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REVIEW

Resolution of inflammation pathways in preeclampsia—a narrative review

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Abstract Preeclampsia (PE) is one of the leading causes of maternal morbidity and mortality worldwide. This disease is believed to occur in two stages with placental dysfunction in early pregnancy leading to maternal clinical findings after 20 weeks of gestation, as consequence of systemic inflammation, oxidative stress, and endothelial dysfunction. Much evidence suggests that PE women display an overshooting inflammatory response throughout pregnancy due to an unbalanced regulation of innate and adaptive immune responses. Recently, it has been suggested that dysregulation of endogenous protective pathways might be associated with PE etiopathogenesis. Resolution of inflammation is an active process coordinated by mediators from diverse nature that regulate key cellular events to restore tissue homeostasis. Inadequate or insufficient resolution of inflammation is believed to play an important role in the development of chronic inflammatory diseases, like PE. In this narrative review, we discuss possible pro-resolution pathways that might be compromised in PE women, which could be targets to novel therapeutic strategies in this disease.

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Introduction

Preeclampsia (PE) has been defined as a new onset of hypertension and either proteinuria or end-organ dysfunction at gestational age ≥20 weeks as consequence of systemic inflammation, endothelial dysfunction, and oxidative stress [1, 2]. Because PE is a heterogeneous disease, different classifications based on severity (mild PE/severe PE) and onset of clinical symptoms (early PE <34 weeks/late PE ≥34 weeks; preterm PE <37 weeks/term PE ≥37 weeks) have been proposed [3, 4]. It is widely accepted that early PE and late PE have different clinical features, prognosis, and probably distinct etiopathogenesis [5, 6].

Traditionally, a "two-stage" theory of PE etiopathogenesis has been considered. According to this theory, an abnormal spiral artery remodeling in early pregnancy causes placental hypoxia (*stage 1*) and the ischemic placenta releases large amounts of soluble factors, such as reactive oxygen species, pro-inflammatory cytokines, and anti-angiogenic factors, into the maternal circulation, which lead to the clinical manifestations and complications of the disease (*stage 2*) [7, 8]. Another paradigm has been recently proposed by Ahmed and Ramma [9], in which they use a metaphor to compare normotensive pregnancy as a car with accelerators and functioning brakes. The "accelerators" represent inflammation, oxidative stress, and an anti-angiogenic state, while the "brakes" are the endogenous protective pathways. According to this theory, PE manifests when the braking systems fail and the accelerators cannot be stopped in early pregnancy. In their review, Ashmed and Ramma focused on the carbon monoxide, hydrogen sulfide, and nitric oxide pathways. These gases have been

associated with protective roles, such as regulation of uteroplacental perfusion and inhibition of oxidative stress and inflammation [10–12]. The new paradigm of dysregulated endogenous protective pathways can be combined with the traditional two-stage theory of PE pathogenesis (Fig. 1). Here, we raise the hypothesis of another protective pathway that may be compromised in PE women, the resolution of inflammation pathway.

Resolution of inflammation

Acute inflammation is usually a self-limited response that can be triggered by infectious or sterile injury and has the physiological purpose to restore tissue homeostasis [13]. Successful resolution of inflammation is an active and highly regulated process that evolves several cellular and biochemical events [14, 15]. During this process, the production of anti-inflammatory/pro-resolving factors prevails over the production of pro-inflammatory mediators. However, inflammation and resolution are not isolated events. In fact, they continuously overlap because pro-inflammatory signals can induce anti-inflammatory and pro-resolving signals aiming to temper inflammation [16, 17].

In recent years, endogenous pro-resolution mediators from diverse nature have been identified, including proteins/peptides, specialized pro-resolving lipid mediators, gaseous mediators, protease inhibitors, and neuromodulators [16, 18, 19]. They inhibit further leukocyte recruitment, induce neutrophil apoptosis, and enhance the efferocytosis of apoptotic neutrophils by macrophages, thus acting as brakes for the inflammatory response. They are also able to switch macrophages from pro-inflammatory (M1) to anti-inflammatory and pro-resolving phenotypes (M2 and Mres), drain non-apoptotic leukocytes to lymph nodes, and participate in tissue repair/healing mechanisms [14–16, 20]. Figure 2 shows the key steps of successful resolution of an inflammatory process.

Inflammation may become chronic and lead to further tissue damage if resolution process fails. Dysfunctional resolution of inflammation can occur due to decreased synthesis of pro-resolving mediators and receptors, altered receptors conformation, and increased inactivation of pro-resolving mediators. Inadequate amount or action of pro-resolving mediators can lead, for example, to persistent recruitment and survival of neutrophils, failure to reprogram macrophage phenotype, and ineffective clearance of apoptotic neutrophils. In this sense, if the inflammatory stimulus is too high, it would be necessary a higher production of anti-inflammatory/pro-resolving molecules to neutralize the overshooting inflammation.

In a recent review, Fullerton and Gilroy proposed that resolution could be a bridge between innate and adaptive

