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Decreased expression of MMP-9 in CD8+ cells in placenta with severe preeclampsia

M Orlovic 1, V Tomic 1,2, K Vukojevic 3,4, I Hudic 5, V Mandic 1, I Azinovic 3, D Sildo 1, M Kajic 1, V Soljic 3,6

1Department of Gynecology, University Hospital in Mostar, 2Faculty of Health Studies, University of Mostar, 3Laboratory of Morphology, Department of Histology and Embryology, School of Medicine, University of Mostar, Mostar, Bosnia and Herzegovina, 4Laboratory for Early Human Development, Department of Anatomy, Histology and Embryology, School of Medicine, University of Split, Split, Croatia, 5Clinic of Gynecology and Obstetrics, University Clinical Center, Tuzla, and 6Department of Pathology, Cytology and Forensic Medicine, University Hospital in Mostar, Mostar, Bosnia and Herzegovina

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Abstract

We compared the number of CD4-positive (CD4+) and CD8-positive (CD8+) cells in severe and non-severe preeclampsia (PE), and in normal pregnancy. We also evaluated the expression of matrix metalloproteinase 9 (MMP-9) in CD4+ and CD8+ cells. Immunohistochemistry for CD4+ and CD8+ was performed on the decidua basalis of 15 severe and 13 non-severe PE women and compared to decidual tissue of 19 normal pregnancies (control group). Co-expression of MMP-9 with CD8+ and CD4+ cells was determined by double immunofluorescence staining. The median number of CD8+ cells/mm² was significantly lower for the severe PE group than for the normal pregnancy group, as was the number of CD4+ cells and MMP-9+CD8+ cells. No statistical difference was found between the non-severe PE group and the normal pregnancy group. The significant decrease of CD4+, CD8+ and MMP-9+CD8+ cells at the fetal-maternal interface only in the severe PE group suggests that immunological disorders play a role in the pathophysiology of severe PE.

Key words: CD4, CD8, decidua basalis, immunohistochemistry, MMP-9, placenta, preeclampsia

Preeclampsia (PE) is a multi-system disorder that affects 5–10% of all pregnancies. It is a major cause of maternal and perinatal morbidity and mortality (Cunningham 2014). The pathophysiology of PE is believed to include various degrees of immunological disorders and CD8+ lymphocytes, among other cells, are thought to play a role in these immunological changes (Redman and Sargent 2010).

The function of CD8+ cells during normal pregnancy is poorly understood. CD8+ cells are a subpopulation of T cells that after antigen stimulation can differentiate into one of many CD8+ T cell subsets that exhibit different functions (Scaife et al. 2006, Strioga et al. 2011, Wang et al. 2015). Decidual CD8+ T cells are the most numerous subpopulation of T cells at the fetal-maternal interface (Vassiliadou and Bulmer 1996) and are considered to be one of the main types of cells that could respond to fetal HLA-C antigens (Shao et al. 2005, Tilburgs et al. 2010, Wang et al. 2015). Tilburgs et al. (2010) reported that decidual CD8+ T cells are mostly CD45RA−CCR7− effector memory, effector and CD8+CD28+ suppressor T cells which, unlike CD8+ T cells in peripheral blood, do not express the cytolytic molecules, granzyme B and perforin; therefore they are likely unable to develop a cytotoxic response (Tilburgs et al. 2009). Decidual CD8+ cells also are related to the production of cytokines during early pregnancy that are crucial for adequate trophoblast invasion (Scaife et al. 2006). It
appears that CD8+ cells are highly differentiated and activated cells at the fetal-maternal interface, but the exact mechanisms of CD8+ T cell activation and differentiation remain unclear. Many factors can influence the CD8+ T cell differentiation pathway. For example, the strength and duration of the T cell antigen receptor is important for differentiation of CD8+ T cells to full effector cells; if the signal is not optimal, they undergo programmed cell death or death by neglect (Kaech and Ahmed 2001, Obar and Lefrancois 2010). Cytokines such as TGF-β and IL-10, and hormones such as progesterone also can influence CD8+ cell differentiation (Tilburgs et al. 2010).

