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Cytokine-polymorphisms associated with Preeclampsia

A review

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Abstract

Background: Preeclampsia (PE) is a syndromic disorder that affects 2% to 8% of pregnancies and is diagnosed principally when hypertension appears in the second-d half of pregnancy. WHO estimates the incidence of PE to be seven times higher in developing countries than in developed countries. Severe preeclampsia/eclampsia is one of the most important causes of maternal mortality, associated with 50,000 to 100,000 annual deaths globally as well as serious fetal and neonatal morbidity and mortality, especially in developing countries. Even though evidence from family-based studies suggest PE has a heritable component, its etiology, and specific genetic contributions remain unclear. Many studies examining the genetic factors contributing to PE have been conducted, most of them are focused on single nucleotide polymorphisms (SNPs). Given that PE has a very important inflammatory component, is mandatory to examine cytokine-SNPs for elucidating all mechanisms involved in this pathology. In this review, we describe the most important cytokine-polymorphisms associated with the onset and development of PE. We aim to provide current and relevant evidence in this regard.

Methods: We searched English databases such as PubMed and the National Center for Biotechnology Information. The publication time of the papers was set from the establishment of the databases to February 2022. All studies about Th1/Th2/Th17 cytokines polymorphisms were included in our study.

Results: SNPs in IFN-γ, TNF-α, IL-4, IL-6, IL-10, IL-17A, and IL-22 are associated with the development, early-onset and severity of PE, being the Th1/Th2/Th17 responses affected by the presence of these SNPs.

Conclusions: The changes in Th1/Th2/Th17 response modify processes such as placentation, control of inflammation, and vascular function. Nonetheless, association studies have shown different results depending on sample size, diagnostic, and population.

Abbreviations: ACE = angiotensin I converting enzyme gene, AGT = angiotensinogen gene, AGTR1 = angiotensin II receptor type 1gene, AGTR2 = angiotensin II receptor type 2 gene, B cells = B lymphocytes, CRP = C-reactive protein, DC = dendritic cells, DNA = deoxyribonucleic acid, F2 = coagulation factor II, F5 = coagulation factor V gene, sFlt-1 = soluble fms-like tyrosine kinase, GWAS = genome-wide association studies, HLA = human leukocyte antigen, HUVEC = human umbilical vein endothelial cell, IFN-γ = interferon-gamma, IgE = immunoglobulin E, IL-1 = interleukin 1, IL-2 = interleukin 2, IL-4 = interleukin 4, IL-6 = interleukin 6, IL-8 = interleukin 8, IL-10 = interleukin 10, IL-17 = interleukin 17, IL-17A = interleukin 17A, IL-22 = interleukin 22, ILCs = innate lymphoid cells, IUGR = intrauterine growth restriction, LTi = lymphoid tissue inducer, MALDI = matrix-assisted laser desorption/ionization, MHC = major histocompatibility complex, MHC-I = major histocompatibility complex class 1, MHC-II = major histocompatibility complex class 2, mRNA = messenger ribonucleic acid, *MTHFR* = methylenetetrahydrofolate reductase gene, NFAT = nuclear factor of activated T cells, NK = natural killer cells, NKT = natural killer T, NO = nitric oxide, NOS3 = nitric oxide synthase 3 gene, PCR = polymerase chain reaction, PE = Preeclampsia, PlGF = placental growth factor, PTGS2/COX-2 = cyclooxygenase-2, RFLP = restriction fragment length polymorphism, RNA = ribonucleic acid, SNP = single nucleotide polymorphism, SOCS = suppressor of cytokine signaling, TGF-β1 = transforming growth factor beta receptor 1, Th1 = T helper 1, Th2 = T helper 2, Th17 = T helper 17, Th22 = T helper 22, Th3 = T helper 3, *F2* = thrombin gene, TLRs = toll-like receptors, TNF = tumor necrosis factor gene, TNF-α = tumor necrosis factor-alpha, Treg = regulatory T cells, UNG = Uracil-DNA glycosylase, VEGF = vascular endothelial growth factor, VNTR = variable number tandem repeat, WHO = World Health Organizations.

Keywords: cytokine-polymorphisms, inflammation, preeclampsia, pregnancy, SNPs

CM-P and MB contributed equally to this work.

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1. Introduction

Preeclampsia (PE) is a syndromic disorder that affects 2% to 8% of pregnancies and is diagnosed when hypertension appears in the second half of pregnancy.[1] World Health Organization (WHO) estimates the incidence of PE to be seven times higher in developing countries (2.8% of live births) than in developed (0.4%).[2] Severe PE/eclampsia is one of the most important causes of maternal mortality, associated with 50,000 to 100,000 annual deaths globally,[3] as well as serious fetal and neonatal morbidity and mortality, especially in developing countries. This syndrome produces new-onset hypertension (>140/90 mm Hg) in the second half of pregnancy[4–6] companied with either proteinuria (>300 mg/24 h), or multiorgan maternal dysfunction, especially kidney and liver failure, neurological complications, thrombocytopenia, or hemolysis.[7]

It is believed that PE results from defective spiral artery remodeling, which leads to an imbalance between anti and pro-angiogenic factors, favoring an anti-angiogenic environment, giving as a result, widespread endothelial dysfunction and organic failure.[8]

Serum samples have shown significantly increased soluble fms-like tyrosine kinase (sFlt-1) and decreased vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) concentrations in PE, compared to normotensive controls. In vitro studies showed that serum from PE inhibited tube formation in human umbilical vein endothelial cell (HUVEC) lines compared to that from controls, and administration of adenovirus expressing sFlt-1 to pregnant rats caused hypertension, albuminuria, and glomerular endotheliosis, similar to that observed in PE.[8]

1.1. The genetic component of PE

The complexity of PE suggests that some women are predisposed to suffering from PE. In this regard, there is evidence supporting that PE has an outsized familial risk, with a heritability factor of approximately 50% to 55%,[9,10] of which 30% to 35% is attributed to maternal genotype, 20% fetal, 13% to a couple, and the rest to other effects.[5,11,12] Family history of PE significantly increases woman's risk of PE (24% and 163%).[13] Besides, it has been proved that the familial form of PE is associated with a more severe phenotype.[14]