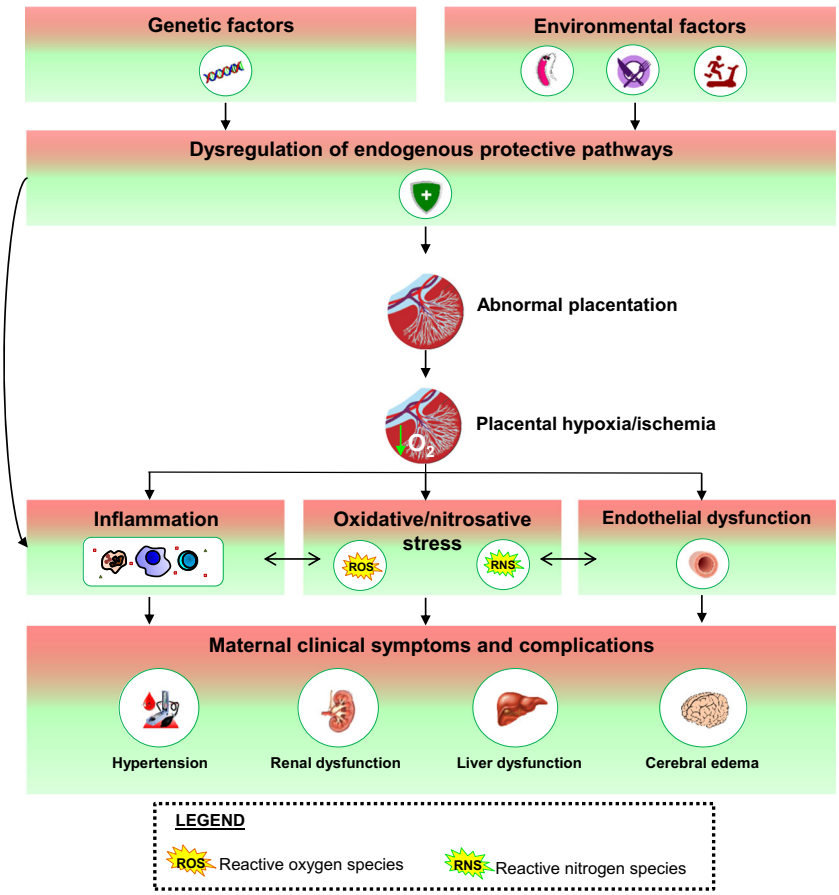

Fig. 1 The combination of "the two-stage" and "the accelerator and brake" theories might explain PE etiopathogenesis. This schematic diagram illustrates the sequential events involved in PE etiopathogenesis. Genetic and environmental factors disrupt endogenous protective pathways, leading to inadequate invasion of uterine spiral arteries by placental trophoblasts and a failure of physiological transformation of uterine spiral arteries. This results in placental hypoxia/ischemia. The dysfunctional placenta releases large amounts of soluble factors into the maternal circulation, which lead to generalized inflammation, oxidative stress/nitrosative stress, and endothelial dysfunction, events that are interconnected and precede PE clinical symptoms and complications. Alternatively, dysregulation of endogenous protective pathways can directly cause inflammation, oxidative stress, and endothelial dysfunction

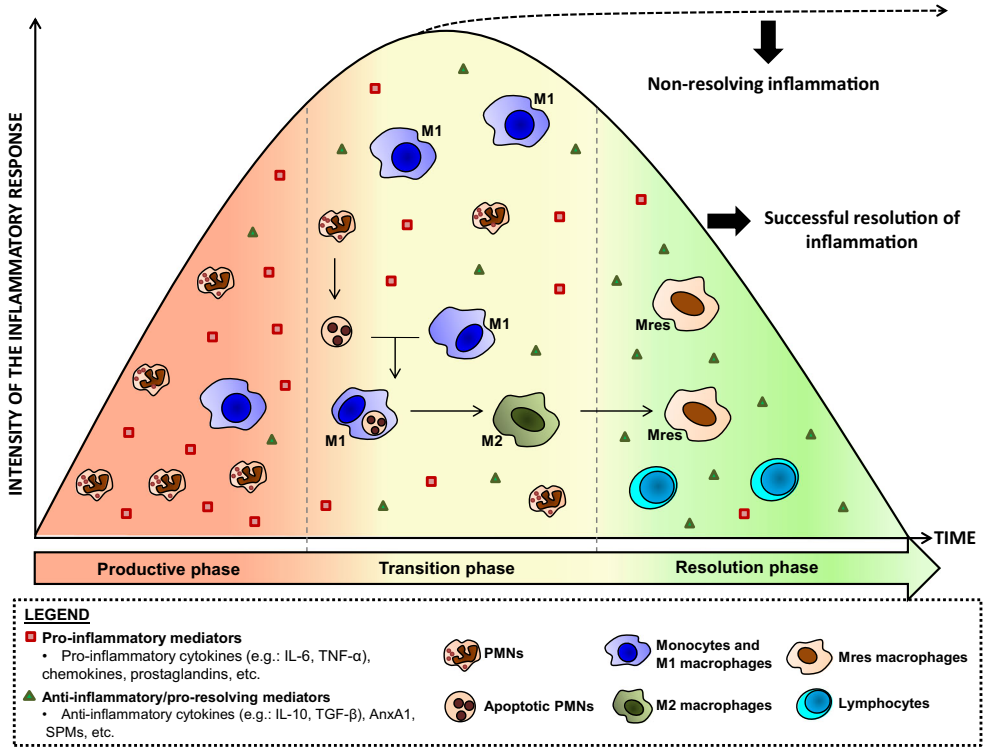

Fig. 2 Success and failure in resolution of inflammation. The productive phase of the inflammatory response is characterized by a significant influx of PMN cells to the inflamed tissue and by an increased generation of pro-inflammatory mediators by endothelial cells, migrated and resident immune cells. As the inflammatory response progresses (transition phase), there is a switch in the production of pro-inflammatory mediators to anti-inflammatory mediators and a reduction of PMN cell migration that parallel an increase in the influx of mononuclear cells. In addition, pro-inflammatory signals induce PMN cell apoptosis and macrophage phagocytosis of apoptotic PMN cells (efferocytosis). During this process, pro-inflammatory macrophages (M1) alter their phenotype to anti-inflammatory macrophages (M2). M2 macrophages have greater ability of efferocytosis and to produce anti-inflammatory/pro-resolving mediators. During the resolution phase of inflammation, the influx of monocytes prevails over the influx of PMN; the synthesis of anti-inflammatory/pro-resolving mediators is increased, while the levels of pro-inflammatory mediators are decreased. Moreover, M2 macrophages are converted into a pro-resolving phenotype (Mres), with greater ability to produce anti-inflammatory/pro-resolving mediators, and lymphocytes repopulate the affected tissue. Collectively, these events lead to successful resolution of acute inflammation. On the other hand, failures in resolution of inflammation pathways lead to persistent inflammation and maladaptive immune responses

immunities. Therefore, unresolved inflammation could lead to maladaptive immune responses, which are commonly associated with chronic inflammatory diseases [21].

