ISSN: 2710-0588 DOI: 10.29556/FSE.202203_2(3).0003

Role and Mechanisms of Ferroptosis in Diabetic Cardiomyopathy

Liangxiu Wu[1], Fangfen Li[2], and Xiaobing Gong[1,*]

[1] Department of Gastroenterology, The First Affiliated Hospital of Jinan University, Guangzhou 510000, China

[2] Department of General Practice, The First Affiliated Hospital of Jinan University, Guangzhou 510000, China

Abstract

Diabetic cardiomyopathy (DCM) is an independent cardiomyopathy that occurs in diabetic patients and is characterized by changing in myocardial structure and function. However, the pathogenesis of DCM is not fully understood. Ferroptosis, a newly discovered regulatory cell death, is s an iron-dependent form of regulated cell death, which differs from other types of cell death in terms of biochemistry, cell morphology, and genetics. Recently, ferroptosis has been shown to be closely associated with the occurrence and progression of DCM. Inhibition of ferroptosis may become a new therapeutic strategy for the treatment of DCM. In this article, we briefly describe the role of ferroptosis in the progression of DCM and its associated mechanisms. This review will highlight further directions for the treatment of DCM and the selection of corresponding drugs to target ferroptosis.

Keywords

Ferroptosis; Diabetic Cardiomyopathy; Reactive Oxygen Species.

1. Introduction

Diabetes is closely related to the occurrence and development of cardiovascular diseases, and is an independent risk factor for cardiovascular complications, increased risk of mortality after myocardial infarction, and increased risk of heart failure 1. Diabetic cardiomyopathy (DCM), a serious diabetic cardiovascular disease, is a special disease of abnormal heart structure and dysfunction in diabetic patients except uncontrolled hypertension, coronary artery disease, severe valvular disease and congenital heart disease 2. Hyperglycemia, fatty acids, insulin resistance, inflammation, oxidative stress, hypertrophy and myocardial fibrosis, mitochondrial dysfunction, endothelial dysfunction, and endoplasmic reticulum stress may be the molecular basis of DCM.

Ferroptosis is recently classified as an form of regulated cell death characterized by the iron-dependent accumulation of lipid hydroperoxides. When ferroptosis occurs, cell cytoplasm presents round and detached, mitochondrial membrane densities condense, mitochondria crista reduces or vanishes, and outer mitochondrial membrane ruptures 3. Previous studies have shown that ferroptosis is closely associated with complications of diabetes, such as diabetic nephropathy and diabetic cardiomyopathy 4, 5. To date, the role of ferroptosis in the development and progression of diabetic cardiomyopathy have not been fully elucidated. Therefore, in this review, we briefly discussed the role of ferroptosis in diabetic cardiomyopathy, with emphasis on the prevention and treatment of new areas of potential research this kind of common and heavy heart disease.

ISSN: 2710-0588 DOI: 10.29556/FSE.202203_2(3).0003

2. Regulation of Ferroptosis

Ferroptosis has recently been identified as a non-apoptotic cell death pathway driven by iron-mediated production of reactive oxygen species (ROS) and subsequent lipid peroxidation (LPO). Iron is an essential element in all living organisms. Iron is closely associated with a wide range of biological processes, including oxygen transport via hemoglobin in red blood cells, DNA synthesis, cellular respiration and electron transport, and overall metabolism 6. The redox properties of iron facilitate the production of reactive oxygen species (ROS) including the most toxic hydroxyl radical 7. In addition, both ferrous (Fe2+) and ferric (Fe3+) iron mediate lipid peroxidation, resulting in the formation of peroxyl (RO2) and alkoxyl (RO)radical 8. These free radical byproducts can also participate in reoxidation reactions in the cytoplasm and mitochondria, which damage DNA, proteins and lipids. Iron may increase the active hydroxylase of lipoxygen (ALOX) or EGLN prolyl, which is responsible for the dynamic balance between lipid peroxidation and oxygen homeostasis, thus further regulating ferroptosis. These may eventually increase oxidative damage through fenton reactions. At the same time, iron metabolism is also regulated by a variety of factors. Oxidative stress increases the synthesis of nuclear factor erythrocyte 2-associated factor 2 (Nrf2) and activates the Nrf2-mediated antioxidant defense system 9. Meanwhile, most genes involved in iron metabolism, such as ferritin heavy chain (FTH), ferritin light chain (FTL), TF, FPN and hemoxygenase-1 (HO-1), can be regulated by Nrf2.

