsia were significantly higher than in normal third trimester pregnant subjects. The percentage of Th2 cells in pre-eclampsia was significantly lower than in the third trimester of normal pregnancy (15, 16).

In our study, we investigated Th1/Th2 balance in pregnant women with pre-eclampsia. Both IL-2, -4, -10, and IFN-γ concentrations in culture supernantants were determined using the ELISA method. We found that, in pre-eclamptic patients, phytohemagglutinin-stimulated IL-2 and IFN-γ production was significantly higher and IL-10 production significantly lower in comparison with the healthy normotensive pregnant women (17).

In our follow-up study, we investigated the intracellular expressions for Th1 and Th2 cytokines in peripheral blood T lymhocytes and NK cells of patients with pre-eclampsia and women with uncomplicated pregnancy. Mononuclear cells were isolated from peripheral blood and stimulated for 5 hours at 37 °C and 5% CO_2. The cells were then stained with antibodies against surface markers for T cell subsets and NK cells. After fixation and permeabilization processes, the cells were again stained with antibodies against intracellular cytokines IL-2, IL-4, IL-10, as well as IFN-γ. The intracellular expressions for Th1 and Th2 cytokines were determined using flow cytometry. We found that, in patients with pre-eclampsia, the expressions for IL-2 were significantly higher when compared to women with uncomplicated pregnancy. Furthermore, in the group of patients with pre-eclampsia the expressions for IL-2 were higher in T $CD8^+$ lymphocytes than in T $CD4^+$ cells. The expressions for IFN-γ did not differ in $CD4^+$ cells and $CD\ 8^+$ cells in both studied groups but they were higher in NK cells in the study group. The expression for IL-10 was lower in lymphocytes of pre-eclamptic patients when compared to controls (18). These results confirm the concept that there is Th1/Th2 imbalance in pre-eclamptic patients with predominant Th1 type immunity.

DENDRITIC CELLS AND CO-STIMULATORY MOLECULES IN PRE-ECLAMPSIA

Dendritic cells (DCs) are antigen-presenting cells with an ability to induce primary activation of immune responses. They capture and transfer information from the outside world to the cells of the adaptive immune system. DCs are not only critical for the induction of primary immune responses, but may also be important for the induction of immunological tolerance, as well as for the regulation of the type of T-cell mediated immune responses. Two distinct lineages of DCs have been described in humans. Myeloid dendritic cells (DC-1) are a major subpopulation. They express myeloid markers (CD13 and CD33) and Fc receptors (CD32, CD64, FcεRI) and are of monocytoid morphology. Furthermore, DC-1 cells expresses BDCA-2 (CD1c) antigen which is characteristic for peripheral blood DC-1 cells. Plasmocytoid (lymphoid) dendritic cells (DC-2) have been described recently in human peripheral blood and lymphoid tissue. Peripheral blood DC-2 cells express a specific BDCA-2 marker. After appropriate activation, DC-2 cells induce T cell differentiation into Th2 cells (19-23). Moreover, DCs are the only antigen-presenting cells that can prime naive T cell to a new antigen. In humans, peripheral blood $CD1c^+$ cells are identified as negative for lymphoid and myeloid cell-specific markers (lin^-) and are $HLA\text{-}DR^+$/$CD11c^+$. $CD1c^+$ cells produce large quantities of IL-12 when stimulated with tumor necrosis factor-α (TNF-α) or ligand for CD40, and drive T cell differentiation into Th1 lymphocytes.

Our further studies were geared towards the populations of myeloid and lymphoid DCs (including $BDCA\text{-}1^+$, $BDCA\text{-}2^+$, $BDCA\text{-}4^+$, and the $BDCA\text{-}1^+$ / $BDCA\text{-}2^+$ ratio) in normal pregnant women and in patients with pre-eclampsia. The cells were isolated from peripheral blood, stained with monoclonal antibodies against blood DC antigens (anti BDCA-1, BDCA-2, and BDCA-4) and measured using flow cytometry. $BDCA\text{-}1^+$, $BDCA\text{-}2^+$ and $BDCA\text{-}4^+$ DCs were present during all trimesters in normal pregnancy and in pre-eclamptic patients. We observed that the numbers of DCs were significantly lower in the second trimester when compared to the first and third trimesters of normal pregnancy. Furthermore, in the second trimester $BDCA\text{-}1^+$: $BDCA\text{-}2^+$ ratio was higher than in the other trimesters of normal pregnancy. All populations of DCs and $BDCA\text{-}1^+$: $BDCA\text{-}2^+$ cell ratio did not differ in the first and third trimesters of physiological pregnancy. The percentage of $BDCA\text{-}2^+$ dendritic cells was significantly lower in pre-eclampsia in comparison with the third trimester of normal pregnancy, while $BDCA\text{-}1^+$: $BDCA\text{-}2^+$ cell ratio was significantly higher in pre-eclamptic patients when compared to controls (24, 25). It appears that dendritic cells may be involved in the immune regulation during physiological