Hypothesis

Embryo implantation, trophoblast invasion of uterine spiral arteries, and labor are inflammatory events. Therefore, inflammation is necessary to successful reproduction [22]. Normotensive pregnancy is characterized by a state of mild/low-grade inflammation, as demonstrated, for example, by increased levels of pro-inflammatory cytokines when compared to the non-pregnant state [23]. Innate immune responses are upregulated in normotensive pregnant women, while adaptive immune responses are modulated in order to maintain maternal immune tolerance to the fetal allograft. By contrast, innate immune responses are even more activated and adaptive immune responses are dysregulated in PE [24]. Indeed, there is a shift from T helper (Th)2/regulatory T cell responses in normotensive pregnant women to a predominant Th1/Th17 immunity in PE women [25]. Furthermore, there are evidences of placental M2 macrophage polarization in normotensive pregnancy and a predominant M1 phenotype in PE [26, 27]. Consequently, PE women display an overshooting inflammatory response throughout pregnancy [23].

Most studies of the literature have focused on the accelerators of the inflammatory response in PE. Here, we propose that the exaggerated inflammatory response seen in this disease may result from failures in a “braking system” called resolution of inflammation. If so, unresolved inflammation may account for maladaptive immune responses in PE women.

Methods

First, we performed a screening on PubMed database results through reading of titles and abstracts about pro-resolving mediators previously described in general works [16, 18, 19]. We used as key terms the specific pro-resolving mediator and preeclampsia. The pro-resolving mediators that had been studied in the context of PE according to this research were annexin A1, galectins, chemerin, lipoxin A4, nitric oxide, hydrogen sulfide, carbon monoxide, acetylcholine, netrin-1, and protease inhibitors. The final selection was based on full reading of each preselected article. Original research articles were included if they addressed these pro-resolving mediators in the context of PE (human disease and animal models). Original articles about pro-resolving mediators in other inflammatory diseases and general review articles were also included to provide a background on the role of these mediators. Articles that had not focused on these issues were excluded.

Results

This review included a total of 225 articles published between 1985 and 2017. The main conclusions obtained from them are described in the next subsections.

Annexin A1

Annexin A1 (AnxA1) is a 37-kDa glucocorticoid-regulated protein that elicits anti-inflammatory/pro-resolving effects through binding to formyl peptide receptor type 2/lipoxin A4 receptor (FPR2/ALXR). These effects lie within AnxA1 N-terminal domain and include inhibition of neutrophil migration to inflamed tissues, induction of neutrophil apoptosis, stimulation of macrophage efferocytosis of apoptotic neutrophils, and induction of macrophage reprogramming to a pro-resolving phenotype [28, 29]. AnxA1 was first recognized by its capacity to inhibit phospholipase A2 activity and the generation of eicosanoids, but subsequent studies revealed that this protein exerts a wider range of actions. It has been suggested that AnxA1 mediates part of neuroendocrine responses of the glucocorticoids, particularly in the hypothalamic-pituitary-adrenocortical axis. In addition, experimental data indicate that AnxA1 may be implicated in processes regulating pregnancy, lactation, and fetal development [30, 31].

Altered AnxA1 synthesis might be involved in the pathogenesis of chronic inflammatory diseases, like asthma [32]. Of importance, intact AnxA1 (37 kDa) can be cleaved in its N-terminal domain by proteases, such as neutrophil elastase, generating various fragments that are believed to be inactive or pro-inflammatory [33]. Indeed, increased levels of AnxA1 cleavage products (e.g., 33 kDa) have been reported in inflammatory samples [34]. Moreover, FPR2/ALXR decreased expression or altered receptor conformation can impair AnxA1 to regulate inflammation [35, 36].

Previously, Perucci et al. investigated AnxA1 in PE and found increased plasma levels when compared to normotensive pregnancy [37]. The increased concentration of AnxA1 combined with an overwhelming inflammatory response suggests a failure in this resolution pathway in PE, which could be a consequence of decreased expression of FPR2/ALXR [38, 39] or presence of anti-AnxA1 auto-antibodies [40]. Considering that neutrophilia is a common feature in PE women and that neutrophil elastase is increased in their plasma and placenta [41–43], it is also plausible to hypothesize that AnxA1 cleavage could interfere with its actions. Although AnxA1 expression has been studied in placental tissues [44], the differential expression of its intact and cleaved forms in preeclamptic and normotensive pregnancies has not been determined, a matter under investigation in our group.

Galectins

Galectins are β-galactoside-binding proteins that were initially known to mediate developmental processes, including tissue organization and embryo implantation [45]. Further research indicated that galectins are secreted in response to inflammatory signals and cellular damage, acting as pattern recognition receptors, immunomodulators, or damage-associated molecular patterns in innate and adaptive immune responses [46, 47]. Galectins are thought to modulate intracellular signaling pathways in immune cells due to their ability to induce the aggregation of specific cell-surface glycoreceptors [48, 49]. Thereby, galectins may elicit pro-resolving effects, as described below. Emerging evidences also suggest that galectins are capable of triggering platelet activation and inducing angiogenesis [50, 51]. Here, we give a general overview on the role of galectin-1 (Gal-1) and galectin-13 (Gal-13), the most studied galectins in PE.

Galectin-1

It has been suggested that Gal-1 plays a role in maternal-fetal tolerance, which is thought to be impaired in PE women. Blois et al. reported that Gal-1 deficient (*LGALS1*$^{-/-}$) mice had increased fetal loss when compared to wild-type mice, an effect that was prevented by the treatment with recombinant Gal-1. According to their results, Gal-1 restored maternal immune tolerance by promoting the expansion of IL-10-secreting regulatory T cells [52]. This data was corroborated by the study of van der Leij et al. [53]. Gal-1 might also improve maternal-fetal tolerance by inducing the apoptosis of activated CD8$^+$ T cells, Th1 cells, and Th17 CD4$^+$ cells [54]. Other

immunomodulatory actions of Gal-1 have been proposed. For instance, Rostoker et al. showed that Gal-1 induced 12/15-lipoxygenase expression (lipoxin A4 synthetizing enzyme; see the "Lipoxin A4" section) in murine macrophages and promoted their conversion into a pro-resolving phenotype [55].

