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The Role of Adipokine Chemerin in Pregnancy Complications*

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1 Introduction

Recurrent pregnant loss, gestational diabetes, premature delivery, intrauterine growth restriction, preeclampsia and other pregnancy-related complications have severe impact on the fetus development and the health and life quality of the mother. These diseases are also causes of unstability and huge economic burden for the family as well as the society. However, pathogeneses of the most pregnancy-related complications are still poorly understood. Recent studies show that lipid and carbohydrate metabolism and hypertension play a role in these diseases. For example, the high incidence of preeclampsia, miscarriage and recurrent early miscarriage, gestational diabetes are closely related to lipid metabolism. Preeclampsia, for instance, is a severe disease that causes 14% of pregnancy-related maternal deaths and 15% of premature deliveries world wide [1-2]. In health statistical data of China for 2012, preeclampsia is the second leading cause of maternal death and responsible for 11.1% of maternal death. The incidence of preeclampsia in obese pregnant women is three times higher than normal weight pregnant women [3], in gestation diabetes pregnant women is two times higher than the normal pregnant women respectively [4]. The incidence of preeclampsia increases dramatically when the pregnant women has hypertension, and usually with an unfavorable prognosis for the patient [5]. Also, the incidence of preeclampsia is significantly higher among pregnant women with metabolic syndrome [6]. Meanwhile, the results from long-term studies [1-2, 7] compared the health condition of women with normal pregnancy and preeclamptic pregnancy upto seven years post delivery showed that the incidences of several diseases were higher in preeclamptic women: hypertension & proteinuria, cardiovascular disease and postpartum diabetes was 10, 1, and 2 times greater in the preeclamptic women respectively [1-2, 7-8]. In another investigation, it was found that the incidence of the postpartum metabolic syndrome was significantly higher in the preeclampsia patients [8]. Also, if preeclampsia pregnancy accompanied metabolic syndrome, the incidence of postpartum cardiovascular diseases and high blood pressure will be 12 times higher than normal pregnancy [9]. So, there is a close association between cardiovascular diseases (such as hypertension) and lipid and carbohydrate metabolism abnormality with pregnancy-related complication. However, the underlying connections remain unclear.

Although the rate of obesity, diabetes, and cardiovascular diseases are already high, it still increases every year with affected people younger and younger. These diseases seriously influence the reproductive health and contribute substantially to the increased incidence of pregnancy-related diseases.

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According the statistical data, the rates of overweight and obesity during 2010~2011, were 32.4% and 13.2% in China, respectively[10]. In 2013, the prevalence rate of adult hypertension was 33.5%. The rate of diabetes for the same year was 11.6%. The total number of patients with hypertension and diabetes for 2013 was more than 114 million [11]. This situation not only endangers the reproductive and overall health of the individual but also brings new, unprecedented challenges to the health of our future generations.

In sum, it is important to identify the etiology of pregnancy-related diseases, as well as their internal connection with the obesity, diabetes, and high blood pressure. The progress in this direction would promote the development of better diagnostic and treatment methods as well as more efficient drugs. These will, in turn, lead to improved the maternal and fetal health and quality of life for both the mom and offsprings during pregnancy and postpartum.

2 Chemerin and its receptors

Chemerin is also called tazarotene-induced gene2 (TIG2) or retinoic acid receptor responder (tazarotene induced) 2 (RARRES2). It is translated as an 18 ku inactive precursor protein and achieved its active 16 ku format by removing the C-terminus with extracellular serine protease [12]. In 2007, Bozaoglu *et al*. [13] first proved that chemerin is an adipokine by using a signal sequence capture technology. Chemerin is highly expressed in white fat tissues, liver, lungs, pituitary, placenta, and ovaries, and participates in different physiological functions[13].

So far, there are three known receptors of chemerin[14]: the chemokine-like receptor 1(CMKLR1), the G protein-coupled receptor 1 (GPR1) and the CC chemokine receptor-like 2 (CCRL2). CMKLR1 has proved to be the natural receptor for chemerin [13]. It plays a role in inflammation, leukocyte recruitment, fat and carbohydrate metabolism process[14]. After chemerin binds to CMKLR1, endocytosis is induced. It leads to the release of intracellular calcium, and suppression of the cAMP accumulation and protein kinase ERK1/2 or PI-3K/Akt phosphorylation pathway [15], and promotes leukocyte chemotaxis. Chemerin binding to GPR1 can stimulate receptor endocytosis, but its physiological role has not yet been explored[14]. Chemerin binding to CCRL2 cannot induce receptor endocytosis or promote leukocyte chemotaxis. Although it has no biological effects, it can increase the concentration of chemerin in the local environment, thereby chemerin binding to CCRL2 plays a role in enriching CMKLR1 high expressing cells[16].

