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Research Progress on the Relationship between Ferroptosis and Insulin Resistance

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Abstract: *Insulin resistance (IR) is a core mechanism leading to obesity and metabolic dysfunction of diabetes, and is the main cause of type 2 diabetes (T2DM). However, the etiology and mechanism of IR are very complex, which has not been clarified yet. Ferroptosis is a new type of iron dependent cell death, which is different from apoptosis, necrosis, autophagy and other typical cell death. It is not clear whether there is a direct relationship between Ferroptosis and IR. At present, only a few studies have explored the relationship between Ferroptosis and T2DM. The article starts from the mechanism of the two, reveals the possible relationship between them, so as to increase the understanding of IR and Ferroptosis, and hopes to lay a foundation for further clarifying the mechanism of insulin resistance.*

Keywords: *Insulin resistance, Ferroptosis, Pathogenesis, Oxidative stress, Iron overload*

1. Introduction

According to the report of the International Diabetes Federation (IDF) in 2021[1], the number of DM patients will continue to grow year by year, and is expected to increase to 783.2 million by 2045, reaching 12.2% of the world's total population, of which Type 2 Diabetes (T2DM) can account for more than 90%. IR is a core mechanism leading to metabolic dysfunction in obesity and diabetes, and is the main cause of T2DM. Ferroptosis is a new type of iron dependent cell death, which is different from apoptosis, necrosis, autophagy and other typical cell death. The etiology and mechanism of IR are very complex, and it is not clear yet. At present, more and more studies have proved that Ferroptosis is related to diabetes and its multiple complications [2], but only a few studies have explored the relationship between Ferroptosis and IR, and its direct relationship has not yet been clear. Based on the mechanism of both, this paper reviews the relevant literature and reviews the latest consensus of Ferroptosis and IR to increase the understanding of IR and Ferroptosis, hoping to lay a foundation for further clarifying the mechanism of IR.

2. Ferroptosis

Ferotosis is a process in which iron dependent lipid peroxides accumulate and eventually lead to cell death, which was first proposed by Dixon et al. in 2012. FERROPTOSIS is different from typical cell death modes such as apoptosis, necrosis and autophagy in terms of mode of action, biochemical characteristics and genetic factors [3]. Its characteristics are mainly reflected in morphological and biochemical changes. The morphological changes are mainly reflected in the mitochondria. The mitochondria shrink obviously, the mitochondrial membrane density increases and the outer membrane breaks, and the mitochondrial crista decreases or disappears [3]. Biochemical changes are mainly due to

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the inhibition of the depletion of the cycstine/glutamateantiporter system (system Xc **-**) on the cell membrane, which causes the depletion of reduced glutathione (GSH) and glutathione peroxidase 4 (GPX4) in the cells, leading to a large amount of deposition of iron and lethal reactive oxygen species (ROS) [4-5].

2.1 Regulatory Mechanism of Ferroptosis

The regulatory mechanism of Ferroptosis is mainly the process of production and elimination of intracellular lipid peroxidation. Iron in cells and ROS and lipid peroxides produced by iron release can promote the occurrence of Ferroptosis. GPX4 can reverse regulate Ferroptosis by eliminating iron, ROS and lipid peroxides. When cells are unable to effectively remove excess ROS in cells through antioxidant mechanism, the accumulated oxidative lipids will induce Ferroptosis [5]. The physiological processes involved in regulating Ferroptosis mainly include iron, lipid and amino acid metabolism.