Some works have demonstrated that the gene expression of Gal-1 was upregulated in placentas from PE women compared with normotensive pregnant women [56–58]. Interestingly, *LGALS1*-knockout dams develop PE symptoms. However, when stratifying PE women according to the onset of clinical symptoms, early PE women showed lower placental expression of Gal-1 than pregnant controls, while an opposite finding was reported for late PE women [58]. It has been proposed that the decreased expression of Gal-1 in early PE could be associated with placental dysfunction, whereas its overexpression might be a compensatory mechanism to attenuate inflammation in late PE [59]. In addition, the circulating levels of Gal-1 may reflect its placental expression in late PE, but not in early PE. Accordingly, Freitag et al. reported increased serum levels of Gal-1 in late PE when compared with early PE and normotensive pregnancies, but no difference was found between early PE women and normotensive women [58]. However, when both clinical forms were included in the same cohort, the serum levels of Gal-1 seemed to be similar between patients and controls [60]. Pregnant women in the second trimester of pregnancy who developed PE also showed lower levels of Gal-1 than healthy pregnant women, indicating that Gal-1 might be an early predictor of PE [58].

Gal-1 seems to be differentially expressed in cells/tissues from women with PE. Gal-1 is downregulated in T and natural killer cells in PE when compared with these cells from normotensive pregnancy, while no difference was detected in Gal-1 messenger RNA (mRNA) expression in decidual samples between these pregnant groups [58, 60]. The decreased expression of Gal-1 expression in these immune cells can be associated with maternal-fetal intolerance and exacerbated inflammatory response in PE women, as discussed above.

Galectin-13

Gal-13 is a galectin uniquely expressed in the placenta, mainly in the syncytiotrophoblast, and it is released from the placenta into the maternal circulation [61]. In vitro studies suggest that Gal-13 participates in the morphological differentiation of the cytotrophoblast into the syncytiotrophoblast [62, 63]. In addition, it has been demonstrated that Gal-13 is able to induce the apoptosis of activated human $CD3^+$ T cells [64]. Interestingly, phagocytosed Gal-13 immunopositive deposits in immune cells coincided with zones of apoptotic and necrotic immune cells in Kliman et al. study [65]. These data indicate that Gal-13 might participate in placentation and in maternal adaptive immune responses at the maternal-fetal interface. Considering that these processes are impaired in PE women, it can be hypothesized that Gal-13 is involved in the pathogenesis of the disease.

Gal-13 placental-specific expression makes it a promising biomarker for PE early prediction. Indeed, Gal-13 protein and mRNA content in blood and placenta are decreased in the first trimester of gestation in women who developed PE, especially in the early clinical form [66–71], and this could be associated with single-nucleotide polymorphisms in the *LGALS13* gene [72]. Moreover, combining Gal-13 with background risk factors, other serum biomarkers and physical parameters increase the accuracy of predicting PE [73]. Low serum levels of Gal-13 in early gestation may lead to impaired placentation and maternal immune intolerance to the fetus [65, 74].

It has been demonstrated that the serum levels of Gal-13 increase throughout normotensive pregnancy and that preterm PE women have higher serum levels of Gal-13 than preterm controls [66]. It was proposed that the increase in maternal serum concentration of Gal-13 during the third trimester of gestation in PE women is a consequence of augmented placental shedding of microvesicles containing Gal-13, and this could be a compensatory mechanism aiming to restore homeostasis [66]. Nevertheless, both decreased and increased expressions of placental Gal-13 have been reported in PE women [66, 75].

Chemerin

Chemerin is an adipocyte-secreted protein originally identified as the natural ligand of chemR23 receptor, which is implicated in several biological processes, such as adipogenesis, glucose homeostasis, and immune cell migration [76]. It has been suggested that chemerin is abundantly expressed in stromal cells and in extravillous trophoblast cells, but not in decidual endothelial cells in early pregnancy [77]. Moreover, chemerin may stimulate angiogenesis and the accumulation of natural killer cells at maternal-fetal interface, and these immune cells have been implicated in uterine spiral artery remodeling [77–79]. Thus, chemerin can be involved in placental development, which is impaired in PE women. Chemerin also acts as a chemoattractant for dendritic cells [80]. Several lines of evidence indicate crucial roles for both natural killer and dendritic cells in the modulation of adaptive immune responses [81, 82]. Based on these data, it can be admitted that chemerin may contribute to maternal-fetal tolerance, but more studies are necessary to clarify this issue.

Fragments with distinct inflammatory actions can be generated after chemerin C-terminal proteolytic processing, depending on the types of proteases predominating in the microenvironment [80, 83]. Some chemerin fragments can induce the chemotaxis of immune cells, in particular dendritic cells, macrophages, and natural killer cells, toward inflammatory sites, thus contributing to the onset of inflammation. By

contrast, other fragments can inhibit the synthesis of pro-inflammatory mediators. In addition, the activation of the chemerin/chemR23 axis may increase the non-phlogistic phagocytosis of apoptotic cells by macrophages, and inhibit neutrophil activation and influx to inflammatory sites, thus promoting the resolution of inflammation. Therefore, chemerin-derived peptides may play a role both in initiation and in resolution of the inflammatory response [80].

