Prenatal inflammation exposure-programmed cardiovascular diseases and potential prevention

Youcai Deng[a,b,1,*], Liang Song[a,b,1], Xuqiang Nie[a,b], Weinian Shou[a,b,c], Xiaohui Li[a,b,*]

[a]Institute of Materia Medica, College of Pharmacy, Army Medical University (Third Military Medical University), 30# Gaotanyan Rd., Shapingba District, Chongqing 400038, China

[b]Center of Translational Medicine, College of Pharmacy, Army Medical University (Third Military Medical University), 30# Gaotanyan Rd., Shapingba District, Chongqing 400038, China

[c]Herman B Wells Center for Pediatric Research, Department of Pediatrics, Indiana University School of Medicine, 1044 W. Walnut Street, R4 W302D, Indianapolis, IN 46202, USA

[1]These authors equally contributed to this work.

***Address correspondence to:**

Xiaohui Li and Youcai Deng

Address: Room 606, Pharmaceutical Sciences Building, 30# Gaotanyan Rd, Shapingba District, Chongqing 400038, China

Tel.: (86) 23-68771632;

Fax: (86)23-68753397

Email address: youcai.deng@tmmu.edu.cn (Y. Deng); lpsh008@aliyun.com (X. Li)

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Abstract

In recent years, the rapid development of medical and pharmacological interventions has led to a steady decline in certain noncommunicable chronic diseases (NCDs), such as cancer. However, the overall incidence of cardiovascular diseases (CVDs) has not seemed to decline. CVDs have become even more prevalent in many countries and represent a global health threat and financial burden. An increasing number of epidemiological and experimental studies have demonstrated that maternal insults not only can result in birth defects but also can cause developmental functional defects that contribute to adult NCDs. In the current review, we provide an overview of evidence from both epidemiological investigations and experimental animal studies supporting the concept of developmental reprogramming of adult CVDs in offspring that have experienced prenatal inflammation exposure (PIE) during fetal development (PIE-programmed CVDs), a disease-causing event that has not been effectively controlled. This review describes the epidemiological observations, data from animal models, and related mechanisms for the pathogenesis of PIE-programmed CVDs. In addition, the potential therapeutic interventions of PIE-programmed CVDs are discussed. Finally, we also deliberate the need for future mechanistic studies and biomarker screenings in this important field, which creates a great opportunity to combat the global increase in CVDs by managing the adverse effects of inflammation for prepregnant and pregnant individuals who are at risk for PIE-programmed CVDs.

Keywords: Cardiovascular diseases; inflammation; prenatal inflammatory exposure; maternal immune activation; developmental reprogramming; NF-κB.

Abbreviations:

ACE, Angiotensin-converting enzyme; ACTH, Adrenocorticotropic hormone; Ang II, Angiotensin II; ApoE, Apolipoprotein E; AT1R, Ang II type 1 receptor; AT2R, Ang II type 2 receptor; AVP, Arginine vasopressin; CMV, Cytomegalovirus; CNS, Central nervous system; CRH, Corticotropin-releasing hormone; CVDs, Cardiovascular diseases; DHA, Dehydroacetic acid; DNMT, DNA methyltransferase; DOCA, Deoxycorticosterone acetate; DOHaD, Developmental origins of health and disease; GHO, Global Health Observatory; GPCR, G protein-coupled receptor; GR, Glucocorticoid receptor; HBV, Hepatitis B virus; HIV, Human immunodeficiency virus; HPA, Hypothalamic-pituitary-adrenal; HPV, Human papillomavirus; HRV, Human rhinovirus; HSCs, Hematopoietic stem cells; HSD, Hydroxysteroid dehydrogenase; HSV, Herpes simplex virus; IFN, Interferon; IL, Interleukin; ISO, Isoproterenol; LPS, Lipopolysaccharide; MAPK, Mitogen-activated protein kinase; NCDs, Noncommunicable diseases; PDTC, Pyrrolidine dithiocarbamate; PGC-1α, Peroxisome proliferator-activated receptor-γ coactivator 1α; PIE, Prenatal inflammation exposure; PVN, Paraventricular nucleus; RAS, Renin–angiotensin system; ROS, Reactive oxygen species; SAM, Sympathetic adrenal medullary; TLR, Toll-like receptor; TNF, Tumor necrosis factor; Treg, Regulatory T cell; WHO, World Health Organization.

1. Introduction

With the decreased prevalence of communicable diseases worldwide, noncommunicable diseases (NCDs) have become the greatest threat and burden of global health expenses, particularly in developing countries and regions that are undergoing socioeconomic transition. NCDs mainly include cardiovascular diseases (CVDs), cancers, respiratory diseases, diabetes and various metabolic diseases, which account for over 70% of global deaths (39.5 million of 56.4 million global deaths), according to the 2015 Global Health Observatory (GHO) of the World Health Organization (WHO) (Mendis, Davis, & Norrving, 2015). Among NCDs, CVDs are the leading causes of death (17.7 million deaths in 2015; 45% of all NCD deaths) (Mendis, et al., 2015). The clinical therapies and preventive measures for CVDs have become one of the highest expenditures in health care systems around the world in the efforts to combat all forms of NCDs (Laslett, et al., 2012). However, the incidence and mortality of CVDs continue to rise rapidly worldwide, and even the treatment strategies toward managing traditional risk factors, such as lipid levels and blood pressure, show significant beneficial effects in the secondary prevention of CVDs (Gaita & Sperling, 2015). CVD risk factors, such as hypertension, hyperglycemia, Type II diabetes, dyslipidemia, atherosclerosis, and metabolic syndrome, are now more prevalent in adults and even in adolescents into the 21st century (Alvarez, Vieira, Sichieri, & Veiga, 2011; Eisenmann, 2003). All of this evidence indicates that other potential critical factors responsible for CVDs were overlooked in the past. The current dominant scientific opinion assumes that genetic predisposition coupled with adult lifestyle contributes to the development of CVDs; however, adult lifestyle changes and weight loss have been relatively unsuccessful in reducing the burden of CVDs at the public health level (Hanson & Gluckman, 2014).

In the past several decades, extensive epidemiological investigations and experimental animal studies have demonstrated that early-life environmental insults, such as maternal exposure to smoking, nicotine, ethanol and caffeine, as well as several maternal disease conditions, such as obesity, bacterial vaginitis, stress, and malnutrition, contribute to an increased risk of NCDs, a process that is termed the developmental origins of health and disease (DOHaD) (D. J. Barker, 2004; D. J. Barker, Osmond, Forsen, Kajantie, & Eriksson, 2005; Costa-Silva, et al., 2015; Hanson & Gluckman, 2014; McMillen & Robinson, 2005). Given the practical constraints of prospective studies and the limited evidence from retrospective studies, the concept of DOHaD may have been largely overlooked in the past two decades but has received much attention in light of the recent, rapidly accumulating evidence from a series of epidemiological investigations and animal model-based studies (D. Barker, Barker, Fleming, & Lampl, 2013; Hanson & Gluckman, 2014; Rando & Simmons, 2015). This concept of DOHaD has a great implication for our understanding of the etiologies and disease-causing mechanisms of many forms of NCDs, including CVDs (Hanson & Gluckman, 2014).

Prenatal inflammation exposure (PIE) has been brought to our attention for more than ten years. The inflammation can be caused by 1) the classic inflammatory pathway, also called "hot" inflammation, which is driven by pathogens usually accompanied by a febrile reaction, such as found in viral, bacterial and parasitic infections (Calay & Hotamisligil, 2013) or 2) an unknown etiology with a chronic and relatively lower degree of inflammation, such as chronic inflammation from the placenta and metabolic inflammation (called "metaflammation"), that is not accompanied by an increased basal energy expenditure—also called "cold" inflammation (Calay & Hotamisligil, 2013). Autoimmune diseases, such as systemic lupus erythematosus, result in chronic inflammation and yield a multitude of adverse reproductive and obstetric outcomes (Oktem, Yagmur, Bengisu, & Urman, 2016). Both maternal "hot" and "cold" inflammatory conditions can lead to an increased incidence of CVDs in offspring; as such, we named this category "PIE-programmed CVDs". In this review, we will discuss the concept derived from epidemiological and experimental studies and the potential mechanisms for PIE-programed CVDs. We hope this analysis will help to understand the overall physiological and pathophysiological bases for PIE-programmed CVDs and to create potential, effective strategies for the early intervention of PIE-programmed CVDs.

2. Epidemiological evidence supporting "PIE-programmed CVDs"

CVDs, which mainly include ischemic heart disease, stroke, hypertensive heart disease, cardiomyopathies, rheumatic heart disease, atrial fibrillation, aortic aneurysm, peripheral vascular disease, and endocarditis, currently contribute most to the total global burden of disease (Moran, Roth, Narula, & Mensah, 2014). PIE remains an important unresolved public health problem worldwide, including the abovementioned "hot inflammation" driven by pathogens (Bastek, Weber, McShea, Ryan, & Elovitz, 2014; Gorgas, 2008; Gravett, et al., 2012) and "cold inflammation" (Kim, Romero, Chaemsaithong, & Kim, 2015) caused by obesity, diabetes and other metabolic diseases (Calay & Hotamisligil, 2013). The initial evidence of maternal inflammation contributing to CVDs comes from association analyses showing that inflammatory diseases during pregnancy are commonly associated with low birth weight and preterm birth (Boggess, Beck, Murtha, Moss, & Offenbacher, 2006; Hay, et al., 1994), which is prone to cause an increased incidence of CVDs in offspring (Arends, et al., 2005; de Boo & Harding, 2006; Eriksson, 2016). One remarkable observation comes from a series of studies on the population born during the period of the influenza pandemic in 1918; this pool of the population has a significant increased level of CVDs (Cocoros, et al., 2014; Mazumder, Almond, Park, Crimmins, & Finch, 2010; Myrskyla, Mehta, & Chang, 2013) (Fig. 1).