Cell death caused by ferroptosis is carried out by phospholipid peroxidation, arachidonic acid -(AA-) OOH and phosphatidylethanolamine (PE) are the most important signals of ferroptosis 10. Specifically, the process from AA to AA-COA is driven by acyl-coA synthase long chain family 4 (ACSL4), resulting in the formation of lipid peroxidation products (such as 4-hydroxynonenal and malondialdehyde) and oxidized and modified proteins , which ultimately lead to the destruction of membrane integrity 11. ACSL4, as a essential indicator and regulator of ferroptosis, is a key determinant of the sensitivity of ferroptosis by regulating cell (phosphorus) lipid composition 11. Glutathione peroxidase 4 (*GPX4*) is a lipid repair enzyme that can catalyze glutathione (*GSH*) to oxidized glutathione disulfide (GSSG), eliminate lipid peroxides, and protect cell membrane against peroxidation of polyunsaturated fatty acids. Thus, *GPX4 is* a common biomarker *of* ferroptosis. GSH is a cofactor of GPX4 and consists of three subunits which are glutamate, glycine and cysteine. Inhibition of cystine undersupply by the XC – system leads to reduced cysteine production and consumption of GSH, ultimately inhibiting the normal activity of GPX4 in the prevention of ferroptosis 12. Therefore, the above mechanisms can be used as a mechanism to regulate ferroptosis and influence the development of disease.

3. Diabetic Cardiomyopathy

Diabetic cardiomyopathy is a myocardial disease characterized by early ventricular diastolic dysfunction and late ventricular systolic dysfunction in the absence of hypertension and coronary artery disease 13.The pathogenesis of diabetic cardiomyopathy is multi-factor and complex. Ferroptosis was coined in 2012 to describe a specific form of cell death by the small molecule Erastin that inhibits cystine input, resulting in glutathione depletion and inactivation of the phospholipid peroxidase glutathione peroxidase 14. Ferroptosis involves metabolic, genetic, and protein regulatory, triggering, and enforcement mechanisms that have not overlap to a large extent with other regulated forms of cell death 15. Oxidative stress, imbalance of ROS production and antioxidant capacity have been widely accepted as a common mechanism leading to diabetic cardiomyopathy . Under normal physiological conditions, ROS production in the heart is low, and they are effectively eliminated by the body's natural antioxidant defenses, such as the superoxide dismutase and glutathione cycle. The excessive production of ROS in diabetes is the main pathogenic factor for the occurrence and development of DCM 16. In the

ISSN: 2710-0588 DOI: 10.29556/FSE.202203_2(3).0003

condition of diabetes, the body produces excessive ROS, through a variety of ways, including mitochondrial dysfunction, uncoupling of nitric oxide synthase, endoplasmic reticulum stress, enzyme activation , leading to hypertrophy of cardiac myocytes and severe death 17. Nrf2 normally maintains metabolism by controlling the expression of selected genomes associated with iron to achieve redox homeostasis and lipid metabolism, as well as redox equilibrium in the heart. Nrf2 and its downstream signaling pathways are key in preventing high glucose-induced oxidative damage in the cardiovascular system. Zang, H. et al. found that Nrf2-regulated metabolism is interrupted when cardiac autophagy becomes inadequate, promoting ferroptosis in cardiomyocytes and exacerbating the progression of cardiomyopathy in patients with type 1 diabetes. Fsp1 has for a long time been regarded as a specific marker for cardiac fibroblasts. Meanwhile, glucolipid toxicity is likely to inhibit Fsp1 expression by activating Nrf2-driven ACSL4 transcription and Nrf2-operated Gpx4 transcription, then destroying Nrf2-coordinated iron metabolism gene network, thus leading to ferroptosis on cardiomyocytes and promoting the progression of diabetic cardiomyopathy 5. Many natural and synthetic activators of Nrf-2 have been shown to favorable therapeutic effects on DCM in animal models of DCM 18. DCM is an indispensable pathophysiological state of diabetes patients, and ultimately cardiac dysfunction characterized by left ventricular longitudinal dysfunction, as well as the direct cause of heart failure. Previous studies have found that ZFAS1 is upregulated in DCM and HG treated cardiomyocytes, and inhibition of ZFAS1 may inhibit ferroptosis in cardiomyocytes by sponging miR-150-5p to activate CCND2, potentially alleviating myocardial fibrosis in DCM 19. These results suggest that ferroptosis may be related to the pathogenesis of DCM.