It has been shown that the serum levels of chemerin increase throughout normotensive pregnancy [84, 85]. Some studies have reported increased circulating levels of chemerin, as well as increased mRNA and protein expressions in placentas from PE women when compared to normotensive pregnant women [86–88]. Higher levels of chemerin were detected in the first trimester of gestation in women who developed PE, were associated with disease severity, and remained significantly higher 6 months after delivery in former PE women compared with controls [87–89]. Moreover, there is a positive correlation among chemerin levels, pro-inflammatory mediators, and blood pressure [86–89]. However, these studies did not specify the types of chemerin-derived peptides quantified. Hence, their role in PE pathogenesis remains unclear.

Specialized pro-resolving lipid mediators

The polyunsaturated fatty acids omega-6 and -3 are substrates for the biosynthesis of lipoxins (LXs), maresins, resolvins, and protectins, which are collectively called *specialized pro-resolving lipid mediators* (SPMs). Prostaglandins and leukotrienes are lipid mediators that play pivotal roles in the initiation of the inflammatory response, while SPMs attenuate inflammation and contribute to its timely resolution [90]. Curiously, aspirin induces the endogenous synthesis of LX 15-epimers [91]. Endogenous LXs and their epimers have been shown to counter-regulate inflammation in a variety of experimental models of inflammatory diseases. They down-regulate pro-inflammatory mediators' synthesis (including prostaglandins and leukotrienes), inhibit neutrophil infiltration, induce macrophage efferocytosis of apoptotic neutrophils, and stimulate interleukin (IL)-10 production [90, 92]. Furthermore, LXs may modulate other biological actions, such as angiogenesis, airway smooth muscle function, and activity of neuronal ion channels that convey nociceptive signals [93–95]. In this sense, LXs and other SPMs may contribute to resolution of both inflammation and pain [94].

Lipoxin A4

Lipoxin A4 (LXA4) is an eicosanoid synthesized from arachidonic acid, an omega-6 derivate, through the metabolism of lipoxygenase enzymes [96]. LXA4 interacts with FPR2/ALXR receptor, which also binds to AnxA1 [97]. An in vitro study showed that LXA4 inhibited the production of IL-1β by monocytes from severe PE women in a dose-dependent manner [98]. In another experiment, 15-epi-LXA4 reduced neutrophil-endothelium cell adhesion triggered by PE plasma [99]. Lin et al. administrated an LXA4 analogue in low-dose-endotoxin-treated pregnant rats and found that it attenuated inflammation and PE symptoms [100]. These experimental data suggest protective roles for LXA4 and its analogues in the disease.

Three works showed higher circulating levels of LXA4 in PE women compared to normotensive pregnant women [39, 101, 102]. However, an opposite finding has also been reported [38]. Different studied populations or methodologies to quantify LXA4 might have contributed to these divergent results. Interestingly, LXA4 plasma levels correlated with maternal blood pressure, white blood cell count, and C-reactive protein levels in Perucci et al. study [102]. Similar to AnxA1 discussion, LXA4 inefficiency to resolve inflammation could be a consequence, for example, of the decreased expression of FPR2/ALXR and/or increased LXA4 inactivation. However, these hypotheses remain to be investigated.

Gaseous mediators

Nitric oxide, hydrogen sulfide, and carbon monoxide are the most studied gaseous mediators, and, for many years, only their toxicity was known [103]. Recently, they have been implicated in key physiological functions, such as angiogenesis, inflammation, and vascular tone regulation [104, 105]. They also participate in trophoblast invasion and in spiral artery remodeling [106]. Experimental studies have demonstrated that these gases act as anti-inflammatory mediators at low concentrations, promoting resolution of inflammation, but exert pro-inflammatory and damaging effects at high concentrations [12]. In line with this data, altered production or signaling of gaseous mediators has been reported in inflammatory diseases, like atherosclerosis and arthritis [107, 108].

Nitric oxide

Nitric oxide (NO) is synthesized by the conversion of L-arginine to L-citrulline by one of the following three isoforms of nitric oxide synthase (NOS): neuronal, endothelial (eNOS), or inducible (iNOS). NO acts as a vasodilatory molecule by inducing cyclic guanosine monophosphate (cGMP) synthesis [109]. However, NO can act by cGMP-independent pathways to regulate other mechanisms, such as leukocyte apoptosis [110, 111]. NO may have pro- or anti-inflammatory actions depending on the concentration used in the experiment, the delivery method, and the system/disease model studied [112]. Low amounts of NO inhibit the synthesis of pro-inflammatory cytokines and reduce leukocyte-endothelium adhesion and transmigration to inflamed tissues, while high levels of NO increase vascular permeability and leukocyte migration [113,

114]. NO might also play a role in resolution of inflammation since it induces neutrophil, but not macrophage, apoptosis [115].

In normal pregnancy, NO and cGMP biosynthesis are increased due to eNOS upregulation. In addition, the biosynthesis of asymmetrical dimethylarginine (ADMA), a competitive inhibitor of NOS, is reduced. These events are important to regulate peripheral and placental bed vascular resistances, angiogenesis, platelet adhesion/aggregation, and trophoblast invasion [116]. On the other hand, most studies have reported decreased activity of placental iNOS and eNOS and increased levels of ADMA in PE, but data on NO levels are inconsistent [117–119]. Moreover, increased levels of ADMA in the first trimester of pregnancy may predict PE [120]. Additionally, ADMA increase seems to be more prominent in early severe PE than in late severe PE and eNOS polymorphisms may influence the onset time of the disease [121, 122].

Other mechanisms may interfere with NO signaling in PE. It has been demonstrated that polymorphisms in the transcription factor STOX1 gene are associated with maternal susceptibility to PE and that the overexpression of placental STOX1 induces a PE-like syndrome in mice [123, 124]. According to the study of Doridot et al., placentas overexpressing STOX1 showed high concentration of reactive nitrogen species (RNS). They proposed that RNS could be rapidly generated in the placenta through the association of NO with reactive oxygen species (ROS) [125]. Therefore, the overexpression of STOX1 could decrease NO bioavailability in endothelial cells, preventing the protective actions of this gaseous mediator in vascular tone and inflammation and also contributing to oxidative and nitrosative stress in PE women [11]. Further evidence suggested a risk allele (Y153H) in STOX1 gene that might be associated with a less invasive trophoblast phenotype [126]. Accordingly, a previous study showed that the ability of trophoblasts to remodel uteroplacental arteries depended on NO produced by extravillous trophoblasts in guinea pig pregnancy [127].

