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Review article

D-chiro inositol phosphoglycans in preeclampsia: Where are we, where are we going?

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ABSTRACT

Preeclampsia results from a complex interaction between immunological alterations, endothelial dysfunction, and insulin resistance. Inositol second messengers are known to be involved in metabolic signaling and are highly expressed during preeclampsia. In the past two decades, several studies were published on different aspects where these molecules are involved. It appears that maternal increase of IPG-P content in all tissues and fluids reflects an increased production of inositol mediators on the fetal side in preeclampsia. This comprehensive review of findings shows a possible role for these molecules as a link between metabolism, immunology, vascular alterations, predisposition to seizures, and cardiovascular disease later in life.

1. Introduction

Preeclampsia is a severe complication of human pregnancy where immunology, metabolic alterations and systemic inflammation interact to determine hypertension, endothelial and kidney damage. According to present knowledge, we can define preeclampsia as a non-linear disease as it is characterized by significant changes and multiple adaptations between the mother and the fetal/placental unit before and during overt clinical signs. Moreover, it is further complicated by preexisting factors such as genetic background, immunological diseases, metabolic alterations, and inflammatory diseases. In fact, the complexity of this disease appears evident in the heterogeneity of its onset, progression and clinical impact (Huppertz 2008; Redman and Sargent, 2010; Redman et al., 2014). The explanation of why the pathophysiology and, therefore, the cure of this severe complication of human pregnancy are still elusive. In the recent years, several papers focused on the exacerbated metabolic syndrome that occurs during preeclampsia (Salzer et al., 2015) and its role in augmented risks of cardiovascular and metabolic disease in later life (Steegers et al., 2010; Bokslag et al., 2016). Altered angiogenesis and increased insulin resistance seems to hold a pivotal role for long term complications (Wolf et al., 2004; Bokslag et al., 2016). This is supported by the observation that interventions to improve insulin sensitivity may reduce the risk of both hypertension in pregnancy and later life cardiovascular complications (Seely and Solomon 2003; Carpenter, 2007). It has been known since 2000 that some second messengers of insulin, namely inositol phosphoglycans (IPGs), were highly expressed during preeclampsia (Kunjara et al., 2000) and this has been proposed as a crucial link between endothelial dysfunction and insulin resistance in preeclampsia (Scioscia et al., 2015). Over these years, many studies on IPGs have been published and research has progressively moved from causative role to screening tests to endothelial dysfunction. A comprehensive review on IPGs and preeclampsia with the support of other laboratory and clinical works may help to understand the present findings and to foresee future researches.

1.1. Inositol between immunology and metabolism

Inositol is involved in many cell functions, especially as a precursor of phophatidylinositol and phosphoinositides. Inositol second messenger system is deeply involved in metabolic and cell signaling pathways and mediates several insulin-like actions (Larner et al., 2010). Main signaling molecules of this family are present in eukaryotic cells as phosphoglycans incorporating myo- or D-*chiro* inositol (also known as IPG-A and IPG-P, respectively). They mediate different actions of insulin on glucose oxidative use and storage as IPG-A stimulates lipogenesis, activates acetyl-CoA carboxylase, inhibits cAMP-dependent protein kinase and modifies the activities of adenylate cyclase and cAMP-phosphodiesterase while IPG-P exerts specific insulin-mimetic properties on the glycogen metabolism through the activation of pyruvate dehydrogenase phosphatase, glycogen synthase phosphatase, and glycerol-3-phosphate acyltransferase (Varela-Nieto et al., 1996). IPG-P was supposed to have an important role in preeclampsia as it is highly expressed in all tissues (Scioscia et al., 2007a, 2007b) as summarized below. Apart from glucose metabolism (Gao et al., 2016), this molecule was shown to modulate insulin post-receptor signaling pathways