Predisposition to PE is multifactorial and probably polygenic. Candidate genes involved in different biological processes including inflammation, coagulation, vascular resistance, cell signaling pathways, and metabolic processes have been associated with PE due to their putative roles in its pathophysiology. Most of the early candidate gene studies have been focused on just nine genes: angiotensinogen (*AGT*), angiotensin I converting enzyme (*ACE*), angiotensin II receptor type 1 (*AGTR1*), angiotensin II receptor type 2 (*AGTR2*), coagulation factor II, thrombin (*F2*), coagulation factor V (*F5*), methylenetetrahydrofolate reductase (*MTHFR*), nitric oxide synthase 3 (*NOS3*) and tumor necrosis factor (*TNF*), which are involved in endothelial function and hemodynamics, immune response, lipid metabolism and oxidative stress, and thrombophilia.[15,16] Attention has been also focused on increased sFlt-1 and decreased VEGF and PlGF were single nucleotide polymorphism (SNP) analyses have also shown association with PE. In this regard, genome-wide association studies (GWAS) have been performed in large cohorts of unrelated cases and controls to identify novel genetic loci through large-scale SNP analyses where the prevalence of specific SNPs is linked to phenotypes or disease.[17] According to Brody et al.[18], SNPs are variants in the genome occurring naturally in the human population, being the most frequent type of variation in the human genome, occurring once every several hundred base pairs throughout the genome.[19] Each individual inherits one allele copy from each parent (the individual genotype at an SNP site is AA, BB, or AB).[18] SNPs are defined as genomic locus where two or more alternative bases occur with appreciable frequency (0.1%).[19] SNPs in genes can impact on messenger ribonucleic acid (mRNA) splicing, nucleo-cytoplasmic export, stability, and translation. When they are present within a coding sequence, lead to an amino acid change (referred to as a non-synonymous SNP or mutation), thus they can modify the protein's activity.[20,21] If the mutation is synonymous (does not change the nature of the amino acid), then translation rates or mRNA half-life may be affected. If the mutation causes a premature stop codon, this can lead to the production of a truncated protein product or a near-null phenotype due to nonsense mediated decay.[20–22] For this, SNPs can be used as genetic markers to follow the inheritance patterns of chromosomal regions through generations and can be used in the study of genetic factors associated with human diseases.[23]

Different technologies have been used to detect SNPs such as restriction fragment length polymorphism (RFLPs), polymerase chain reaction (PCR) and genome shotgun sequencing, but they can be classically divided in technologies targeted SNP discovery (Denaturing gradient gel electrophoresis, chemical cleavage of mismatch, ribonuclease cleavage of mismatched deoxyribonucleic acid (DNA), single stranded conformation polymorphism, cleavage fragment length polymorphism analysis, MutS protein-binding assay, mismatch repair detection, T4 endonuclease VII cleavage of heteroduplex DNA, heteroduplex analysis, denaturing high performance liquid chromatography, uracil-DNA glycosylase (UNG)-mediated sequencing, ribonucleic acid (RNA) mediated finger printing with matrix-assisted laser desorption/ionization (MALDI) MS detection, sequencing by hybridization, direct DNA sequencing) and technologies for genotyping known SNPs (hybridization, primer extension, ligation, invasive cleavage, reaction formats, homogeneous reactions, reactions on solid support, detection mechanisms, luminescence detection, fluorescence detection, time- resolved fluorescence detection, fluorescence resonance energy transfer, fluorescence polarization, mass spectrometry, electrical detection).[24]

Specifically, in PE, genetic predisposition is thought to be a significant etiological representative and SNPs in various genes were found to be associated with the risk of PE. In this regard, emerging evidence proposes that excessive maternal inflammatory response with cytokine-mediated endothelial damage may play a role in PE's pathogenesis.[25,26]

1.2. Immunology of PE

Even though the main cause of the abnormal placentation remains unclear, genetic, environmental, and immunological factors have been associated.[27] In this regard, it is believed that both, innate and adaptive immune processes are involved in the pathogenesis of PE, proposing that Th1 immunity is responsible for poor placentation and exacerbated inflammatory response and endothelial dysfunction seen in PE.[28,29] This is relevant since T helper 1 (Th1) and T helper 2 (Th2) cytokine balance is important to maintain the success of normal pregnancy.[30,31] In normal pregnancy, the production of Th1 cytokine is inhibited, and their overexpression predisposes to PE development.[32]

Moreover, fetal trophoblast acts as an alloantigen producing a systemic inflammatory response in the mother, but this is controlled and mild.[33–35] Inflammatory response onset during the first twelve weeks could be given by interactions occurring between the decidual immune cells and trophoblast cells, then in the second and third trimester, a secondary inflammatory response could be due to syncytiotrophoblast microparticles that are released into the mother´s vascular system and are detectable in maternal circulation.[36]

Thus, two stages of the PE are proposed: poor trophoblastic invasion, given by altered production of immunoregulatory cytokines and angiogenic factors and a systemic, maternal-inflammatory response, primarily involving the endothelium,

which is stimulated by the liberation of necrotic/apoptotic syncytiotrophoblast cells into the maternal circulation.[37] This second stage of could be involved in poor fetal growth and can be linked with the development of intrauterine growth restriction.[38] The pathophysiology of PE may involve several factors, including persistent placental hypoxia companied of the release of high amounts of syncytiotrophoblast microparticle. Besides, damage-associated molecular pattern molecules released during hypoxia and syncytiotrophoblast microparticle, which bind Toll-like receptors (TLRs), may activate monocytes, dendritic cells (DCs), natural killer (NK) cells, and neutrophils, enhancing persistent inflammatory conditions.[37] The development of hypertension in preeclamptic women from an immunological point of view is also related with endothelial dysfunction induced by neutrophil activation and neutrophil extracellular trap formation. Moreover, preeclamptic women have higher levels of nonclassic and intermediate monocytes and lower levels of positive lymphoid blood DC antigen 2 DCs.[39] In this regard, the inflammatory process may be due to the cytokines secreted by these cells and to changes in adaptive-immunesystem cells, which are also modulated in PE.

The changes in T cell subsets that may be seen in PE include low regulatory T cells (Treg) activity, a shift toward Th1 responses, and the presence of T helper 17 (Th17) lymphocytes. B lymphocytes (B cells) can participate in the pathophysiology of PE by producing autoantibodies against adrenoreceptors and autoantibodies that bind the angiotensin-1 receptor.[40] It is believed that both, innate and adaptive immune processes are involved in the pathogenesis of PE, proposing that Th1 immunity is responsible for poor placentation and exacerbated inflammatory response and endothelial dysfunction seen in PE.[28,41] This is relevant since Th1/Th2 cytokine balance is important to maintain the success of normal pregnancy.[30,31] In normal pregnancy, the production of Th1 cytokine is inhibited, and their overexpression predisposes to PE development.[32] There are also reports showing excessive innate immune activity and a change toward an inflammatory cytokine profile in PE.[28,41] For instance, preeclamptic patients show high levels of Th1 cytokines, tumor necrosis factor-alpha (TNF-α) and interferon-gamma cytokine (IFN-γ) and low interleukin 4 (IL-4) production by phytohemagglutinin-stimulated peripheral blood mononuclear cells. Besides, their placentas show suppression of interleukin 10 (IL-10) and transforming growth factor beta receptor 1 (TGF-$_{\beta 1}$) and altered interleukin 2 (IL-2) IL-2/IL-10 and TNF-α/IL-10 ratios.[42] PE is also associated with increased numbers of Th17 cells that secrete interleukin 17 (IL-17) and interleukin 22 (IL-22) and play critical roles in disease development.[43] Given that IL-22 shares 22% sequence identity with IL-10, and IL-22 is overexpressed in the preeclamptic mother and neonate cord blood exposed to PE, it is thought that IL-22 may be an important inflammatory biomarker of PE.[44]

From a clinical perspective, proinflammatory cytokines, have been studied to find a panel of markers for diagnosing PE. In this regard, a systematic review showed that interleukin 6 (IL-6), interleukin 8 (IL-8), TNFα, and C-reactive protein (CRP) could be useful to identify pregnant women at risk of developing PE, particularly in the second and third trimesters.[45] Nevertheless, there is not a single inflammatory marker for routine clinical use to predict/ identify PE onset or progression.[45] Even though increased sFlt-1 and decreased VEGF and PlGF (and their SNPs) have been related with early onset of PE (Fig. 1), they are not used commonly as clinical markers. As a single cytokine is not reliable markers for early identification of PE, a combination of markers in conjunction with identification of clinical risk factors is mandatory.[46] Therefore, a broad examination of factors affecting inflammatory markers in PE could help to predict/ identify PE. Given that SNPs in genes can impact on mRNA splicing, nucleo-cytoplasmic export, stability, and translation, they must be studied. This review aims to compile the most recent information regarding SNPs in Th1, Th2 and Th17 cytokines and their association with PE.