Considering that NO interferes with several pathways that are known to be compromised in PE women, such as vascular tone, inflammation, and oxidative/anti-oxidative status, impaired bioavailability and/or action of this gaseous mediator may be associated with the pathogenesis of the disease. In this sense, the therapeutical potential of drugs that enhance NO availability, inhibit cGMP degradation, or reduce ADMA levels has been investigated in vitro and in experimental models of PE. PE was mimicked by inducing reduced uterine perfusion pressure (RUPP) model and the overexpression of the anti-angiogenic molecule soluble fms-like tyrosine kinase (sFlt1) and by administrating the NOS inhibitor N^G-nitro-L-arginine methyl ester (L-NAME) in rodents [128]. Although some of these findings seem promising, there is insufficient clinical evidence to use these drugs for PE treatment or prevention [128, 129].

Hydrogen sulfide

Endogenous hydrogen sulfide (H_2S) is primarily synthetized by the conversion of L-cysteine or homocysteine by two enzymes, which are cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) [130]. H_2S is a vasodilatory mediator, an effect that can be mediated through eNOS activation and NO production [131]. H_2S exert anti-oxidant effects on cells and it seems to be cytoprotective at low concentrations, while higher H_2S exposure favors oxidative stress and cell apoptosis [132]. As for NO, H_2S role in inflammation is complex and not fully elucidated. H_2S might act as a pro-inflammatory mediator, as demonstrated in experimental sepsis [133, 134], or as an anti-inflammatory/pro-resolving molecule, for example, in gastrointestinal inflammation [135]. Evidences suggest that H_2S promotes resolution of inflammation by inducing neutrophil apoptosis, M2 macrophage polarization, and clearance of apoptotic neutrophils by macrophages [136–138]. Recently, it has been suggested that part of H_2S anti-inflammatory/pro-resolving effects are mediated by AnxA1 [139].

H_2S has been implicated in placental vascular development and function due to its pro-angiogenic and vasodilatory activities [131, 140]. Both H_2S-synthetizing enzymes CBS and CSE are expressed in human placenta during normal pregnancies [141], but the studies on their expression in PE have conflicting results. Wang et al. reported a downregulation of CSE (mRNA and protein) in placentas from PE women [142]. Moreover, placentas with abnormal Doppler have increased expression of microRNA-21, which negatively regulates CSE expression [143]. By contrast, in Holwerda et al. study, mRNA levels of CSE in the placenta were unchanged, while mRNA levels of CBS were decreased in early PE [144]. These divergent results might be attributed to differences in the studied clinical forms of PE [128]. Furthermore, Wang et al. reported decreased plasma levels of H_2S in PE women [142]. Abnormal synthesis of H_2S could contribute to endothelial dysfunction, oxidative stress, and overwhelming inflammation observed in PE women [128].

H_2S-based therapies have been studied in animal models of PE and in human disease. The administration of a slow-releasing H_2S-generating compound (GYY4137) ameliorated PE-like symptoms induced by the treatment with an inhibitor of H_2S synthesis (DL-propargylglycine) [142]. However, oral administration of an H_2S donor (N-acetylcysteine) to severe early PE women did not improve maternal outcomes [145]. More studies should be conducted in order to evaluate the therapeutical potential of H_2S-releasing compounds in PE.

Carbon monoxide

Heme oxygenase (HO) enzymes convert heme to biliverdin, free iron, and carbon monoxide (CO) in the endoplasmatic

reticulum. HO enzymes exist as inducible (HO-1) and constitutive (HO-2) isoforms [146]. HO-CO system regulates many biological processes, such as vascular tone, oxidant-anti-oxidant status, and platelet aggregation. Further, CO acts as a signaling molecule in the neuronal system, where it regulates the release of neurotransmitters. Like NO and H_2S, CO is toxic at high concentrations but has cytoprotective actions at low concentrations [147, 148]. It has been suggested that part of the protective and deleterious effects of CO are due to its ability to regulate different types of ion channels [149]. Most studies have reported counter-regulatory actions for CO in inflammatory responses. Low CO exposure inhibits neutrophil-endothelial adhesion and transmigration to inflamed tissues, suppresses the production of pro-inflammatory cytokines, promotes neutrophil apoptosis, and enhances macrophage efferocytosis of apoptotic neutrophils [150–153]. Moreover, CO accelerates resolution of inflammation by shifting the lipid profile in the inflammatory milieu [153].

Both HO-1 and HO-2 are expressed in human placenta [154]. During pregnancy, CO regulates perfusion and oxidant-anti-oxidant status within placental tissues, as well as spiral artery transformation [154–156]. Adequate expression of HO might also be important to maintain maternal-fetal tolerance [157]. Considering the importance of CO in regulating multiple processes during pregnancy, alterations in the HO-CO system in PE would be expected. Indeed, PE women seem to have lower CO breath levels and carboxyhemoglobin concentration in the umbilical cord blood than normotensive pregnant women [158, 159]. These data are in line with the observation that CO exposure in cigarette smoke decreases the risk of developing PE [160, 161]. However, HO placental expression during PE is not clear. Either decreased, increased, or unchanged, placental expressions of HO-1 and HO-2 have been reported in PE women [162–166].

Compounds that induce HO expression have been studied in experimental and in human PE [128]. A recent work showed that pravastatin treatment stabilized blood pressure, proteinuria, and serum uric acid levels in severe PE women [167]. These effects seem to be partially mediated by upregulating HO-1 placental expression [168]. McCarthy et al. studied rosiglitazone effects using the RUPP rat model of PE and found that this drug prevented the development of disease-like symptoms via HO-dependent pathway [169]. Moreover, CO application at low doses prevented hypertension and proteinuria in adenovirus sFlt1 PE-like mouse model [170]. In conclusion, the administration of the CO or HO-inducing agents might be beneficial for treating or preventing PE, but further investigation is necessary.

