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Short Communication

The Cytokine Regulatory Network of Natural Killer Cells: Involvement in the Regulation of Blood Pressure in Pre-Eclampsia

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ABSTRACT

Natural Killer (NK) cells play an important role in the early development of fetal. Pre-eclampsia is also related to the dysfunction of NK cells in the first trimester of pregnancy. Dysfunction of cytokines secreting in NK cells, including VEGFA, CXCL8, CXCR4, CXCR3 and Growth-Promoting Factors (GPFs) Pleiotrophin (PTN) and Osteoglycin (OGN), promotes the occurrence of pre-eclampsia. And the imbalance of CD158a (KIR2DL1) and CD158b (KIR2DL3) expression on NK cells is correlated with hypertension, while in pre-eclampsia patients CD158a+ NK cells downregulated the expression of ERAP2 and GCH1, which genes are believed to regulate blood pressure. Here we summarize the function of NK cells in pre-eclampsia, including NK cells cytokine regulatory network and function in blood pressure regulation.

Keywords: Natural killer cells; ERAP2; GCH1; Blood pressure; Pre-eclampsia

ABOUT THE STUDY

Pre-eclampsia is a multisystem pregnancy disorder, which affects 3%-5% of pregnant women, characterised by hypertension and proteinuria, seriously threatening the lives of both mother and baby [1]. Trophoblast cells, decidual stromal cells, and immune cells form the maternal-fetal interface in pregnancy. In the first trimester, decidual Natural Killer (dNK) cells account for about 70% of the immune cells [2]. The role of dNK cells in promoting vascular recasting has been considered as an important factor affecting pre-eclampsia [3]. In women with pre-eclampsia, NK cells imbalanced and downregulated expression of genes about blood pressure regulation [4]. However, whether NK cells can directly intervene in the regulation of blood pressure is a noteworthy issue in the potential regulation mechanism of hypertension.

A complex cytokine regulatory network is constructed around NK cells

NK cells produce large amounts of cytokines including VEGF, CXCL8, angiogenin and large amounts of IFNγ [5,6]. They play critical roles in decidual vascularization and spiral artery formation. A group of cytokines participate in the regulation of angiogenesis, including VEGFA and CXCL8, upregulate in NKs of patients with pre-eclampsia [4]. NK cells upregulate VEGFA, CXCL8, CXCR4, and CXCR3 in a hypoxic environment [7]. This showed that NK cells may be extremely sensitive to hypoxia in the maternal fetal environment of pre-eclampsia. The dNK cells can also secrete Growth-Promoting Factors (GPFs), including Pleiotrophin (PTN) and Osteoglycin (OGN), in both humans and mice [8]. PTN has been shown to be implicated in many processes such as endothelial cell properties during normal and pathological angiogenesis [9], neurite growth during brain development [10], and the development and regeneration of bone and cartilage [11]. OGN is a Proteoglycan (PG) in the Small Leucine-Rich Proteoglycan (SLRP) family, which has key roles in heart development [12], and regulates the thickness of collagen fibrils in skin and eye [13]. These studies speculate that the abnormal function of NK cells at the hypoxia maternal fetal interface of pre-eclampsia patients may lead to various complications, including Fetal Growth Restriction (FGR) [1], newborn cerebral palsy [14] and newborn Bronchopulmonary Dysplasia (BPD) [15], which are

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in high incidence in newborns of women with pre-eclampsia.

NK cells express ERAP2 and GCH1 responsible for regulating blood pressure

As we have known the dNK cells regulate key developmental processes in the first trimester of pregnancy [5], the detailed functions of dNK cells in the maternal-fetal interface are complicated and still indistinct. The imbalance in the expression of the dominant KIRs, CD158a (KIR2DL1) and CD158b (KIR2DL3), on NK cells of patients with pre-eclampsia has been reported [4]. This imbalance is correlated with hypertension, while CD158a+ NK cells from pre-eclampsia patient's downregulated the expression of ERAP2 and GCH1.