2.1.1 Iron Metabolism

Iron is an essential trace element for human body, which plays an important role in metabolism, energy production, DNA synthesis and other cellular levels, as well as in physiological and pathological processes in human body such as oxygen transport. Normally, the iron inside and outside the cell is coordinated and balanced through a special transport system and membrane carriers. Cells can control the intake, excretion, storage and transformation of iron to maintain normal iron homeostasis. Iron in cells exists in two forms: Fe^{2+} and Fe^{3+}. The iron in food is mainly Fe^{3+}, which combines with transferrin, enters cells through Transferrin Receptor 1 (TFR1) on the membrane, and is reduced to Fe^{2+} in cells [6]. Fe^{3+} is relatively stable as a form of iron storage and transportation. Fe^{2+} dissociates in the cytoplasm or combines with serum ferritin to form an iron pool. Ferritin in the iron pool (composed of two subunits of ferritin heavy chain and ferritin light chain, which are encoded by corresponding genes respectively [7]) can be encapsulated by autophagic lysosome under the guidance of nuclear receptor coactivator 4 (NCOA4), and then degraded and released a large amount of Fe^{2+} [8], which is called ferritin autophagy [9]. Fe^{2+} can participate in oxygen reaction and generate hydroxyl free radicals and hydrogen peroxide and other reactive oxygen species through Fenton chemical reaction. These reactive oxygen species and lipid peroxidation can induce iron death [10].

2.1.2 Lipid Metabolism

ROS is a group of active oxygen clusters with partial reducing oxygen, including peroxides, superoxide, singlet oxygen, free radicals, etc. They can cause cell death mainly by damaging DNA, RNA and lipid molecules [11]. The accumulation of ROS is the key link to induce Ferroptosis. Lipid peroxides, especially phospholipid peroxides, are the final executors leading to Ferroptosis. The accumulation of lipid peroxides is considered to be a landmark event of Ferroptosis [12]. The presence of polyunsaturated fatty acids (PUFAs), especially arachidonic acid (AA) and adrenaline acid (AdA), react with phosphatidylethanolamine (PE) under the action of special enzymes to generate excessive lipid peroxides, thus inducing Ferroptosis [13-14]. The compound AA/AdA **-** PE was synthesized from AA and AdA complexes via acylcoa synthase long 4 (ACSL4) and Recombinant Lysophosphatidyl choline Acyltransferase 3 (LPCAT3) respectively. Some studies have shown that reducing the expression of ACSL4 and LPCAT3 is helpful to inhibit Ferroptosis [5, 15-16]. Only when GPX4 is directly or indirectly inactivated, the highly oxidative PUFAs (such as AA) in the membrane can induce the development of cellular Ferroptosis [17].

2.1.3 Amino Acid Metabolism

GPX4 is a GSH dependent peroxidase, which can reduce lipid peroxides (LOOH) to lipid alcohols (L-OH), thus preventing ROS accumulation and inhibiting cell Ferroptosis [17-18]. GSH is a cofactor in the synthesis of GPX4. It is a tripeptide molecule synthesized by cysteine, glutamate and glycine in an ATP dependent form [19], and the synthesis of GPX4 requires two molecules of GSH. Therefore, the level of GSH in cells is crucial to the activity of GPX4. The exchange of extracellular cystine and intracellular glutamic acid depends on system Xc^-, which is formed through disulfide bond connection between light chain subunit (solid carrier family7A11, SLC7A11 is also called x-CT) and heavy chain subunit (solid carrier family3member2, SLC3A2) [20-21]. Cystine enters cells and is reduced to cysteine to synthesize GSH, thus regulating the downstream lipid peroxidation process. Therefore, cysteine directly restricts the biosynthesis of glutathione [3]. The imbalance of amino acid metabolism caused by inhibition of system Xc^- will lead to Ferroptosis. Moreover, glutamate itself can also affect the function of system Xc^-. When the concentration of extracellular glutamate is high enough, it can inhibit system Xc^-, thus inducing Ferroptosis [22]. Under reducing conditions, cysteine can be directly transported into

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cells through the alanine-serine-cysteine (ASC) system, thereby inhibiting iron death [22].

3. IR

The essence of IR is insulin mediated glucose metabolism dysfunction, which was first proposed by Himsworth in the 1930s [23]. When insulin resistance occurs, the effector organs of insulin (such as adipose tissue, skeletal muscle and liver) produce lower than normal biological effects on normal dose of insulin. IR is a core mechanism leading to metabolic dysfunction in obesity and diabetes, and is the main cause of T2DM.