2. Methods

A systematic search was performed on PubMed, National Center for Biotechnology Information, Web of Sciences, Google scholar, Cochrane library and Embase from 2010 to July 2022 to articles matching the following criteria: "single-nucleotide polymorphisms," "SNP," "polymorphisms," "IFN-γ," "IFN gamma," "TNF-alpha," "TNF-α," "IL-4," "IL-6," "IL-10," "IL-17A," "IL-22," and "PE," and their combinations in lowercase letters. The Boolean operators "OR" and "AND" were used, and the strategy was carried out both individually and jointly. The titles and abstracts were screened and acquired relevant full-text manuscripts for further analysis.

No ethics committee or institutional review board needed to revise the study.

2.1. Cytokine-polymorphisms associated with PE

For a long time, single-nucleotide polymorphisms (SNPs) in cytokine have been associated with certain inflammatory diseases and obstetric complications.[47,48] Nevertheless, factors such as selection criteria, ethnic groups, and linkage disequilibrium patterns can lead to differences in results. Besides every pathophysiologic feature could have different clinical patterns. Several studies have investigated SNPs in inflammatory mediator genes and risk of PE; however, the results between studies showed inconsistencies (Franchim et al[49]; Ghasemi et al[50]; Andraweera et al[51]; Li et al[52]; Goddard et al[53]). This could be possible due to variations in the ethnic groups and heterogeneity of PE included in different studies. Additionally, controversial results reported by different investigators may in part be because of selection criteria. Genotype frequencies of SNPs and linkage disequilibrium patterns can differ among ethnic groups, leading to different results.[54] Moreover, distinct clinical patterns may involve different pathological mechanisms.[55,56]

2.2. Th1 cytokines

2.2.1. IFN-γ. The interferon-gamma cytokine (IFN-γ) is encoded by the *IFNG* gene, also known as IFG and IFI. It is localized on chromosomal region 12q15[57] and encodes a soluble cytokine, a member of the type II interferon class. The protein is secreted by cells of the innate and adaptive immune responses. The main functions of IFN-γ are activation of macrophages for destroying phagocytosed microorganism, stimulation, and differentiation of naive LT CD4$^+$ into subpopulation Th1 by inhibiting differentiation into Th2 phenotype, stimulation of the expression of major histocompatibility complex class 1 (MHC-I) and class 2 (MHC-II), and finally, co-stimulate antigen-presenting cells.[58,59] Moreover, IFN-γ has been associated with increased susceptibility to viral, bacterial, and parasitic infections, and it has been also related to leukemia and several autoimmune diseases.[60,61]

High levels of IFN-γ and other cytokines such as interleukin 1 (IL-1), IL-2, IL-8, and tumor necrosis factor-alpha (TNF-α) are associated with pregnancy complications such as preterm labor and intrauterine growth retardation.[32,62] In this regard, IFN-γ as well as IL-2 and TNF-α, induce trophoblastic apoptosis, restrained trophoblast differentiation that produces an incomplete trophoblastic invasion of spiral arteries, and impaired placental implantation, leading to PE.[42,63] There is only a +874A/T SNP associated with PE, in which T/T genotype in that position is related to high levels of IFN-γ production and has been associated with an increased risk of severe PE in the Brazilian population (Table 1).[48] On the other hand, the same SNP was

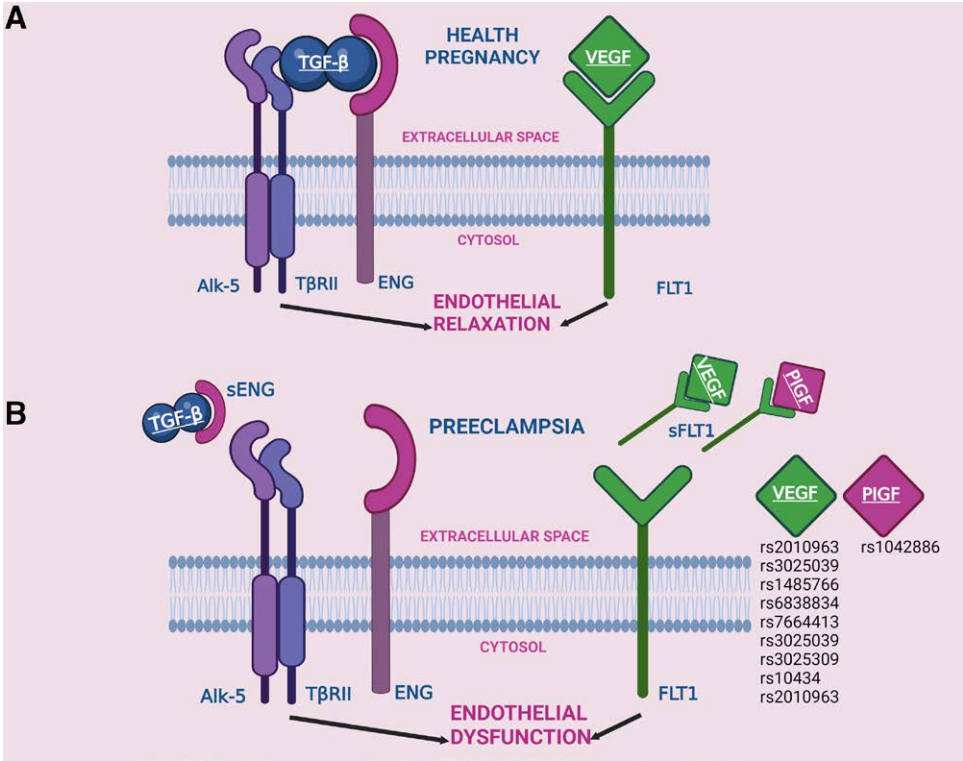

Figure 1. (A) VEGF, PlGF, and TGF-β are required to maintain endothelial function in placenta. During normal pregnancy, endothelial homeostasis is maintained by signaling of theses growth factors. (B) In PE, the secretion of sFlt1 and sEng (antiangiogenic regulators) inhibits VEGF, PlGF, and TGF-β signaling resulting in endothelial cell dysfunction. Besides, SNPs presence in VEGF and PlGF can also alter their function, and have been associated with PE.[156–167] Flt-1 = soluble fms-like tyrosine kinase, PE = preeclampsia, SNP = single nucleotide polymorphism, TGF-β1 = transforming growth factor beta receptor 1, PlGF = phosphatidylinositol glycan anchor biosynthesis class F, VEGF = vascular endothelial growth factor.

investigated in the Brazilian and Iranian populations, were no found association (Table 2).