Matrix metalloproteinases (MMPs) also are associated with T cell activation and tissue infiltration (Graesser et al. 2000, Owen et al. 2003, Benson et al. 2011). MMP-9 is the main protease that supports cytotrophoblast invasion and it is highly expressed at the fetal-maternal interface, especially by uterine natural killer cells, decidual cells and the trophoblast (Plaks et al. 2013). Benson et al. (2011) reported a significant decrease in the percentage of CD4+ and especially CD8+ T cells in murine lung after MMP-9 inhibition. More specifically, inhibition or deficiency of MMP-9 increased the intracellular calcium flux, which led to a significant decrease in cellular activity of the T cells by decreasing the surface expression of CD25 and IL-2. These investigators suggested that MMPs may function intracellularly to regulate T cell activation and/or migration. Others also have described the role of MMPs in T cell functions (Graessser et al. 2000, Fares et al. 2013). Defects in decidual CD8+ T cell regulation and activation may contribute to placental pathology. The role of MMP-9 in the activation and function of T cells, especially CD8+ cells, is largely unknown and to the best of our knowledge, has not been studied in PE.

CD4+ T cells are a heterogeneous group of cells composed of several subsets including Th1, Th2, Th17 and CD4+ T regulatory cells. In women whose pregnancies are complicated by PE, Th1 and Th17, subsets are increased, while Th2 and T regulatory subsets are decreased compared to women with normal pregnancies (Amaral et al. 2015). Decidual CD4+ T cells also are thought to possess fetal specificity and are assumed to react to fetal alloantigens (Piccinni et al. 2015).

To understand better the role of CD8+ and CD4+ cells at the fetal-maternal interface, we analyzed these cells in third trimester decidua basalis of both severe and non-severe PE, and compared them to the decidua basalis of normal pregnancies. We also measured the expression of MMP-9 in these cells to evaluate its role in T cell activation.

### Material and methods

We analyzed placental tissue containing decidua basalis from 13 women with non-severe PE, 15 women with severe PE and 19 women in the control group with healthy term deliveries. The placental tissue for all three groups (control, non-severe, severe, PE) were macroscopically normal. PE was defined as a gestational onset of hypertension (systolic blood pressure ≥18.9 kPa or ≥140 mmHg, diastolic blood pressure ≥11.9 kPa or ≥90 mmHg) and either proteinuria ≥300 mg/24 h or 300 mg/l urine in one sample, or signs/symptoms of end organ dysfunction after 20 weeks gestation in women with no prior history of hypertensive disorders. Non-severe and severe PE were defined according to the criteria of American College of Obstetrics and Gynecology (ACOG; American College of Obstetricians and Gynecologists 2013). The excluding criteria for all groups were chronic hypertension, renal disease before pregnancy, clinical or pathological diagnosis of chorioamnionitis, any kind of infectious disease, previously recorded diabetes mellitus (type 1 or 2), conception by assisted reproductive technology or multiple gestations.

### Tissue preparation

Placentae were collected after vaginal or cesarean section deliveries and fixed in 4% formalin. Tissue specimens were excised and after washing in phosphate buffer, they were dehydrated through ascending concentrations of alcohol. After clearing in xylol, tissue blocks (1 cm × 1 cm) were embedded in paraffin, and sections were cut at 4 µm and mounted on silanized slides (Kraljevic et al. 2015, Prusac et al. 2011). For immunohistochemical evaluation of the markers, one placental section was taken from the central part of a macroscopically normal placental disc (for all groups including control, non-severe and severe PE), close to the umbilical cord insertion. All placental samples contained basal decidua.

