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REVIEW ARTICLE

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T lymphocytes and preeclampsia: The potential role of T-cell subsets and related MicroRNAs in the pathogenesis of preeclampsia

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Abstract

Innate and adaptive immune systems have a crucial role in initiating and progressing some pregnancy disorders such as preeclampsia (PE), which is one of the pregnancy-specific disorders that could result in neonatal and maternal morbidity and mortality. The dysregulation of the spiral artery and inadequate trophoblast invasion lead to PE symptoms through producing various inflammatory cytokines and anti-angiogenic factors from the placenta. T lymphocytes play a special role in the epithelium and stroma of the human endometrium. CD4+ T helper (Th) cells, Th1/Th2, and Th17/T regulatory (Treg) balance mainly contribute to the establishment of a pregnancy-favorable environment. This review examined the dysregulation of some cytokines produced from T cells, the dysregulation of the transcription factors of Th cells, the expression of chemokine receptors on T cells, as well as the effects of some factors including vitamin D on the activity of T cells, and finally, the dysregulation of various miRNAs related to T cells, which could cause PE.

KEYWORDS
miRNA, preeclampsia, pregnancy, T cell

1 | INTRODUCTION

Adaptive and innate immune systems have a major role in the initiation and development of different types of pregnancy disorders such as preeclampsia (PE).[1] Approximately, 5%-8% of pregnant people suffer from PE worldwide. PE is one of the pregnancy-specific disorders which could result in neonatal and maternal morbidity and mortality.[2] It is diagnosed by different symptoms such as thrombocytopenia, pulmonary edema, renal insufficiency, proteinuria, visual or cerebral symptoms, and the presence of de novo hypertension after the 20th gestational week.[3,4] PE can be categorized into early- (before 34 weeks) and late-onset (after 34 weeks) types. The dysregulation of the spiral artery and inadequate trophoblast invasion lead to the symptoms of PE by producing various inflammatory cytokines and anti-angiogenic factors from the placenta.[5] In recent years, research has expanded on the disorders of different subtypes of T lymphocyte cells, the dysregulation of releasing cytokines from T cells, and the expression of microRNAs (miRNAs) related to T cells in PE. This review also focuses on the advances in our knowledge about the role of T lymphocytes in the pathogenesis of PE.

2 | LYMPHOCYTES AND PREGNANCY

Lymphocytes are the largest resident immune cell population found in the decidualized endometrium and include uterine or decidual natural killer (NK) cells and the T-cell subsets, namely CD4 T helper 1 (TH1), Th2 CD8, T regulatory (Treg), and Th17 cells. T lymphocytes are located in the decidual stroma and glandular epithelium where they play a critical role in the establishment of a favorable pregnancy environment.[6] Th1/Th2 and Th17/Treg cell balance have an essential part in the establishment of a pregnancy-favorable environment. During the peri-implantation period, a controlled shift toward Th1 responses is involved in immune surveillance and avoids the excessive invasion of trophoblast.[7,8] After the placental implantation, making a shift toward Th2 is essential for the preservation and development of a normal embryo, the suppression of Th17 and Th1 cells by releasing interleukin (IL)-13 and IL-4, respectively, and an increase in allograft tolerance.[8,9] Additionally, Treg cells are the main factors for immunological tolerance, the acceptance of the fetus by the mother's immune system, and embryo implantation. Peripheral and decidual Treg cells increase during normal pregnancy.[10,11] Tregs exert suppressive functions through different mechanisms, including the modulation of antigen presentation, the cytolysis of target cells, and the secretion of inhibiting cytokines.[12,13] Treg cells prevent the operation and proliferation of Th17 and Th1 cells via different mechanisms, including programmed cell death protein 1 (PD-1) and the Ca + influx-clapin-caspase 1 pathway. Over the years, studies have shown that different subsets of Tregs have various effects on pregnancy. Zenclussen et al revealed the exact type of thymus Treg (tTreg) cells that are vital for the establishment of pregnancy.[14] In this regard, the activity of induced Treg (iTregs) is demonstrated in the late fertility stages.[15] During pregnancy, Th17 cells make immunity against extracellular pathogens and induce NK cell activation.[8] IL-17 promotes tissue invasion and progesterone secretion.[16] Low levels of Th17 cells are observed during normal pregnancy as compared to infertile women, and Th17 cell levels do not vary in fertility processes. In addition, the level of Th17 in the decidual is higher compared to the peripheral blood.[17,18] According to a study, the placental trophoblast through making a shift toward Th2 responses and inhibition of Th17 cells leads to the maintenance of pregnancy.[19]