2.1 Maternal hot inflammation and PIE-programed CVDs

Strong evidence to support the notion that maternal inflammation is causally associated with CVDs came from a series of studies of offspring in the influenza pandemic era, which was further supported by observations that maternal influenza exposure (Acs, Banhidy, Puho, & Czeizel, 2005; Ou, et al., 2016) and febrile genitourinary infections (Botto, et al., 2014) cause cardiovascular malformations in the fetus. In 2010, a retrospective study of 1918–1919 influenza pandemic (Influenza A, H1N1 subtype) cohorts (over 101,068 individuals) in the United States that was conducted by the National Center for Health Statistics (USA) revealed that prenatal influenza infection was closely associated with a ≥ 20% excess amount of CVDs, including ischemic heart disease and diabetes in 62-82-year-old individuals, relative to cohorts born without exposure to the influenza (Mazumder, et al., 2010). This study found that the population born in the first quarter of 1919 that was exposed to the influenza in the second trimester of pregnancy had an overall 10.9% excess of heart disease, with 25.4% excess ischemic heart disease and 20.8% excess diabetes compared to the cohorts born in other periods of this influenza epidemic. Gender differences showed differential birth quarter effects, with only men born in the first quarter of 1919 having a significantly higher percentage of total heart diseases (23.1%), with more ischemic heart diseases (32.7%) and hypertensive heart diseases (21.6%) compared to women (Mazumder, et al., 2010). Another independent study in the United States, conducted by the National Health Interview Survey, also confirmed the above findings that prenatal influenza exposure resulted in an increased incidence of CVDs. However, the study revealed that the cohorts exposed to the second or third waves of influenza during early gestation had decreased risk levels for developing CVDs (Myrskyla, et al., 2013). Recently, another study of a Danish cohort reported that the overall incidence of myocardial infarction showed an increased trend in the 1918 and 1968 influenza pandemic cohorts, despite lacking statistical significance (Cocoros, et al., 2014), which might be attributed to the ungroup analysis based on the specified exposure time during pregnancy. Taken together, these findings suggest that the time window of viral exposure during gestation is critical to the development of future CVDs, of which the second trimester might be the most important window (Fig. 1 and Table 1).

2.2 Maternal cold inflammation and PIE-programed CVDs

Cold inflammation is the consequence of disease conditions such as obesity, maternal diabetes or hyperglycemia, hypertension, preeclampsia, and smoking. Several studies have shown that maternal cold inflammation has a significant positive correlation with CVDs in offspring. Maternal pre-pregnancy obesity, diabetes and excessive gestational weight gain, whose inflammatory pathways are activated (Burton, Fowden, & Thornburg, 2016) together with macrophage accumulation and inflammation in the placenta (Challier, et al., 2008), are considered important risk factors for the development of cardiovascular and metabolic diseases in early postnatal life and adulthood. This topic has been extensively reviewed in several recent publications (Aceti, et al., 2012; Costa-Silva, Simoes-Alves, & Fernandes, 2016; Ma, Tutino, Lillycrop, Hanson, & Tam, 2015; Roberts, Frias, & Grove, 2015). Early onset of maternal higher blood pressure or preeclampsia during pregnancy can lead to an imbalance between inflammatory and anti-inflammatory profiles in $CD4^+$ T cell subsets, accompanied by higher plasma levels of interleukin-6 (IL-6), IL-17 and tumor necrosis factor (TNF)-α in mothers (Ribeiro, et al., 2017). This imbalance can affect early childhood blood pressures and cardiovascular health in the offspring. For example, the GUSTO Birth Cohort Study showed that the peripheral systolic blood pressure of offspring increased by 0.08 mmHg at 3 years of age with every 1 mmHg increase in the maternal central systolic blood pressure; another study found that the systolic blood pressure of offspring born to mothers with early-onset preeclampsia increased by 7.88 mmHg compared with those born to mothers with late-onset preeclampsia at the age of 6 to 13 years. (Himmelmann, Svensson, & Hansson, 1993, 1994; Jayet, et al., 2010; Lazdam, et al., 2012; Lim, et al., 2015; Tenhola, Rahiala, Halonen, Vanninen, & Voutilainen, 2006). Maternal smoking or even second-hand smoke exposure, causing a proinflammatory status including elevated maternal serum levels of TNF-α and interleukin (IL)-1β (Niu, et al., 2017; Niu, et al., 2016), is recognized as an independent risk factor for CVDs (Behl, et al., 2013; Cohen, Vella, Jeffery, Lagercrantz, & Katz-Salamon, 2008; Lawlor, et al., 2004). However, the direct causal relationship between the maternal cold inflammation and these abovementioned diseases needs to be further determined.

Collectively, the evidence discussed here indicates that both "hot" and "cold" maternal inflammation can lead to an increased incidence of CVDs (Fig. 2 and Table 1).

2.3 Maternal hot and cold inflammation-induced preterm birth and low birth weight

The close link of PIE to offspring CVDs can also be traced from the close association of preterm birth and low birth weight in PIE-offspring, as preterm birth and low birth weight are known to be related to the development of CVDs (Bertagnolli, Luu, Lewandowski, Leeson, & Nuyt, 2016; Eriksson, 2016; Ligi, Grandvuillemin, Andres, Dignat-George, & Simeoni, 2010; Norman, 2010) (Fig. 1 and Fig. 2). There are many epidemiological observations that maternal viral infections are closely related to preterm birth and low birth weight. For example, individuals infected with influenza produce a lower proportion of preterm births (8.0%) and low birth weight newborns (4.7%) (Acs, Banhidy, Puho, & Czeizel, 2006; Doyle, Goodin, & Hamilton, 2013; S. S. Lee & Wong, 2012); women with circulating hepatitis B virus (HBV) DNA show a higher proportion of spontaneous preterm births (7.3%) than women without HBV infection (1.6%) (Elefsiniotis, et al., 2010; Mouloudi, et al., 2012; Sirilert, Traisrisilp, Sirivatanapa, & Tongsong, 2014); the incidence of preterm delivery is 19.7% in human immunodeficiency virus (HIV)-infected women and 8.5% in healthy women (López, et al., 2016; Lopez, et al., 2012; Lopez, et al., 2015; Rollins, et al., 2007; Uneke, Duhlinska, & Ujam, 2009); prematurity is 77% higher in infants of mothers with malaria caused by *Plasmodium falciparum* than in infants of mothers with malaria by caused by *Plasmodium vivax* (Botto-Menezes, et al., 2015; Nair & Nair, 1993; Tobon-Castano, Solano, Sanchez, & Trujillo, 2011). In addition, urogenital infections during pregnancy, such as bacterial vaginosis (Klebanoff, et al., 2005), placental malaria infection (Menendez, et al., 2000; Oraneli, Okeke, & Ubachukwu, 2013), *Chlamydia trachomatis* infection (Baud, et al., 2015; Rours, et al., 2011), schistosomiasis (Mombo-Ngoma, et al., 2017), *Mycoplasma hominis* (Paul, et al., 1998), *Ureaplasma parvum* infection (Agger, et al., 2014), and sexually transmitted diseases (H. L. Johnson, Ghanem, Zenilman, & Erbelding, 2011), also show a close association with preterm birth and low birth weight. Other inflammatory diseases without an undefined pathogen infection during pregnancy, including chorioamnionitis (Botet, Figueras, Carbonell-Estrany, Arca, & The Castrillo Study, 2010; Botet, Figueras, Carbonell-Estrany, & Narbona, 2011), intra-amniotic inflammation (Shim, et al., 2004), periodontitis (Kumar, et al., 2013; Lauren, Minire, Maldi, Mirton, & Aferdita, 2012; Macedo, et al., 2014), systemic lupus erythematosus (Clark, Spitzer, Nadler, & Laskin, 2003; M. J. Johnson, Petri, Witter, & Repke, 1995), and primary sclerosing cholangitis (Ilhan, Ilhan, Gok, Gunay, & Ertekin, 2016; Ludvigsson, et al., 2014), have also been reported to cause preterm birth and low birth weight.

3. Development of experimental animal models for PIE-programmed CVDs

Experimental animal models for PIE-programed CVDs were established in 2004 by treating pregnant rats with human IL-6 during the entire second or third trimester (Samuelsson, et al., 2004). IL-6 is known as one of the critical proinflammatory cytokines produced by various cell types after immune activation or in a chronic disease status (Hunter & Jones, 2015). Offspring from mothers that were treated with 9 μg/kg recombinant human IL-6 on gestational days 8, 10 and 12 (in the second trimester) or on days 16, 18 and 20 (in the third trimester) showed a higher blood pressure at 5 weeks of age and eventually developed hypertension (increased by over 40 mmHg at 24 weeks of age) and an increased heart rate by 11 weeks of age (Samuelsson, et al., 2006; Samuelsson, et al., 2004) (Fig. 3 and Table 2).

To better mimic the complexity of persistent maternal inflammatory stimulation *in vivo*, our laboratory developed a protocol by treating pregnant rats or mice with a lower dose of lipopolysaccharide (LPS), a main component of the gram-negative bacterial cellular wall and a specific ligand for Toll-like receptor (TLR) 4, to serve as a nonspecific immunostimulant of bacterial infection (Lien, et al., 2000). We also developed a similar model mimicking a fungal infection-mediated inflammatory response by treating animals with zymosan, a key component of yeast cell walls and a specific ligand for TLR2/6 (Volman, Hendriks, & Goris, 2005). Similar to IL-6 treatment, treating pregnant rats with LPS or zymosan on gestational days 8, 10 and 12 was able to effectively increase blood pressure levels (increased by 8.0 mmHg) in the offspring by 6 weeks of age and eventually caused hypertension (increased by 40 mmHg) at an older age (Liao, et al., 2008; Y. L. Wei, Li, & Zhou, 2007) (Fig. 3). The offspring also demonstrated pathological alterations in their vascular structure at the neonatal stage and finally progressed to significant dysfunctions in adulthood (S. Zhao, Zhang, Cao, Liu, & Li, 2014). In addition, animals that were maternally exposed to LPS or zymosan had increased levels of myocardial fibrosis and myocardial remodeling (Chen, et al., 2015; Y. Wei, et al., 2013), significantly reduced glomerular numbers and creatinine clearance rates, but higher urinary protein levels, indicating renal injury (Hao, Zhang, Yuan, et al., 2010) (Fig. 4). Our ongoing studies indicated that a short-term- or transient-stimulus inflammatory challenge by using a one-time LPS or poly (I:C) (a synthetic double-stranded RNA that mimics a viral infection) treatment on gestational day 10 was also able to increase the blood pressure levels in rat offspring [Ji, Deng, et al., unpublished observation]. As previous findings showed that poly(I:C) injection with different dosages and at different time points during pregnancy could lead to different outcomes of behavioral abnormalities by perturbing brain development at different stages (Chow, Yan, & Wu, 2016; Meyer, Feldon, Schedlowski, & Yee, 2005), it would be interesting to systematically characterize the different dosages and different time points of prenatal LPS or poly (I:C) challenge on the development of PIE-programed CVDs (Table 2).

