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DJ-1 upregulates the Nrf2/GPX4 signal pathway to inhibit trophoblast ferroptosis in the pathogenesis of preeclampsia

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Ferroptosis is a newly discovered mode of cell death that involves disorders in iron metabolism and the accumulation of reactive oxygen species (ROS) in the plasma membrane. Preeclampsia (PE) is a gestational idiopathic disease that is characterized by hypertension and albuminuria, begins after 20 weeks of pregnancy. DJ-1 is a prerequisite for activating and stabilizing Nrf2 to allow translocation to the nucleus to carry out further functions. Detecting the expression levels of DJ-1, the Nrf2/GPX4 signaling pathway and ferroptosis markers in placental tissues of pregnant women with and without PE. Analyzing the effects of the ferroptosis inducer (RSL3) and the inhibitor (Fer-1) on the mortality rate of BeWo cells and DJ-1+/+, DJ-1−/− BeWo cells. Ferroptosis markers (MDA concentration and morphology of trophoblast cells) and DJ-1 and its downstream the Nrf2/GPX4 signaling pathway increased significantly in PE pathological state. The expression levels of DJ-1 protein in the control group and the PE group were positively correlated with the expression levels of Nrf2/GPX4 signaling pathway protein, and negatively correlated with the MDA concentration. BeWo cells were sensitive to the ferroptosis inducer (RSL3) and the inhibitor (Fer-1). The high expression levels of DJ-1 in BeWo cells can resist ferroptosis by regulating the Nrf2/GPX4 signaling pathway. Ferroptosis is involved in the pathogenesis of PE. DJ-1 can mediate the trophoblast cells ferroptosis and play a protective role in the pathogenesis of preeclampsia by regulating the Nrf2/GPX4 signaling pathway.

Preeclampsia (PE) is a gestational idiopathic disease that is characterized by hypertension and albuminuria, begins after 20 weeks of pregnancy, and can cause damage in the liver, kidney, brain, and the functionality of other organs. The global incidence of PE is 5% to 8%. PE is one of the most common causes of maternal and perinatal morbidity and death, especially in developing countries[1]. Ferroptosis is a newly discovered mode of cell death that involves disorders in iron metabolism and the accumulation of reactive oxygen species (ROS) in the plasma membrane[2]. Ferroptosis can be triggered by excessive levels of Fe^{2+} or reagents that can increase the levels of intracellular ROS (such as NADPH oxidase)[3]. Ferroptosis can be pharmacologically inhibited by iron chelating agents (e.g., deferrioxamine), lipophilic antioxidants (e.g., ferristatin), and enzymes that can reduce lipid peroxidation and inhibit iron uptake[4]. However, ferroptosis does not respond to inhibitors that are related to apoptosis or necrosis[5]. Over recent years, there has been significant interest in the correlation between increasing ferroptosis and lipid peroxidation in plasma membrane and the pathogenesis of PE[6]. Many studies have observed the characteristics of ferroptosis in the physiological and pathological states of PE[7]. In a previous study, Siddiqui et al.[8] reported that the concentration of malondialdehyde (MDA) in the serum of pregnant women with PE and eclampsia was significantly increased. In another study, Yang et al.[9] reported that the accumulation of lipid peroxidation can inhibit a variety of cellular functions in trophoblast cells, including invasion, and participate in the pathogenesis of PE. These findings suggest that cellular ferroptosis is involved in the pathogenesis of PE, although the specific mechanisms underlying these observations remain unclear.

DJ-1 is a small molecular binding protein that is located in cell membranes. DJ-1 is an important sensor for the redox state in cells and a prerequisite for activating and stabilizing Nrf2 to allow translocation to the nucleus

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