3.1 Pathogenesis site of IR

There are three sites that cause IR, namely, the functional defects of insulin receptor pre, receptor and post receptor levels. Among them, the most common site is the functional defect of post receptor level, which refers to the abnormality of transmembrane signal transduction after insulin binds to the receptor. At present, it is found that there are mainly three related signaling pathways: phosphatidylinositol 3 kinase (PI3K) pathway, mitogen activated protein kinase (MAPK) pathway and Cap-Cb1 related protein (CAP/Cb1) pathway [24-25]. The functional defect of insulin receptor pre level means that IR has appeared before insulin has combined with insulin receptor, such as insulin gene mutation, multiple endogenous or exogenous insulin antibodies generated in the body, and rapid insulin degradation [26-27]. Defects at the receptor level can be divided into receptor functional abnormalities (such as the reduction of the number of insulin receptors) and structural functional abnormalities (such as gene mutation) [28].

3.2 Hypothesis of pathogenesis

The etiology and mechanism of IR are very complex and have not been fully elucidated. At present, there are two mainstream hypotheses about the mechanism of IR, namely, inflammatory hypothesis and hypothesis of signal transduction [29].

3.2.1 Inflammatory hypothesis

Many studies have shown that inflammation may be one of the pathogenesis of IR [30-32]. There are two main mechanisms of the inflammation hypothesis. On the one hand, inflammatory factors interfere with the insulin signal transduction system. Some studies have shown that in the case of chronic inflammation, the secretion of inflammatory factors such as IL-TNF-CRP increases in the body, which decreases the rate of the tyrosine phosphorylation of insulin receptor, thereby weakening the biological effect of insulin [33]. And TNF- α can activate C-Jun N-terminal kinase (JNK), and enhance the expression of Ser307 phosphorylation of IRS-1, and reduce the expression of tyrosine phosphorylation of IRS-1, thus causing IR [34]. On the other hand, inflammation leads to endothelial dysfunction [35-36].

3.2.2 Hypothesis of Signal transduction

The signal transduction hypothesis mainly refers to the impairment of insulin signaling pathway. IR is mainly caused by abnormal phosphorylation or insufficient expression of insulin receptor. For example, studies have shown that overexpression of protein kinase C (PKC) can induce phosphorylation of IRS-1 serine, and negative feedback regulates tyrosine phosphorylation of IRS-1 to reduce its expression, thereby weakening signal transduction of PI3K pathway [37-38]. It has also been shown that protein tyrosine phosphatase non receptor type 1 (PTPN1) can phosphorylate tyrosine residues of insulin receptor, leading to the decrease of insulin receptor activity, signal transduction and insulin biological response, thus causing IR [39-40]. Evans et al. found that oxidative stress can activate threonine kinase, block insulin action signal pathway and reduce insulin sensitivity in peripheral tissues to cause IR [41].

3.2.3 Other hypotheses

At present, some studies have shown that obesity [42], leptin resistance [43], vitamin D [44-46], smoking [47], mitochondrial dysfunction [48] and other factors can also cause IR, but the relevant molecular mechanism is still controversial, and the specific mechanism needs further study.

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4. The Relationship Between Ferroptosis and IR

At present, the relationship between the mechanism of Ferroptosis and of IR is not clear, but through the above overview, we can find that the mechanisms of both have a lot in common, and more and more studies have proved that Ferroptosis is related to multiple complications of diabetes [49]. How IR causes Ferroptosis and how Ferroptosis affects the occurrence and development of IR have not been fully clarified. Now through the existing research, the relationship between them is analyzed and elaborated from the following aspects.