ERAP2 has been shown to cleave and hydrolyze angiotensin III (AngIII) and was also reported to act in synergy with ERAP1, which can cleave angiotensin II (AngII) to AngIII and AngIV [16,17]. Several studies in Australian, New Zealand, Norway, Iran, Brazil and America, have shown that ERAP2 gene is associated with the risk of pre-eclampsia [18-21]. The reduced expression or the variation of the ERAP2 gene during the first trimester is significantly correlated with regulation of blood pressure, especially systolic blood pressure, no matter the disorder happened in placenta, fetal or gravida. GCH1 promotes de novo synthesis of tetrahydrobiopterin (BH4) [22]. GCH1 is the rete-limiting enzyme and play key role in the production of BH4. BH4 is essential for the activity of NO Synthase (eNOS) and the production of NO [23]. Therefore, both ERAP2 and GCH1 play effective roles in blood pressure downregulation.

ERAP2 and GCH1 downregulated in NK cells from pre-eclampsia patients [4]. This indicates NK cells may play a potentially important role in the blood pressure regulation of pregnancy women. The disorder of NK cells in gravida, especially in the first trimester of pregnancy, which is the time for placenta forming, may leads to blood pressure raising and even pre-eclampsia.

The potential role of NK cells in blood pressure regulation in gravida

Impaired spiral arteriole remodeling is seen in some women who develop pre-eclampsia, and is often present when the disease results in preterm delivery with fetal growth restriction [1]. In this progress, NK cells play important roles. In the first weeks of pregnancy, NK cells infiltrate and accumulate around spiral arteries [24]. The relationship between NK cells and the vascular remodeling necessary for the proper development of pregnancy indicates that one of the possible key factors that may be failing when pre-eclampsia develops is related to the NK cells3. Disordered NK cells in maternal-fetal interface are associated with impaired spiral arteriole remodeling. In another way, NK cells secrete cytokines to regulate blood pressure. Angiotensin II (ATII) induced vascular dysfunction depends on vascular entry and IFNγ production by NK cells [25]. Down-regulated ERAP2 and GCH1 of NK cells capable lead the disorder of blood pressure in women with pre-eclampsia [4]. In turn, NK cells may play a crucial role in maintaining normal blood pressure of gravida. As high blood pressure is harm for kidney, heart and brain, dNK cells residence in placenta while pNK cells migration around the body in circulation, function of blood pressure reduction of pNK cells may be more effective and direct to non-placental organs harmed in pre-eclampsia. Because the damage of these organs is serious and lasting, it is necessary to explore and develop the roles of NK cells in maintaining blood pressure, and may provide new ideas and methods for controlling blood pressure, especially refractory hypertension.

CONCLUSION

NK cells have a wide and complex cytokine regulatory network, which is involved in the regulation of blood pressure in pre-eclampsia. Function of NK cells secreting VEGFA and CXCL8 upregulate in patients with pre-eclampsia, that may lead to pre-eclampsia and hypoxia environment in decidua. Hypoxic environment further upregulates VEGFA, CXCL8, CXCR4, and CXCR3 secreting in NK cells, and may also leads to various complications of pre-eclampsia. The imbalance of CD158a and CD158b expression on NK cells is correlated with hypertension in patients with pre-eclampsia. And two important genes, ERAP2 and GCH1, play important and direct roles in regulatory function of blood pressure, and worthy of further study and application in the protection of damaged organs in pre-eclampsia.

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CONFLICT OF INTEREST

All authors declare no competing interests.

AUTHOR`S CONTRIBUTIONS

Conceptualization: Weidong Zhao and Jieqi Ke; wiring original draft preparation: Jieqi Ke; writing, review and editing: Ting Gao and Yanhuan Zhang; supervision: Weidong Zhao and Jieqi Ke. All authors have read and agreed to the published version of the manuscript

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