Many studies indicates that ferroptosis may be related to the formation of DCM to a certain extent, but the exact mechanism is still unclear, however, it can be used as a new approach for the treatment of DCM in the future.

4. Conclusion

Ferroptosis is an iron-dependent non-apoptotic form of cell death, which is closely related to the occurrence and development of diabetic complications, especially DCM. However, we suggest that further mechanistic studies are needed to better understand the role of ferroptosis in DCM. Nevertheless, the study of ferroptosis in DCM is still at a relatively early stage, and the specific mechanism, node molecules and related signaling pathways remain unclear. Therefore, the exploration of ferroptosis in diabetic cardiomyopathy will provide new ideas for its clinical prevention and treatment.

References

[1] Eckel, R.H., Kahn, R., Robertson, R.M. & Rizza, R.A. Preventing cardiovascular disease and diabetes: a call to action from the American Diabetes Association and the American Heart Association. Circulation 113, 2943-2946 (2006).

[2] Dillmann, W.H. Diabetic Cardiomyopathy. Circ Res 124, 1160-1162 (2019).

[3] Xie, Y. et al. Ferroptosis: process and function. Cell Death Differ 23, 369-379 (2016).

[4] Li, S., Zheng, L., Zhang, J., Liu, X. & Wu, Z. Inhibition of ferroptosis by up-regulating Nrf2 delayed the progression of diabetic nephropathy. Free Radic Biol Med 162, 435-449 (2021).

[5] Zang, H. et al. Autophagy Inhibition Enables Nrf2 to Exaggerate the Progression of Diabetic Cardiomyopathy in Mice. Diabetes 69, 2720-2734 (2020).

[6] Abbaspour, N., Hurrell, R. & Kelishadi, R. Review on iron and its importance for human health. J Res Med Sci 19, 164-174 (2014).

[7] Aisen, P., Enns, C. & Wessling-Resnick, M. Chemistry and biology of eukaryotic iron metabolism. Int J Biochem Cell Biol 33, 940-959 (2001).

ISSN: 2710-0588 DOI: 10.29556/FSE.202203_2(3).0003

[8] Valko, M., Jomova, K., Rhodes, C.J., Kuca, K. & Musilek, K. Redox- and non-redox-metal-induced formation of free radicals and their role in human disease. Arch Toxicol 90, 1-37 (2016).

[9] Majzunova, M., Dovinova, I., Barancik, M. & Chan, J.Y. Redox signaling in pathophysiology of hypertension. J Biomed Sci 20, 69 (2013).

[10] Kagan, V.E. et al. Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis. Nat Chem Biol 13, 81-90 (2017).

[11] Doll, S. et al. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. Nat Chem Biol 13, 91-98 (2017).

[12] Imai, H., Matsuoka, M., Kumagai, T., Sakamoto, T. & Koumura, T. Lipid Peroxidation-Dependent Cell Death Regulated by GPx4 and Ferroptosis. Curr Top Microbiol Immunol 403, 143-170 (2017).

[13] Bugger, H. & Abel, E.D. Molecular mechanisms of diabetic cardiomyopathy. Diabetologia 57, 660-671 (2014).

[14] Yang, W.S. et al. Regulation of ferroptotic cancer cell death by GPX4. Cell 156, 317-331 (2014).

[15] Dixon, S.J. et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell 149, 1060-1072 (2012).

[16] Thandavarayan, R.A., Giridharan, V.V., Watanabe, K. & Konishi, T. Diabetic cardiomyopathy and oxidative stress: role of antioxidants. Cardiovasc Hematol Agents Med Chem 9, 225-230 (2011).

[17] Shah, M.S. & Brownlee, M. Molecular and Cellular Mechanisms of Cardiovascular Disorders in Diabetes. Circ Res 118, 1808-1829 (2016).

[18] Zhou, S. et al. Potential drugs which activate nuclear factor E2-related factor 2 signaling to prevent diabetic cardiovascular complications: A focus on fumaric acid esters. Life Sci 134, 56-62 (2015).

[19] Ni, T., Huang, X., Pan, S. & Lu, Z. Inhibition of the long non-coding RNA ZFAS1 attenuates ferroptosis by sponging miR-150-5p and activates CCND2 against diabetic cardiomyopathy. J Cell Mol Med 25, 9995-10007 (2021).