It has been postulated that a “multihit” mechanism (i.e., exposure to multiple risk factors prenatally and postnatally) contributes to the induction of various diseases, such as autism and schizophrenia (Estes & McAllister, 2016). Consistent with this hypothesis, our studies also demonstrated that disease conditions of myocardial remodeling (Q. Zhang, et al., 2016), hypertension (Deng, Zhang, et al., 2016) and atherosclerosis [Ji, Deng, et al., unpublished observation] are similar to the “multihit” mechanism, a combination of prenatal exposure of unwanted inflammatory stimulation and postnatal exposure to various pathogenic stresses. For example, adult rat offspring with PIE at 20 weeks of age with two weeks of postnatal isoproterenol (ISO) challenge, a critical component that can activate the sympathetic nervous system and trigger stress-induced cardiomyopathy (Lymperopoulos, Rengo, & Koch, 2013), displayed augmented left-ventricular systolic dysfunction, cardiac hypertrophy and myocardial fibrosis (Q. Zhang, et al., 2016). Furthermore, the offspring with PIE at the age of 16 weeks with 4 weeks of deoxycorticosterone acetate (DOCA) and salt (DOCA-salt) treatment, an aldosterone analogue that mimicked the hyperaldosteronism-induced hypertension (Aronova, Iii, & Zarnegar, 2014), showed a significantly greater hypertensive response leading to increased arterial vascular remodeling and endothelial dysfunction in both conduit and resistance vasculature (Deng, Zhang, et al., 2016). As such, PIE is likely to serve as a CVD-primer (Fig. 4 and Table 2).

4. Molecular mechanisms of PIE-programmed CVDs

The rapidly growing interest in biomedical research to determine the complicated molecular pathogenic mechanisms that underlie the early development of various NCDs is considered the first and critical step for the eventual identification of preventative and therapeutic strategies. Previously, a series of studies identified several potential common pathways relevant to PIE-programmed CVDs, including the crosstalk among reprogramed inflammatory pathways, oxidative stress, over-activation of the renin–angiotensin system (RAS), NF-κB dyshomeostasis, epigenetic reprograming, and dysregulation of the immune system and hypothalamic-pituitary-adrenal (HPA) axis (Fig. 5).

4.1 Crosstalk among inflammation, oxidative stress, RAS and NF-κB in PIE models

It has been shown that inflammatory responses are synergistically activated with oxidative stress and RAS, which play critical roles in the development and progression of CVDs, such as hypertension, atherosclerosis, nephropathy, and cardiomyopathy (Ayoub, Pothineni, Rutland, Ding, & Mehta, 2017; Guzik & Touyz, 2017; Pacurari, Kafoury, Tchounwou, & Ndebele, 2014). Current findings suggest that this crosstalk mechanism is involved in the pathogenesis of PIE-programed CVDs (Fig. 5).

4.1.1 Strong inflammatory response in utero and the proinflammatory state in the adult cardiovascular system

Inflammation plays critical roles in the development of CVDs (Marchant, et al., 2012; McMaster, Kirabo, Madhur, & Harrison, 2015). In PIE models, in addition to some proinflammatory cytokines that may cross the placental barrier to the embryo (Aaltonen, Heikkinen, Hakala, Laine, & Alanen, 2005; Zaretsky, Alexander, Byrd, & Bawdon, 2004), inflammatory cytokines (e.g., TNF-α, IL-1β and IL-6) can be robustly activated in embryos shortly after maternal exposure to LPS and poly (I:C) (Ashdown, et al., 2006; Cardenas, et al., 2010; Deng, Deng, et al., 2016; Liverman, et al., 2006; Urakubo, Jarskog, Lieberman, & Gilmore, 2001). The proinflammatory cytokines TNF-α and IL-6 are strong risk factors for PIE-induced CVDs in offspring. Prenatal exposure to IL-6 alone was able to result in hypertension in adults (Samuelsson, et al., 2004), which is in contrast to IL-6 knockouts, in which hypertension induced by angiotensin II and acute stress was attenuated (D. L. Lee, et al., 2004; D. L. Lee, et al., 2006). We also have found that offspring from mothers receiving maternal LPS stimulation showed modest but significantly increased levels of the proinflammatory cytokines IL-6, TNF-α and IL-1β in vascular tissues and kidney (Deng, Deng, et al., 2016; Guo, et al., 2016). Our more recent studies further revealed that dysregulation of the NF-κB signaling pathway plays a critical role in mediating the elevated inflammatory response and PIE-programmed CVDs (Deng, Deng, et al., 2016; Deng, Zhang, et al., 2016). NF-κB is known as a common key transcription factor in various inflammatory responses. It is downstream of nearly all danger-sensing receptors of innate and adaptive immune systems (Smale, 2012). Prenatal exposure to LPS causes NF-κB activation in fetal and adult aortic tissues (Deng, Deng, et al., 2016; S. Zhao, et al., 2014), which is likely due to a persistently lower level of IκBα (Deng, Deng, et al., 2016), a critical molecule for retaining NF-κB dimers in the cytoplasm in an inactive state (Ruland, 2011). Both prenatal or postnatal NF-κB inhibition by pyrrolidine dithiocarbamate (PDTC) was able to prevent hypertension and alleviate damage to the myocardium (Chen, et al., 2015), vasculature system (Deng, Deng, et al., 2016) and kidney (Guo, et al., 2016). Dyshomeostasis of NF-κB was found to be associated with abnormal RAS overactivation in thoracic aortic tissues (Deng, Deng, et al., 2016), sensitizing the offspring to hypertensive damage induced by DOCA-salt through impaired peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α)-mediated antioxidation (Deng, Zhang, et al., 2016). In addition, PIE in obese pregnant females elevated the activity of TLR4/NF-κB signaling in the offspring, which was likely responsible for enhanced adipogenesis and insulin resistance in the fetal skeletal muscle at late gestation (X. Yan, et al., 2010), and exaggerated atherosclerotic lesions of the entire aorta in the offspring through augmenting the periaortic adipose tissue-specific proinflammatory response in apolipoprotein E (ApoE)-deficient mice (Wakana, et al., 2015). Taken together, all these findings suggest that the

NF-κB-mediated inflammatory response plays a critical role, possibly through a common pathogenic pathway, in the development of PIE-programed CVDs.

4.1.2 Oxidative stress

Reactive oxygen species (ROS), a fundamentally important aspect in cellular physiology, are generated by both enzymatic and nonenzymatic systems and are scavenged by endogenous antioxidant enzymes (Nathan & Cunningham-Bussel, 2013). Once the balance between the generation and clearance of ROS is disrupted, oxidative stress occurs, which leads to cellular and tissue damage triggering a vicious spiral cycle of inflammation and oxidative stress (Niemann, et al., 2017). Oxidative stress is involved in the pathogenesis of CVDs (Munzel, et al., 2017; Niemann, et al., 2017; Sack, Fyhrquist, Saijonmaa, Fuster, & Kovacic, 2017). Mounting evidence has shown oxdative stress as pervasive pathological changes in the cardiovascular system in offspring experiencing prenatal adverse stimuli, including maternal high-fat intake, maternal nicotine exposure and maternal protein restriction (Chisaka, et al., 2016; Resende, et al., 2013; Xiao, et al., 2015).

In a PIE rat model with prenatal LPS exposure, ROS levels were found to be significantly increased, but no significant oxidative damage was found in both myocardial and vascular tissues in the offspring. However, under a second insult in adulthood, significant oxidative damage was found in the cardiovascular system in adults (Deng, Zhang, et al., 2016; Q. Zhang, et al., 2016). Interestingly, it seemed that two different mechanisms were involved in oxidative stress in response to a second insult between myocardial and vascular tissues in PIE offspring. In the myocardium of adult PIE offspring, increased expression of both oxidase and antioxidant enzymes together with p38 mitogen-activated protein kinase (MAPK) activation maintained the relative modest ROS activation but without oxidative damage. As ISO could directly activate the p38 MAPK signal pathway through the G protein-coupled receptor (GPCR) (Magocsi, Vizi, Selmeczy, Brozik, & Szelenyi, 2007), a positive feedback loop between the p38 MAPK signal pathway and ROS was ignited when challenged with ISO as a second insult, augmenting the oxidative stress by the dramatic upregulation of NADPH (Q. Zhang, et al., 2016). In the vascular system, the PGC-1α-mediated antioxidant capacity was impaired by the NF-κB overactivation, but not the ROS-p38 MAPK-ROS positive feedback loop, which apparently was the key responsible pathway for the aggravated oxidative damage induced by the postnatal DOCA-salt treatment (Deng, Zhang, et al., 2016) (Fig. 4).