3 Chemerin is highly expressed in obesity, diabetes, hypertension and metabolic syndrome

The level of chemerin was significantly higher in the peripheral blood of obesity and metabolic syndrome patients [13, 17], and was associated with abnormalities in the lipid metabolism and insulin resistance [17], and chemerin might be the causative factor of obesity induced type 2 diabetes[18]. Meantime, experimental evidence had shown that the antagonists of CMKLR1 receptor had beneficial effects on type 2 diabetes treatment from both cellular level and *in vivo* aspect [19]. All these findings indicate that the occurrence of high level of chemerin is related to diabetes. Also, it was found that the blood level of chemerin was positively correlated with the incidence of coronary artery disease in adult Chinese [20]. The intensities of chemerin expression in periadventitial fat and foam cell were positively correlated with the severity of atherosclerosis, and moreover, the expression of CMKLR1 in foam cells was also significantly correlated with aortic atherosclerosis[21]. In addition, chemerin secreted by periadvantitial fat can promote arterial vasoconstriction through CMKLR1 receptor [22]. So, chemerin might serve as a key molecular connecting obesity and hypertension. These studies showed that the high expression level of chemerin and CMKLR1 receptor signal pathway is a common risk factor for obesity, diabetes, hypertension and metabolic syndrome.

4 Chemerin and pregnancy

To date, the function of chemerin and its receptor CMKLR1 in pregnancy is still unclear. Chemerin mRNA is highly expressed in extra villas trophoblast (EVT) and placental trophoblast cells, uterine stromal cells except the decidual endothelial cells [23-24]. By analyzing the serum levels of chemerin in non-pregnant, early, mid and late pregnant women, Garces *et al* [25] found that chemerin levels were markedly increased in late pregnancy compared to early and middle pregnancy. Meantime, its receptor CMKLR1 is expressed in trophoblast cells, decidual cells, decidual natural killer cells and peripherial natural killer cells[24]. In addtion, chemerin can support

peripherial natural killer cells migration through both deciduas and stromal cells, promote decidual cells to form capillary-like tube structure [24]. These results suggest that chemerin and its recepter CMKLR1 may involve with uterine spiral artery remodeling process. However, their function in this process remains unclear. Also, it is still unclear why the expression of chemerin tends to increase with the progress of the pregnancy.

5 Chemerin and pregnancy-related complications

The fastest fat accumulation period in women is weight gain during pregnancy. With the increasing of the maternal fat mass, both the synthesis and secretion of adipokines increase, and they participate in the regulation of energy metabolism and insulin activity in normal pregnancy. Since the rate of obesity in the modern society increases, the study on the relationship between the abnormal levels of adipokines during pregnancy and pregnancy-related complications attracts more attention. Recent studies show that chemerin is closely related to reproductive functions. For example, increased expression of chemerin was observed in the blood and adipose tissues from polycystic ovary syndrome patients[26], as well as in the circulation system of preeclampsia patients [27–29]. Besides, chemerin concentraton is correlated to insulin sensitivity of pregnant women, and the concentration of chemerin is higher in the fetus of obese pregnant women[30]. In the following paragraph, the relationship between chemerin and pregnancy-related diseases and the potential pathogenesis will be discussed.