3 | Th1 AND Th2 CELL FUNCTION AND RELATED FACTORS IN PE

Preeclampsia patients exhibit chronic inflammation.[20] The balance between the functions of Th1/Th2 changes toward a Th1-dominated phenotype, and a high level of IL-12 can cause the severity of PE.[21] In this respect, the ratio of Th1/Th2 cells elevates as well.[22] Th1 cells have a critical role in systematic inflammation by secreting the amounts of tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), IL-1β, and IL-12. The domination of Th1 responses can induce chronic inflammatory reactions in the fetal-maternal interface, endothelial dysfunction, and the impairment of placentation.[23,24] Some studies represented the transfusion of Th1 cells into normal pregnant mice that demonstrated PE symptoms including proteinuria, blood pressure, inflammation of the decidua, and changes in kidney functions. However, the transfer of Th1 cells into non-pregnant mice does not induce any alterations in renal function and blood pressure.[22]

T-bet and GATA binding protein 3 (GATA-3) as the transcription factors of Th1 and Th2 cells regulate the expression of Th1 and Th2 cytokine, respectively, and have critical roles in the differentiation of Th cells.[25] According to a study, higher and lower percentages of T-bet and GATA-3 were found in peripheral and decidual T cells in PE patients, respectively, as compared to normal pregnant.[25,26]

4 | Treg AND Th17 CELL FUNCTION AND RELATED FACTORS IN PE

It has been shown that number of Treg cells is decreased and their function impaired in peripheral blood and decidua in PE patients.[27,28] There is an altered prevalence of Treg subtypes in PE compared with healthy pregnant. The prevalence of fully functional effector Tregs ($CD4^+$ FoxP3hi $CD45RA^-$) is reduced, while naïve Tregs ($CD4^+$ $FoxP3^+$ $CD45RA^+$) remain to be unaffected.[29] Feger et al[30] described HLA-G^+ Treg cell subsets. These cells do not express Foxp3 and CD25 molecules, are of hypo-proliferative and thymic-derived types, and are detected in HIV-1 infection, multiple sclerosis, and transplantation.[31] The frequency of $CD4^+$ HLA-G^+, $CD8^+$ HLA-G^+, and $CD4^+$ $CD25^+$ $CD127^{low}$ peripheral cells in the PE group is lower compared to a healthy pregnant group.[32] According to these results,

decreased frequencies of regulatory T cells can lead to immunological maladaptation and inadequate tolerance to the fetus in PE.[33] Higher numbers of $CD4^+$ CD25high $FoxP3^+$ $CD279^+$ identified as exhausted Tregs were found in peripheral T cells in PE patients.[34,35] The exhausted T cell is a state of T-cell dysfunction that decreases the strength of the immune system in controlling infection and cancer.[36] CD279 (PD-1) expression has been considered as a marker of T-cell exhaustion.[37] PD-1 expression on T cells is associated with restricted proliferative capacity and decreased suppression of the immune system.[29] Higher expression of PD-1 and interactions with its ligand (PDL-1) generate a strong co-inhibitory signal in exhausted T cells.[36] Thereby, this molecule may involve in reducing the number and function of Tregs in PE.[34] During pregnancy, the PD-1/PDL-1 pathway plays a major role in maintaining feto-maternal tolerance by regulating the immune response.[38] According to Zhang et al, the PD-1/PD-L1 pathway contributes to the Treg/Th17 balance during pregnancy by promoting Treg cell generation and preventing Th17 proliferation. However, PD-1/PD-L1 pathway dysfunction may exert a role in the Treg/Th17 imbalance in peripheral blood and decidua, leading to the development of PE.[39] The Treg-related factors are summarized in Table 1.