4.1.3 Overactivation of the RAS in the cardiovascular system

The RAS is a momentous endocrine, paracrine and intracrine vasoactive system that plays critical roles in the normal physiological regulation of cardiovascular functions and contributes to the development of cardiovascular, hypertensive, and renal diseases (Li, Zhang, & Zhuo, 2017). The RAS family mainly includes angiotensinogen, renin, angiotensin I, angiotensin-converting enzyme (ACE), ACE2, angiotensin II (Ang II), Ang II type 1 receptor (AT1R), and Ang II type 2 receptor (AT2R). Some of the key members of the RAS (including ACE, AT1R and AT2R) have already been developed as pharmacological targets to effectively treat heart, hypertensive and renal diseases (Bader, 2010). Plasma angiotensinogen is primarily generated in the liver and is then converted into angiotensin I by kidney-derived renin in plasma. Ang I is then converted into Ang II by ACE, which is primarily present on endothelial cells. The actions of Ang II are then transmitted into the target cells by AT1R and AT2R, leading to an increase in blood volume and blood pressure via the stimulation of vasoconstriction, sodium retention, thirst, aldosterone synthesis and secretion from the adrenal cortex, and the sympathetic nervous system (Li, et al., 2017). However, angiotensin could also be generated in local tissue, such as the brain, heart, blood vessels and kidney. Compared to the circulating RAS, the local RAS components are known to regulate the function of these organs and are involved in the tissue damage that eventually contributes to the pathogenesis of CVDs (e.g., hypertension) (Li, et al., 2017).

In PIE-programmed CVD models, our laboratory has found that the circulating Ang II level is not altered in the offspring of LPS-treated mothers. However, the tissue Ang II, ACE and AT1R expression levels are significantly increased in the offspring's kidneys (Hao, Kong, Zhang, & Zhao, 2013; Hao, Zhang, Li, et al., 2010), vascular system (He, et al., 2011), hearts (Y. Tang, Zhou, & Li, 2014) and adipose tissue (Gao, et al., 2014). Elevated local RAS activities are also found in the kidneys of offspring from zymosan-treated mothers (Hao, Zhang, Li, et al., 2010). In addition, the induction of proinflammatory factors by hyperglycemia exposure in utero alters the gene expression of RAS components in the offspring, which may in part account for the programmed hypertension (J. Yan, Li, Su, Zhang, & Yang, 2014).

Interestingly, the intrarenal Ang II level is decreased in PIE neonates, suggesting that the elevated RAS activity might be a secondary event of other signaling pathways. As we found that the prenatal or postnatal NF-κB inhibitor PDTC was able to reverse the RAS over-activation in the hearts (Y. Tang, et al., 2014), vascular tissues (Deng, Deng, et al., 2016) and kidneys (Guo, et al., 2016; Hao, Zhang, Li, et al., 2010), we believed that NF-κB has crosstalk with RAS. In addition, Wang et al. found that administering 4-hydroxy-2, 2, 6, 6-tetramethylpiperidine-N-oxyl (TEMPOL) (a ROS scavenger) to PIE-offspring could also reverse RAS overactivity in the vascular system (X. Wang, et al., 2015).

Taken together, the evidence in Section 4.1 suggests that the crosstalk among inflammation, oxidative stress and local RAS activity in cardiovascular tissues has important roles in the development of CVDs in PIE offspring, whereas the dysfunctional NF-κB signal pathway may act as a checkpoint in this process.

4.2 Epigenetic reprograming

Epigenetic mechanisms, such as DNA methylation, histone modification or noncoding RNA molecules, are believed to be involved in the developmental reprograming of adult diseases, especially metabolic syndrome and neuropsychological diseases caused by early life adverse exposure, which is well reviewed in several recent articles (Bale, 2015; Dunford & Sangster, 2017; Kirchner, Osler, Krook, & Zierath, 2013). DNA methylation and histone modification are believed to be involved in the development of and predisposition to metabolic diseases. For example, maternal and paternal periconceptional nutrition, such as protein restriction or high-fat diets, alters the DNA methylation state of ribosomal DNA (rDNA) in germ cells, which is involved in the development of metabolic syndrome (Holland, et al., 2016). In a sheep model, maternal undernutrition leads to tissue-specific epigenetic modification of the glucocorticoid receptor (GR) (including decreased GR promoter methylation, decreased histone lysine 27 trimethylation, and increased histone H3 lysine 9 acetylation) in different brain areas of adult offspring, participating in regulating the offspring's energy balance (Begum, et al., 2013). Maternal obesity or weight loss altered the balance between "writers" and "erasers" of histone acetylation in the fetal liver and placental labyrinth, leading to fetal growth restriction in mice (Panchenko, et al., 2016).

In animal models of PIE-programmed neurodevelopmental disorders, several studies have reported that PIE can provoke the alteration of enzymatic activities that are responsible for DNA methylation or histone modification (Reviewed in (Weber-Stadlbauer, 2017). Unfortunately, it has not been well-studied whether the potential changes of epigenetic regulation contribute to PIE-programmed CVDs. We made initial efforts to analyze the global DNA methylation level of the renal cortex, and we found it was dramatically increased in PIE-offspring (J. Wang, et al., 2017). Consistent with this finding, DNA methyltransferase (DNMT) 1 and DNMT3B, enzymes responsible for DNA methylation (Lyko, 2017), were found to be increased in renal tissue (J. Wang, et al., 2017). In addition, we found an increased level of histone H3 acetylation of the ACE promoter in the renal cortex of PIE-offspring (J. Wang, et al., 2016). This limited evidence suggests that epigenetic alteration is pivotal for the development of PIE-programmed CVDs. It is important to further profile the changes in DNA methylation, histone modification or noncoding RNAs genome wide in the cardiovascular tissues in PIE-offspring (Fig. 5).

4.3 Dysregulated immune system and HPA axis in PIE-offspring

4.3.1 Reprogrammed immune system in PIE-offspring

The immune response almost participates in every phase of CVD development and progression, including hypertension, atherosclerosis and heart disease. Overactivation of both the innate and the adaptive immune systems is involved in the damage of hypertensive end-organs, the formation and activation of atherosclerotic plaques, and cardiac injury (Epelman, Liu, & Mann, 2015; Rodriguez-Iturbe, Pons, & Johnson, 2017; Tabas & Lichtman, 2017).

For the adaptive immune system, pregnant mice challenged with poly (I:C) at E12.5 (second trimester), a critical time window for the initiation of the immune system and hematopoietic stem cells (HSCs) during fetal development (Clements & Traver, 2013; Dzierzak & Speck, 2008), exhibit a significantly reduced total number of regulator T (Treg, $CD4^+CD25^+Foxp3^+$) cells in the spleen but an increased production of IL-6 and IL-17 produced by $CD4^+$ T cells (Hsiao, McBride, Chow, Mazmanian, & Patterson, 2012; Mandal, et al., 2013; Mandal, Marzouk, Donnelly, & Ponzio, 2010, 2011). When treated with zymosan (a TLR2 agonist) or MOG35-55 (an encephalitogenic peptide), the offspring also showed increased cellular and cytokine responses, respectively, which led to a preferential differentiation toward Th17 cells

(Mandal, et al., 2013). PIE-offspring treated with LPS at E12.5 also showed an elevated percentage of interferon (IFN)- γ^+ and IL-17A$^+$ CD4$^+$ T cells in the spleen and liver (Luan, et al., 2015). At a later stage (E17.0) of treatment with LPS, the offspring also showed a similar trend with increased cell-mediated immunity, including increased levels of IL-12, IL-6 and IFN-γ when postnatally challenged with ovalbumin (Zager, Pinheiro, Ferraz-de-Paula, Ribeiro, & Palermo-Neto, 2013). These findings suggest a proinflammatory phenotype in PIE offspring, likely due to the alterations in development and/or immunological memory of the adaptive immune system.

Changes in the innate immune system have also been analyzed in PIE animal models. PIE-offspring from poly (I:C) treatment at E12.5 showed elevated levels of peripheral Gr-1$^+$ cells in the spleen and increased myeloid lineage differentiation by HSCs (Hsiao, et al., 2012). Bone marrow-derived macrophages generated from the offspring of poly (I:C)-treated mothers showed an increased potential to differentiate into M1 macrophages, which suggests activated inflammatory macrophages in PIE-offspring (Onore, Schwartzer, Careaga, Berman, & Ashwood, 2014).

In PIE-programmed CVDs, we found similar changes in PIE-offspring prenatally treated with poly (I:C) or LPS at E10.5, an earlier time window that is critical for HSC differentiation (Clements & Traver, 2013; Dzierzak & Speck, 2008), including a decreased abundance of Treg cells [Ji, Deng, et al., unpublished observation]. In addition, we also found an elevated ratio of matured dendritic cells and macrophages but a reduced ratio of monocytes in PIE-offspring prenatally treated with poly (I:C) or

LPS at E10.5 [Ji, Deng, et al., unpublished observation]. The alteration of the immune system in PIE-offspring is likely responsible for the atherosclerogenesis because the transfer of bone marrow cells from PIE-offspring prenatally treated with poly (I:C) or LPS to ApoE-deficient mice resulted in more atherosclerotic plaques in the aorta [Ji, Deng, et al., unpublished observation]. These findings suggest that dysregulation of both the innate and adaptive immune system contributes to the pathogenesis of PIE-programed CVDs.

Due to the dramatic changes in both HSC and lymphocyte differentiation during different time windows of embryonic development (Clements & Traver, 2013; Dzierzak & Speck, 2008), the phenomenon of different alterations of immune cell subsets by different time points of inflammatory stimulation could be conceivable. For example, PIE-offspring prenatally treated with LPS at E12.5 showed a decreased number of Treg ($CD4^+$ $Foxp3^+$) cells in the thymus (Luan, et al., 2015), but PIE-offspring prenatally treated with poly (I:C) or LPS at E10.5 showed reduced numbers of Treg cells in the spleen [Ji, Deng, et al., unpublished observation]. However, the overall proinflammatory phenotype due to the imbalanced immune homeostasis exists in the offspring of PIE models, which merits further studies to find the common initiating factors responsible for the imbalanced immune homeostasis. This research will help to elucidate the mechanisms of PIE-programmed CVDs (Fig. 5).