5.1 Chemerin and gestational diabetes

Gestational diabetes mellitus (GDM) refers to any degree of glucose intolerance with onset or first recognition during pregnancy. Its rate is about 8%～14%, with a trend of increasing every year. GDM is one of the common pregnancy complications and endangers the health both of the pregnant women and the fetus. It may lead to maternal energy metabolic disorders, which in turn increase the risk to mother and child, such as, large for gestational age in unmanaged GDM, small for gestational age and intrauterine growth retardation in managed GDM, spontaneous abortion, fetal malformations, neonatal hypoglycemia, jaundice, polycythemia, hypocalcemia and hypomagnesemia. However, the pathogenesis of GDM is still unclear. Insulin resistance (IR) and reduced insulin secretion from islet β cells are important to the pathogenesis of GDM. IR is a physiological condition in which cells fail to respond to the normal actions of the hormone insulin, and normal pregnancy is a physiological IR condition. When beta cells in the pancreas cannot produce enough insulin to compensate this abnormal IR, GDM will occur. One large data analysis showed that GDM of overweight pregnant women was 2.14 times higher than normal weight pregnant women, the rate of GDM in obese pregnant women is 3.56 times higher than normal weight pregnant women, and the occurence of GDM in the pregnant women that suffer from severe obesity was 8.56 times higher than normal weight pregnant women [31]. Increased maternal fat content during pregnancy may lead to increased secretion of adipokines which are involved in the regulation of the IR. Recent studies showed that the concentration of chemerin is significantly higher in the serum of the GDM group than in the control group, and is significantly correlated with the weight gain during pregnancy and antepartum BMI [32]. These findings suggest that the onset of GDM is related to the increase of chemerin concentration and the weight gain during pregnancy. Meantime, there are also reports shown that the concentration of chemerin in GDM pregnancy is lower than normal pregnancy[8]. Also, in the control group, the chemerin level was related to the blood glucose level and the lipid metabolism, which indicates that chemerin plays a role in maintaining the normal blood glucose level and serum lipid metabolism during pregnancy[33]. Therefore, there is a correlation between the level of chemerin and the incidence of GDM. However, chemerin is highly expressed both in the placenta and fat tissues. So, the origin of abnormal expression of chemerin during GDM pregnancy, the pathways which chemerin invovled with IR, and the mechanism of chemerin in GDM development are all need further investigation.

5.2 Chemerin and preeclampsia

Preeclampsia (PE) is a disorder of pregnancy characterized by high blood pressure and proteinuria after 20 weeks of gestation. To date, PE treatment is limited to treat the hypertension and edema symptoms, and the only effective treatment is still the termination of pregnancy by removing the fetus and placenta [1–2]. Although pregnant termination can reduce the maternal and child mortality rate, it results in the development issues and high cost of medical care for

preterm birth children. Rescent study showed that the concentration of chemerin was significantly higher in the serum of preeclampsia patients compared to normal pregnant women[27–29]. Also, regression analysis results indicate that serum concentrations of chemerin were positively correlated with systolic blood pressure, serum creatinine concentration, and free fatty acids. Other studies showed that high serum chemerin concentration could serve as an independent marker for dyslipidemia, the severity of preeclampsia [29] and predictive biomarker for preeclampsia and important causative factor in the pathogenesis of preeclampsia[28]. In addition, the serum chemerin level is significantly higher in PE patient then normal pregnant women 6 months postpartum[27], this could be one of the causes for higher incidence of diabetes, hypertension and metabolic syndrom occuring postpartum in PE patients. However, so far, there are no direct experimental proof that chemerin can induce PE. Hence, how chemerin causes PE pathogenesis remains unclear.

As mentioned above, the signaling pathway between high expression of chemerin and its receptor CMKLR1 is the common pathogenic factor of obesity, diabetes, hypertension and metabolic syndrome. Meanwhile, chemerin is also overexpressed in preeclampsia. It is a matter of further investigation to determine whether the chemerin/CMKLR1 signaling pathway is an internal factor between preeclampsia and obesity, diabetes, hypertension and metabolic syndrome.

6 Chemerin regulatory mechanisms may be involved with pregnancy complications

6.1 Chemerin and the regulation of trophoblast cell invasion

Chemerin and its receptors are all expressed by placental trophoblast cells, and they are also expressed by a variety of cells during the decidualization process [23–24]. Current studies indicate that chemerin expression is correlated with the malignant degree of tumors, for example, in small cell lung cancer, decreased chemerin expression is an indicator of tumor progression, and high levels of chemerin indicate a good prognosis[34]. Similarly, chemerin expression level in liver cancer cells were significantly lower than the surrounding healthy liver cells, and its expression level were negatively correlated with tumor size [35]. Trophoblast cells also have invasion features similar to the tumor cells, and can invade into the decidua tissue and uterine sprial arteries in an restrictive manner. Also, the restrictive invastion of trophoblasts is also related to the CMKLR1 expressing natural killer cells, dendritic cells, and innate immune cells. So, chemerin/CMKLR1 may involve with trophoblast cell proliferation and invasion processes. However, the role of the chemerin/CMKLR1 pathways in these processes has not been revealed and needs further study. Meanwhile, chemerin level is high in preeclampsia, and superficial trophoblastic invasion and incomplete spiral artery remodeling are typical pathological changes in the placenta of preeclampsia patients. So, further studies are required to determine whether chemerin regulates the trophoblast invasion is the causes of typical pathological changes in preeclampsia.

