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Review

The NLRP3 inflammasome role in the pathogenesis of pregnancy induced hypertension and preeclampsia

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Abstract: Pregnancy-induced hypertension and preeclampsia are associated with significant maternal and fetal mortality. A better understanding of those diseases, delineation of molecular pathomechanism, and efficient treatment development are some of the most urgent tasks in obstetrics and gynecology. Recent findings indicate a crucial role of inflammation in the development of hypertension and preeclampsia. Although the mechanism is very complex and needs further explanation, it appears that high levels of cholesterol, urate, and glucose activates NLRP3 inflammasome, which produces IL-1β, IL-18 and gasdermin D. Production of these proinflammatory chemokines is a beginning of local and general inflammation, what results in sympathetic outflow, angiotensin II production, proteinuria, hemolysis, liver damage, immunothrombosis, and coagulopathy. NLRP3 inflammasome is a critical complex in the mediation of inflammatory response, which makes it crucial for the development of pregnancy-induced hypertension and preeclampsia, as well as its complications, such as placental abruption and HELLP syndrome. Herein presented the article delineate molecular mechanisms of those processes, indicating directions of future advance.

Keywords: NLRP3; inflammation; preeclampsia; pregnancy-induced hypertension; HELLP syndrome; immunothrombosis

1. Introduction

Pregnancy-induced hypertension (PIH), defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg, complicates approximately 6-10 % of all pregnancies[1]. PIH is related to significant maternal and fetal mortality and increased risk of placental abruption, cerebrovascular events, organ failure, and disseminated intravascular coagulation. Gestational hypertension most frequently occurs as the component of preeclampsia (PE), defined as de-novo hypertension present after 20 weeks of gestation combined with proteinuria (>300 mg/day), other maternal organ dysfunction, hematological complications, uteroplacental dysfunction, or fetal growth restriction [1]. PE afflicts 2-8 % of pregnancies and is one of the three leading causes of maternal morbidity and mortality worldwide [2]. Preeclampsia can be complicated with eclampsia, stroke, abruptio placentae, disseminated intravascular coagulation (DIC), liver hemorrhage/rupture, pulmonary edema, or HELLP syndrome, and the last one is the cause of 83 % of deaths in the course

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of PE [1,2]. Recognizing the gravity of this problem, scientists for decades tried to discover precise pathomechanism of PE, and introduce efficient therapeutic options. Regarding that pursue Weel et al. performed immunohistochemical analysis of placental tissues collected from 20 women with PE and 20 healthy controls [3]. Researchers discovered the significantly higher expression of NOD-like receptor family, pyrin domain-containing protein 3 (NLRP3), and related mediators such as caspase-1, IL-1β, and IL-18 in samples from women with PE in compare to controls [3]. Moreover, Xu et al. and Pontillo et al. reported that specific NLRP3 gene polymorphisms are associated with a significantly higher risk of PE development [4,5]. This article aims to delineate the role of NLRP3 in the development of preeclampsia, its symptoms, and complications.

2. Role of NLRP3 in PE and PIH

2.1. General information

The innate immune system is a host's first line of defense against invading pathogens or environmental irritants in order to maintain homeostasis. Every cell expresses germline-encoded pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and nucleotide-binding domain leucine-rich repeat-containing receptors (NLRs), which role is surveillance and recognition of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). Among 22 recognized members of the NLR family, NLRP3 is most extensively investigated, among other things, due to its ability to associate with other proteins in large multimeric complexes, called inflammasomes (Figure 1) [6]. PAMPS and DAMPs induce inflammatory response through the activation of inflammasomes [7]. NLRP3 inflammasome consists of NLRP3, ASC, and cysteine protease precursor procaspase-1 [8]. NLRP3 is composed of C-terminal leucine-rich repeats (LRRs), a central nucleotide-binding and oligomerization domain (NACHT), and an effector domain, which is an N-terminal pyrin domain (PYD). ASC is an abbreviation of apoptosis-associated speck-like protein containing an N-terminal PYD and a C-terminal caspase recruitment domain (CARD) what indicates what it is composed of. ASC has been also termed Pycard. Cysteine protease precursor procaspase-1 is composed of the CARD and caspase domain. Activation of NLRP3 inflammasome is composed of two signals, both initiated by DAMPs or PAMPs [6–8]. The first signal leads to the activation of nuclear factor κ B (NF-κB) through different receptors such as NLRs, TLRs, IL-1R1, etc. NF-κB is a transcription factor that interacts with a vast number of genes, and among other things induce expression of pro-IL-1β and NLRP3. These proteins are not constitutively expressed. Therefore their concentrations in cells are insufficient to form inflammasomes [7]. The second signal mechanism is not fully delineated. However, it appears that it involves the direct binding of DAMPs to NLRP3. Activated NLRP3 multimerize and interact with ASC, which is responsible for the recruitment and activation of procaspase-1 into caspase-1 [7,8]. Active caspase-1 transforms pro-IL-1β, pro-IL-18, and gasdermin D (GSDMD) into their active forms (Figure 1) [6–8].