2.2.2. TNF-alpha. The tumor necrosis factor-alpha cytokine (TNF-α) is encoded by the *TNF* gene, also known as DIF, TNFSF2, and TNLG1F. It is located in the human leukocyte antigen (HLA) class II region of the major histocompatibility complex (MHC) on chromosomal region 6p21.33.[84,85] TNF-α is multifunctional proinflammatory Th1 cytokine, mainly secreted by macrophages, recognized for its receptors TNFRSF1A/TNFR1 and TNFRSF1B/TNFBR.[85] TNF-alpha is involved in the regulation of a variety of biological processes such as cell proliferation, differentiation, apoptosis, lipid metabolism, and coagulation.[86,87] Moreover, this cytokine has been implicated in a variety of diseases, including autoimmune diseases, Alzheimer, and cancer.[88,89]

During pregnancy, TNF-α has been involved with PE etiology. In this regard, increased plasma levels of TNF-α in trophoblastic cells of the placenta have been found in preeclamptic patients while IL-10 and IL-4 levels are decreased.[90–92] This cytokine imbalance leads to chronic peripheral and placental inflammation.[93] In addition, there is evidence pointing to some SNPs that act as transcriptional regulators of this cytokine in the promoter region (-308G/A, -238G/A) (Table 1),[94] such as the G/A polymorphism at position -308 that has been associated with an increased risk of PE.[64,65] Additionally, preeclamptic women are significantly more likely to carry the upregulating TNF-a -308 A/G than normotensive women.[69,82] Besides, the allele frequency (AA) in -308 position is significantly higher among preeclamptic Slovak, Finnish, Iranian and the Turkish population[65,67–69] and eclamptic Turkish women.[67] Interestingly, the AA allele frequency has been found significantly higher among preeclamptic patients with intrauterine growth restriction (IUGR) compared to those without IUGR in Hungary population.[66]

Regarding G/A polymorphism at position -238, the allele G distribution is significantly higher in the PE group, moreover, is related to high levels of TNF-α production compared with the control group 136. Furthermore, the haplotype C/A, of two polymorphisms, -850C/T and -308G/A, have been associated with an increased risk of PE in the Finnish population.[68] On the other hand, the same SNPs were investigated in the Brazilian, American, Austrian, Scottish, Italian, Finnish, and Turkish populations, where no found any association with the risk of PE (Table 2).

2.3. Th2 cytokines

2.3.1. IL-4. The interleukin 4 cytokine (IL-4) is translated by the *IL4* gene, also known as BSF1; IL-4; BCGF1; BSF-1; BCGF-1 and IL4 is localized on chromosomal region 5q31.1.[95] IL-4 protein encodes a pleiotropic cytokine Th2 produced by activated T cells. In this regard, IL-4 is considered an important cytokine for tissue repair, counteracting the effects of proinflammatory Th1 cytokines, however, it also promotes allergic airway inflammation.[96,97] Moreover, IL-4 regulates a variety of human host responses such as allergic, anti-parasitic, wound healing, and acute inflammation.[98–100] This protein has been reported to promote the resolution of neutrophil-mediated acute lung injury. In an allergic response, IL-4 plays a key role in the production of immunoglobulin E (Ig E).[101,102] IL-4 cytokine is implicated in a wide variety of disease as chronic asthma, gastric cancer, breast cancer, leukemia, oral carcinoma, bladder carcinoma, colonic cancer, chronic periodontitis, and inflammatory dilated cardiomyopathy.[103,104]

In pregnancy the Th2 cytokines, such as IL-4, play an important role in the regulation and control of inflammation, leading to the normal development of gestation. In this regard, the

Table 1

Cytokine-SNPs associated with preeclampsia.

Authors	Population studied	Population size	Methodology	SNP	Finding
IFN-γ					
Pinheiro et al[48]	Brazilian	SPE: 116 Ctl: 107 NP: 58	PCR-SSP	rs2430561	+874T/T genotype seems to plays a role in PE occurrence
TNF-α					
Tavakkol Afshari et al*	Iranian	PE: 153 Ctl: 150	PCR-RFLP	rs1800629rs361525	Significant association between TNF-alpha G-308A and G-238A genotype and PE
Mohajertehran et al[64]	Iranian	PE: 54 Ctl: 50	PCR-RFLP	rs1800629	Significant association between SNP of promoter region of TNF-alpha G-308A with PE
Mirahmadian et al[65]	Iranian	PE: 160 Ctl: 100	ASO-PCR	rs1800629rs361525	Both, -308A and -238G allele were associated with risk of PE
Molvarec et al[66]	Hungarian	PE: 140 Hellp: 69 Ctl: 144	PCR-RFLP	rs1800629	SNP G-308A was associated with risk of complicated PE with severe IUGR
Pazarbasi et al[67]	Turkish	E: 40 PE: 113 NP: 80	PCR-RFLP	rs1800629rs1799724	Both SNPs were associated with the PE susceptibility
Saarela et al[68]	Finnish	PE: 133 Ctl: 115	PCR-RFLP	rs1799724rs1800629	Both SNPs showed a significant haplotype association with susceptibility to PE
Harmon et al†	American	PE: 1598 Ctl: 918	Illumina Golden-Gate Plataform	rs1800629	Association was for PE among European Americans
Naderi, et al‡	Iranian	PE: 153 Ctl: 140	PCR-RFLP	rs361525	The AA genotype and the A allele may carry an increased risk for PE
Puppala et al[10]	Indian	PE: 100 Ctl: 100	PCR-RFLP	rs1800629	SNP -308G/A was associated with risk of PE
Zubor et al[69]	Slovak	PE: 38 Ctl: 38	PCR-RFLP	rs1800629	-308A allele was associated with risk of PE
IL-4					
Fraser et al[70]	England	PE: 117 Ctl: 146	PCR-RFLP	rs2243250	-590T/T homozygous were associated in risk of PE
Salimi et al[71]	Iranian	PE: 192 Ctl: 186	PCR	rs79071878	VNTR polymorphism of IL-4 gene has significantly increased the risk of PE
IL-6					
Puppala et al[72]	Indian	PE: 100 Ctl: 100	PCR-RFLP	rs1800795	SNP -174G/C was associated with risk of PE
IL-10					
Fan et al[30]	Chinese	PE: 142 Ctl: 260	PCR-RFLP	rs1800872	CC genotype of -592A/C was observed to be associated with PE
Liu et al[73]	Chinese	PE: 177 Ctl: 182	PCR-RFLP	rs1800871	CC genotype of -819T/C was associated with risk of PE.
Song and Zhong[74]	Chinese	PE: 177 Ctl: 182	PCR-RFLP	rs1800872	-592A/C was associated with an increased risk of early-onset PE
Sowmya et a[75]	Indian	PE: 120 Ctl: 120	ARMS-PCR	rs1800872rs1800871	-819C allele and - 592A allele were associated with PE
Sowmya et al§	Indian	PE: 120 Ctl: 120	ARMS-PCR	rs1800871	Significant association of C allele of IL-10 -819 promoter polymorphism with PE
Vural et al[76]	Turkish	PE: 101 NP: 95	ASO-PCR	rs1800896	AA genotype has 3.38-fold-increased risk of developing PE
Mirahmadian et al[65]	Iranian	PE: 160 Ctl: 100	ASO-PCR	rs1800871rs1800872	-819C/C and -592C/C were associated with risk of PE
Kamali-Sarvestani et al[77]	Iranian	PE: 134 Ctl: 164	ASO-PCR	rs1800896	-1082G allele in PE may be considered as a genetic susceptibility to development of PE
Daher et al[78]	Brazilian	PE: 151 Ctl: 189	PCR-SSP	rs1800896	SNP of IL-10 -1082 is associated with PE
Zhou et all	Chinese	PE: 117 Ctl: 286	Multiplex PCR	rs1800896	A-1082G allele frequency was significantly higher in PE
Elhawary et al[79]	Egyptian	PE: 20 Ctl: 20	PCR-RFLP	rs1800896	Significant difference between the frequency of genotype in GG, AA and A and G allele and development of PE
Raguema et al¶	Tunisian	PE: 345 Ctl: 300	RT-PCR	rs1800871	-819T/T variant and the ATA haplotype represent genetic risk for PE
IL–17A					
Lang et al[80]	Chinese	PE: 120 Ctl: 120 NP: 150	PCR-RFLP	rs2275913	Heterozygous (GA) and minorallele (A) were significantly more prevalent in PE women