### Immunohistochemistry

Tissue sections were deparaffinized in xylol, then rehydrated through descending concentrations of alcohol and twice in distilled water. The sections then were incubated in 3% H2O2 for 15 min at room temperature to block endogenous peroxidase. Antigen retrieval was performed by heating the sections in EDTA buffer, pH 9, in a microwave oven for 17 min. After cooling to room temperature, sections
were washed in phosphate-buffered saline (PBS) and incubated for 1 h with the following primary antibodies: mouse monoclonal CD8 antibody (C8/144B; DAKO, Glostrup, Denmark) diluted 1:100 in PBS and mouse monoclonal CD4 antibody (4B12; DAKO) diluted 1:100 in PBS. After a wash with PBS, sections were incubated in HRP rabbit/mouse system (K5007; DAKO) for 30 min. Antigen-antibody binding was developed by adding 3,3′-diaminobenzidine (DAB + chromogen) diluted 1:50 in substrate buffer, both provided in the kit together with HRP rabbit/mouse system (K5007, DAKO). Tissue then was washed with distilled water and stained with hematoxylin. The membranes of cells that reacted with primary antibodies were brown. All tissue sections were examined using an Olympus CX41 light microscope (Olympus, Tokyo, Japan). Negative control tissue sections underwent the same procedure except they were incubated with PBS instead of primary antibody. The negative control exhibited only hematoxylin stained nuclei and no brown coloration of the membrane. Lymph node tissue was used as a positive control.

**Double immunofluorescence staining**

We used double immunofluorescence staining to examine co-expression of MMP-9 with CD8 and CD4 in placental decidua tissue sections. Sections were deparaffinized and rehydrated as described above for immunohistochemistry. After antigen retrieval, sections were incubated with both CD8 or CD4 primary antibodies for 1 h and rabbit monoclonal MMP-9 antibody (A0150; DAKO). All primary antibodies were diluted 1:100 in PBS. Sections were washed in PBS, then incubated with a combination of secondary antibodies: goat anti-mouse rhodamine (AP124R; Jackson Immuno Research Lab, West Grove, PA) diluted 1:300 with PBS and goat anti-rabbit FITC (AP132F; Jackson Immuno Research Lab) diluted 1:300 with PBS. After rinsing in PBS, sections were counterstained with DAPI and coverslipped (Imuno-mount; Shandon Inc., Pittsburgh, PA). Sections then were examined using a fluorescence microscope (Olympus CX41; Olympus, Tokyo, Japan) equipped with a digital camera.

**Quantification and data analysis**

All sections were analyzed in blinded manner by two observers (VS and MO). Images were captured using a DP71 digital camera mounted on an Olympus CX41 microscope. The Olympus software, Cell B, was used to measure the area at 40 ×. The number of stained cells was counted in placental decidua basalis. All empty spaces were excluded from the measurement. Ten areas were used to analyze a minimum of 1 mm² of tissue for each placenta. Results were recorded as numbers of cells/mm².

**Statistical analysis**

The data were analyzed by Kruskal–Wallis and Dunn’s post hoc test using GraphPad Prism statistical software (GraphPad software, Inc., San Diego, CA). The data are reported as medians or means ± SD. Values for $p \leq 0.05$ were considered significant.

**Results**

Clinical data for the patients in the different groups are shown in Table 1.

Figure 1 shows the number of CD8⁺, CD4⁺, MMP-9⁺ cells and the proportion of MMP-9⁺ CD8⁺/total CD8⁺ cells in the decidua basalis in the groups examined. The total number of CD8⁺ cells/mm² in decidua basalis of the severe PE group (median = 20) was decreased significantly compared to the control group (median = 59.3; $p < 0.0001$). The difference between the non-severe and control groups was not statistically significant (Fig. 1A). The total number of CD4⁺ cells/mm² in the severe PE group (median = 4.5) was decreased significantly compared to the control group (median = 18.7; $p < 0.01$). The difference between the non-severe and control groups was not statistically significant (Fig. 1B). The differences in the total number of MMP-9⁺ cells in decidua tissue among the groups examined were not statistically significant (Fig. 1C).