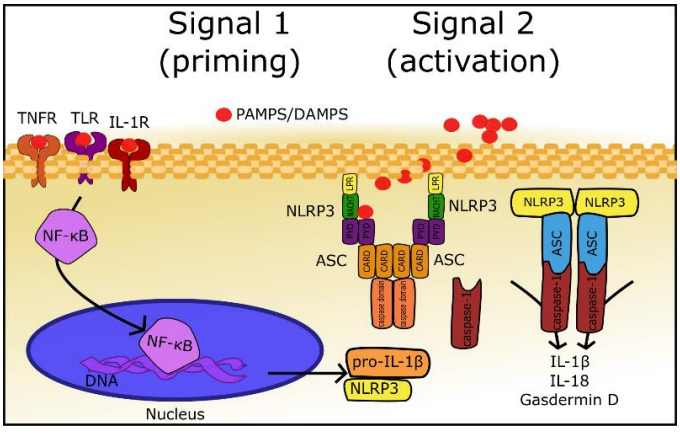

Figure 1. Mechanism of formation and activation of NLRP3 inflammasome.

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2.2. *NLRP3 as an inductor of hypertension*

Many scientists noticed the role of the immune system in a pathomechanism of hypertension. A vast number of studies indicating inflammation and elevated levels of plasma interleukins among patients with hypertension were analyzed by Krishnan et al. in order to answer if IL-1β and IL-18 are markers or mediators of hypertension [9]. As was described above, IL-1β and IL-18 are products of the activated NLRP3 inflammasome. Therefore its role in the development of hypertension was investigated [8]. Omi et al. examined 1 911 patients (987 with hypertension, 924 controls), discovering that homozygotes of high activity NLRP3 alleles had a greater risk of hypertension development then heterozygotes and low activity NLRP3 alleles homozygotes combined (odds ratio 1.24, $p = 0.03$) [10]. Crucial for the development of hypertension is an activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic system. Van der Meiraker and Boomsma indicated a connection between these two systems by discovering that the activity of both is increased in hypertension. Moreover, ACE or AT1 inhibitors resulted in a decrease of sympathetic system outflow despite predictions, that lowering blood pressure will increase sympathetic system activity [11]. Torretti reported increased renin excretion and production under sympathetic system stimulation through activation of β-adrenergic receptors in juxtaglomerular cells, indicating balance and cooperation of RAAS and sympathetic system in order to maintain proper blood pressure and sodium homeostasis in case of low sodium intake what afflicted humans for thousands of years [12]. Rust and Eckmekcioglu investigated the role of salt intake in the pathogenesis of hypertension, describing the potential of increased natrium chloride concentrations to induce inflammation in the brain, leading to sympathetic system outflow, and as a result increase of renin concentrations, all resulting in blood pressure elevation [13]. Analysis of these findings and NLRP3 activation by NaCl prompt Liu et al. to the conclusion that high salt intake induces NLRP3 mediated inflammation in the hypothalamic paraventricular nucleus leading to sympathoexcitation and RAAS activation [8]. Furthermore, Platten et al. show a significant reduction of inflammatory lesions, amount of Th lymphocytes, and an increase of the number of Treg lymphocytes in rat experimental autoimmune encephalitis model after treatment with ACE or AT-1 inhibitors, indicating a notable role of RAAS in inflammation induction and maintenance [14]. In order to confirm the role of NLRP3 in the development of hypertension in preeclampsia, Shirasuna et al. induced PE in pregnant wild type mice, NLRP3 knock-out mice, and ASC knock-out mice [15]. Researchers divided female mice aged 8-12 weeks into seven groups approximately 4 individuals each: wild type vehicle, wild type 500 ng/kg, wild type 1500 ng/kg, NLRP3 -/- 500 ng/kg, NLRP3 -/- 1500 ng/kg, asc -/- 500 ng/kg, asc -/- 1500 ng/kg. All animals were implanted into dorsal space with osmotic minipump on the 10th day of gestation, which administered continuously 500 or 1500 ng/kg of angiotensin II daily for eight days. Angiotensin II elevated systolic blood pressure (SBP) in dosage dependant fashion. However, in both NLRP3 -/- and asc -/- SBP was significantly lower in comparison to wild type, and this effect was considerably more expressed among NLRP3 -/- than asc -/-, indicating the substantial role of NLRP3 in development of hypertension in preeclampsia [15]. Moreover, Krishnan et al. describe the contractile response of arteries directly after exposition to IL-1β, and augmented contraction after activation of α1-adrenergic receptors in IL-1β rich environment. Furthermore, IL-1β and IL-18 are associated with increase expression of pro-oxidant enzymes in blood vessels and increased thickness of intima-media complex in carotid arteries [9]. Considering aforementioned data induction of NLRP3 i.e. by high concentrations of NaCl induce inflammation in paraventricular nucleus of hypothalamus, leading to sympathetic outflow resulting in activation of RAAS, and angiotensin II leads to further induction of inflammation and NLRP3 activation, what closes the cycle of hypertension pathomechanism.