pregnancy. BDCA-1$^+$ and BDCA-2$^+$ dendritic cells could influence the Th2 phenomenon which is observed during physiological pregnancy. Furthermore, it seems possible that lower BDCA-2$^+$ cells percentage and higher BDCA-1$^+$: BDCA-2$^+$ cell ratio can be associated with increased Th1 type immunity in patients with pre-eclampsia. The possible regulatory mechanisms that might be involved in the alterations of the myeloid and lymphoid dendritic cells in pre-eclampsia remain obscure. Cytokines such as GM-CSF, IL-4 and TNF-α, which are the growth factors for myeloid DCs maturation, are likely to be engaged in CD1c$^+$: BDCA-2$^+$ shift.

Significantly lower BDCA-2$^+$ myeloid cells percentage and higher CD1c$^+$: BDCA-2$^+$ cell ratio associated with increased Th1-type immunity in pre-eclampsia were intriquing. Thus, we investigated the expressions for B7-H1 and B7-H4 molecules on myeloid and plasmacytoid DCs in peripheral blood of patients with pre-eclampsia, normal pregnant women and healthy non-pregnant women. DCs were isolated from peripheral blood, stained with monoclonal antibodies against blood DC antigens and B7-H1 and B7-H4 molecules and estimated using flow cytometry. The expressions for B7-H1 and B7-H4 molecules were significantly higher on CD1c$^+$ myeloid and CD303$^+$ plasmacytoid DCs in the first trimester of normal pregnancy when compared to the luteal phase of the ovarian cycle. Moreover, the expressions for B7-H1 molecule on CD1c$^+$ DCs in the second trimester of normal pregnancy were significantly higher when compared to the first trimester, but decreased in the third trimester when compared to the second trimester. The expressions for B7-H1 molecule on CD1c$^+$ myeloid and CD303$^+$ plasmacytoid DCs were significantly lower in pre-eclampsia when compared to healthy third trimester pregnant women (26). Higher expressions for B7-H1 and B7-H4 molecules on CD1c$^+$ myeloid and CD303$^+$ plasmacytoid DCs in the first trimester of normal pregnancy suggest their role in the immunomodulation during early pregnancy. The decrease in the expressions for B7-H1 molecule on myeloid CD1c$^+$ DCs in the third trimester of normal pregnancy may suggest their diminished tolerogenic activities before labor. Lower expressions for B7-H1 tolerance molecule on CD1c$^+$ myeloid and CD303$^+$ plasmacytoid DCs in pre-eclampsia may be associated with the increased inflammatory response which is observed in pre-eclampsia.

The purpose of our next study was to test the hypothesis that the expressions for CD200 and CD200R tolerance molecules are increased on peripheral blood DCs in normal pregnancy and decreased in pre-eclampsia. Consequently DCs were isolated from peripheral blood, stained with monoclonal antibodies against blood DCs antigens, as well as CD200 and CD200R antigens, and estimated using flow cytometry. The expressions for CD200 and CD200R molecules on CD1c$^+$ myeloid and BDCA-2$^+$ lymphoid DCs in the first trimester of normal pregnancy were significantly higher when compared to the luteal phase of the ovarian cycle. The expressions for CD200 molecule on CD1c$^+$ myeloid DCs were significantly lower in the third trimester of normal pregnancy when compared to the second trimester. The expressions for CD200R molecule on CD1c$^+$ myeloid DCs and BDCA-2$^+$ lymphoid DCs did not differ in pre-eclampsia and healthy third trimester pregnant women. However, the expressions for CD200 molecule on CD1c$^+$ myeloid and BDCA-2$^+$ lymphoid DCs were significantly higher in pre-eclampsia when compared to the healthy third trimester pregnant women (27). These results suggest increased tolerogenic properties of myeloid and lymphoid DCs in normal pregnancy. Moreover, they suggest a decrease in tolerogenic properties of DCs before delivery. Interestingly, higher expressions for CD200 molecule on CD1c$^+$ myeloid and BDCA-2$^+$ lymphoid DCs in pre-eclampsia may constitute the tolerogenic mechanism secondary to the proinflammatory response which is observed in this syndrome. The systemic inflammatory response during pregnancy might be a major cause of pre-eclampsia because chronic inflammation can reverse the suppressive effect of Treg cells.