Neuromodulators

Acetylcholine

Cholinergic neurons release acetylcholine (ACh), a neurotransmitter known to regulate skeletal, smooth, and cardiac muscle contractions. ACh also acts as neuromodulator in the central nervous system, where it alters neural excitability, synaptic transmission, and plasticity, thus interfering with learning, memory, and mood [171, 172]. ACh can induce endothelium vasodilatation through NO-dependent and independent mechanisms, for example, by inducing the production of prostaglandins [173]. Indeed, it has been demonstrated that pharmacological administration of ACh reduces blood pressure in rats [174]. These data suggest that Ach-deficient synthesis or action may be associated with PE pathogenesis.

Studies on the role of neural reflexes in inflammation and immunity are recent. It has been demonstrated that ACh binding to α7-nicotinic receptors in macrophages inhibits the synthesis and the release of pro-inflammatory cytokines [175–178]. Alternative anti-inflammatory cholinergic mechanisms have been proposed. For instance, nicotine (a cholinergic agonist drug) attenuates inflammation by upregulating the expression of HO-1 in macrophages [179, 180]. Other anti-inflammatory and pro-resolving effects of nicotine include inhibition of neutrophil migration and stimulation of its apoptosis [181, 182]. Moreover, ACh receptor activation by nicotine enhances macrophage phagocytosis and protects M2 macrophages from apoptosis [183, 184]. The role of this neural pathway in controlling inflammatory responses was further confirmed by studies showing that vagus nerve lesions enhance pro-inflammatory cytokines' production and are associated with non-resolving inflammation [176, 185, 186]. Accordingly, chronic inflammatory conditions, such as inflammatory bowel disease, have decreased vagus nerve function [176].

Yang et al. reported reduced vagus nerve function in PE women [187]. Thus, Ach-reduced synthesis in these women might contribute to excessive inflammation and hypertension. Accordingly, nicotine binding to ACh receptor supresses ex vivo placental cytokines' production [188]. In a recent study, nicotine was able to reduce systolic blood pressure in LPS-induced PE rat model [189]. This effect might be associated with nicotine protective effects on the endothelium, as previously demonstrated by Mimura et al. [190]. These data corroborate with the theory that nicotine, and also CO, in cigarette smoke might protect from PE [160, 161]. Some studies have also shown that nicotinic ACh receptors are upregulated in PE women [191, 192], which could be a compensatory mechanism to decreased ACh levels.

Netrin-1

Netrin-1 was originally described as a laminin-related protein that guides axonal trajectories during the development of central nervous system, by repulsing/abolishing the attraction of neuronal cells expressing the UNC5b receptor [193]. Subsequently, it was implicated in the regulation of various biological processes, including angiogenesis and, recently, inflammation. Netrin-1 suppresses neutrophil trafficking, probably as consequence of the strong expression of UNC5b receptor in these cells [194, 195]. It also inhibits prostaglandin E2 synthesis, regulates Th1/Th2/Th17 cytokines' production, induces M2 polarization, increases apoptotic polymorphonuclear (PMN) cell efferocytosis, and stimulates the endogenous biosynthesis of SPMs [196–199]. In accordance, in vivo studies have reported protective functions of netrin-1 in inflammatory conditions [199–202]. Interestingly, Mirakaj et al. found that netrin-1 stimulated the resolution of peritoneal inflammation induced by zymosan via resolvin D1, a pro-resolving lipid mediator [186]. Yang et al. investigated the placental expression of netrin-1 and found that it was downregulated in severe PE women [203]. More studies are needed to understand the association between netrin-1 and inflammation in PE.

Protease inhibitors

Proteases are enzymes that hydrolyze peptide bonds of proteins, releasing polypeptides or free amino acids. They regulate the activity and the localization of several proteins, modulate the interactions among them, and participate in cellular signaling events. Currently, proteases are classified based on their mechanisms of catalysis into the following four classes: serine proteases, metalloproteases, aspartic proteases, and cysteine proteases. Their activities are tempered by protease inhibitors or anti-proteases [204, 205]. Proteases are usually upregulated in inflammatory conditions, and defective anti-proteolytic control mechanisms may participate in the pathogenesis of chronic inflammatory diseases, like cystic fibrosis [206, 207]. Thus, protease inhibitors have the potential to be developed as new therapeutic agents for these diseases.

Metalloproteinase inhibitors

Metalloproteinases are proteolytic enzymes that hydrolyze extracellular matrix components, playing important roles on tissue repair. They participate in extracellular matrix remodeling during trophoblast invasion and in uterine spiral artery transformation. This family of enzymes comprises, among other members, matrix metalloproteinases (MMPs) and membrane-anchored disintegrin metalloproteinases (ADAMs) [208, 209]. Activated metalloproteinases can be regulated by general or specific protease inhibitors (tissue inhibitors of metalloproteinases (TIMPs)) [210].

Several non-matrix substrates for metalloproteinases have been identified, including cytokines, chemokines, and their receptors. Metalloproteinases cleave these substrates in short fragments, altering their bioactions, and, in the case of receptors, interfering with their responsiveness and downstream signaling. Metalloproteinases modulate additional aspects of inflammation, such as integrity of physical barriers,