We also evaluated the proportion of MMP-9⁺ CD8⁺ cells among the total CD8⁺ cells and found a significantly decreased number in the severe PE group (16.58%) compared to the non-severe (65.5%) and control groups (74.7%; $p < 0.001$) (Fig. 1D). We did not find co-expression of MMP-9 and CD4⁺ in lymphocytes (data not shown).

Figure 2 shows examples of CD4 and CD8 staining of decidua basalis among the groups studied. Many CD8⁺ cells were evident in decidua basalis of the control and non-severe PE groups (Fig. 2A, B). CD8⁺ cells mainly formed a large group of cells with villi especially at the border. We found only a few CD8⁺ cells in the decidua basalis of the severe PE group (Fig. 2C).

We found a greater number of CD4⁺ cells in the decidua basalis of the control group (Fig. 2D) compared to the severe PE group. We observed only a few CD4⁺ cells dispersed among decidual cells in the non-severe PE group (Fig. 2E). We observed also a
Table 1. Clinical features of the patients in the study groups

<table>
<thead>
<tr>
<th></th>
<th>Non-severe preeclampsia (n = 13)</th>
<th>Severe preeclampsia (n = 15)</th>
<th>Control (n = 19)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years) mean ± SD</td>
<td>30.30 ± 6.78</td>
<td>28.50 ± 5.50</td>
<td>29.47 ± 4.26</td>
<td>0.730</td>
</tr>
<tr>
<td>Gestational age (weeks) median (IQR)</td>
<td>39 (34–41)</td>
<td>34 (33–39)</td>
<td>40 (37–41)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Systolic RR (mm Hg) mean ± SD</td>
<td>142 ± 7.55</td>
<td>175 ± 18.02</td>
<td>116 ± 6.94</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diastolic RR (mm Hg) median (IQR)</td>
<td>90 (85–100)</td>
<td>120 (110–140)</td>
<td>75 (65–80)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Neonatal birth weight (g) median (IQR)</td>
<td>3325 (1800–3950)</td>
<td>1830 (1270–2200)</td>
<td>3250 (2250–4500)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cesarean deliveries (%)</td>
<td>4 (31)</td>
<td>15 (100)</td>
<td>4 (21.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body mass index (BMI) mean ± SD</td>
<td>23.54 ± 2.06</td>
<td>23.49 ± 2.49</td>
<td>25.92 ± 4.18</td>
<td>0.084</td>
</tr>
<tr>
<td>Intrauterine growth restriction (IUGR) (%)</td>
<td>1 (7.69)</td>
<td>11.25 (75)</td>
<td>1 (5.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Postpartum complications (%)</td>
<td>1 (7.69)</td>
<td>6.25 (41.7)</td>
<td>0 (0.0)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD analyzed by ANOVA, medians (IQR = interquartile range) analyzed by Kruskal–Wallis test, and percentages using Chi-square tests.

Fig. 1. Distribution of CD8⁺ (A), CD4⁺ (B), MMP-9⁺ (C), MMP-9⁺CD8⁺/total CD8⁺ cells (D) in the decidua basalis of the control group (n = 19), non-severe PE (n = 13) and severe PE (n = 15). Data are medians for CD8⁺, CD4⁺ and MMP-9⁺. Double-positive MMP-9⁺CD8⁺ cells were calculated as a proportion of total CD8⁺ cells. Significant differences indicated by *p < 0.01, **p < 0.001, ***p < 0.0001.
significantly reduced number of CD4+ cells in decidua tissue of the severe PE group compared to the control group (Fig. 2F).

Double immunofluorescence staining of MMP-9 and CD8 markers in the decidua basalis of the groups examined is shown in Fig. 3. Many MMP-9+CD8+ cells with granular membrane expression were found in the control group. In addition to lymphocytes, decidual cells also co-expressed MMP-9, which appears as moderate staining of the cytoplasm (Fig. 3A–D). Like the control group, the non-severe PE group showed many MMP-9+CD8+ cells with distinct granular expression of only part of the lymphocyte membrane. Apart from MMP-9+CD8+ lymphocytes and MMP-9+ decidual cells, there also were a few MMP-9+ lymphocytes that did not express CD8 (Fig. 3E–H). In the severe PE group, only a few MMP-9+CD8+ positive were found and these exhibited mild staining intensity. Decidual cells, however, expressed MMP-9 similarly in all groups. We also observed a few MMP-9+CD8− lymphocytes in the decidual tissue of the severe PE group (Fig. 4I–L).