Th17 cells are involved in pro-inflammatory and autoimmune diseases by secreting IL-17 cytokine.[40] Studies have confirmed that Th17 cell populations and their cytokines are elevated in PE women.[41] Moreover, both TH17 and IL-17 increase in reduced uterine perfusion pressure (RUPP) rats.[42] The dysregulation in NK cell subtypes, agonistic autoantibodies to the ANGII type 1 receptor (AT1-AA), inflammatory cytokines, and placental oxidative stress are the main factors for proteinuria, high blood pressure, and low birthweight in PE patients.[43] As reported by a study, separating and transferring RUPP Th17 to normal pregnant (NP) rats can induce the levels of inflammatory cytokines such as IL-17, IL-6, IFN-γ, TNF-α, cytolytic NK functions, markers of blood pressure, placenta perforin, and AT1-AA production, and placenta oxidative stress including reactive oxygen species.[44] Moreover, Travis et al investigated the role of IL-17, which is secreted by Th17, in hypertension and pregnant rats. They concluded that IL-17 infusion into a subset of NP rats can induce the activation of NK cells, the plasma level of TNF-α, the reduction of placental vascular endothelial growth factor and fetal weight, the production of a high level of granzymes A and B, and finally, the impairment of the vascular reactivity of uterine arteries and PE defects.[45] The Th17-related factors are presented in Table 1.

Orphan nuclear receptor γt (RORγt) and forkhead box p3 (Foxp3) are specific transcription factors that are involved in the production of Th17 and Treg cells.[46] Eghbal-fard et al[46] approved an increasing Th17/Treg ratio in PE by detecting the percentages of CD4+ CD25+ CD127- and CD4+ IL-17+ cells. Additionally, the mRNA level of RORγt increased while that of Foxp3 decreased in peripheral and decidual T cells in the PE patients as compared to healthy pregnant.[25,46] An imbalance between Treg and Th17 cells can induce chronic inflammation in PE.[33] Moreover, the mRNA levels and the secretion of inflammatory cytokines in peripheral blood mononuclear cells (eg, IL-6, IL-23, and IL-17) are meaningfully higher in PE women. On the other hand, anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta (TGF-β) are remarkably lower in PE.[46]

TABLE 1 Dysregulation of T-cell subsets and related factors in PE

Dysregulation of various factors in PE	Function
Th1	Inducing chronic inflammatory reactions in the fetal-maternal interface by secreting the amounts of TNF-α, IFN-γ, IL-1β, and IL-12
T-bet, GATA-3	High expression of T-bet and low expression of GATA-3 may lead to Th1/Th2 imbalances toward to Th1
PD-1/PD-L1	PD-1/PD-L1 pathway dysfunction may exert a role in the Treg/Th17 imbalance in peripheral blood and decidua
IL-17	IL-17 is found by Th17 and elevation in angiotensin II type I receptor (AT1-AA) production
Th17	Inducing cytolytic NK cell's function, placenta perforin production, IFN-γ, and TNF-α cytokines
RORγt, Foxp3	High expression of RORγt and low expression of Foxp3 may lead to Th17/Treg imbalances toward to Th17
iNKT	Have an augmented cytotoxic potential along with exhibiting Th1 dominant profile
CXCL16	Interaction with CXCR6 receptors on T cells and subsequently inflammation
IFN-γ	Inducing the expression of CXCL9 chemokines which are involved in inflammatory responses
25 (OH) vitD	Increasing IL-6 and decreasing TGF-β secretion from Th1 and Treg
Adenosine	Th1/Th2 balances toward Th1 and subsequently hypertension
DCR3	Suppressing Th2 cells function and Th1/Th2 imbalances

5 | NKT CELLS IN PE

These cells are a subset of lymphocytes that express NK cell receptors and can be classified into the invariant NKT (iNKT) cells with the T-cell receptor (TCR) alpha-chain (TCRα) or variant NKT (vNKT) cells without the expression of the invariant T-cell receptor (TCR) alpha-chain.[1] NKT cells can control the immune response in decidua and peripheral blood through the production of Th1-type cytokines (IFN-γ) and Th2-type cytokines (IL-4).[24] In the decidua, NKT cells can regulate Th1/Th2 balance and are involved in maintaining pregnancy.[1] An alteration in the balance of NK cell activating and inhibitory receptors on peripheral iNKT cells in women with PE indicates a lower chance of inhibitory signal transduction as compared with healthy pregnancies.[47] Thereby, the frequency of activated peripheral iNKT cells is fully higher in PE women, and they have an augmented cytotoxic potential along with exhibiting Th1 dominant profile, suggesting the important role of iNKT cells in making a systemic inflammation.[24,48]