2.3. *NLRP3 role in kidney injury*

Along with hypertension, proteinuria is a major sign of PE, and it indicates kidney injury. Kwon et al. assessed urine of 45 patients with confirmed lupus nephritis, 36 of them had no or mild tubulointerstitial inflammation (TI), and 9 had moderate to severe TI. Results show significant correlation between proteinuria and moderate to severe TI (odds ratio [OR] 3.166, 95% confidence interval [95% CI] 1.145–8.757, $p = 0.026$) describing proteinuria as a diagnostic and prognostic

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parameter [16]. As was described in the previous section NLRP3 and inflammation stimulate angiotensin II (Ang II) production, in which high concentration appears to be harmful to kidneys not only due to induction of hypertension. Li and Zhuo report that Ang II initiates tubulointerstitial inflammation through activation of NF-κB, which, as a transcription factor, increases expression of proinflammatory chemokines [17]. Grande et al. shed more light on that process, indicating that Ang II activates NF-κB through transforming growth factor β (TGFβ), and production of reactive oxygen species (ROS). Furthermore, NF-κB leads to macrophage infiltration of renal interstitium and apoptosis of renal tubular cells [18]. Tashiro et al. assessed kidney biopsy specimens of 28 patients with TI [19]. IL-β1 was elevated in all samples and positively correlated with the severity of the tubulointerstitial injury. Moreover, there was a positive correlation of NLRP3 mRNA with the severity of TI as well [19]. As it was described above, NLRP3 inflammasome products not only IL-β1 and IL-18 but also gasdermin D. Li et al. reported gasdermin D mediated pyroptosis of renal tubular cells in the course of treatment with cisplatin [20]. This information implicates that gasdermin D is a possible inductor of renal cell apoptosis in Ang II induced TI. Neßelhut et al. determined the urinary protein profile in 21 healthy males, 25 healthy females, 64 patients with an uncomplicated pregnancy, and 110 hypertensive pregnant women [21]. Researchers detected that Tamm-Horsfalls glycoprotein was present in the urine of healthy individuals, but was significantly decreased or absent in the urine of 83 % of hypertensive pregnant women. Based on studies indicating that Tamm-Horsfalls glycoprotein is, in fact, uromodulin and has a significant affinity to the IL-1, Neβelhut et al. hypothesized that the immunological system has a substantial role in the development of PIH and PE. Therefore reduction of urine Tamm-Horsfalls glycoprotein concentration is a result of its immunosuppressive activity and association with IL-1 [21]. Considering data above the activation of NF-κB and NLRP3 through Ang II, leading to inflammation, renal tubular cell pyroptosis, and proteinuria is a pathomechanism of kidney injury in hypertension, i.e., in PE or PIH. However, it appears that TI is not the only cause of kidney injury and proteinuria in PE. Yamamoto et al. examined urine of 34 preeclamptic patients, dividing protein profiles into four patterns: low molecular weight (L) pattern (tubular damage), high MW (H) pattern (glomerular damage), high and low MW (HL) pattern, and middle MW (M) pattern. The incidences of the HL, H, L, and M patterns were 26.5 %, 14.7 %, 11.8 %, and 47.1 % respectively [22]. Kaltenbach et al. performed a similar study investigating 107 pregnant women with PE, additionally dividing patients based on MAP: 80-100 mmHg, 100-120 mmHg, 120-200 mmHg. 47 % of all patients had mixed patterns, indicating both glomerular and tubular pathology. Interestingly glomerular pattern prevalence in 80-100 mmHg, 100-120 mmHg, 120-200 mmHg groups was 3 %, 7 %, and 12 %, respectively indicating the correlation of glomerulopathy with blood pressure [23]. According to this data kidney injury in PE occurs not only due to TI, but also glomerulopathy with could be a result of coagulopathy and/or hemolysis which are described in following sections of this article.