(Continued)

Table1

(Continued)

Authors	Population studied	Population size	Methodology	SNP	Finding
IL-22					
Niu et al[81]	Chinese	PE: 107 Ctl: 1263	RT-PCR	rs2227485	A significant difference under the recessive model of the T allele (TT/CC + CT genotype)

Ctl = control (normotensive pregnancy), E = Eclampsia, GH = gestational hypertension, NP = Non-pregnant women, PE = preeclampsia, SNP = single nucleotide polymorphism, SPE = Severe preeclampsia.

*Tavakkol Afshari Z, Rahimi HR, Ehteshamfar SM, et al. Tumor necrosis factor-alpha and nterleukin-1-beta polymorphisms in pre-eclampsia. Iranian J Immunol. 2016;13:309–16.

†Harmon QE, Engel SM, Wu MC, et al. Polymorphisms in inflammatory genes are associated with term small for gestational age and preeclampsia. Am J Reprod Immunol. 2014;71:472–84.

‡Naderi M, Yaghootkar H, Tara F, et al. Tumor necrosis factor-alpha polymorphism at position -238 in preeclampsia. Iran Red Crescent Med J. 2014;16:e11195.

§Sowmya S, Ramaiah A, Sunitha T, et al. Role of IL-10 -819(T/C) promoter polymorphism in preeclampsia. Inflammation. 2014;37:1022–7.

‖Zhou L, Cheng L, He Y, et al. Association of gene polymorphisms of FV, FII, MTHFR, SERPINE1, CTLA4, IL10, and TNFalpha with pre-eclampsia in Chinese women. Inflamm Res. 2016;65:717–24.

¶Raguema N, Gannoun MBA, Zitouni H, et al. Interleukin-10 rs1800871 (-819C/T) and ATA haplotype are associated with preeclampsia in a Tunisian population. Pregnancy Hypertens. 2018;11:105–10.

production of IL-4 is enhanced at the feto-maternal interface during pregnancy, this production has been observed depressed in pregnant that suffering from recurring spontaneous abortions.[105] In rats, IL-4 has proved that decrease the inflammation and ultimately, improve hypertension in response to placental ischemia.[106] On the other hand, the -590C/T SNP in IL-4 has been associated with PE, in T/T genotype in that position has been associated with marked trend of PE in UK population.[70] Moreover, another SNP, the variable number tandem repeat (VNTR) RP2 allele has been associated with PE susceptibility in Iranian pregnant.[71]

2.3.2. IL-6. The interleukin 6 cytokine (IL-6) is translated by the *IL6* gene, also known as CDF; HGF; HSF; BSF2; IL-6; BSF-2; IFNB2; IFN-beta-2 and *IL6* is localized on chromosomal region 7p15.3.[107] IL-6 protein encodes a proinflammatory cytokine is primarily produced by activated cells at sites of acute and chronic inflammation. This cytokine is a soluble mediator with pleiotropic effects on inflammation and the maturation of B cells.[108] Additionally, has been observed to be an endogenous pyrogen capable of inducing fever in patients with autoimmune diseases or infections.[109,110] The IL-6 cytokine is implicated in a wide variety of inflammatory disease, for instance, juvenile rheumatoid arthritis, rheumatoid arthritis or susceptibility to diabetes mellitus.[111,112]

There are two faces of IL-6 on Th1/Th2 differentiation.[113] IL-6 promotes Th2 differentiation and at the same time inhibits Th1 polarization through two independent molecular mechanisms: IL-6 activates transcription mediated by nuclear factor of activated T cells (NFAT) leading to production of IL-4 by naive $CD4^+$ T cells and their differentiation into effector Th2 cells. The inhibition of Th1 differentiation by IL-6 is IL-4- and NFAT-independent. IL-6 inhibits Th1 differentiation by upregulating suppressor of cytokine signaling (SOCS)-1 expression interfering with IFN-γ signaling and the development of Th1 cells. Thus, by using two independent molecular mechanisms, IL-6 plays a dual role in Th1/Th2 differentiation.[113]

IL-6 is a cytokine highly expressed in the feminine tract reproductive and gestational tissues and has a differential effect during pregnancy how in the development the placenta and the requirements of immunological adaptation on the fetus tolerances, in this regard IL-6 plays an important function on the pathophysiology of infertility and gestational disorders.[114,115]

Preterm labor has been associated with elevated levels of maternal serum IL-6 cytokine, whereas it is observed that serum IL-6 levels increase with preeclamptic women and decreased production of IL-6 in placental tissue,[116,117] in this regard, IL-6 is not essential for the success of the pregnancy, however, it is important in modulation during the implantation of the embryo.[118]

Regarding SNPs, in IL-6, the -174G/C genotype has been associated with the risk of PE in the Indian population.[72] But these results differ from other investigations, where a lot of groups have evaluated this SNP in Brazilian, American, Sri Lanka, Saudi, Austrian, Scottish, Turkish, Finnish, Chinese and Mexican populations and them no found any association with the risk of PE (Table 2).

