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Review

Toll-like receptor activation, vascular endothelial function, and hypertensive disorders of pregnancy

Dakshnapriya Balasubbramanian[a], Catalina A. Lopez Gelston[a], Brett M. Mitchell[a,*], Piyali Chatterjee[b]

[a] Texas A&M University Health Science Center, Department of Medical Physiology, 361A Reynolds Medical Building, College Station, TX 77843, USA
[b] Baylor Scott & White Health, Department of Internal Medicine, 702 SW HK Dodgen Loop, Temple, TX 76504, USA

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ABSTRACT

Aberrant innate immune system activation in the mother contributes greatly to the development of hypertension during pregnancy. Numerous groups have elicited vascular inflammation, endothelial dysfunction, and hypertension in animals during gestation by directly activating Toll-like receptors. Additionally, several experimental therapies that reduce pro-inflammatory immune cells and cytokines restore vascular endothelial function and normalize blood pressure.

This review will summarize the research demonstrating that an excessive maternal innate immune response is sufficient to cause vascular inflammation and endothelial dysfunction, which contributes to the development of hypertension during pregnancy. Dampening the vascular inflammation caused by immune responses may reduce the incidence and severity of hypertensive disorders of pregnancy.

Contents

Abbreviations: AngII, angiotensin II; APCs, antigen presenting cells; Aza, azathioprine; CO, carbon monoxide; DAMPs, danger-associated molecular patterns; DOCA, deoxycorticosterone acetate; dsRNA, double-stranded RNA; EDHF, endothelial-derived hyperpolarizing factor; ET-1, endothelin-1; HO, heme oxygenase; IFN, interferon; IL, interleukin; IRF, interferon regulatory factor; MMF, mycophenolate mofetil; NF-kappaB, nuclear factor kappa B; NO, nitric oxide; NOD, nucleotide-binding oligomerization domain-like; PAMPs, pathogen-associated molecular patterns; P, pregnant; PDGF, platelet-derived growth factor; PE, preeclampsia; PIC, polyinosinic:polycytidylic acid; PlGF, placental-derived growth factor; PLX-PAD, placental expanded cells (Pluristem Therapeutics Inc.); PRR, pattern recognition receptor; r, recombinant; R, R-837; ROS, reactive oxygen species; RUPP, reduced uterine perfusion pressure; sEng, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase-1; SHR, spontaneously hypertensive rat; ssRNA, single-stranded RNA; TGF-beta, , transforming growth factor beta; TLR, Toll-like receptor; Tregs, , regulatory T cells; Th, helper T cell; TxA2, thromboxane receptor A2; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cell; vWF, von Willebrand factor.

* Corresponding author.
E-mail addresses: bmitchell@tamhsc.edu (B.M. Mitchell), Piyali.Chatterjee@BSWHealth.org (P. Chatterjee).

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1. Introduction

Preeclampsia (PE) is a serious pregnancy related complication that causes 75,000 maternal deaths and is a leading cause of premature birth annually [1]. According to the new guidelines set forth by the American College of Obstetricians and Gynecologists and the International Society for the Study of Hypertension in Pregnancy, PE is diagnosed by new onset hypertension and proteinuria or without proteinuria but the presence of other end-organ injury including edema, thrombocytopenia, impaired liver function, renal insufficiency, and visual or cerebral disturbances [2]. Symptoms of PE usually resolve after the delivery of the placenta. However, growing evidence suggests that the vascular dysfunction that accompanies PE increases the risk of cardiovascular disease by two-fold in these women later in life compared to women who had normotensive pregnancies [3]. Currently, both detection and treatment options for women with PE are limited due to the lack of our complete understanding of the disease etiology.

To meet the demands of the growing fetus during pregnancy blood flow needs to increase significantly in the placenta. Thus, decidual spiral artery remodeling by the invading trophoblasts in the placenta is an important step for creating a low resistance system facilitating increased blood flow. Besides the placenta, the maternal vasculature undergoes systemic vasodilation resulting in a fall in total peripheral resistance to compensate for increases in cardiac output and maternal blood volume [4]. To compensate for the dramatic increase in cardiac output, the uterine vessels have low resistance and increased blood flow (30–50%) [5]. During normal pregnancy, blood pressure decreases until mid-gestation and gradually normalizes thereafter. In PE, spiral artery remodeling is impaired due to shallow trophoblast invasion thus restricting intrauterine blood flow. In addition, both uterine and systemic vascular resistance fails to drop during PE. Together, these factors contribute to hypertensive diseases of pregnancy including PE [5]. Redman and Sargent proposed a two-stage model for PE where inadequate spiral artery remodeling leads to poor placental perfusion during the early stages of placentation and subsequently contributes to widespread maternal endothelial dysfunction and disease manifestation [6]. This two-stage model failed to explain several clinical observations of PE and more recently, Roberts et al. suggests that low grade inflammation and metabolic changes that are characteristic of normal pregnancy are exaggerated in PE [7].