6 | CHEMOKINES AND PE

Chemokines are a superfamily of chemotactic cytokines that have an important impact on the regulation of leukocyte and lymphocyte transport from the bone into the inflammation sites. The dysregulation of chemokine expression has been attributed to some diseases such as PE, as well as habitual and spontaneous abortions.[49] CXC chemokine ligand (CXCL) 16 is a plasma membrane chemokine and consists of a short cytoplasmic tail, a single transmembrane helix, and a chemokine domain with a glycosylated mucin-like stalk.[50] CXCL16 are expressed on smooth muscle cells, endothelial cells, fibroblasts, dendritic cells, B and T cells, macrophages, and platelets.[51] Some of the functions of CXCL16 include being a chemo-attractant for cells carrying chemokine receptor CXCR6, which is known as Bonzo, inducing cell migration into inflammatory areas, and promoting matrix metalloproteinases, which cause the degradation of the matrix.[52] Previous research reported that CXCL16 expression increases in inflammatory diseases, endothelial dysfunction, and hepatic damages.[53] Increased CXCL16 expression has been shown to be associated with inflammation and is induced by inflammatory mediators such as TNF-α and IFN-γ. Tok et al[54] showed that the serum level of CXCL16 is meaningfully higher in PE patients, and there exists a positive correlation between CXCL16 and renal and hepatic damages in PE. Elevated CXCL16 levels could be related to systemic inflammation which is involved in the pathogenesis of PE. This study suggested that the CXCL16/CXCR6 axis can be a predicting marker for the development of PE.

Interferon-gamma is a pro-inflammatory cytokine produced by immune cells such as Th1 cells, CD8+ lymphocytes, and NK cells.[55] It is well known that IFN-γ is highly expressed in serum/plasma of PE.[56] IFN-γ can induce CXCL9 and CXCL10 chemokines, which have a major impact on the recruitment of immune cells into infected/inflamed organs.[57] CXCL9 and CXCL10 exhibit anti-angiogenic features.[58] It has been shown that in the plasma of PE women the levels of CXCL9 and CXCL10 are increased, in line with the increase in IFN-γ.[59] Similarly CXCL9 has been shown to increase in the PE placenta while CXCL10 was unaffected.[60]

Collectively, these findings suggest that the CXC chemokines may contribute to the inflammatory pathogenesis of PE and may present good therapeutic targets.

7 | OTHER FACTORS AND PE

7.1 | Vitamin D

Vitamin D is a critical modulator of vital biological events including immune function, hormone secretion, cell differentiation, and proliferation.[61] It also has a role in the bone synthesis, metabolism, and the regulation of phosphor-calcium metabolism.[62] The vitamin D receptor is expressed on some immune cell members (Th17 and Treg).[63] Vitamin D impedes the lymphocyte proliferation and cytotoxic cell stimulation by alloantigen in the maternal-fetal interface [64] and meaningfully decreases inflammation in PE [65] by the expansion of Treg and Th2 responses.[66] Furthermore, vitamin D inhibits the IL-6 secretion and increases the expression of TGF-β.[67,68] As reported by some studies, the level of plasma 25 (OH) D is lower in women with PE as compared with normal pregnancy.[69-71] Moreover, a lower level of vitamin D can be a risk factor for severe PE.[72-74] According to Muyayalo et al[66], lower levels of vitamin D in PE patients can cause Treg/Th17 cell imbalance and promotion of IL-6 levels.

7.2 | Adenosine

Adenosine is produced in reaction to hypoxia and ischemia in the placenta and is a degradative metabolic agent of adenine nucleotides.[75] In addition, it has several roles in different regulatory processes (eg, the regulation of local blood flow and metabolic rate) and has a strong influence on shifting the Th1/Th2 balance toward Th2 dominance and immune-triggered cytokine production.[76] Consequently, adenosine can have a protective role at the maternal-fetal interface. However, plasma adenosine concentrations remarkably increase in PE women [77] and can involve in the regulation of Th1/Th2 ratio imbalance based on the severity of hypertension.[78]

7.3 | Decoy receptor 3

Decoy receptor 3 (DCR3; Figure 1) is introduced as tumor necrosis factor receptor superfamily member 6B (TNFRSF6B)/TR6/M68 and a soluble receptor that can neutralize inflammation and apoptosis inducers such as TNF-like molecule 1A (TL1A/TNFSF15), Fas ligand (Fasl/CD95L/TNFSF6), and LIGHT (TNFSF14).[79,80] The expression of DCR3 on tumor cells can lead to evasion from immune-cytotoxic attack by preventing the LIGHT-mediated apoptosis and the Fas ligand.[81] According to one study, DCR3 can bind to TL1A on immune cells and lead to T-cell differentiation, favoring Th1 and Th17 cells.[82] Moreover, DCR3 skews