2.3.3. IL-10. The interleukin 10 cytokine (IL-10) is encoded by the *IL10* gene, also known as CSIF, TGIF, GVHDS and IL10A. It is located on the chromosomal region 1q32.1.[119] The IL-10 is produced primarily by monocytes and to a lesser extent by lymphocytes. It has two principal roles, immunoregulation and inflammation. Additionally, IL-10 produces downregulation of Th1 cytokines expression, MHC class II, and co-stimulatory molecules on macrophages.[120] It also helps with B cell survival, proliferation, and antibody production.[119] IL-10 cytokine has been implicated in a wide variety of disease as pancreatitis, diabetic nephropathy, asthma susceptibility, ischemic stroke, and coronary artery disease.[121,122]

In normal pregnancy, IL-10 has three major beneficial roles since this cytokine plays a key role in Th2 response: promoting successful placentation, controlling inflammation, and regulating vascular function.[123–125] In this regard, levels of serum IL-10 are increased during a normal pregnancy and remain high until delivery. Besides, in normal human placental tissue, it has been observed higher levels of IL-10 during first and second trimesters compared to the third trimester of pregnancy, which means that provides an important balance for inflammation at the fetal-maternal interface.[90,126]

Interestingly, some SNPs in the proximal (-1082A/G, -819T/C and -592A/C) and distal regions of the promoter region of the *IL-10* gene[127] are transcriptional regulators (Table 1).[128] For instance, the A/G polymorphism at position -1082 is related to lower IL-10 production.[77,129,130] It has been associated with an increased risk of PE in Turkish, Brazilian, and Egyptian populations.[76,78,79]

The T/C polymorphism at position - 819 found an increased distribution of the normal allele in patients[75] and was associated with increased risk of PE in Chinese[73] population, and with early-onset PE in an Indian population[75] were specifically diplotypes of IL-10: -1082A with -819C; -1082G with -819C; -819C with -592C; -1082A with -592C; and -1082G with -592C were associated.

Several studies have shown that A/C polymorphism at position -592 is associated with low levels of IL-10 production.[129,131,132] Its presence has been correlated with an elevated risk of developing PE in Iranian population[65] and the CC and AC + CC genotypes of IL-10 -592A/C are also associated with high risk when compared to the AA genotype in Chinese population.[30] Besides, this SNP has been related to early-onset PE in Indian[75] and Chinese[74] populations.

On the other hand, these three SNPs in IL-10 have been widely studied in different populations as Iranian, Brazilian,

Table 2

Cytokine-SNPs not associated with preeclampsia.

Authors	Population studied	Population size	Methodology	SNP	Finding
IFN-γ					
Daher et al[78]	Brazilian	PE: 151 Ctl: 189	PCPCR-SSP	rs2430561	No association in 874A/T SNP and PE was observed
Kamali-Sarvestani et al[77]	Iranian	PE: 134 Ctl: 164	ASO-PCR	rs2430561	No association between 874A/T polymorphism and PE was observed
de Lima et al[56]	Brazilian	PE: 92 E: 73 Ctl: 101	PCR-SSP	rs2430561	SNP of 874A/T was not association with PE women
TNF-α					
Daher et al[78]	Brazilian	PE: 151 Ctl: 189	PCR-SSP	rs1800629	SNP of -308G/A was no associated with PE
Pinheiro et al[48]	Brazilian	SPE: 116 Ctl: 107 NP: 58	PCR-SSP	rs1800629	SNP of -308G/A was no associated with PE
Livingston et al*	American	SPE: 112 Ctl: 106	PCR-RFLP	rs1800629	Neither genotypic frequency and mutant alleles were associated with severe PE
Stonek et al[6]	Austrian	PE: 107 Ctl: 107	Multiplex PCR	rs1800629	SNP in G-308A was no associated with PE
Haggerty et al[82]	American	PE: 150 Ctl: 661	TaqMan	rs1800629	-308 G/A was no associated with PE
de Lima et al[56]	Brazilian	PE: 92 E: 73 Ctl: 101	PCR-SSP	rs1800629	SNP of -308G/A was no associated with PE
Freeman et al‡	Scottish	PE: 106 Ctl: 212	PCR-RFLP	rs1800629	No association between -308G/A and the risk of PE
Previtera and Restaino[9]	Italian	SPE: 20 Ctl: 10	Sanger sequencing	rs1800629	No association was observed in -308G/A
Heiskanen et all	Finnish	PE: 133 Ctl: 115	PCR-RFLP	rs1799724	No association was observed in C-850T and risk of PE
Vural et al[76]	Turkish	PE: 101 NP: 95	PCR-RFLP	rs1800629	No significant differences was found in genotype or allele frequencies in -308G/A
IL-6					
Pinheiro et al[48]	Brazilian	SPE: 116 Ctl: 107 NP: 58	PCR-SSP	rs1800795	No association between -174G/C polymorphisms and PE was observed
Andraweera et al[51]	Sri Lanka	PE: 175 Ctl: 171	SequenomMass ARRAY system	rs1800795	No significant differences was found in-174G/C and PE risk
Freeman et al‡	Scottish	PE: 106 Ctl: 212	PCR-RFLP	rs1800795	No association between -174G/C and the risk of PE
Vural et al[76]	Turkish	PE: 101 NP: 95	PCR-RFLP	rs1800795	No significant differences was found in genotype or allele frequencies in -174G/C
Saarela et al¶	Finnish	PE: 133 Ctl: 115	PCR-RFLP	rs1800795	No significant difference was found in -17G/C and PE risk
Fanet al[30]	Chinese	PE: 142 Ctl: 260	PCR-RFLP	rs1800795rs1800796rs1800797	No significant differences were found in genotype or allele frequencies in -174G/C, -597G/A and -572 G/C
Harmon et al#	American	PE: 1598 Ctl: 918	Illumina GoldenGate Plataform	rs1800795	There was no association between IL-6 SNP and the risk of PE
Daher et al[78]	Brazilian	PE: 151 Ctl: 189	PCR-SSP	rs1800795	SNP of IL-6 -174G/C was no associated with PE
Bayoumy et al**	Saudi	GH: 60 PE: 49 Ctl: 100	PCR Allele Discrim-ination	rs1800795	No association was observed in-174G/C and risk of PE
Stonek et al††	Austrian	PE: 14 Ctl: 1367	ASO-PCR	rs1800795	-174 G/C is not a genetic marker for risk of PE
de Lima et al[56]	Brazilian	PE: 92 E: 73 Ctl: 101	PCR-SSP	rs1800795	No significant difference was found in SNP of -174G/C and PE risk
Valencia Villalvazo et al‡‡	Mexican	PE: 411 Ctl: 613	RT-PCR	rs1800795	SNP of IL-6 -174G/C was no association with PE women
Stonek et al†	Austrian	PE: 107 Ctl: 107	Multiplex PCR	rs1800795	IL-6 G174C was no associated with PE
IL-10					
Kamali-Sarvestani et al[77]	Iranian	PE: 134 Ctl: 164	PCR-RFLP	rs1800871 rs1800872	No association between -819T/C, -592A/C polymorphisms and PE was observed

(Continued)

Table2

(Continued)