2.4. NLRP3 impact on the coagulation system

Engelmann and Massberg created a review regarding immunothrombosis, its activation, and its role in fighting with pathogens [24]. Authors show that lipopolysaccharide (LPS), PAMPs, and DAMPs associated with infections can activate macrophages through TLRs, inducing proinflammatory chemokine production. Inflammation leads to the recruitment of more macrophages and other white blood cells, inter alia neutrophils. Interestingly LPS, DAMPs and PAMPs can directly activate and induce aggregation of thrombocytes, due to expression of TLRs (TLR2 and TLR4) on their surface. Moreover, neutrophils produce neutrophils extracellular traps (NETs), which are composed of DNA associated with histones, and histones H3 and H4 can activate platelets [24]. Furthermore, activated macrophages, neutrophils, and platelets present active tissue factor. Tissue factor activates the extrinsic pathway of coagulation by interaction with factor VIIa, which activates coagulation factor X, and Xa induces the production of thrombin. The role of immunothrombosis is to trap pathogens, i.e., bacteria, and prevent them from spreading with blood, which facilitates the destruction of pathogens and limits inflammatory response to small loci instead of the whole body. Interestingly, the hemolytic abilities of some bacteria are known for decades, and

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it appears that this property is a counteraction against immunothrombosis [24]. Murthy et al. conducted a study aiming to determine whether NLRP3 is involved in the formation of thrombus through platelet activation and aggregation. Researchers assessed the expression of NLRP3 and ASC in non-activated and collagen-activated platelets by immunofluorescence staining, showing significant up-regulation of NLRP3 and ASC in activated platelets [25]. Moreover, western blot showed a notable increase of active IL-1β concentration in collagen-activated platelets specimen in comparison to resting platelets. Furthermore, platelet aggregometry and flow chamber with a collagen-coated surface showed a significant reduction of platelet activation and aggregation in the blood of NLRP3 knock-out mice in comparison to the blood of wild type mice [25]. The same tests were performed using blood samples of healthy humans. Platelets were isolated and pretreated for 30 minutes with a specific inhibitor against NLRP3 (MCC950; 100 nM, Cayman Chemical, Ann Arbor, MI) or against caspase-1 (YVAD-CHO; 100 nM, Calbiochem, Darmstadt, Germany). Platelets of both groups showed a significant reduction of activation and aggregation in comparison to samples without inhibitors, proving that NLRP3 inflammasome is crucial for that process and thrombus formation [25]. Brown et al. experimented on platelets isolated from human blood samples, indicating that IL-1β and IL-1α stimulate pro- IL-1β production in platelets [26]. Flow cytometry showed 1ILR1 expression on platelets surface, and recombinant IL1R antagonist abolished the aforementioned effect of IL-1, leading to the conclusion that this receptor is responsible for signal transduction. Moreover, as it was described above, platelets through NLRP3 and caspase-1 can activate pro-IL-1β. Considering this data, Brown et al. claimed the existence of an IL-1β autocrine loop, which is a part of immunothrombosis [26]. In relation to the previous section, thrombosis in renal microvessels can lead to glomerulopathy. Therefore, to the development of proteinuria [27]. The data mentioned above confirm the crucial role of NLRP3 in the mechanism of immunothrobosis. Moreover, platelets constitutively express NLRP3. Therefore, it does not need a priming signal for activation of the inflammasome, which highlights its importance in thrombus formation [28]. Considering the correlation of PE with NLRP3 and all described pathomechanisms, this inflammasome appears to play a significant role in the development of PE associated coagulopathy.