6.2 Chemerin and insulin resistance

Circulation chemerin levels are significantly higher in obesity and metabolic syndrome patients[13, 17]. The level of chemerin is associated with the lipid metabolism and IR [17], and chemerin could be the potential internal cause of obesity induced type 2 diabetes [18]. Previous studies has shown that chemerin induced IR may be associated with the activity changes of the Akt and ERK signaling pathways in the muscle system. By treating human skeletal muscle cells with chemerin, Sell *et al*.[36] found that chemerin induces IR in human skeletal muscle cells at the level of insulin receptor substrate 1, Akt and glycogen synthase kinase 3 phosphorylation, and glucose uptake. Meanwhile, chemerin-induced IR can be prevented by inhibiting the ERK signaling pathway. In addition, by overexpressing human chemerin in LDL receptor knockout mice on high-fat diet, Becker *et al*.[37] found that overexpression chemerin did not affect body weight, lipid levels and atherosclerosis. However, in the insulin tolerance test and glucose tolerance experiments, blood glucose levels increased significantly. This is mainly because that chemerin inhibited insulin-induced activation of Akt1 and AMPK phosphorylation in skeletal muscles while no effects on Akt1 phosphorylation and the activation of AMPK in the liver and gonadal fat tissues. Recently, Zhang *et al*. found that the glucose intake of myocardial cells and insulin-induced phosphorylation of Akt were reduced after treating rat cardiomyocytes with chemerin. Meanwhile, chemerin activated the phosphorylation of p38MAPK and ERK1/2 after ERK pathway, and inhibition of ERK singnal pathway can

partially relieve the chemerin-induced IR [38]. The correlation between the changes of chemerin-induced Akt and ERK and the occurence of GDM, needs further study.

6.3 Chemerin with hypertension and atherosclerosis

Stejskal *et al*. [39] found a positive correlation between chemerin levels and systolic/diastolic blood pressure in white population. Also, Wang *et al*. [40] found that the chemerin level was also positively correlated with blood pressure in Kazak hypertension patients. These results indicate that chemerin is possibly a new factor regulating the blood pressure balance. Previous study showed that chemerin can activate the inhibitory intracellular G proteins and inhibit adenylate cyclase activity after binding to CMKLR1, resulting reduced content of cyclic adenosine monophosphate significantly, increased content of intracellular Ca^{2+}, vasoconstriction and elevated blood pressure [13]. Other study showed that chemerin secreted from periadventitial fat acts as an arterial vasoconstrictor through the CMKLR1 receptor [22]. In addition, blood chemerin level is positively correlated with the onset of coronary artery disease in adult Chinese [20], and chemerin expression intensity in the periadventitial fat and foam cell were positively correlated with the severity of atherosclerosis, and moreover, the expression of CMKLR1 in foam cells was also significantly correlated with aortic atherosclerosis [21]. Meanwhile, hypertension and acute atherosclerotic lesions in the uterine spiral artery are also typical symptoms and pathological changes in patients with preeclampsia [41]. The relationship of preeclampsia with chemerin/CMKLR1 signaling pathway involved blood pressure regulation and atherosclerosis changes, needs further investigation.

6.4 The possible mechanism of preeclampsia induced by chemerin

Summarizing the above latest research progresses, we hypothesize the pathogenesis of chemerin induced pregnancy-related complications by using preeclampsia as an example (Figure 1). Studies had shown that obesity, diabetes, hypertention and metabolic syndrome could increase the incidence of preeclapsia, and the incidence of above diseases are increase in postpartum of PE gestation. Meanwhile, the level of chemerin was increased in obesity, diabetes, hypertension, metabolic syndrome and preeclampsia. Studies found that high levels of chemerin can induce high blood pressure through CMKLR1 receptor, and is