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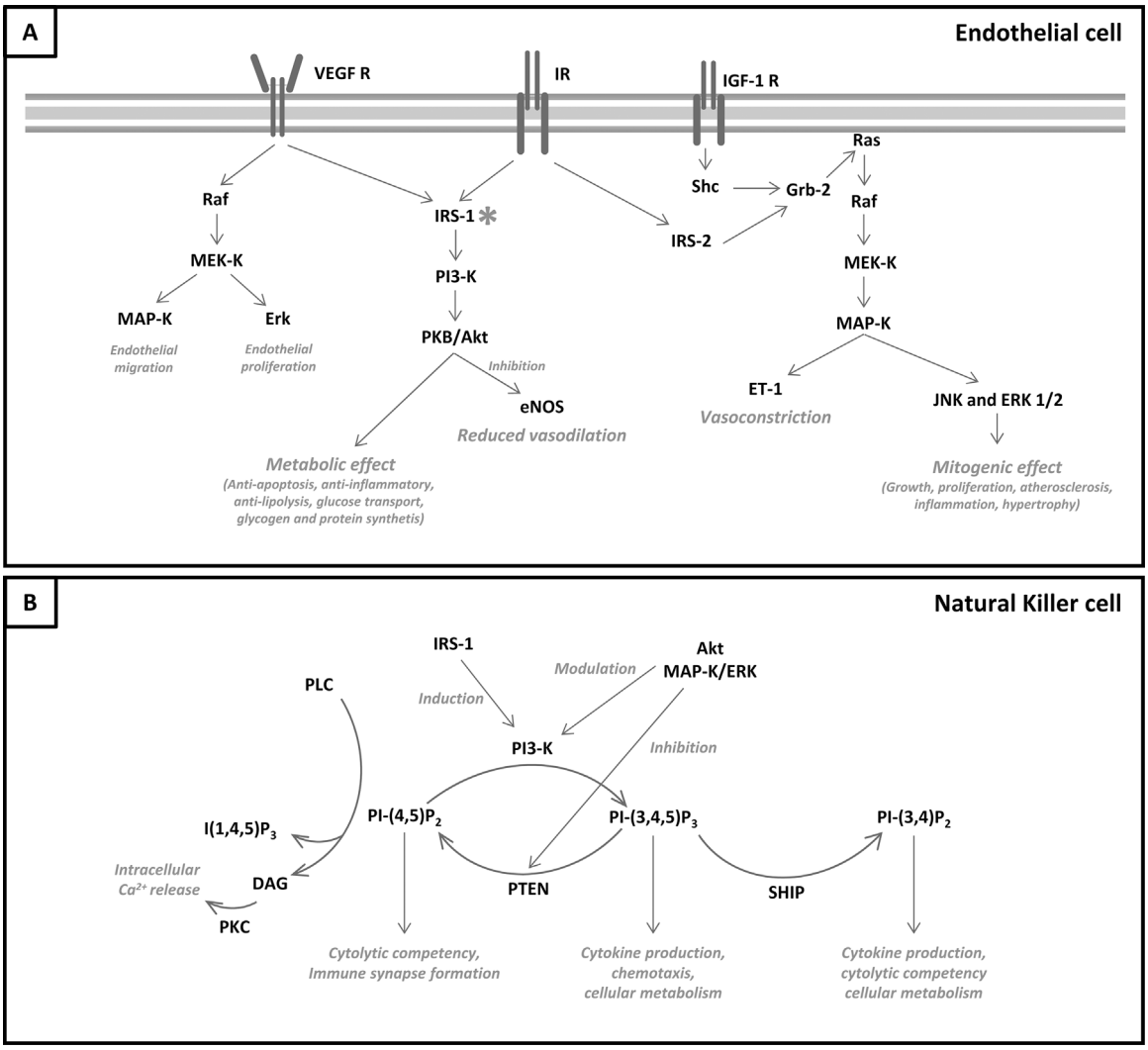