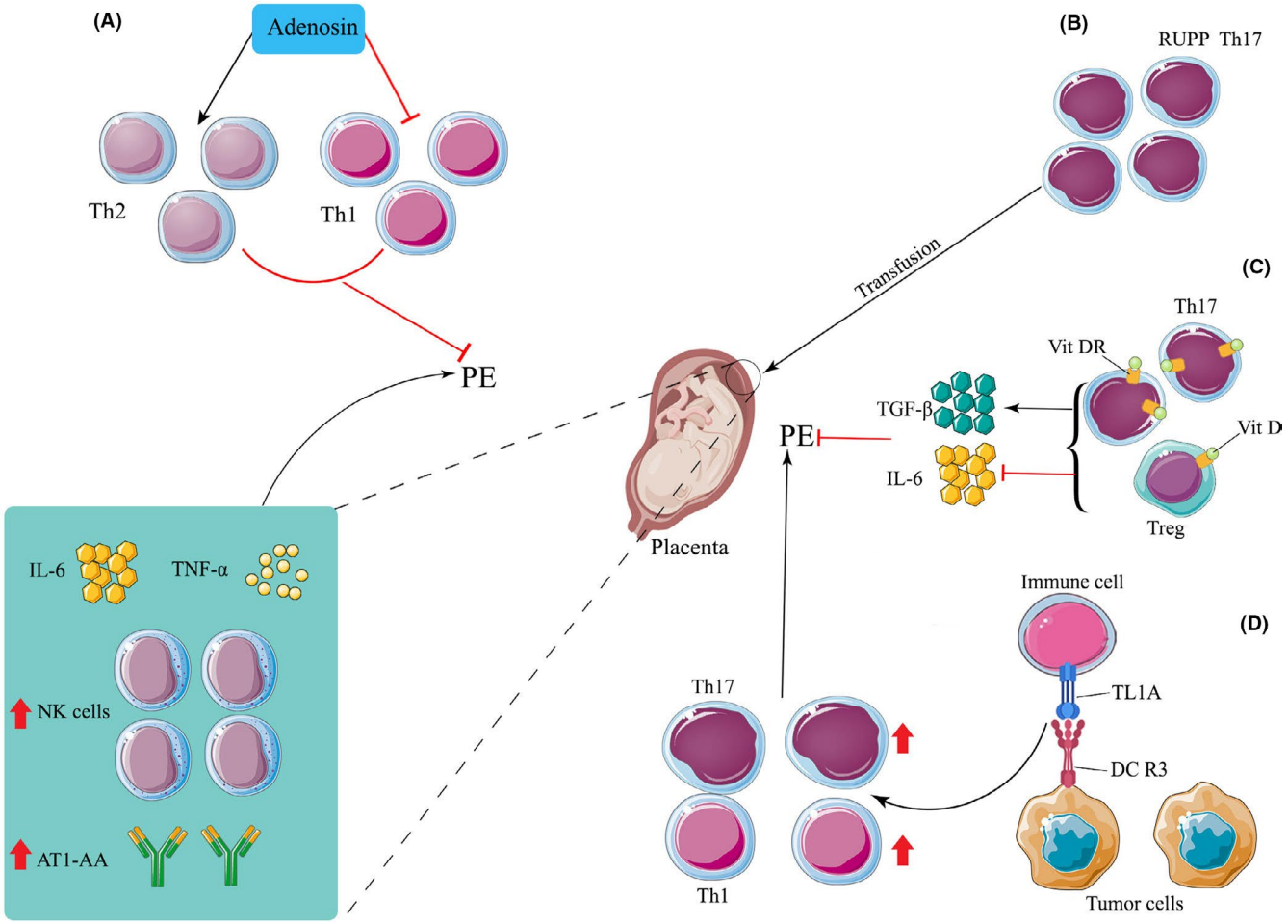

FIGURE 1 Function of different subtypes of Th cells in PE. Note. TH: T helper; PE: Preeclampsia; Treg: T regulatory; IL: interleukin; TNF-α: tumor necrosis factor-alpha; NK: Natural killer. A, Adenosine has a strong influence on shifting the Th1/Th2 balance toward Th2. B, Transfusion can elevate the risk of PE by increasing IL-6, TNF-α, NK cells, and AT1-AA. C, The interactions between vitamin D and its receptors in the cytoplasm of Treg and Th17 cells can release TGF-β, block IL-6 cytokines, and suppress PE development. D, Decoy receptor 3 can bind to TL1A on immune cells and lead to T-cell differentiation, favoring Th1 and Th17 cells, and finally, causing PE