2.5. NLRP3 as an inductor of placental abruption

Preeclampsia is a risk factor of placental abruption, a major obstetric complication, with fetus mortality around 49.5 % and mothers mortality in a range of 4-8 % [29,30]. For decades scientists struggled to delineate pathomechanism of placental abruption and development of more efficient therapies. Nath et al. performed a histological examination of placenta samples of 160 patients with placental abruption, and 176 patients with no evidence of placental abruption. All women delivered at the gestation of 20 weeks or longer, and samples were taken a right after parturition [31]. Chorioamnionitis was defined as the presence of inflammatory infiltrates of neutrophils at two or more sites on the chorionic plate and extraplacental membranes. The odds ratio for chorioamnionitis for women with placental abruption in compare to controls was 3.6 (95% CI 1.7 to 10.5), and 2.8 (95% CI 1.3 to 6.1) for preterm and term gestation groups respectively, indicating the participation of immunology system in placental abruption process [31]. Moreover, analysis of the placental tissue of 20 normotensive pregnant women and 20 patients with severe PE, performed by Weel et al., revealed a significant increase of NLRP3, caspase-1 and IL-1β expression [3]. This data indicates the occurrence of NLRP3 inflammasome mediated inflammation in the placentae of women with PE. In their histological study of placental abruption, Braila et al. reported edema and inflammation in both uterus and placenta [32]. Moreover, researchers discovered thrombosis and coagulant imbalance in the uterus, and placental infarctions in examined samples. Furthermore, myometrium presented a vascular network poor in small blood vessels [32]. These findings can be explained by the aforementioned placental inflammation and NLRP3 associated coagulopathy. Moreover, Major et al. report the production of soluble fms-like tyrosine kinase-1 (sFlt-1) by monocytes stimulated by activated platelets in the blood of women with PE [33]. Soluble fms-like tyrosine kinase-1 is a vascular endothelial growth factor (VEGF) inhibitor, and due to this property, it can impede angiogenesis. Therefore it can be hypothesized that placental NRLP3 mediated inflammation leads to

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immunothrombosis, and monocyte-platelet aggregates produce sFlt-1. Both coagulopathy and angiogenesis inhibition possibly contributes to placental incapacity and placental abruption. However, this hypothesis needs confirmation.