Fig. 1. Inositol derivates can mediate many aspects of intracellular cascades that lead to metabolic, mitogenic, and activity of insulin-sensitive cells. The convergence of signaling pathways subsequent of the activation of specific receptors for VEGF, insulin, and IGF-1 is reported in figure A. IRS-1 and 2 hold a pivotal role in this scenario as inositol phosphoglycans (*) can activate these substrates through a tyrosine phosphorylation or, when IPGs are excessively expressed, they can promote IRS inactivation via serine phosphorylation. Dynamic regulation and activity of natural killer cells is mediated by inositol derivates (B) in a sequence of phosphorylation/dephosphorylation of phosphatidylinositol. In endothelial and NK cells PKB/Akt and MAP-K/ERK show a relevant role in modulation of the signaling. VEGF-R, vascular endothelial growth factor receptor; IR, insulin receptor; IGF-1 R, insulin-like growth factor 1; ERK, extracellular receptor kinase; IRS-1/2, insulin substrate receptor-1/2; PBK/Akt, protein kinase B also known as Akt,; JNK, c-jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase/extracellular receptor kinase; PI3-K, phosphatidylinositol(PI)3-kinase; eNOS, endothelial nitric oxide synthase; ET-1, endothelin 1; PLC, phospholipase C; DAG, diacylglycerol; PKC, protein kinase C; PTEN, phosphatase and tensin homologue; SHIP, SH2-containing inositol phosphatase.

involving IRS – PI3K – PKB/Akt (Insulin Receptor Substrate; Phosphatidyl Inositol 3-Kinase; Protein Kinase B) promoting trophic effects of insulin, enhancing protein synthesis, cell growth, differentiation, and cell survival (Fig. 1A) (Lizcano and Alessi, 2002; Scioscia et al., 2014). These effects of inositols were demonstrated also in lymphocytes (Okkenhaug and Vanhaesebroeck, 2003; Huang and Sauer, 2010; Fayard et al., 2010; So and Fruman, 2012) where IL-2-inducible T cell kinase (ITK) and BTK (Bruton agammaglobulinemia tyrosine kinase) represent important mediators of PI3K signaling pathway respectively in T and B cells (Srivastava et al., 2013). PTEN and SHIP1 are two important phosphatase that dephosphorylate $PtdIns_{(3,4,5)}P_3$, the principal second messenger of PI3K, and their deficiency leads respectively to impaired T cell immune response and to severe myeloproliferative disorders and impaired NK cell function (Fig. 1B) (Helgason et al., 1998; Suzuki et al., 2001; Suzuki et al., 2007; Suzuki et al., 2008). A fine balance between inositol phosphatases and PI3K is necessary for the proper activation and development of T cells (Srivastava et al., 2013). Uterine NK cells contribute to blastocyst implantation in species with invasive hemochorial placentation through secretion of cytokines, chemokines, and angiogenic factors prompting the physiological changes of the endometrium into decidual basalis and triggering cytotrophobalst invasion and spiral artery remodeling (Zhang et al., 2011). Jiang et al. (2000) reported that integrity of PI3K-MEK-ERK pathway is fundamental for degranulation in NK cells. This was confirmed by subsequent studies that demonstrated that inositol phospholipids have a prominent role in NK cell biology mainly through SHIP1 (Kerr and Colucci, 2011; Anderson et al., 2015). Apparently, PI3-K seems to run the critical phase in NK cells for antibody-dependent cellular cytotoxicity and for production of cytokines including IFNγ, TNFα, and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Ståhls and Carpén, 1989; Gumbleton and Kerr, 2013) as demonstrated in PI3-KR1$^{-/-}$ NK cells that resulted cytolytically incompetent (Awasthi et al., 2008). Intracellular signaling in NK cells can be summarized as a sequence of phosphorylation/dephosphorylation of phosphatidylinositol (PI) that can trigger intracellular Ca^{2+} release ($PI(4,5)P_2$ is hydrolyzed by phospholipase C into diacylglycerol to activate protein kinase C and inositol 1,4,5-trisphosphate), promote cytolytic competency, cytokine formation, chemotaxis, and modulate cellular