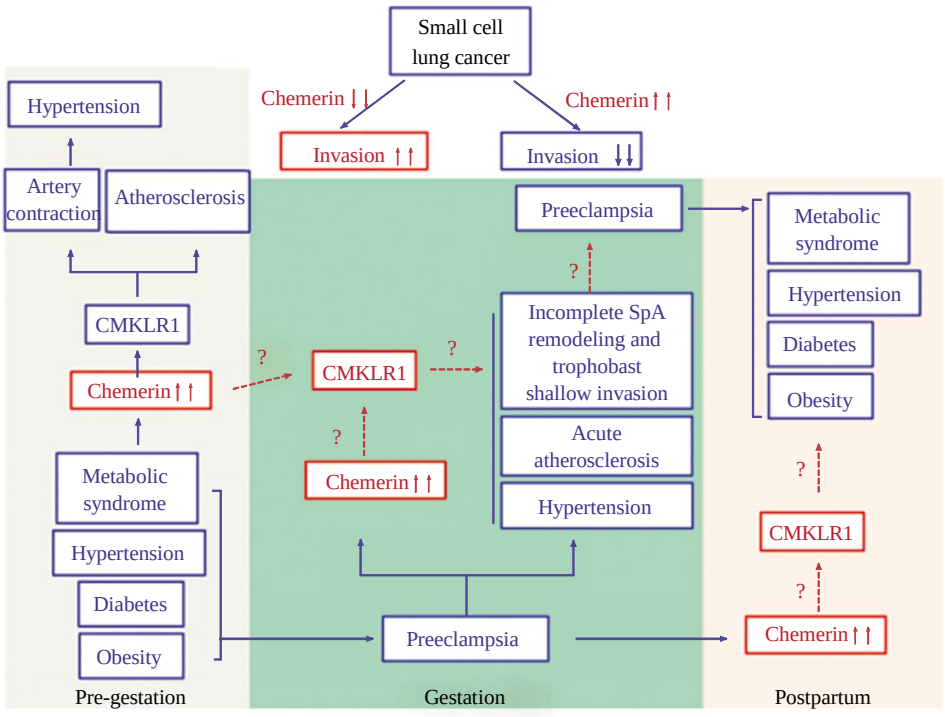

Fig. 1 A schematic illustration of mutual induction between obesity, diabetes mellitus, hypertension, metabolic syndrome, and preeclampsia

The existed findings (the blue line) and the possible pathogenesis pathway of preeclampsia (the red dashed line).

positively correlated with the degree of atherosclerosis. Hypertension and acute atherosclerosis are also typical pathological changes of preeclampsia. Are the upregulation of chemerin before or during pregnancy resulting in the typical hypertension in preeclampsia? In addition, chemerin was highly expressed in small cell lung cancer cells and could inhibit tumor invasion, suggesting that chemerin may be involved in regulation of trophoblastic invasion. During pregnancy, trophoblast cells invade maternal decidua, modify the spiral arteries and establish the maternal-fetal blood supplying in the early pregnancy, and the invastion ability is reduced after placentation. These changes are matching with the gradually increasing serum chemerin level during the pregnancy. Al s o, the levels of chemerin in preeclampsia were increased compared to those of normal pregnancy, companied with superficial trophoblast cells invasion and incomplete spiral artery remodeling. Does this mean that chemerin participate in the development of preeclampsia by regulating the trophoblast cell invasion? Finally, the serum chemerin level was significantly higher in patients from PE postpartum than normal pregnancy, and high levels of chemerin are associated with abnormal glucose and lipid metabolism and high incidence rate of hypertension. Therefore, does the high level of chemerin contribute to the high incidence of postpartum hypertension, obesity and diabetes? To answer these questions, in-depth investigation is needed.

7 Prospective

Pre-pregnancy abnormal glucose and lipid metabolism and hypertension are associated with elevated circulation chemerin levels, and the accumulated adipose tissue and placenta are all chemerin highly expressed tissues during pregnancy. So, the relationship of high chemerin concentration before or during pregnancy with gestational diabetes, preeclampsia and other pregnancy complications needs further in-depth study. The application of chemerin and CMKLR1 gene deficient mice, placental- and endometrial- specific manipulation of chemerin and CMKLR1 gene expression methods will finely dissect out the roles of chemerin from different oringins and the CMKLR1 receptor signal pathway on pregnancy related complications, discover the etiology of these pregnancy-related diseases, and provide new basis and targets for diagnosis and treatment of these diseases.

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