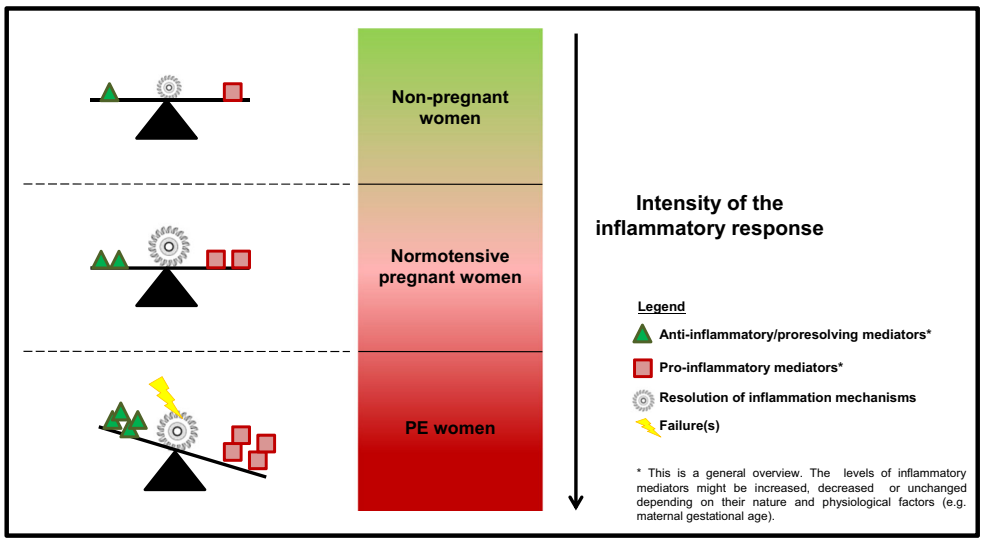

Fig. 3 Schematic representation of inflammatory and counter-regulatory mechanisms in non-pregnant women, normotensive pregnant women, and PE women. Healthy non-pregnant women have basal levels of anti-inflammatory/pro-resolving mediators and pro-inflammatory mediators, which are in a state of equilibrium due to functioning resolution of inflammation mechanisms. Normotensive pregnant women show higher levels of pro-inflammatory mediators than non-pregnant women, but the inflammatory response is mild and controlled, because resolution of inflammation mechanisms are able to adjust properly to this physiological state (increased gear symbol). By contrast, failures in pro-resolving mechanisms probably lead to an exacerbated inflammatory response in PE women, despite the upregulation of some anti-inflammatory/pro-resolving mediators

leukocytes' transmigration, and survival [211, 212]. Metalloproteinases may have pro-inflammatory or anti-inflammatory/pro-resolving actions. For instance, ADAM17, also known as tumor necrosis factor alpha (TNF-α) converting enzyme, releases the membrane-bound TNF-α, increasing the bioavailability of this pro-inflammatory cytokine. By contrast, ADAM17 sheds TNF-α soluble receptors (sTNFRs) in the circulation, which sequester TNF-α, neutralizing its systemic effects [213]. ADAM17 also prevents neutrophil transmigration trough the endothelium by shedding L-selectin from them, without altering monocyte recruitment. In addition, ADAM17 induces neutrophil apoptosis [214, 215].

There is increasing evidence of metalloproteinase/TIMP imbalance in inflammatory diseases, like inflammatory bowel diseases [216]. Metalloproteinases and their inhibitors may also participate in PE pathogenesis. Ma et al. reported that ADAM17 was upregulated in placentas from PE women and induced TNF-α production by placental trophoblasts [217]. Later, they showed that the placental levels of TIMP3 (ADAM17 inhibitor) were decreased in PE women and that TIMP3 downregulation increased TNF-α production by placental trophoblasts [218]. Further reports on increased circulating levels of TNF-α and sTNFRs in PE women corroborated with these findings [219–221], since increased ADAM 17 levels and decreased TIMP3 levels may induce TNF-α release and the consequent shedding of neutralizing sTNFR receptors in the circulation of PE women. Decreased, increased, or similar levels of other metalloproteinases and TIMPs have been described in PE [222]. These discrepancies are probably due to differences in the types of specimens analyzed, gestational age of specimen collection, and quantification methodologies. Therefore, the role of metalloproteinases and their inhibitors in PE pathogenesis requires further investigation.

Concluding remarks

Several evidences support that there is a balance of pro-inflammatory and anti-inflammatory/pro-resolving pathways in normotensive pregnant women as consequence of functioning mechanisms of resolution of inflammation, leading to a state of controlled inflammatory response in these women. On the other hand, inflammation is overwhelming in PE women, probably because of dysregulated resolution of inflammation mechanisms (Fig. 3). Moreover, pro-inflammatory and anti-inflammatory/pro-resolving mediators from diverse nature might be at higher, lower, or similar levels in PE women compared with normotensive pregnant women, reinforcing the complex regulation of resolution pathways.

The apparently contradictory findings regarding the measurement of pro-resolving mediators in PE can be a mirror of the biological sample tested (serum/plasma—systemic vs. placenta—local) and moment (onset vs. established inflammation), in which such mediators were measured. It is known that some of the pro-resolving mediators may have dual activities during the inflammatory response; i.e., they can be pro-inflammatory at the beginning of inflammation to assure proper activation of the immunologic system and, as inflammation progresses, they can be pro-resolving, acting as brakes for the inflammatory response. In addition, the activity of some mediators may be influenced by several factors, such as molecule structure (e.g., AnxA1 cleavage generates short peptides believed to have pro-inflammatory activities), the cell type in which they act (e.g., LXA4 induces apoptosis of neutrophils while rescue macrophage from death), or concentration (e.g., NO and H_2S have anti-inflammatory actions at low concentrations but pro-inflammatory actions at high concentrations) [33, 113, 114, 133–135, 223, 224]. However, whether these activities may be applied in the context of PE remains to be determined.

There are few mechanistic studies in the literature for most of the pro-resolving mediators described in this work in the context of PE. Further investigation about the role of pro-resolving mediators in PE pathogenesis is warranted, for example, using knockout animals and therapeutic strategies in animal models. However, none of the available animal models of PE can mimic the full spectrum of the human disease [225]. Prospective studies with standardized methodologies would also be valuable to assess whether altered levels and/or actions of pro-resolving mediators in PE women are causes or consequences of the disease. The knowledge acquired from these studies will provide a basis for future clinical trials about novel therapies targeting pro-resolving mechanisms in PE.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

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