In conclusion, the above results suggest increased tolerogenic properties of myeloid and lymphoid DCs in normal human pregnancy. The decreased expressions for CD200 molecule on CD1c$^+$ myeloid DCs in the third trimester of normal pregnancy suggest that tolerogenic properties of DCs decrease before delivery. It seems possible therefore that the higher expressions for CD200 molecule on CD1c$^+$ myeloid and BDCA-2$^+$ lymphoid DCs in pre-eclampsia may constitute the tolerogenic mechanism secondary to the proinflammatory response which is observed in this syndrome.

CD40 LIGAND IN PRE-ECLAMPSIA

The antigen CD40 is a 50 kD glycoprotein bound to cellular membranes. It belongs to the TNF receptor protein superfamily. The antigen CD40 participates in many biological processes between immune cells and other cell types. The ligand for CD40L antigen (CD154 antigen) is expressed on the surface of activated T CD4$^+$ lymphocytes, basophils and mast cells. Furthermore, a biologically active form of the ligand for CD40 (CD40L) has been shown to exist in circulation. This soluble molecule is an 18 kDa protein homotrimer which arises as a result of enzymatic proteolysis of CD40L, following the interactions between CD40 antigen and CD40L. The increase in concentrations for soluble CD40L (sCD40L) reflects the augmentation of CD40-CD40L interaction processes which play an important role in the activation of innate response (28). Our continued study concerned surface expressions for CD154 antigen on peripheral blood T CD4$^+$ lymphocytes and serum concentrations of sCD40L antigen in normal nonpregnant and pregnant women in their first, second, and third trimesters of pregnancy, and patients with pre-eclampsia. Mononuclear cells were isolated from peripheral blood and stained with monoclonal antibodies against surface markers (CD4, CD154). The expressions for CD154 antigen on T CD4$^+$ lymphocytes were determined using flow cytometry. The serum sCD40L concentrations were measured using ELISA method. The CD154 expression on T CD4$^+$ lymphocytes and concentration of CD40L were significantly higher in pre-eclampsia when compared to normal third trimester. There was a positive correlation

between the percentage of $CD4^+CD154^+$ cells and sCD40L concentrations in pre-eclampsia. In the first trimester of normal pregnancy, the expressions for CD154 antigen on T $CD4^+$ lymphocytes and the concentrations for sCD40L were significantly lower when compared to non pregnant women (29). These results indicate increased CD40-CD40L interactions of T $CD4^+$ lymphocytes with antigen presenting cells in pre-eclampsia. Moreover, our findings suggest that activated T $CD4^+$ lymphocytes expressing CD154 antigen are an essential source of sCD40L in pre-eclampsia.

HLA-G IN PRE-ECLAMPSIA

The fetus is a semi-allograft because half of its histocompatibility antigens comes from the father. Recent data show that the fetoplacental unit may not be the only mechanical barrier which reduces the possibilities of contact between maternal lymphocytes and fetal tissues. There are also many protective mechanisms which alter paternal antigen presentation and may influence the development of potentially harmful reactions of the mother's immune system. For example, there is no human leukocyte antigen (HLA) class II molecules expression on syncytio- and cytotrophoblast (30).

It has been proven that the only non-classic HLA molecule expressed on the placenta is the class I HLA-G molecule. It is thought that this molecule protects the trophoblast from the activation of decidual NK cells, but it is not the only role of the HLA-G molecule in the development of protective immunological mechanisms during normal pregnancy (31). Possibly, alterations in the expression for HLA-G molecule could influence the secretion of cytokines in pre-eclamptic patients. The only known polymorphic histocompatibility antigens on the fetal trophoblast are HLA-C molecules. It has been suggested that the recognition of these molecules by killer immunoglobulin receptors (KIRs) on maternal decidual NK cells is a key factor in the development of pre-eclampsia. Mothers lacking most of or all activating KIR (AA genotype) when the fetus possessed HLA-C2 group were at a greatly increased risk of pre-eclampsia. This was true even if the mother herself also had HLA-C2 (30, 31).