2.6. NLRP3 as an inductor of HELLP syndrome

HELLP is an abbreviation of hemolysis, elevated liver enzymes, and low platelets. HELLP syndrome is a grave obstetric complication with severe maternal mortality and afflicts 10-20 % of women with preeclampsia [34]. Abildgaard and Heimdal delineated pathomechanism of HELLP syndrome, indicating a significant role of thrombotic microangiopathy in the development of this disease [35]. Pathomechanism of coagulopathy and thrombosis in small vessels among women with PE, as well as the role of NRLP3 in that process, is described in section 2.4. Red blood cells are fragmented as they pass through vessels with fibrin strands, which results in microangiopathic hemolytic anemia [35]. Moreover, hem released from fragmented erythrocytes acts as a DAMP, therefore stimulates NLRP3 inflammasome activation and further induction of immunothrombosis and erythrocyte destruction [36]. Furthermore, Mustafa and Bano discovered that bilirubin deactivates cystatin, an inhibitor of cathepsin, which increases its activity [37]. Cathepsin is a protease that initiates apoptosis of hepatocytes through caspase-3 and caspase-9, leading to liver damage. Therefore bilirubin from fragmented erythrocytes can indirectly induce liver parenchyma destruction [37,38]. Moreover, cathepsin and thrombin directly cleave complement component 5 (C5) to C5a, facilitating the formation of membrane attack complex (C5b-9) [39]. Burwick et al. examined blood and urine samples of 25 women with severe PE, 25 women with chronic hypertension, and 25 healthy controls discovering higher concentrations of C5a and C5b-9 in plasma of women from the first two groups in comparison to controls. Furthermore, researchers detected high concentrations of C5b-9 in urine samples of 94 % of women with severe preeclampsia, and none in other groups, indicating the participation of C5b-9 and C5a in the pathomechanism of PE [40]. Membrane attack complex directly haemolyse red blood cells in the intravascular hemolysis process, contributing to DMAPs production and spread of inflammation [41]. If the inflammatory response occurs in the liver, activated NLRP3 inflammasome leads to the production of gasdermin D and pyroptosis of hepatocytes [42]. Interestingly, placentas with thrombotic and ischaemic alterations, as it was described in section 2.4, show higher expression of death receptor Fas ligand (FasL) [35]. FasL can induce apoptosis of hepatocytes, which maintain the constitutive expression of Fas. Thus this could be another component of liver damage in HELLP syndrome among preeclamptic women [43]. Considering aforementioned data HELLP syndrome is most likely a result of NLRP3 mediated inflammation (Figure 2).

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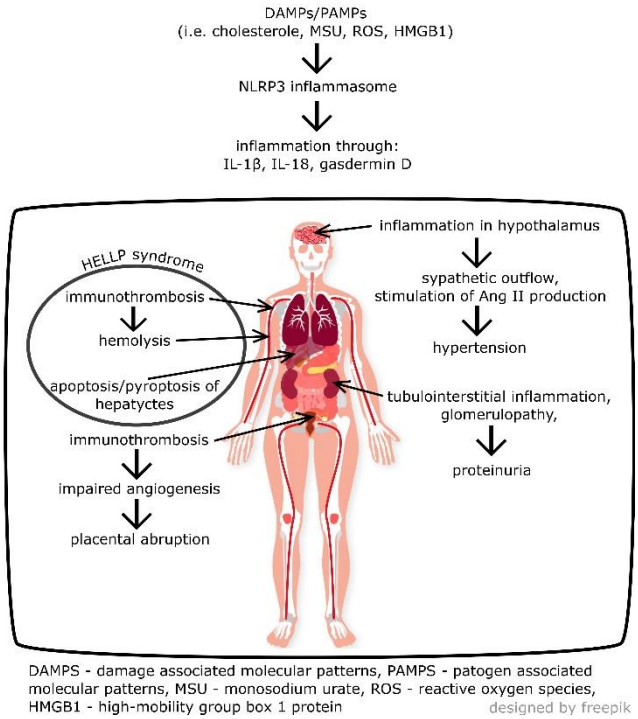

Figure 2. Pathomechanism of PIH and PE development by the NLRP3 inflammasome.