4.3.2 Dysregulation of HPA axis activity in PIE-offspring

Exposure to environmental, physical, or physiological stresses causes systematic activation of various biological stress responses. The stress response, including the endocrine, immune, and cardiovascular systems, comprises a complex interaction between components of the central nervous system (CNS) and peripheral systems (Kadmiel & Cidlowski, 2013; Selye, 1956). The HPA axis, including the paraventricular nucleus (PVN) of the hypothalamus, the anterior pituitary gland, and the cortex of the adrenal gland, plays a critical role in homeostatic maintenance in response to stress through regulating adrenal hormones and glucocorticoids. Stress can activate the hypophysiotropic neurons in the PVN that can release corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). CRH and AVP travel through the median eminence and hypophyseal portal vessels and reach the anterior pituitary, where they stimulate the synthesis and secretion of adrenocorticotropic hormone (ACTH). ATCT reaches the zona fasciculata of the adrenal cortex and promotes the synthesis and release of the primary stress hormones, namely, glucocorticoids (Burford, Webster, & Cruz-Topete, 2017). Through circulation, glucocorticoids reach various cardiovascular tissues (such as the heart, vasculature, adipose tissue, and muscle) and bind to the GR, which triggers beneficial actions on the cardiovascular function, immune system, and secondary metabolism in response to stress. Glucocorticoids could also create negative feedback to inhibit activation of the HPA axis through their levels in the hypothalamus and pituitary gland (Burford, et al., 2017). However, if there is sustained elevation of glucocorticoid levels induced by chronic stress, the levels of CVD incidence will increase (Burford, et al., 2017; Kadmiel & Cidlowski, 2013); similarly, the incidence of metabolic diseases and psychiatric symptoms will increase as well (Chrousos, 2009; Constantinof, Moisiadis, & Matthews, 2016).

The activity of the HPA axis is dramatically affected by pregnancy, causing increased cortisol and ACTH levels during gestation (J. R. Lindsay & Nieman, 2005). The activity of the HPA axis is highly susceptible to maternal adverse stimulants such as alcohol (X. Zhang, Sliwowska, & Weinberg, 2005), a protein-restricted diet (Bertram, Trowern, Copin, Jackson, & Whorwood, 2001; Langley-Evans, 1997; Langley-Evans, Gardner, & Jackson, 1996), a high-fat diet (Sasaki, de Vega, St-Cyr, Pan, & McGowan, 2013), smoking (McDonald, et al., 2006; Stroud, et al., 2014), preeclampsia (Henley, Brown, Pennell, Lye, & Torpy, 2016), which contribute to many CVDs (van Montfoort, Finken, le Cessie, Dekker, & Wit, 2005). Direct evidence shows that early-life overactivation of the HPA axis by excessive maternal glucocorticoids exposure leads to reprograming of the HPA axis in offspring and elevates their incidence of CVDs, such as hypertension (Edwards, Benediktsson, Lindsay, & Seckl, 1993; R. S. Lindsay, Lindsay, Edwards, & Seckl, 1996; J. I. Tang, Kenyon, Seckl, & Nyirenda, 2011). Several studies have revealed that PIE contributes to the reprogramming of the HPA axis. Epidemiological investigations indicate that infants exposed to chorioamnionitis with funisitis show increased levels of salivary cortisol at the corrected age of 18 months compared to infants with no infections or chorioamnionitis alone (Gover, et al., 2013). In a rat animal model, prenatal IL-6 exposure resulted in hypertension and dysregulation of HPA axis activity in adult rats, such as reducing the mRNA expression of the mineralocorticoid receptor (*Nr3c2*) and glucocorticoid receptor (*Nr3c1*) in the hippocampus and increasing the corticotropin-releasing factor (CRF) level in the hypothalamus and CRF receptor type 1 (*Crhr1*) mRNA expression in the pituitary (Samuelsson, et al., 2004). Prenatal LPS exposure leads to an increase in maternal corticosterone levels (Babri, Doosti, & Salari, 2014; Kirsten, Lippi, Bevilacqua, & Bernardi, 2013) and heightens the corticosterone responses in adult PIE-offspring (Lin, Lin, & Wang, 2012).

The altered crosstalk between the immune response and the HPA axis has important roles in the development and progression of CVDs. For example, psychological stress induces atherosclerosis, and under psychological stress, activation of the HPA and sympathetic adrenal medullary (SAM) axes activates immune reactions in immune cells, which results in elevated levels of proinflammatory cytokines, such as IL-1β, TNF-α and IL-6. These proinflammatory cytokines can change the level of stress hormones, which leads to either activation or suppression of the HPA or SAM regulatory feedback loop. If the positive feedback between the immune response and the HPA axis is established, it will damage the vascular endothelium function and increase the recruitment of circulating monocytes and their conversion into foam cells (Gu, Tang, & Yang, 2012). Given the evidence that fetal programming of the HPA-immune system plays critical roles in the development of metabolic diseases (Fisher, Steele, & Karrow, 2012), it is conceivable that analyzing details of the HPA-immune system will provide more potential targets for developing a therapeutic intervention for PIE-programmed CVDs (Fig. 5).

4.4 Immuno-inflammatory changes at the maternal-fetus interface of PIE models

The placental origin of various adult chronic diseases has been extensively studied and well appreciated in previous studies (Burton, et al., 2016). The placenta is the organ that performs various activities (including nutrient transport and endocrine functions) and forms the interface between the fetus and its mother, underpinning fetal development. The maternal-fetus interface acts as a physical barrier, impeding the entry of pathogens and some maternal immune molecules and immune cells into the fetal circulation (Burton, et al., 2016). A dysfunctional placenta leads to insufficient nutrients or excessive unneeded materials arriving at the fetus, which causes embryonic defects or embryonic development reprogramming, resulting in future postnatal chronic diseases. For example, mothers treated with glucocorticoids exhibited reduced activity of 11β-hydroxysteroid dehydrogenase (HSD) in the placenta, followed by exposure of the fetus to excess levels of glucocorticoids, which is associated with adult hypertension (Edwards, et al., 1993).

Elevated levels of the placental inflammation response may have some adverse effects on placental transport capacity, infiltration of immune cells, and placental hemorrhage (Abrahams, et al., 2005; Baines, Duclos, Antecka, & Haddad, 1997; Huang, et al., 2008; Kim, et al., 2015; Liong & Lappas, 2017; H. Zhao, et al., 2015). These effects in turn will lead to intrauterine growth restriction, low birth weight, and higher proinflammatory cytokines in the fetus, which is also associated with adult CVDs (Bukowski, et al., 2017; Burton, et al., 2016; Straughen, et al., 2017).

In PIE rat models, there are several direct lines of evidence supporting this hypothesis. Prenatal exposure to LPS or poly (I:C) leads to robustly elevated levels of proinflammatory cytokines, such as TNF-α, IL-1β, IL-6 and IL-10 in the placenta and amniotic fluid, irrespective of the high or low dose of inflammatory stimulants (Ashdown, et al., 2006; Cai, Pan, Pang, Evans, & Rhodes, 2000; Deng, Deng, et al., 2016; Urakubo, et al., 2001). In other chronic inflammatory statuses during pregnancy, smoking mothers have more natural killer cells and inflammatory macrophages in the first-trimester decidua (Prins, et al., 2012); obesity in pregnancy can stimulate the accumulation of macrophage and proinflammatory mediators in the placenta (Challier, et al., 2008). The similar changes in the placenta as those in PIE models further support our idea that the chronic inflammatory status caused by other diseases during pregnancy, such as obesity, diabetes, hyperglycemia, hypertension, preeclampsia, and smoking, plays critical roles in mediating the development of CVDs in adults. However, the ratio and functional changes of each immune cell subset in the placenta after PIE challenge and the role of these changes in the development of PIE-programmed CVDs are still largely unknown.

5. Potential preventive strategies for PIE-programmed CVDs

Timely symptom-based treatments for CVDs are beneficial, but such treatments have a limited degree or are often too late to be effective. Interventions in young and even fetal individuals are now believed to be more effective and lower the risk factors in the next generation via the reproductive cells (Hanson & Gluckman, 2014). Therefore, an increasing number of countries, especially those with aging societies, have adopted an important measure for early-life prevention of NCDs. As a successful example, the intense promotion of breastfeeding initiated by East Germany yielded a lower prevalence of obesity in young individuals compared to that in the corresponding West Berlin population, which was not introduced to intense breastfeeding (Dörner, Rodekamp, & Plagemann, 2008).

There are some limited exploratory studies seeking potential effective preventive strategies during pregnancy or in young offspring by using PIE animal models. We found that pharmacological treatments in the second trimester with PDTC could effectively prevent PIE-programmed hypertension, vascular damage (Deng, Deng, et al., 2016; Hao, Zhang, Yuan, et al., 2010), and myocardial remodeling (Chen, et al., 2015; Y. Wei, et al., 2013) in rats. Interestingly, early postnatal treatment with PDTC, NAC, or TEMPOL could also prevent PIE-programmed CVDs (Deng, Deng, et al., 2016; Deng, Zhang, et al., 2016; X. Wang, et al., 2014; X. Wang, et al., 2015; Q. Zhang, et al., 2016), suggesting that both prenatal and early postnatal life can be considered the therapeutic window for the prevention of PIE-CVDs.

As the concept of DOHaD has been accepted in our community, the avoidance of various adverse insults during gestation seems obvious to preclude PIE-programmed CVDs. Some risk factors are easier to control, such as avoiding malnutrition, smoking, and the intake of nicotine, ethanol and caffeine. The more difficult measure to prevent PIE-programmed CVDs is the control of infection-induced inflammation or chronic inflammatory states due to various disease conditions during pregnancy. Therefore, the first and critical step for the eventual identification of preventative and therapeutic strategies is to determine the complex molecular pathogenic mechanisms that underlie the early development of various NCDs. Another important challenge for us is to search for specific diagnostic biomarkers (including various proinflammatory cytokines) in both maternal serum and umbilical cord blood after a definite inflammatory challenge in individuals who have the potential for developing PIE-programmed CVDs. Given the limitations of screening for targets in humans, PIE animal models become an important resource, especially with respect to their usefulness for comparing the types and differences of PIE-programmed CVDs triggered at various time windows during pregnancy. Such research will help us to understand the vulnerability of infected individuals to various PIE-programmed CVDs.