Discussion

Although the regulatory mechanisms remain largely unknown, the pathophysiology of PE is associated with immunological disorders in which T cells play an important role. We determined the number of
CD4$^+$ and CD8$^+$ T cells in severe and non-severe PE patients compared to normal pregnancies. We also evaluated the expression of MMP-9 in these cells and in decidual cells.

We found that the number of decidual CD8$^+$ cells was significantly decreased in the severe PE group compared to the normal pregnancy group. Our findings were consistent with some earlier reports (Rieger et al. 2009, Williams et al. 2009), but contrary to others in which increased levels of CD8$^+$ cells were found in PE (Wilczynski et al. 2003, Quinn et al. 2011). A possible explanation for the disparate results may be related to the different methods used for determining immune cells. For example, Rieger et al. (2009) used flow cytometry to determine decidual T cells, whereas Quinne et al. (2011) used immunohistochemistry to evaluate decidual T cells. Some of these investigators counted T cells in peripheral blood while others counted decidual T cells, which is another likely reason for disparate results, because the number of peripheral blood lymphocytes does not equal the lymphocytes at the fetal-maternal surface and activated T cells are enriched in decidual tissue (Tilburgs et al. 2006, Toldi et al. 2008).

Tilburgs et al. (2010) reported a significant increase in the number of CD8$^+$ cells in normal early pregnancy decidua compared to peripheral blood. These investigators described highly differentiated CD8$^+$ cells at the fetal-maternal interface of normal pregnancy. K lentzeris et al. (1994) reported more CD8$^+$ cells at implantation and fewer of these cells in the endometrium of women with unexplained infertility. Wang et al. (2015) reported that decidual CD8$^+$ cells, unlike peripheral tissue cytotoxic CD8$^+$ cells, provided protective immunity and exhibited suppressive and regulatory functions that permitted fetal development. The literature suggests that CD8$^+$ cells play an important role in maintaining normal pregnancy. Our findings are consistent with the reports described above concerning the importance of CD8$^+$ cells in normal pregnancy; however, the number of CD8$^+$ cells and their function in PE remains unclear. Others have explained the increased number of cytotoxic CD8$^+$ cells in PE as a result of inflammation that leads to clinically manifested PE (Wilczynski et al. 2003, Quinn et al. 2011, Saito and Sakai 2003). Our findings and those of others concerning the large number of CD8$^+$ cells at the fetal-maternal interface during early pregnancy suggest a protective role for these cells for maintaining a normal pregnancy (K lentzeris et al. 1994, Wang et al. 2015, Tilburgs et al. 2010). CD8$^+$ T cells, after encountering specific antigens, can develop suppressive and regulatory functions (Konya et al. 2009, Wang et al. 2015); however, the exact mechanisms of CD8$^+$ T cell differentiation into suppressor cells in decidual tissue is largely unknown.