Authors	Population studied	Population size	Methodology	SNP	Finding
Previtera and Restaino§	Italian	SPE: 20 Ctl: 10	Sanger sequencing	rs1800872	No association was observed in -592A/C
Pinheiro et al[48]	Brazilian	SPE: 116 Ctl: 107 NP: 58	PCR-SSP	rs1800896	No association in -1082G/A SNP and PE was observed
Sowmya et al§§	Indian	PE: 88 Ctl: 100	ARMS-PCR	rs1800896	No association was observed in -1082G/A and risk of PE
de Lima et al[56]	Brazilian	PE: 92 E: 73 Ctl: 101	PCR-SSP	rs1800871 rs1800896 rs1800872	No association between -819T/C, -1082G/A and - 592A/C polymorphisms and PE was observed
Valencia Villalvazo et al‡‡	Mexican	PE: 411 Ctl: 613	RT-PCR	rs1800896	SNP in -1082G/A was no association with PE women
Stonek et al†	Austrian	PE: 107 Ctl: 107	Multiplex PCR	rs1800896	IL-10 G-1082A was no associated with PE
Haggerty et al[82]	American	PE: 150 Ctl: 661	TaqMan	rs1800871 rs1800896	There were no differences in -819C/T and -1082G/A allele distribution
IL-17A					
Lang et al[80]	Chinese	PE: 120 Ctl: 120 NP: 150	PCR-RFLP	rs1974226 rs3748067	No significant genetic association were observed in the distribution *1245C/T and 1249C/T and risk of PE
Wang et al‖‖	Chinese	PE: 1031 Ctl: 1.298	RT- PCR Allele Discrimination	rs2275913	-197A/G was no associated with risk of PE
Anvari et al[83]	Iranian	PE: 261 Ctl: 278	PCR-RFLP	rs2275913	No significant differences in genotypic and allelic frequencies was found in -197A/G

Ctl = control (normotensive pregnancy), E = Eclampsia, GH = gestational hypertension, NP = Non-pregnant women, PE = preeclampsia, SNP = single nucleotide polymorphism, SPE = Severe preeclampsia.
*Livingston JC, Park V, Barton JR, et al. Lack of association of severe preeclampsia with maternal and fetal mutant alleles for tumor necrosis factor alpha and lymphotoxin alpha genes and plasma tumor necrosis factor alpha levels. Am J Obstet Gynecol. 2001;184:1273–7.
†Stonek F, Hafner E, Metzenbauer M, et al. Absence of an association of tumor necrosis factor (TNF)-alpha G308A, interleukin-6 (IL-6) G174C and interleukin-10 (IL-10) G1082A polymorphism in women with preeclampsia. J Reprod Immunol. 2008;77:85–90.
‡Freeman DJ, McManus F, Brown EA, et al. Short- and long-term changes in plasma inflammatory markers associated with preeclampsia. Hypertension (Dallas, Tex: 1979). 2004;44:708–14.
§Previtera F, Restaino S. Gene polymorphism in five target genes of immunosuppressive therapy and risk of development of preeclampsia.Healthcare (Basel). 2021;9:821.
‖Heiskanen J, Romppanen EL , Hiltunen M, et al. Polymorphism in the tumor necrosis factor-alpha gene in women with preeclampsia. J Assist Reprod Genet. 2002;19:220–3.
¶Saarela T, Hiltunen M, Helisalmi S, et al. Polymorphisms of interleukin-6 , hepatic lipase and calpain-10 genes, and preeclampsia. Eur J Obstet Gynecol Reprod Biol. 2006;128:175–9.
#Harmon QE, Engel SM, Wu MC, et al. Polymorphisms in inflammatory genes are associated with term small for gestational age and preeclampsia. Am J Reprod Immunol. 2014;71:472–84.
**Bayoumy NM, Al-Sharaidh AS, Babay ZH, et al. The role of interleukin-6 promoter polymorphism -174G/C in Saudi women with hypertensive disorders of pregnancy. Saudi Med J. 2013;34:689–94.
††Stonek F, Metzenbauer M, Hafner E, et al. Interleukin 6 -174 G/C promoter polymorphism and pregnancy complications: results of a prospective cohort study in 1626 pregnant women. Am J Reprod Immunol. 2008;59:347–51.
‡‡Valencia Villalvazo EY, Canto-Cetina T, Romero Arauz JF, et al. Analysis of polymorphisms in interleukin-10, interleukin-6, and interleukin-1 receptor antagonist in Mexican-Mestizo women with pre-eclampsia. Genet Test Mol Biomarkers. 2012;16:1263–9.
§§Sowmya S, Ramaiah A, Sunitha T, et al. Evaluation of interleukin-10 (G-1082A) promoter polymorphism in preeclampsia. J Reprod Infertil. 2013;14:62–6.
‖‖Wang H, Guo M, Liu F, et al. Role of IL-17 variants in preeclampsia in Chinese Han Women. PloS One. 2015;10:e0140118.

American, Italian, Indian, Mexican, and Austrian not having found any association with risk of PE (Table 2).

2.4. Th17 cytokines

2.4.1. IL-17A. The interleukin 17A cytokine (IL-17A) is translated by *IL17A* gene, also known as IL17; CTLA8; IL-17; CTLA-8; IL-17A and *IL17A* is localized on chromosomal region 6p12.2,[133] and this gene encoded a proinflammatory cytokine produced by activated T cells and by other cell subsets, such as γδT cells, cytotoxic $CD8^+$ T cells, innate tissue-specific cells, innate lymphoid cells (ILCs), and myeloid cells.[134,135] This cytokine regulates the activities of NF-kappaB and mitogen-activated protein kinases. The IL-17A can stimulate the expression of IL-6 and cyclooxygenase-2 (PTGS2/COX-2), as well as enhance the production of nitric oxide (NO). The IL-17A cytokine has been implicated in several chronic inflammatory diseases like rheumatoid arthritis, psoriasis, multiple sclerosis, and autoimmune diseases.[133,136,137]

The IL-17 family has six members IL-17A (IL17), IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F. In fact, IL-17A and IL-17F are the most closely related, are coexpressed in linked genes and usually are coproduced by Th17 cells.[138–140] The IL-17A promotes hypertension, because is traditional cardiovascular risk factor that contributes to myocardial infarction and stroke.[141–143] The Th17 cells participate in pregnancy related pathologies, including recurrent spontaneous abortion and PE, and imbalances between Th1/Treg/Th17 subsets in blood circulation and uterus have been reported.[83,144–147] In humans, it has been suggested that IL-17 can increase in the invasive capacity of JEG-3 cells (trophoblast-like human choriocarcinoma cell line) and increase progesterone secretion significantly.[148] In normal pregnancy, the size of peripheral blood TH17 cells decrease, but in PE cases, this change is not observed, being higher in the peripheral blood and decidua.[149]

Only one SNP has been reported affecting the expression of IL-17, causing recurrent pregnancy loss.[150] There is an association between the heterozygous GA and the minor allele A at position -197 and PE in Chinese women, and is related to high levels of IL-17A production compared with the control group.[80] However, another studies did not found association with PE in Chinese and Iranian population (Table 2).