3. NLRP3 activators in PE and PIH

Regarding previous sections of this article, the role of NLRP3 inflammasome as a risk factor of PIH and PE, and its crucial part in the pathomechanism of these diseases appear to be quite well established. However, the cause of primary NLRP3 inflammasome activation still needs an explanation. Assessment of blood samples performed by Stødle et al. revealed elevated plasma concentrations of monosodium urate (MSU) and cholesterol among women with PE in comparison to healthy controls [44]. Moreover, MSU and cholesterol showed a positive correlation with plasma concentrations of high sensitivity C-reactive protein and soluble sFlt-1 (a marker of PE), indicating the association of MSU and cholesterol with inflammation and PE [44]. Matias et al. assessed monocytes isolated from blood samples of 23 women with PE and 23 normotensive pregnant women [45]. Monocytes of women with PE showed significantly higher expression of NLRP3, caspase-1, IL-1β, and IL-18 mRNA. Interestingly, monocyte stimulation with MSU resulted in increased expression of NLRP3, caspase-1, and IL-18 in samples of PE women but not in samples of controls. Moreover, MSU increased the expression of caspase-1 and IL-1β in dosage-dependent fashion in monocytes of non-pregnant healthy women. Furthermore, this effect was abolished by glibenclamide, an NLRP3 inhibitor [45]. Another, similarly designed studies confirmed that NLRP3 is activated by cholesterol, ROS, MSU, hyaluronan, and glucose [45–49]. These findings led to the creation of NLRP3 crystal-induced activation theory, where MSU, alum, silica, asbestos, β-amyloid, cholesterol crystals, and calcium crystals, induces NLRP3 inflammasome activation [6,45]. Although the exact mechanism is not yet comprehended, this theory is vital for PE research, because it explains why high BMI, which is usually connected with hypercholesterolemia, is a significant risk factor for PE development [1]. Therefore, crystal-induced NLRP3 inflammasome activation theory can facilitate the development of effective prophylaxis and treatment of preeclampsia.

4. Discussion

Immunological and hormonal balance is very complex and fragile, mainly during pregnancy, when many changes occur. One of them is an alteration of cholesterol concentration, which typically decrease at the beginning of pregnancy achieving nadir in the second month, and significant increase

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above concentrations from before pregnancy, with zenith in the month of parturition [50]. As was described above, cholesterol is an activator of the NLRP3 inflammasome, thus physiological for pregnancy increase of its concentration could be a primer of preeclampsia development. However, cholesterol level elevation is typical for pregnancy, but PE afflicts only 2-8 % of pregnancies. Therefore there is another factor, which makes some women more susceptible to DAMPs like cholesterol, and/or which facilitate greater inflammatory response and/or impairs self-restraint ability of the immunological system. Interestingly Stødle et al. revealed no difference of NLRP3 expression in placenta samples of healthy and preeclamptic patients. However, if IUGR occurred, it was associated with an increased level of IL-1β, a product of NLRP3 inflammasome [44]. Similar expression of NLRP3 exclude the previous priming, but higher IL-1β production could be an effect of NLRP3 polymorphism and the presence of its more active forms. This finding indicates that on top of the general inflammatory response, there are local inflammations, which could be a reason for the variable PE spectrum. Despite many unknowns in the pathomechanism of PE development studies proving the crucial role of NLRP3 in that process and delineating DAMPs, which can activate the inflammasome can be a source of great change in therapy and prophylaxis of preeclampsia. For example, by monitoring and lowering levels of cholesterol and monosodium urate, or the introduction of new pharmacotherapy guidelines. High glucose concentrations activate the NLRP3 inflammasome in trophoblasts, and a recent study showed that metformin inhibits NLRP3 through AMPK/mTOR pathway. Therefore this drug could be used as a PE prevention among pregnant patients with DM2 or gestational diabetes [49,51]. Moreover, researchers investigate the potential of different NLRP3 inhibitors, which, if safe for fetuses, would significantly decrease PE morbidity and mortality, which is the future of obstetrics [1,52].

5. Conclusions

NLRP3 plays a crucial role in the development of PIH and PE, leading to the occurrence of hypertension, through sympathetic outflow and RAAS activation, to proteinuria, through tubulointerstitial inflammation and glomerulopathy, to placental abruption, through immunothrombosis, and to development of HELLP syndrome, through immunothrobosis, cytokine-mediated hemolysis, and induction of hepatocyte apoptosis and pyroptosis. NLRP3 inflammasome can be activated by high concentrations of cholesterol, glucose, MSU, ROS, etc., although other factors, like genetic susceptibility, appear to be important in the excessive activity of inflammasome and development of PIH and PE. Therefore, inhibitors of NLRP3 could be very effective in the treatment of pregnancy-induced hypertension and preeclampsia.

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