During a normal pregnancy, the maternal decidual innate immune cells (macrophages, natural killer cells, dendritic cells) and adaptive immune cells (T cells, regulatory T cells or Tregs) facilitate implantation of the embryo and migration of the invading trophoblast cells for proper spiral artery remodeling. The local milieu of immune cells and the cytokines they produce promote a successful pregnancy outcome by inducing immune tolerance. During PE, excessive inflammation may result from invading pathogens (pathogen-associated molecular patterns, PAMPs) or release of endogenous factors (damage-associated molecular patterns, DAMPs). The conserved molecular patterns in PAMPs and DAMPs are recognized by pattern recognition receptors (PRRs) including Toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like (NOD) receptors, scavenger receptors, and C-type lectins,which lead to the activation of the signaling cascade and persistent production of pro-inflammatory cytokines [8]. Phagocytes are the early responders and then antigen presenting cells (APCs) activate the leukocytes to trigger the adaptive immune system. In PE, pro-inflammatory cytokines are produced by trophoblasts and immune cells in the placenta and released to the maternal circulation [9]. In contrast, anti-inflammatory cytokines are decreased which offsets the balance and polarizes even further towards a pro-inflammatory state. In concert, these factors contribute to the increased maternal systemic inflammation [10]. Vascular function is impaired as a consequence of an increased number of circulating leukocytes in the vascular wall that results in increased production of adhesion molecule and cytokines [11]. Increased vascular permeability also occurs due to endothelial cell barrier dysfunction [12]. Thus, both local and systemic inflammatory changes during PE induce widespread maternal endothelial dysfunction resulting in altered blood flow and arterial pressure (Fig. 1).

The contribution of excessive activation of the innate immune system during pregnancy causing maternal endothelial dysfunction and hypertension is only beginning to emerge. Our previous studies and others in rodents have demonstrated that TLR activation during mid-gestation contributes to the development of PE-like features only if the animals are pregnant [13–20]. In a TLR3-induced mouse model of PE, plasma levels of the pro-inflammatory cytokines TNF-alpha, interleukin (IL)-6, and IL-17 are increased that can contribute directly to increased vasoconstriction and reduced endothelium-dependent relaxation during pregnancy [13,14]. Likewise, similar observations were made more recently in a TLR9-induced rat model of PE [17]. We have also demonstrated that administration of the anti-inflammatory cytokines IL-10 and IL-4 either alone or in combination attenuates endothelial dysfunction, normalizes blood pressure, and restores the pro-inflammatory T helper cell-1/anti-inflammatory T helper cell-2 (Th1/Th2) balance, and that the genetic deficiency of either of these cytokines exacerbates TLR3-induced PE-like features in mice [13,21,22]. This review will primarily focus on the new relevant findings in our understanding of the activation of innate immune system leading to systemic maternal vascular dysfunction, and how inhibition of inflammation can improve maternal vascular function and attenuate PE-like features.

2. Tlr activation induces vascular endothelial dysfunction during pregnancy

Endothelial dysfunction is evident in patients with PE and occurs due to reduced endothelium-dependent vasodilation or increased vasocontraction via altered production or responsiveness to vasodilators and vasoconstrictors. Several factors have profound effects on vascular cells. Endothelium-derived vasodilators nitric oxide (NO) and prostacyclin are decreased in PE, and deficiency of myoendothelial gap junctions in subcutaneous arteries leads to a reduced contribution of various endothelium-derived hyperpolarizing factors (EDHFs) in women with PE [23–27]. In contrast, endothelium-derived vasoconstrictor levels of and/or sensitivity to endothelin-1 (ET-1), angiotensin II (AngII), and thromboxane A2 (TxA2) are increased during PE [28–30]. A dysfunctional endothelium is also characterized by an inflammatory phenotype due to increased expression of pro-inflammatory and/or decreased anti-inflammatory cytokines and increased production of reactive oxygen species (ROS).

The effect of excessive activation of PRRs on the vasculature and immune cells and the subsequent maternal vascular adaptation during pregnancy that contribute to hypertension are currently topics of great interest. Among the phylogenetically conserved germline-encoded PRRs, TLRs are the best characterized. These receptors are present in both immune and non-immune cells, sense PAMPs and DAMPs, and invoke an appropriate immune response [8,31]. TLR profiles of human medium and large arteries found that TLR2 and TLR4 are ubiquitously expressed, TLR7 and TLR9 are mostly absent, and TLR1, 3, 5, 6, and 8 are expressed more selectively [32]. TLRs are type-I integral transmembrane glycoproteins composed of a toll-interleukin 1 homology domain, a single transmembrane domain, and a solenoid domain. TLR1-13 subtypes have been reported in mammals, where TLR1-10 is present in humans