2.4.2. IL-22 Interleukin-22 cytokine (IL-22) is a member of the IL-10 family (along with IL-10, IL-19, IL-20, IL-24, IL-26, IL-28, and IL-29). IL-22 is key for the host defense against extracellular pathogens at mucosal surfaces strengthening epithelial barrier

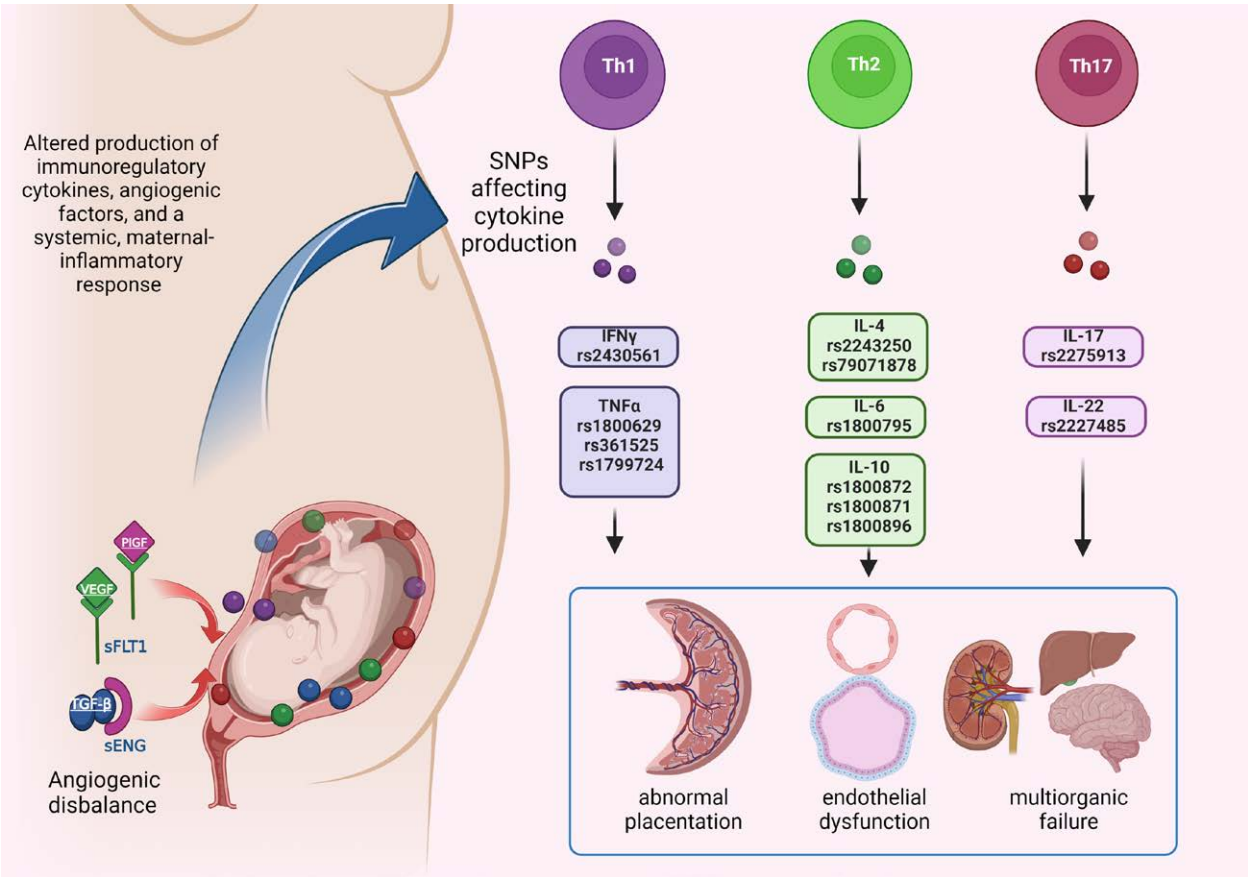

Figure 2. SNPs in IFN-γ, TNF-α, IL-4, IL-6, IL-10, IL-17A, and IL-22 have a clear association with the development, early-onset and severity of PE, modifying the Th1, Th2, and Th17 responses, affecting processes such as placentation, control of inflammation, and vascular function, which in turn affects organs such as kidney, liver and brain. This Altered production of immunoregulatory cytokines, a disbalance in angiogenic factors and maternal inflammatory response are responsible of PE severity. IFN-γ = interferon-gamma, IL-4 = interleukin 4, IL-6 = interleukin 6, IL-10 = interleukin 10, IL-17A = interleukin 17A, IL-22 = interleukin 22, PE = preeclampsia, SNP = single nucleotide polymorphism, Th1 = T helper 1, Th2 = T helper 2, Th17 = T helper 17.

functions and is involved in tissue homeostasis, tissue repair and wound healing.[151] Although IL-22 is classified a Th17 cytokine, since is mostly coexpressed with IL-17 can be produced by a wide variety of cells from adaptive and the innate immune system: $CD4^+$ T cells (Th1, Th17, T helper 22; Th22), $CD8^+$ T cells (Tc17, Tc22) γδT cells, natural killer T (NKT) cells, lymphoid tissue inducer (LTi) cells, and certain NK cell subset.[152,153]

IL-22 has been related to PE. For instance, IL-22 concentration is significantly higher in PE patients group compared with the control group, resulting in the predominance of Th17- and Th22-mediated immunity in PE. This suggests that the immune imbalance among $CD4^+$ T helper cells could lead to PE through placental ischemia.[154] Also, Stefańska et al,[155] showed that the IL-22, MDC, and IL2/IL-4 ratio can be used to discriminate between PE, gestation hypertension and healthy pregnancy.

As for IL-17, only one SNP has been reported affecting the expression of IL-22 (rs2227485) involved in the development of PE in the Chinese Han population. Significant differences were found between PE patients and controls for this SNP in terms of genotypic frequencies ($P < .001$). Then rs2227485 was assessed under the dominant model of the C allele (CC/CT + TT genotype) or the recessive model of the T allele (TT/CC + CT genotype), and observed a significant difference under the recessive model of the T allele ($P < .001$, OR = 0.620, 95% CI 0.495–0.776).[81]

3. Discussions

Pathophysiology of PE is multifactorial, being the abnormal placentation a key factor that can trigger endothelial system dysfunction and dysregulation of the inflammatory process. Nevertheless, genetic aspects also play a very important role in the development of PE.

PE is a complex and multi-symptomatic disease in which onset time, severity, and development can be a reflex of multiple genotypes. In this regard, considering that cytokines are involved in PE pathogenesis and that cytokine gene polymorphism may affect cytokine production it is obvious to seek for association between these candidate SNPs and PE.

Until now, SNPs in IFN-γ, TNF-α, IL-4, IL-6, IL-10, IL-17A, and IL-22 have shown a clear association with the development, early-onset, and severity of PE. In this regard, Th1, Th2, and Th17 responses are modified by the presence of these SNPs, affecting processes such as placentation, control of inflammation, and vascular function (Fig. 2). Nevertheless, association studies have shown different results depending on sample size, diagnostic, and population. More extensive studies could help to have more accurate conclusions about how cytokine genotypes should be considered in clinical practice since PE remains a very serious public health problem.

4. Conclusions

SNPs in IFN-γ, TNF-α, IL-4, IL-6, IL-10, IL-17A, and IL-22 have a clear association with the development, early-onset and severity of PE, modifying the Th1, Th2, and Th17 responses, affecting processes such as placentation, control of inflammation, and vascular function. Nevertheless, association studies

have shown different results depending on sample size, diagnostic, and population.

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