Hence, we need to focus our efforts on the disease-causing mechanisms and search for specific diagnostic biomarkers to develop a universal therapeutic strategy for the prevention of PIE-programmed CVDs, especially from the aspect of stress-response and hormone-secretion regulation in both the mother and offspring. Our future studies in this important field will provide a great opportunity to uncover novel interventions by managing the adverse effects of inflammation in prepregnant and pregnant individuals who are at risk for PIE-programmed CVDs.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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Tables

Table 1 Epidemiological studies linking maternal insults with diseases in offspring

Key studies	Maternal insults	Offspring disease	Country	Major findings
Boggess et al., 2006	Periodontal disease	Preterm birth, low birth weight	USA	Moderate or severe periodontal disease early in pregnancy is associated with the delivery of a small-for-gestational-age infant.
Hay et al., 1994	Bacterial infection	Preterm delivery	England	Late miscarriage and preterm delivery are associated with the presence of bacterial vaginosis in early pregnancy.
Arends et al., 2005	Preterm birth	Type 2 diabetes mellitus and cardiovascular diseases	Netherlands	The development of type 2 diabetes mellitus and CVDs are already present during childhood in short

				prepubertal children born small for gestational age (SGA).
Erikssonet al., 2016	Low birth height and weight	Heart disease, type 2 diabetes	Finland	Early growth patterns are associated with coronary heart disease, type 2 diabetes and other health outcomes.
Cocoros et al., 2014	Influenza	Cardiovascular events	Danish	Prenatal exposure to the 1918 influenza pandemic is associated with cardiovascular events in adulthood.
Mazumder et al., 2010	Influenza	CVDs	USA	Maternal infections in the fetus result in the programming of cardiovascular risk factors that are independent of maternal malnutrition.
Myrskyla et al., 2013	Influenza	Respiratory and	National Health	Early disease exposure increases old-age

		cardiovascular diseases	Interview Survey	mortality through noncancer causes, which include respiratory and cardiovascular diseases.
Acs et al., 2005	Influenza	Cardiovascular congenital abnormalities		Maternal influenza during pregnancy results in the risk of congenital abnormalities in offspring.
Ou, et al., 2016	Fever, diabetes, influenza, and threatened abortion	Congenital heart defects	China	Maternal fever, diabetes and influenza are dominant risk factors associated with congenital heart defects.
Botto, et al., 2014	Febrile genitourinary infections	Congenital heart defects	USA	Febrile genitourinary infections are associated with selected heart defects, particularly right-sided obstructive

				defects.
Mazumder et al., 2010	Influenza	Ischemic heart disease	USA	Prenatal exposure to the 1918 influenza pandemic resulted in ≥20% excess cardiovascular diseases in the offspring at 60 to 82 years of age.
Aceti et al., 2012	Type 2 diabetic	Higher systolic blood pressure		Offspring of diabetic mothers have a higher systolic BP than controls.
Roberts et al., 2015	Obesity	CVDs		Maternal obesity during pregnancy results in a subsequent impact on fetal cardiovascular development.
Tenhola et al., 2006	Preeclampsia	Hypertension	Kuopio	Maternal preeclampsia is associated with elevated BP in offspring.
Himmelman	Hypertensio	Higher blood	Sweden	Maternal histories of

n et al., 1993, 1994	n	pressure		hypertension maintain their rank with regard to left ventricular mass during adolescence.
Jayet, et al., 2010	Preeclampsia	Pulmonary and systemic vascular dysfunction	Switzerland	Preeclampsia leaves a persistent defect in the systemic and pulmonary circulation of the offspring.
Lazdam et al., 2012	Preeclampsia	Hypertension	England	Mothers who develop early-onset preeclampsia and the offspring of these pregnancies display specific adverse blood-pressure characteristics later in life.
Lim et al., 2015	Hypertension	Hypertension	Singapore	Maternal central pulsatile blood pressure components (SBP and PP) during pregnancy

				are associated with higher blood pressures in offspring.
Cohen et al., 2008	Smoking	Hypertension	Sweden	There is early postnatal programming of human cardiovascular dysfunction by maternal smoking.
Lawlor, et al., 2004	Smoking	Hypertension	Switzerland	Childhood blood pressure tracks into adulthood; interventions are aimed at early-life risk factors, such as quitting smoking during pregnancy.

Table 2 Experimental animal models for PIE-programmed CVDs

Animal model	Disease phenotypes	Reported molecular mechanism	Age at evaluation	Ref.
Pregnant rats injected with human IL-6 during the entire second or third trimester	Higher blood pressure	Not studied	5 and 11 weeks	Samuelsson, et al., 2004 , 2006
Pregnant rats treated with LPS or zymosan on gestational days 8, 10 and 12	Higher blood pressure	Not studied	6 weeks of age and older	Liao, et al., 2008; Y. L. Wei, Li, & Zhou, 2007
Prenatal rats injected with LPS in the second trimester	Endothelium dysfunction in thoracic aortas; hypertension	NF-κB dyshomeostasis contributes to RAS overactivity, resulting in	7 and 16 weeks	Deng et al., 2016

		hypertension in offspring.		
Adult offspring rats of LPS-treated mothers with 4 weeks of DOCA-salt treatment	Hypertension; increasing sensitivity to DOCA-salt challenge	NF-κB over-activation impairs the PGC-1α-mediated antioxidant capacity, which results in an increased sensitivity of offspring to hypertensive damage induced by DOCA-salt	20 weeks	Deng et al., 2016
Adult offspring rats of LPS-treated mothers with 2 weeks of ISO treatment at 20	Cardiac hypertrophy and myocardial fibrosis; increasing sensitivity to	Activated ROS-p38 MAPK predisposes offspring to heart damage caused by ISO via augmenting ROS	22 weeks	Zhang et al., 2016

weeks	ISO challenge	generation		

Figure Legends

Fig. 1. Direct and indirect epidemiological evidence for PIE-programed CVDs. Timeline of the initial reported epidemiological studies for both direct and indirect evidence for PIE-programed CVDs. The direct evidence from the cohorts with prenatal influenza exposure indicates that the second trimester of gestation is the most sensitive time window for PIE-programed CVDs.

Abbreviations: CVDs, cardiovascular diseases; PIE, prenatal inflammatory exposure.

Fig. 2. Both systemic maternal or placental "hot" and "cold" inflammation are associated with adult CVDs in offspring. This schematic summarizes the etiologies for both maternal systemic or placental "hot" and "cold" inflammation associated with PIE-associated CVDs. Abbreviations: CMV, cytomegalovirus; CVDs, cardiovascular diseases; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; HRV, human rhinovirus; HSV, herpes simplex virus; PIE, prenatal inflammatory exposure.

Fig. 3. Animal models for PIE-programed CVDs. This schematic depicts the current models for PIE-programed CVDs with the injection of LPS (Y. L. Wei, et al., 2007), Poly (I:C) [Guan, Deng, et al. Unpublished data], zymosan (Liao, et al., 2008) or IL-6 (Samuelsson, et al., 2006; Samuelsson, et al., 2004) at the indicated time points during pregnancy by using a rat or mouse. The time points for the onset of circulation and occurrence of primitive macrophages, aortic clusters, AGM and HSCs are also added

to the timeline of pregnancy (Clements & Traver, 2013; Dzierzak & Speck, 2008).

Abbreviations: AGM, aorta-gonad-mesonephros; CVDs, cardiovascular diseases; HSCs, hematopoietic stem cells; PIE, prenatal inflammatory exposure.