It has been shown that CD4$^+$ and CD8$^+$ cells can produce MMP-9 after antigen stimulation, which is important for T cell activation and optimal suppressor activity (Graesser et al. 2009, Benson et al. 2011). Benson et al. (2011) reported that MMP-9 gene deficiency or specific MMP-9 inhibition resulted in significant impairment of T cell function and activation in mice. Experiments in vivo have shown that MMP-9 inhibition causes a significant decrease in the percentage of CD8$^+$ cells in murine lung, which affects their migration and cellular activation (Benson et al. 2011). We evaluated the expression of MMP-9 in CD8$^+$ and CD4$^+$ cells and found a significant decrease in MMP-9/CD8$^+$ cells in the severe PE group compared to the non-severe and control groups. This could mean that decidual CD8$^+$ cells exhibit suppressor activity and that overall reduction in the number of these cells causes immune disorders at the fetal-maternal interface. Regulatory mechanisms are important for maintaining normal pregnancy and that decidual tissue is enriched with a large number of T regulatory cells (Aluvihare et al. 2004, Sasaki et al. 2004, Saito et al. 2007); our findings support this concept. We did not observe MMP-9 expression in CD4$^+$ T cells. Also, the difference in MMP-9 expression by decidual cells among the groups studied was not statistically significant, which is consistent with previous reports that described stable expression of MMP-9 throughout pregnancy (Anacker et al. 2011). The role of MMP-9 in T cell function and activation remains unclear and further research is required to determine how MMP-9
regulates T cell activation and function. It is noteworthy, however, that MMP-9 expression was greater in CD8+ cells than in CD4+ cells (Fares et al. 2013).

The underlying pathophysiology mechanism of PE is poorly understood. Namely, in PE we have reduced placental perfusion because of the uterine spiral arterioles impairment, which develops from inadequate trophoblast migration toward the arterioles (Dekker and Sibai 1998, Ditisheim et al. 2013). Additionally, trophoblast invasion can be regulated by cytokines produced by CD8+ lymphocytes (Scaife et al. 2006). However, we were unable to determine yet whether the decreased number of CD8+ cells during the third trimester is a cause or a consequence of PE.

Successful pregnancy is related to the presence of CD4+ cells, which, together with regulatory T cells, are thought to play a role in maintaining normal human pregnancy. Specifically, regulatory T cells can produce cytokines that make the fetal-maternal interface a more acceptable environment for an allogenic fetus (Piccinni et al. 2015). We found a significant decrease in CD4+ lymphocytes in the severe PE group. A decrease in CD4+ cells may indicate a decrease in monocytes, macrophages and dendritic cells, because CD4+ is also a marker of these cells.

The severe PE cases in our study mostly were delivered by week 34 of gestation (Table 1), so they could be categorized as early onset PE. It is widely considered that early and late onset PE exhibit different pathophysiology and should be regarded as different forms of the disease (Crispi et al. 2006). Our findings were consistent with this concept, because we found that the decreased number of CD8+ and MMP9+CD8+ cells compared to the control group is significant only in the severe PE group.

A potential limitation of our study was the difference in gestational ages between the severe PE and the normal pregnancy group; the difference was unavoidable. Considering that pre-term labor is associated with various immunological changes, especially in the T cell pool (Steinborn et al. 2012, Hamilton et al. 2013), we believe that finding gestational age-matched controls for the severe PE group would be unreliable for obtaining an accurate count of immunological cells. In addition, only term delivery is confirmation of a normal, healthy pregnancy. We found that PE, especially its severe form, is associated with immunological disorders and that T cells serve important functions at the fetal-maternal interface. Findings during early pregnancy of a high number of CD8+ cells in the decidua of a normal pregnancy and the decreased number in pathological pregnancies indicate that these cells play an important role in the immunological maintenance of pregnancy. The MMP-9 expression in CD8+ cells could have an immune regulatory effect, which could offer therapeutic possibilities. Finally, the significant decrease of MMP9+CD8+ cells in the severe PE group is an interesting finding that requires further research to determine the functions of these cells in PE.

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**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

**ORCID**

M Orlovic  http://orcid.org/0000-0002-5337-0780  
V Tomic  http://orcid.org/0000-0002-1015-4463  
K Vukojevic  http://orcid.org/0000-0003-2182-2890  
I Hudic  http://orcid.org/0000-0002-7819-3530  
V Mandic  http://orcid.org/0000-0001-9867-1977  
I Azinovic  http://orcid.org/0000-0003-0285-7684  
D Soldo  http://orcid.org/0000-0001-8486-3177  
M Kajic  http://orcid.org/0000-0002-3769-6983  
V Soljic  http://orcid.org/0000-0002-1534-6229

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