macrophages to the M2 phenotype and regulates dendritic cell differentiation, resulting in a Th1-suppressing effect and Th2 polarization.[83] Transgenic mice who highly express DCR3 show attenuated Th2 differentiation. DCR3 has different roles in decreasing major histocompatibility complex class II expression and dampening T-cell response to alloantigen via interfering with the LIGHT-TR2/HVEM interaction.[84] In pregnancy, DCR3 expression is detected in preeclamptic placentas and is elevated in the excessive inflammatory activities of PE.[85] Ching Yeh et al[86] revealed that the plasma level of DCR3 in PE patients was meaningfully lower than that of the normal pregnant group, suggesting that a potential involvement of DCR3 in normal pregnancy and the reduced levels of DCR3 may be related to immune dysregulation in PE.

8 | MicroRNAs AND THEIR FUNCTION IN PE

Similar to short endogenous regulatory RNAs, miRNAs are approximately 22-24 nucleotides long.[87,88] Their main function is to pair with the 3′-untranslated region of target mRNA and regulate gene translation. Further, miRNAs exert a key role in different physiological and pathological disorders, and the evidence demonstrates that miRNAs are important regulators in placental development and the immune environment.[89-91] Moreover, miRNAs are highly stable in the plasma, serum, and urine, offering the possibility of miRNA to diagnostic or prognostic markers for different illnesses. Dysregulation in the expression of miRNA or abnormal miRNA levels is found in placentas from women who have pregnancy complications such as PE, recurrent miscarriage, and fetal growth restriction, which can affect cell cycle, migration, adhesion, and antiapoptotic survival.[92,93] Differential expression of miRNA has been revealed in PE patients. As reported in previous research, the expression of miR-181a, miR-210, miR-155, miR-182, miR-196, miR-195, and miR-26 increases while that of miR-144 and miR-223 represents a decrease.[93] The modification of miRNAs is critical in the expansion of PE because of their effect on the regulation of immune response and inflammation.[94] In recent years, the association between alterations in miRNA expression and the function of T lymphocytes or the secretion of

different cytokines has been an interesting subject of research. The dysregulation of miRNA-related T lymphocytes is provided in Table 2.

8.1 | Dysregulation of miRNAs related to T lymphocytes in PE

8.1.1 | miR-106b/miR-326

miR-106b induces cell cycle progression, modulates cell cycle-related proteins, and controls cell proliferation.[95] The upregulation of miR-106b targets and suppresses two pivotal effectors of the TGF-β signaling pathway, including cyclin-dependent kinase inhibitor 1A (CDKN1A/p21) and BCL2L11/Bim.[96] TGF-β is necessary for the maturation and differentiation of Treg cells, and any dysregulation in this miRNA may alter the activity of Treg cells.[96] Moreover, miR-326 affects the differentiation of Th17 lymphocytes by preventing Ets-1 activity.[97] It has been proven that Ets-1 has an important role in the modulation of Treg and Th17 cell responses.[98] Eghbal-fard et al[46] reported that the expression of miR-106b and miR-326 is upregulated in PE women, and the dysregulation of these two miRNAs can affect the Th17/Treg balance and make a shift toward Th17 response in PE patients.

8.1.2 | miR-106_363 cluster

The cluster of miR-106_363 is located on chromosome X. A previous study revealed that the upregulation of miR-20a, miR-17, and miR-106a can lead to macrophage activation and increase Th1 cells as compared with Th2 cells.[99] Thus, this miRNA cluster is expressed at the intermediate levels in the Th2, the highest level in the Th1, and the lowest level in Th17 cells.[100] The expression of miR-363-3p, miR-106a, and miR-18b can decrease IL-17 gene expression and prevent the production and activity of IL-17a and Th17, respectively. miR-20b and miR-182 are the other members of the miR-106_363 cluster and target RORγt and the signal transducer and the activator of transcription 3 (STAT3), which are Th17 cell transcription factors and suppress Th17 cells and experimental autoimmune encephalitis.[101] Therefore, the expression of the cluster of miR-106_363 can impede Th17-mediated inflammations such as chronic disease, asthma, and PE. Therefore, using miR-18b, miR-106a, and miR-363-3p may be a therapeutic approach for Th17 cell-mediated preeclampsia.