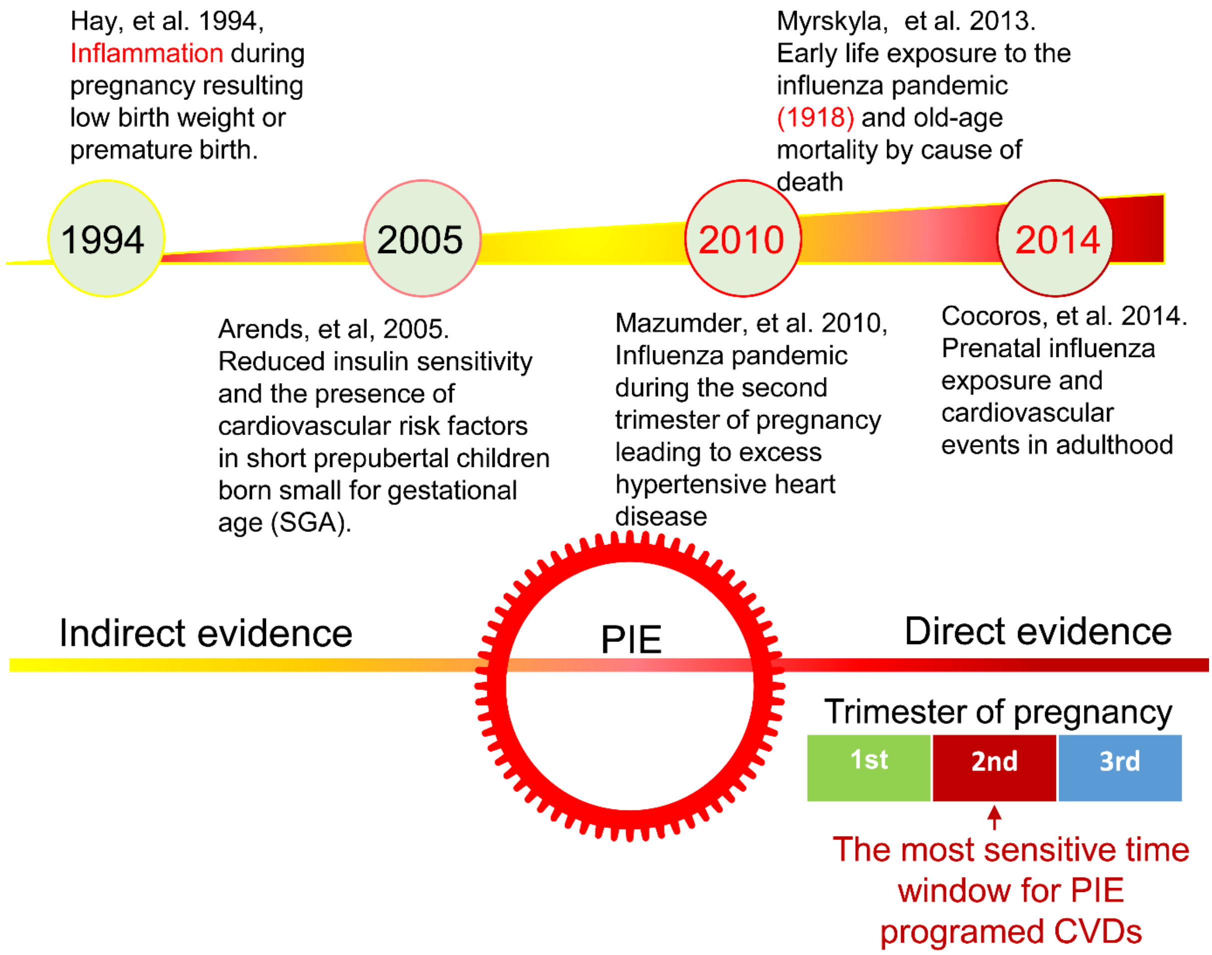
Fig. 4. Proposed model of PIE as a CVDs primer. Early-life NF-κB dyshomeostasis plays essential roles in the aging-related development of hypertension and heart diseases through triggering the crosstalk among inflammation, RAS overactivity and ROS activation (Deng, Deng, et al., 2016; Deng, Zhang, et al., 2016; Y. Wei, et al., 2013). Two different mechanims may be involved in oxidative stress responding to a second insult between myocardial and vascular tissues in PIE offspring. In the heart, the positive feedback loop between the p38 MAPK signal pathway and ROS is ignited when challenged with ISO as a second insult, augmenting oxidative stress by dramatically upregulating the expression of NADPH oxidase (Q. Zhang, et al., 2016). However, in the vasculature, NF-κB overactivation impairing the PGC-1α-mediated antioxidant capacity, but not the p38 MAPK-ROS positive feedback loop, is the key responsible pathway for the aggravated oxidative damage by DOCA-salt treatment at the adult stage (Deng, Zhang, et al., 2016).

Abbreviations: CVDs, cardiovascular diseases; DOCA-salt, deoxycorticosterone acetate (DOCA) and salt; ISO, isoproterenol; MAPK, mitogen-activated protein kinase; PIE, prenatal inflammatory exposure; RAS, renin–angiotensin system; ROS, reactive oxygen species.

Fig. 5. Mechanisms underlying PIE-programed CVDs. Schematic representation of the multiple signal pathways (such as inflammation, oxidative stress, RAS, NF-κB

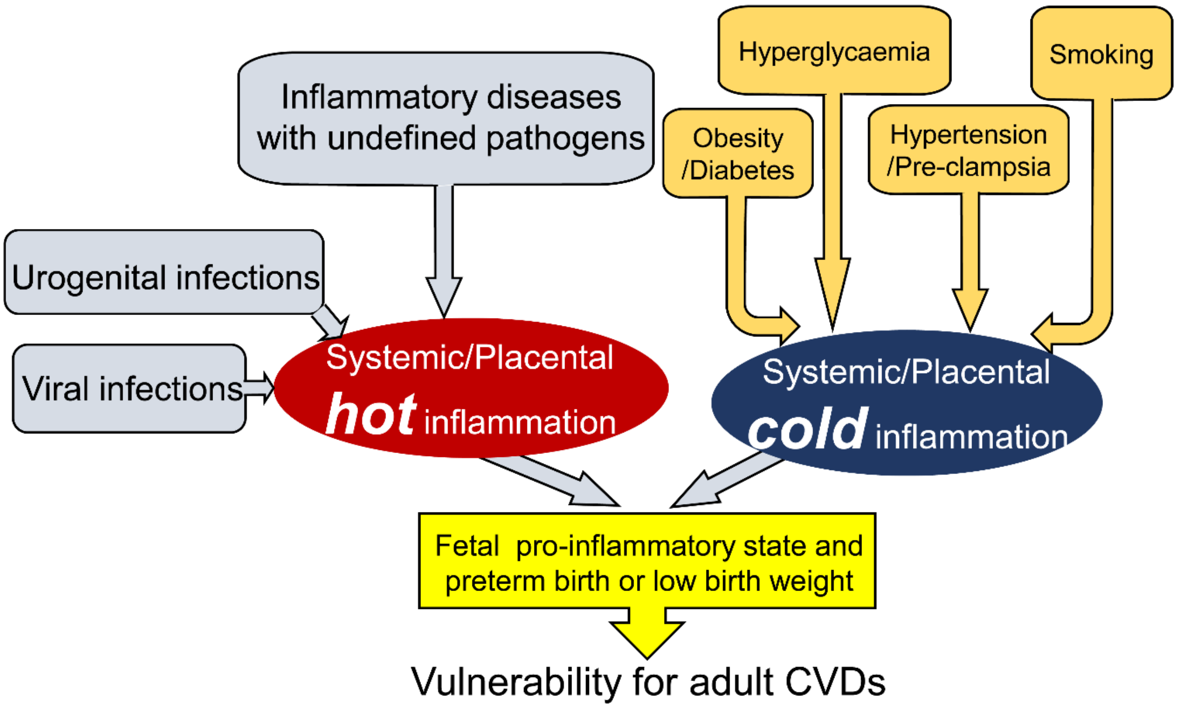
and epigenetic reprograming) in cardiovascular tissues and the dysregulation of the immune system and HPA axis, which may predispose PIE offspring to CVDs. ↑ indicates upregulation of protein expression or increased cell abundance; ↓ indicates downregulation of protein expression or decreased cell abundance.

Abbreviations: ACE, angiotensin-converting enzyme; Ang II, angiotensin II; AT1R, Ang II type 1 receptor; CRF, corticotropin-releasing factor; CRFR, hypothalamus and CRF receptor type 1 (Crhr1); CVDs, cardiovascular diseases; DNMT, DNA methyltransferase; GR, glucocorticoid receptors; HPA, hypothalamic-pituitary-adrenal; MR, mineralocorticoid receptors; PIE, prenatal inflammatory exposure; RAS, renin–angiotensin system; ROS, reactive oxygen species; Treg, regulator T; Th17, T helper cell type 17.



Hay, et al. 1994, Inflammation during pregnancy resulting low birth weight or premature birth.
Myrskyla, et al. 2013. Early life exposure to the influenza pandemic (1918) and old-age mortality by cause of death
1994
2005
2010
2014
Arends, et al, 2005. Reduced insulin sensitivity and the presence of cardiovascular risk factors in short prepubertal children born small for gestational age (SGA).
Mazumder, et al. 2010, Influenza pandemic during the second trimester of pregnancy leading to excess hypertensive heart disease
Cocoros, et al. 2014. Prenatal influenza exposure and cardiovascular events in adulthood
Indirect evidence
PIE
Direct evidence
Trimester of pregnancy
1st
2nd
3rd
The most sensitive time window for PIE programed CVDs

Fig. 1



Inflammatory diseases with undefined pathogens
Hyperglycaemia
Smoking
Obesity /Diabetes
Hypertension /Pre-clampsia
Urogenital infections
Viral infections
Systemic/Placental hot inflammation
Systemic/Placental cold inflammation
Fetal pro-inflammatory state and preterm birth or low birth weight
Vulnerability for adult CVDs

Fig. 2.

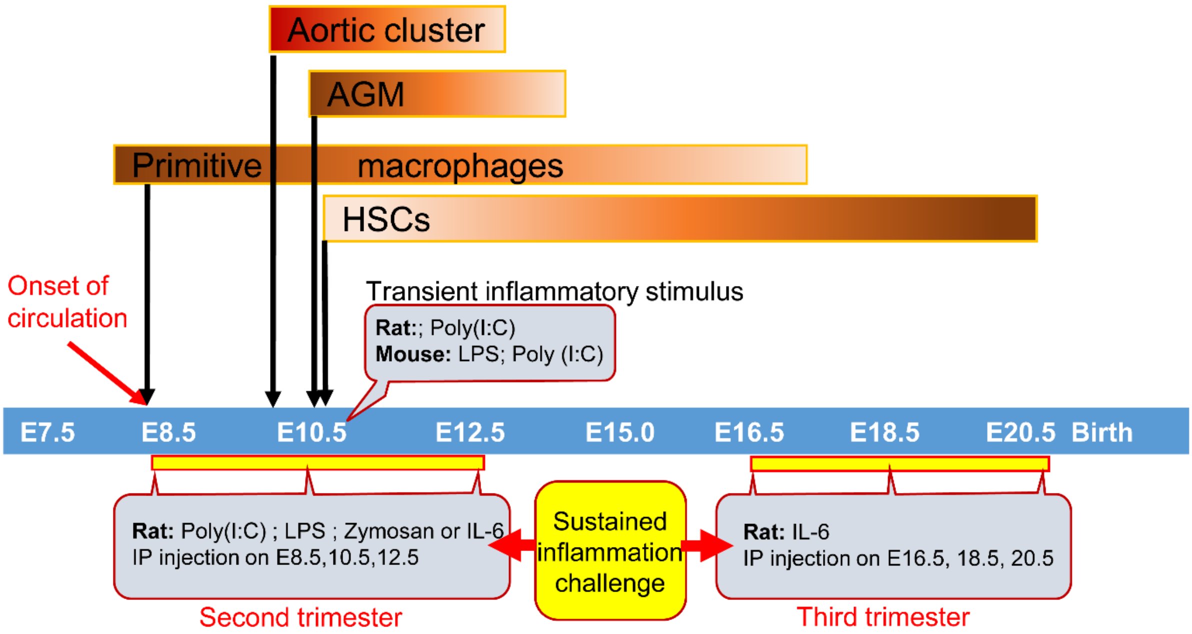

Aortic cluster
AGM
Primitive macrophages
HSCs
Onset of circulation
Transient inflammatory stimulus
Rat:; Poly(I:C)
Mouse: LPS; Poly (I:C)
E7.5 E8.5 E10.5 E12.5 E15.0 E16.5 E18.5 E20.5 Birth
Rat: Poly(I:C) ; LPS ; Zymosan or IL-6
IP injection on E8.5,10.5,12.5
Sustained inflammation challenge
Rat: IL-6
IP injection on E16.5, 18.5, 20.5
Second trimester
Third trimester

Fig. 3.

