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Research Progress on the Role of Autophagy and Preeclampsia

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Abstract

Objective:Preeclampsia (PE) is an idiopathic disorder of pregnancy and an important type of hypertension in pregnancy. The current causes and mechanisms of preeclampsia have not been fully elucidated, which poses a great threat to the health of mothers and children, and there is no effective treatment. At present, it is believed that inflammation and oxidative stress are potential stimulating factors for the change of placental autophagy, which can cause placental dysfunction and pathological pregnancy. Therefore, this article discusses the research progress of the role of autophagy and preeclampsia.

Keywords

Preeclampsia; Autophagy; Placental tissue.

1. Introduction

Preeclampsia (PE) is an idiopathic disorder of pregnancy and an important type of hypertension in pregnancy. The clinical manifestations are high blood pressure, proteinuria, edema and various degrees of damage to the function of multiple organs throughout the body after 20 weeks of pregnancy, which can cause intrauterine hypoxia and growth restriction, and are the main causes of death of pregnant women and fetuses. The worldwide incidence rate is 3%-5% [1, 2], and the incidence rate is increasing year by year. The cause and mechanism of preeclampsia have not yet been fully elucidated. Current studies suggest that under normal pregnancy conditions, Extravillous trophoblast (EVTs) invade and penetrate deep into the spiral artery of the uterus, destroying the muscularis and elastic layers of the blood vessels, replacing vascular endothelial cells , So that the spiral artery expands and the uterine placental blood flow increases. If this process fails, the uterine placental blood flow will decrease, and hypoxic stress will further affect the formation and function of the placenta [3]. Preeclampsia poses a great threat to the health of mothers and children, and there is no effective treatment method. Timely termination of pregnancy is currently the only reliable treatment method [4].

2. Pathogenesis of Preeclampsia

PE is a pregnancy-specific disease. The pathogenesis and etiology are not very clear. Studies have shown that [5-7] The pathogenesis of preeclampsia includes factors such as abnormal placental function, poor placental vascular remodeling, and systemic oxidative stress. There are also studies that [8-10] abnormal placental function and angiogenesis are the main potential causes of preeclampsia. Other studies have shown that [11] abnormal immune response is also involved in the occurrence and development of preeclampsia. The hypothesis on the pathogenesis of pre-eclampsia is mainly based on the two-stage theory of pre-eclampsia. The first stage mainly indicates that long-term hypoxia of placental trophoblasts in early pregnancy leads to placental trophoblast cell invasion disorder and poor uterine spiral artery recasting [12]. The second stage indicates that the mother has a systemic oxidative stress response, an inflammatory response, and an increase in blood pressure due to damage to the vascular

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endothelium [13]. At present, it is believed that inflammation and oxidative stress are potential stimulating factors for the change of placental autophagy, which may cause superficial placental implantation, dysfunction and pathological pregnancy. Shallow infiltration of the placental trophoblast in preeclampsia, placental dysplasia [14,15], may be more suitable to explain the relatively early preeclampsia process.

3. The Relationship Between Autophagy and Preeclampsia

Autophagy is a mechanism by which cells self-regulate to maintain homeostasis. It can occur in a steady state and can also be activated under stress. Studies have shown that autophagy is involved in the occurrence and development of many diseases and is one of the current research hotspots [16]. When the body is in a normal physiological state, the cells are in a state of low autophagy; when the cells are in a bad environment such as hypoxia, oxidative stress, the cells express a large number of autophagy-related protein molecules to form autophagy membrane-like structures, phagocytic cells and organelles Cellular components form autophagosomes, which combine with lysosomes to form autophagy-lysosomes, which degrade large molecules such as proteins in the autophagosome into small molecules. When the internal environment is destroyed, it can be the body Provide energy and synthesize new molecules to ensure homeostasis [17]. When autophagy is overactivated, too much cell material is swallowed, which can lead to cell death. Therefore, moderate autophagy is conducive to cell proliferation and differentiation, and overactivation of autophagy leads to cell death. Autophagy is related to many diseases, but the relationship between the abnormal regulation of autophagy and the pathological state of the disease is currently unclear. Cells have the ability to maintain their own integrity and can activate the autophagy process under internal and external environmental stimuli. Autophagy markers such as microtubule-associated protein 1 light chain 3B (MAP1 LC3B) and Beclin-1, (MAP1LC3B/Beclin-1) ratio The change can reflect the situation of the autophagy process. If a cell cannot maintain its integrity, it will enter the process of cell death. Therefore, the ratio of MAP1LC3B/Beclin-1 not only reflects the level of autophagy, but also reflects the viability of cells [18]. As an important marker protein for autophagy, LC3 on the autophagosome membrane exists in two forms: LC3 I and LC3 II. When autophagy occurs, LC3 I is transformed into LC3 II and localized in the autophagosome membrane, so LC3 II/I can reflect the level of autophagy [19]. Studies [20] have shown that the autophagy of trophoblasts is enhanced under hypoxic conditions, and the expression of LC3 II/LC3 I and Beclin 1 in placental trophoblasts is significantly reduced under hypoxia [21].