4.1 Oxidative Stress

Oxidative stress is a pathological state in which the production of active oxides exceeds the clearance and breaks the redox balance. When the blood sugar rises in the body, mitochondria will produce a large amount of ROS, and the mitochondrial function will be damaged, thus causing oxidative stress reaction, which is an important factor in the occurrence of T2DM. In addition, in the high glucose state, antioxidants such as GSH will be consumed in large quantities, which will further lead to the accumulation of ROS. Oxidative stress can activate threonine kinase, block the insulin action signal pathway, and reduce the sensitivity of peripheral tissue to insulin to cause IR [21]. Some studies have shown that, the IR can be improved by removing a large amount of ROS and restoring the balance of oxidation and reduction [50]. The depletion of GPX4 with GSH as substrate and the accumulation of ROS are very important in the mechanism of Ferroptosis. It has also been shown that curcumin and epigallocatechin gallate (EGCG), two polyphenols, as well as quercetin, can protect mouse pancreaticβcells from iron poisoning and Erstin induced Ferroptosis. The mechanism is to act as an iron complexing agent to prevent GSH depletion and lipid peroxidation [51-52]. Ellagic acid (EA) can improve the insulin resistance of HepG2 cells treated with oxidative stress and high glucose through miR-223/keap1-Nrf2 pathway [53].

4.2 Iron Overload

Fat, liver and skeletal muscle are all important organs regulating glucose metabolism. Iron ions can participate in and promote lipid oxidation, especially the oxidation of free fatty acids. The increase of free fatty acid oxidation will reduce the use of glucose in muscle tissue and increase the gluconeogenesis of liver to cause IR [54]. In the regulatory mechanism of Ferroptosis, the large release of $Fe2^{+}$ is a key link. Moreover, the relationship between IR and iron has been revealed in early studies [55]. It is reported that the accumulation of iron can promote the production of ROS in large quantities, thus causing IR of myocardial cells [56]. There is also a hypothesis that excessive iron storage in the human body will increase the risk of T2DM [57-58]. For example, the mouse model of hereditary hemochromatosis that leads to iron overload shows that iron deposition in skeletal muscle, fatty acid oxidation increases, glucose oxidation decreases, and finally increases IR [59-60]. From the perspective of improving diabetes, some studies have shown that insulin secretion and insulin sensitivity have improved, and blood sugar has also been better controlled after reducing the level of iron storage in the body [61-62]. However, it is not completely reliable to calculate the iron storage in the body by the level of serum ferritin, because ferritin can also increase in inflammation, cancer and liver disease [63]. Therefore, it is still unclear whether the ferritin in the blood is the cause or the result of diabetes.

4.3 Mitochondrial dysfunction

When the structure, quantity and activity of mitochondria change, it will cause mitochondrial dysfunction, which will also lead to IR. Studies have shown that IR caused by abnormally high triglyceride levels in liver and muscle is often accompanied by mitochondrial dysfunction such as decreased mitochondrial oxidation activity and ATP synthesis [64]. The morphological change characteristics of Ferroptosis are also reflected in mitochondria, such as obvious shrinkage of mitochondria, increase of mitochondrial membrane density and rupture of outer membrane, reduction or disappearance of mitochondrial crista, etc. At present, there is still some controversy about the occurrence of IR due to mitochondrial dysfunction. Whether the morphological changes of mitochondria in Ferroptosis have an impact on IR remains to be studied. However, studies have shown that FeS clusters can regulate the iron homeostasis of mitochondria [65]. The accumulation of iron in mitochondria caused by the lack of iron sulfur clusters can further lead to the production of ROS in mitochondria [66], and then Ferroptosis occurs due to the accumulation of lipid peroxidation [67]. This is the focus of current research, which needs to be further studied in the future to determine whether the two are related.

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5. Conclusion and Perspective

As a new way of programmed cell death, Ferroptosis is different from cell apoptosis, necrosis, and autophagy. It is a kind of cell death caused by iron dependent lipid structure peroxidation through abnormal intracellular iron metabolism. Although there are many studies on Ferroptosis, diabetes and its complications, they are still in the early stage. Most of the studies are just revealing that Ferroptosis occurs in various complications of diabetes. The research on its mechanism is not deep enough, and many problems have not yet been solved. For example, the relationship between IR and Ferroptosis, how Ferroptosis interacts with IR, and these related mechanisms need to be further clarified. Ferroptosis is related to changes in many signaling pathways, and the mechanism of the relationship between Ferroptosis and IR may be different in different tissues. Therefore, it is possible to provide new molecular targets for the prevention and treatment of IR by further studying the mechanism of Ferroptosis and IR and clarifying their related signal pathways.

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