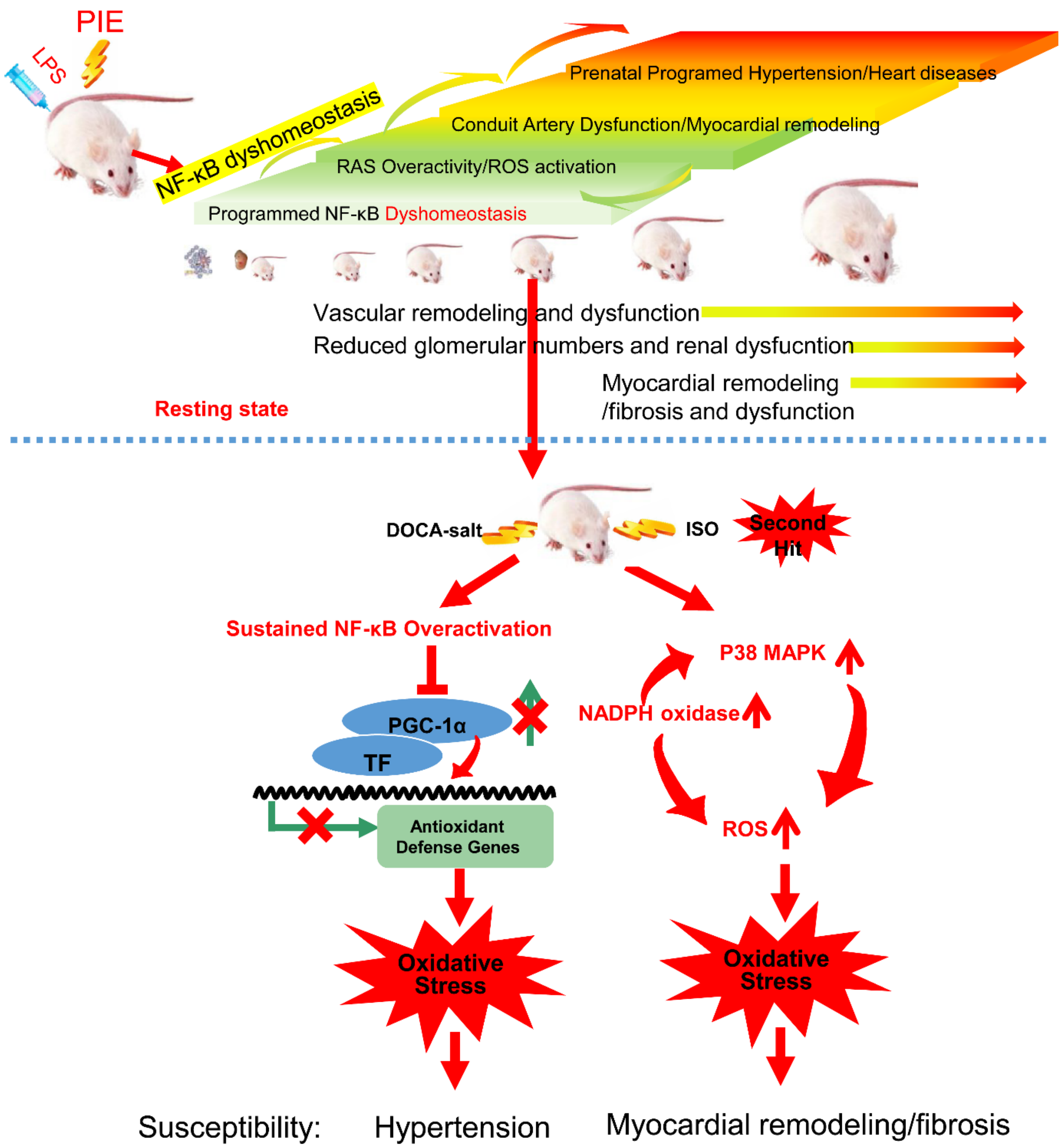

PIE
LPS
NF-κB dyshomeostasis
Prenatal Programed Hypertension/Heart diseases
Conduit Artery Dysfunction/Myocardial remodeling
RAS Overactivity/ROS activation
Programmed NF-κB Dyshomeostasis
Vascular remodeling and dysfunction
Reduced glomerular numbers and renal dysfucntion
Myocardial remodeling
/fibrosis and dysfunction
Resting state
DOCA-salt
ISO
Second Hit
Sustained NF-κB Overactivation
PGC-1α
TF
Antioxidant Defense Genes
P38 MAPK
NADPH oxidase
ROS
Oxidative Stress
Oxidative Stress
Susceptibility:
Hypertension
Myocardial remodeling/fibrosis

Fig. 4.

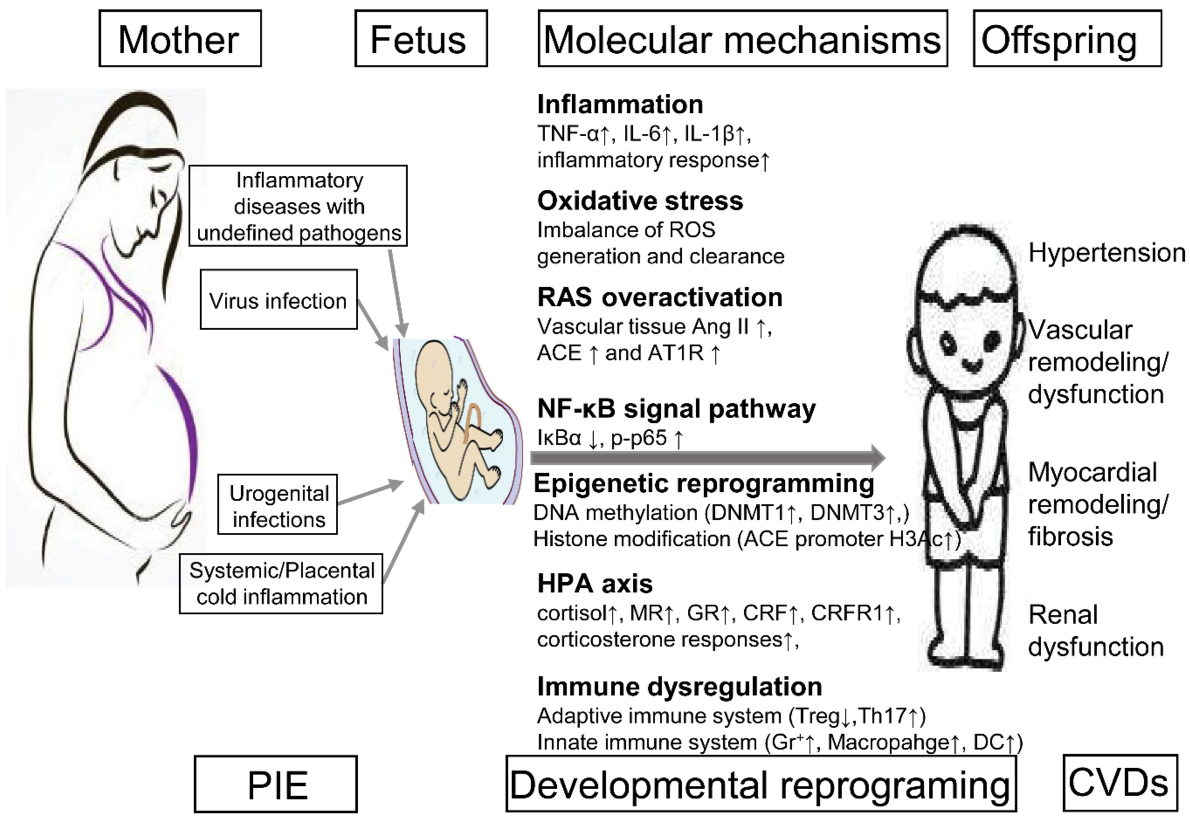

Mother
Fetus
Molecular mechanisms
Offspring
Inflammatory diseases with undefined pathogens
Virus infection
Urogenital infections
Systemic/Placental cold inflammation
Inflammation
TNF-α↑, IL-6↑, IL-1β↑, inflammatory response↑
Oxidative stress
Imbalance of ROS generation and clearance
RAS overactivation
Vascular tissue Ang II ↑, ACE ↑ and AT1R ↑
NF-κB signal pathway
IκBα ↓, p-p65 ↑
Epigenetic reprogramming
DNA methylation (DNMT1↑, DNMT3↑,)
Histone modification (ACE promoter H3Ac↑)
HPA axis
cortisol↑, MR↑, GR↑, CRF↑, CRFR1↑, corticosterone responses↑,
Immune dysregulation
Adaptive immune system (Treg↓,Th17↑)
Innate immune system (Gr⁺↑, Macropahge↑, DC↑)
Hypertension
Vascular remodeling/ dysfunction
Myocardial remodeling/ fibrosis
Renal dysfunction
PIE
Developmental reprograming
CVDs

Fig. 5.