Some studies [22-23] evaluated the role of autophagy in the placenta of preeclampsia, indicating that oxidative stress and hypoxia are important mechanisms for the occurrence and development of preeclampsia [24-29], and are increasingly considered It is an important mechanism of placenta formation in pregnancy. The serum of pregnant women with normal blood pressure promotes the induction of autophagy, the serum of pregnant women with preeclampsia contains autophagy inhibitors, and the disorder of autophagy induction may lead to the pathophysiology of this disease [30]. The results of the experiment [31] showed that the expression of LC3II in the placenta tissue of severe PE was significantly higher than that in the normal pregnancy group, and the expression was positively correlated with 24-hour urine protein, suggesting that the autophagy process of trophoblast cells in severe PE placenta is obviously activated, which is related to the severity of PE Related. Studies have also shown that the autophagy of PE placental trophoblasts is over-activated, the invasion of trophoblasts is significantly inhibited, and the apoptosis of trophoblasts is increased [32-34]. Chang Ying [35] showed that the autophagy activity is different in syncytiotrophoblast cells in preeclampsia and EVTs in preeclampsia. Studies have also shown that autophagy is dominant in placental syncytiotrophoblast cells [36]. Mizushima N [37-38] et al. showed that LC3 and p62/SQSTM1

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are used as autophagy marker molecules, and the combination of the two participates in the process of autophagy. In preeclampsia, compared with normal pregnancy, the increase of LC3-II and the decrease of p62/SQSTM1 indicate that autophagy activation occurs in the placenta of preeclampsia [39]. Fetal growth restriction is an important clinical manifestation of preeclampsia[40]. In rodent pregnancy, the inhibition of autophagy is closely related to fetal growth restriction. Ceramide-mediated autophagy activation and oxidative stress- The combined effect of reductase activity impairs the function of the placenta in preeclampsia and indirectly leads to the deterioration of the fetal growth environment.

In autophagy inhibition, EVTs under hypoxic conditions with impaired invasion and vascular remodeling suggest that inhibition of autophagy may lead to poor placenta formation. Studies have shown that p62, a substrate for autophagy degradation in preeclampsia-positive EVTs, accumulates more frequently than normal women, indicating that autophagy suppression occurs in the placenta of preeclampsia, and at the same time, in EVTs of preeclampsia patients The positive rate of p62 molecule is also higher than that of normal pregnant women. The serum of patients with preeclampsia can induce preeclampsia-like symptoms in model mice, such as hypertension, proteinuria, and fetal growth restriction [41].

Seng [42] inhibited the invasion and vascular remodeling of vascular endothelial cell lines by inhibiting autophagy under hypoxic conditions. This experiment confirmed that the substrate p62/SQSTM1 degraded by autophagy is cytokeratin 7 in placental biopsy specimens of preeclampsia. The accumulation frequency of positive EVT cells in women with normal blood pressure is higher than that in women with normal blood pressure, suggesting that the placenta has autophagy inhibition in preeclampsia. Another study showed that the positive rate of p62/SQSTM1 in EVT cells was also significantly higher than that in normal pregnant women [43]. Autophagy activation has also been reported in the placenta of preeclampsia. In patients with preeclampsia, compared with normal pregnancy, the autophagy activating protein LC3-II in the placenta of hypertensive patients is increased, and p62 is decreased [44]. Yung [45] examined the plasma samples of 2002 women, divided the samples into pregnancy group and pre-eclampsia group, and performed circulating plasma DAPK-1 detection. The results showed that DAPK-1 in the plasma of patients with pre-eclampsia was significantly increased ($p<0.01$). At the same time, the expression of DAPK-1mRNA and protein in placental tissues of patients with preeclampsia increased.

Autophagy activity is inhibited, so that damaged, senescent or degenerated organelles and macromolecules cannot be degraded in time, leading to the production of some inflammatory substances, which can damage cells, induce apoptosis and death, and limit the infiltration of trophoblasts. Poor recasting of uterine spiral arteries can cause placental ischemia and hypoxia, which can lead to preeclampsia. When hypoxia worsens, it causes vascular endothelial cell damage and inflammatory response. Inflammatory mediators stimulate vascular endothelial dysfunction, which can lead to microthrombosis and infarction, and may cause systemic endothelial cell activation, leading to preeclampsia happened.

4. Concluding Remarks

Autophagy activity is closely related to preeclampsia. In preeclampsia, the placenta is in a persistent state of hypoxia, and the autophagy of the placental nourishing vesicles is overactivated, leading to cell death, causing systemic oxidative stress, inflammation, etc., and aggravating nourishment Decreased cell invasion ability and poor uterine blood vessel remodeling can cause "superficial placental implantation", which can further aggravate the symptoms of hypoxia and cause various clinical manifestations of preeclampsia. Preeclampsia poses a great threat to the health of mothers and children, and there is no effective treatment method. Timely termination of pregnancy is currently the only reliable treatment method.

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Finding an effective treatment target for the disease is an important means to achieve effective intervention. Studies have shown that 1,25-dihydroxyvitamin D can activate the autophagy process of placental trophoblasts, inhibit cell apoptosis, and achieve the purpose of early prevention of preeclampsia. It is hoped that in the future, the study of preeclampsia using autophagy as an entry point will further explain the relevant mechanisms of the diagnosis or treatment of preeclampsia, and provide new ideas for clinical preeclampsia research.

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