We investigated the dynamics of the alterations of soluble HLA-G (sHLA-G) concentrations in sera of healthy nonpregnant women, as well as healthy pregnant women in the first, second and third trimesters. Furthermore, the aim of the study was to test the hypothesis that sHLA-G concentrations are decreased in patients with pre-eclampsia. Serum concentrations for sHLA-G protein were determined using immunoenzymatic ELISA method. The sHLA-G protein concentrations in pregnant women in all the trimesters of normal pregnancy were significantly higher in comparison with healthy nonpregnant women. Interestingly, the sHLA-G concentrations in the second trimester were significantly higher than in the first and third trimesters. The concentrations for sHLA-G in sera of patients with pre-eclampsia tended to be lower than in pregnant women in the third trimester of normal pregnancy but the difference was not statistically significant (32). These results indicate that normal pregnancy is associated with elevated serum concentrations of the particulary sHLA-G molecule. The increased concentrations for sHLA-G in the mid-gestation could reflect a role of this protein in the second phase of the invasion of extravillous cytotrophoblast into the spiral arteries.

TH17/TREG CELLS IMBALANCE IN PRE-ECLAMPSIA

It was proposed that regulatory T lymphocytes $CD4^+CD25^{bright}$ (Tregs) play an important role in the development and maintenance of tolerance in peripheral tissues. When they are absent, allogenic fetuses are resorbed, suggesting that the presence of regulatory T cells is necessary for a successful gestation in allogenic pregnancy. Furthermore regulatory T cells have a role in the induction of transplantation tolerance. They express high levels of CD25 (IL-2Rα), as well as cytotoxic T lymphocyte antigen 4 (CTLA-4) and transcription factor Foxp3 (33, 34). This functional activity requires cell-to-cell contact.

Treg cells are said to be responsible for mediating maternal tolerance for fetal antigens (35-38). There are some evidences that Treg lymphocytes play an essential role in controlling and preventing fetal rejection. This is possible because of their capacity to regulate the activation of allo-reactive T cells. It has been observed that normal human pregnancy is associated with the expansion of Treg cells (35-38). Some authors found that the populations of decidual and peripheral blood Tregs are reduced in pre-eclampsia (39). On the other hand, there were reports that the numbers of peripheral blood Tregs were similar in preeclampsia and normal pregnancy (40). But it should be taken into account that in those studies the numbers of observations were small and the authors estimated, rather than precisely evaluated, $CD4^+CD25^{high}$ Treg cells (40).

Th17 lymphocytes are a recently discovered subset of T $CD4^+$ lymphocytes which produce IL-17. The discovery of the family of IL-17 shed a new light on the understanding of host defense, as well as the pathogenesis of some immunological disorders. A new hypothesis concerning regulatory mechanisms of chronic inflammatory diseases draws attention to the imbalance which led to the predominance profile of Th1/Th17 over Th2/Treg in inflammatory conditions. The upregulation of Th17 immunity can contribute to the development and progression of autoimmune diseases, chronic inflammatory diseases and graft rejection. Furthermore, IL-17 may induce allergic disorders. On the other hand, the deficiency of Th17 cells is one of the causes why immune deficiencies result in recurrent viral, bacterial and fungal infections (33, 34).

We investigated the prevalence of T $CD3^+CD4^+$ lymphocytes producing IL-2, IL-4, IL-17, and IFN-γ, as well as $CD4^+CD25^+FoxP3^+$ T regulatory cells in peripheral blood of both patients with pre-eclampsia and healthy pregnant women in the third trimester. Our additional goal was to assess the immunosuppressive activity of T regulatory cells in pre-eclamptic patients as compared with third trimester controls. The percentage of $CD4^+CD25^+FoxP3^+$ Treg cells and $CD3^+CD4^+$ T lymphocytes with intracellular expressions for cytokines was estimated using monoclonal antibodies

and flow cytometry. The *in vitro* functional assays were performed with the use of Treg Cells Isolation Kit and ^{3}H-thimidine. The percentage of $CD3^{+}CD4^{+}$ T lymphocytes producing IL-17A was significantly higher in pre-eclampsia when compared to healthy pregnant women in the third trimester. The population of $CD4^{+}CD25^{+}FoxP3^{+}$ Treg cells was significantly lower in the study group when compared to the controls. There were no changes in the proliferative response of $CD3^{+}CD4^{+}CD25^{-}$ T lymphocytes of patients with preeclampsia during *in vitro* assay without Treg cells and after the addition of autologous Tregs (39, 41, 42). In normal pregnancy, the proliferative response of $CD3^{+}CD4^{+}CD25^{-}$ T lymphocytes was significantly higher without Treg cells when compared to a similar response after the addition of autologous Tregs. These results testity to the upregulation of Th17 immune response in preeclampsia. It seems that the decreased number and reduced function of Treg cells may be responsible for the activation of inflammatory response in this disorder. The predominance of Th17 immunity in preeclampsia could act through the modulation of Th1/Th2 immune response.