8.1.3 | miR-210

miR-210 has been implicated in several pathophysiological pathways such as cancer, apoptosis, and oxidative stress.[102,103] Recently, it has been found that miR-210 levels meaningfully increase in the placental and plasma-derived samples from PE patients.[104] Trophoblast cell migration and invasion reduce following miR-210 overexpression in PE.[93] Further, this component causes reductions in STAT6 and IL-4 levels that contribute to the expansion of PE.[105] Additionally, the overexpression of miRNA-210 can suppress the expression of Foxp3 and impair Treg cell functions.[106] The expression of miR-210, which targets Foxp3 and inhibits Treg cell functions, is high in the PE placenta.[107]

8.1.4 | miR-155

miR-155 is processed from the human nonprotein coding exon 3 of B-cell integration cluster RNA [108] and is effectively upregulated in T and B cells as a response to antigen stimulation.[109,110] In addition, this miRNA could be induced by Toll-like receptor ligation in dendritic cells and macrophages.[111,112] miR-155 is extremely expressed in Treg cells and is essential for the production of normal thymic-derived Treg cells.[113] Altered miR-155 has been reported in adverse pregnancy outcomes including recurrent miscarriage, recurrent implantation failure, and preeclampsia, suggesting that miR-155 plays

TABLE 2 Dysregulation of miRNAs related to T cell subsets in PE

miRNAs	Expression level in PE	Function
miR-106b miR-326	↑	Increasing RORγt mRNA and elevating Th17 cell differentiation, and decreasing Foxp3 mRNA expression in Treg cells
miR-363-3p miR-106a miR-18b	↑	Increasing IL-17 gene expression and high production of IL-17a and Th17 activity
miR-20b miR-182	↑	High expression of RORγt and STAT3, which are transcription factors of Th17 cells
miRNA-210	↑	Suppressing expression of Foxp3 and impairing Treg cells function
miR-155	↑	induced podocyte apoptosis through increasing in IL-17 production
miR-320a	↑	Repressing IL-4 expression via binding to 3/ untranslated region

an important role in modulating the immune system during pregnancy. Furthermore, it is essential for inducing Treg cells regarding achieving tolerance and preventing miscarriage.[113] As reported by one study, in PE following the maternal and fetal inflammation, the overexpression of miR-155 was found in the placenta.[114] Recently, it has been revealed that the upregulation of miR-155 induced podocyte apoptosis through increasing in IL-17 production.[115]

8.1.5 | miR-320a

The expression of miR-320a, which is a tumor inhibitor via decreasing the expression of several target genes, is downregulated in various tumor cells.[116] According to previous research, miR-320a has low expression in human non-small lung cancer cells and acts as a crucial regulator in gastric cancer by targeting Ras-related protein Rab-14.[117] Overexpression of miR-320 isoforms in activated T cells can reduce the TGF-β signaling pathway by suppressing TGFBR2 and Smad2 genes.[118] miR-320a has an important impact on the invasion and proliferation of trophoblast cells.[119] Recently, it has been found that miR-320a levels increase in serum of PE patients.[120] XI et al[119] reported that the upregulation of miR-320a in PE patients may contribute to the expansion of PE through repressing IL-4 expression via binding to the 3′untranslated region, which leads to the inhibition of trophoblast proliferation and invasion. The results of this study suggested that the miR-320a/IL-4 pathway may represent a new therapeutic approach for PE.

9 | CONCLUSION AND PROSPECT

T lymphocyte cells have four main subsets including Th1, Th2, Th17, and Treg. A normal association between these T cells is necessary for preventing pregnancy disorders such as PE. In recent years, studies have examined the variation of T-cell functions, as well as the cytokines and chemokines that they release in PE. High levels of adenosine and DCR3 or low levels of 25 (OH) vitamin D can lead to imbalances in the Th1/Th2 and Th17/Treg ratios, and eventually, cause PE. Moreover, changing the expression of some miRNAs related to T cells can be a potential molecule for the development of inflammation and PE. In the future, using some blockers for suppressing cytokine or chemokine receptors on T cells or using some siRNAs for inhibiting or activating miRNAs related to T cells can affect the functions of T cells, thus decreasing pregnancy inflammation and preventing PE disease.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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