Subsequently, we focused on the role of apoptosis of T cells in the etiopathogenesis of pre-eclampsia. Specifically, we investigated the surface expressions for CD95 (APO-1/Fas) antigen and the intracellular expressions for antiapoptotic protein Bcl-2 and proapoptotic protein Bax in $CD4^{+}CD25^{+}FoxP3^{+}$ T regulatory lymphocytes (Tregs), as well as the percentage of $CD8^{+}CD28^{+}$ T cytotoxic cells in peripheral blood of patients with pre-eclampsia in comparison with healthy pregnant women in the third trimester. The population of $CD4^{+}CD25^{+}FoxP3^{+}$ Treg cells was significantly lower in peripheral blood of patients with pre-eclampsia when compared to the third trimester of normal pregnant women. The percentage of $CD4^{+}CD25^{+}FoxP3^{+}$ Treg cells that express Bcl-2 was significantly lower in peripheral blood of pre-eclamptic patients and healthy pregnant women, whereas the percentage of $CD4^{+}CD25^{+}FoxP3^{+}$ Treg cells with the expression for Bax did not differ in both groups. Moreover, the mean fluorescence intensity (MFI) for Bcl-2 protein in $CD4^{+}CD25^{+}FoxP3^{+}$ Treg cells was significantly lower, whereas the MFI for Bax protein was significantly higher in pre-eclampsia when compared to the control group. The percentage of $CD8^{+}CD28^{+}$ T cells did not differ in both studied groups whereas MFI for CD28 antigen on T $CD8^{+}$ cells was significantly higher in pre-eclampsia as compared to controls (43-45). Overall, the deficit of $CD4^{+}CD25^{+}FoxP3^{+}$ Treg lymphocytes which is observed in pre-eclampsia may be associated with the alterations in the apoptosis markers.

CONCLUDING REMARKS

Pre-eclampsia is characterized by systemic inflammatory response. However, our results indicate that the pathogenesis of this disease may be more complex than the mere activation of inflammatory response alone. Inflammatory response could be observed in other complications of pregnancy, such as unexplained recurrent pregnancy loss. It is puzzling that similar inflammatory mechanisms may cause early pregnancy loss in some cases but other circumstances could lead to the development of pre-eclampsia. It seems possible, therefore, that in pre-eclampsia some protective mechanisms are triggered parallel to the activation of the inflammatory response. This may be a key point to understand the pathogenesis of the syndrome. In pre-eclampsia, the inflammation causes the inappropriate invasiveness of trophoblast but the development of pregnancy is continued.

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From the Vice-Editor

As indicated by the heading, this invited review was specifically written for our request. The paper comes from a leading Polish tertiary referral perinatal center. Professors Dorota Darmochwał-Kolarz and Jan Oleszczuk share with us the knowledge stemming from their long-term interests in and in-depth investigations on fine immunological aspects of pre-eclampsia.

At the beginning of the XXI century, the causes of pre-eclampsia and eclampsia still remain not fully elucidated. Over decades, many causative pathomechanisms have been proposed, such as Page's mosaic theory, circulatory thromboxane A_2-prostacyclin imbalance, abnormal placentation concept put forth by Kingdom and Kaufmann, altered oxygenation of the product of conception in early pregnancy (oxygen has been considered as the main regulator of trophoblast proliferation and differentiation), placental production of antiangiogenic factors, and chronic systemic inflammation, to name just a few. These lines of previous research are now more and more frequently supplemented by immunological studies.

From a review of the data from their own laboratory and those generated by others, Darmochwał-Kolarz and Oleszczuk draw our attention to the fact that pre-eclampsia is a T helper 1 to T helper 2 immunity disorder (with predominance of T helper 1 type immunity). Furthermore, higher expressions for CD200 molecule on $CD1c^+$ myeloid and $BDCA\text{-}2^+$ lymphoid dendritic cells are found and a deficit of $CD4^+CD25^+FoxP3^+$ Treg lymphocytes is observed, among others. Kindly consider how graciously these findings now fit into many pieces of the information known from previous work on pre-eclampsia.

This illustrative contribution published in our *Developmental Period Medicine* was supposed to add to our way of thinking of pre-eclampsia, and it truly did.

Professor Maciej Jóźwik