Ferroptosis's Newly Discovered Roles in Cardiovascular Disorders

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Abstract

Cardiovascular Diseases (CVDs) have a complicated process that jeopardises human health. Cardiomyocyte death plays a significant role in the pathophysiology of CVDs. A novel kind of iron-dependent programmed cell death called ferroptosis is brought on by aberrant iron metabolism, excessive accumulation of iron-dependent lipid peroxides, and reactive oxygen species (ROS). The recognised cell death processes of apoptosis, necrosis, necroptosis, autophagy, and pyroptosis are all different from ferroptosis. It has been demonstrated that a number of substances can either cause or prevent ferroptosis by controlling relevant critical players or signalling pathways. In order to stimulate the development of new therapeutic approaches, we have outlined the traits and associated mechanisms of ferroptosis in this review and highlighted its contribution to CVDs.

Keywords: Cardiovascular diseases • Surge responses • Atherosclerosis

Introduction

The heart can pump blood to every region of the body and supply oxygen and nutrients to other organs and tissues as the blood's power source. It is one of the most important organs in the human body. However, the incidence and mortality of CVDs are rising every year, especially in emerging nations, and CVDs have overtaken all other causes of death due to an unhealthy food pattern and lifestyle as well as the acceleration of ageing. Heart failure (HF), myocardial hypertrophy, atherosclerosis (AS), hypertension, Diabetic Cardiomyopathy (DCM), and doxorubicin (DOX)-induced cardiomyopathy are the most common CVDs (DIC). Three-quarters of the volume of the mammalian heart is made up of cardiomyocytes, which make up the biggest amount of the tissue. Individual cardiac function is also somewhat influenced by the condition of cardiomyocytes. It is important to note that in adult animals, the ability of cardiomyocytes to proliferate in vivo becomes constrained, and harmful environmental variables will determine the fate of cardiomyocytes. Cell death is a stress reaction triggered by outside damaging stimuli. Cardiomyocyte death has a crucial physiological role in controlling heart senescence, development, and homeostasis. Apoptosis, necrosis, necroptosis, autophagy, pyroptosis, and ferroptosis are among the more prevalent types of cell death that have recently been identified. Most cardiac cell death is under the direction of a complex regulatory network. Cell atrophy, a rise in cytoplasmic density, the disappearance of Mitochondrial Membrane Potential (MMP), a change in permeability, and the formation of an entirely apoptotic body are the primary characteristics of apoptosis. Necrosis is typically an unplanned and uncontrolled type of cell death that occurs in response to physical or chemical injury. Specific signalling networks are also responsible for controlling necroptosis.

Necroptosis is mostly regulated by the death receptor TNFR1. In order to maintain intracellular metabolic balance, autophagy is a prosurvival mechanism that transports unneeded or damaged cellular components to lysosomes for destruction. The process of pyroptosis is thought to be an inflammatory and controlled type of cell death that typically takes place during the body's defence against foreign invaders such viruses, bacteria, and fungi. Iron is an essential metal found in the human body. About 72% of the iron in the body is found in haemoglobin, 3% is myoglobin, and 0.2% is present in other compounds. The remaining 25% of the iron is reserve iron, which is kept in the liver, spleen, and bone marrow as ferritin. Oxygen transport, cell respiration and electron transfer, DNA synthesis, immunological control, and other functions essential to life all involve iron. Numerous physiological processes become distorted as a result of iron metabolism that is aberrant. When lipid peroxides build up to deadly amounts, the condition known as ferroptosis occurs. This causes oxidative damage to cell membranes. In terms of shape and mechanism, ferroptosis is different from other types of cell death. Ferroptosis is said to be a major factor in CVDs in an increasing number of studies. In this review, we outline the mechanism of ferroptosis and highlight the development of the field's understanding of the condition in relation to CVDs in order to offer suggestions for creative therapeutic approaches.

Overview of ferroptosis mechanisms

Research has shown that the Ras-Selective Lethal (RSL) chemical can also cause cell death, and that the application of inhibitors of apoptosis, necroptosis, autophagy, and pyroptosis cannot prevent the cell death caused by RSL. An iron-chelating substance, however, might stop this process. Therefore, it is thought that this novel type of cell death is iron-dependent. In vivo, iron is a critical cofactor in the metabolism of numerous enzymes and a catalyst for REDOX cycle events, contributing to a variety of vital physiological and biochemical activities. Ferroptosis can be caused by a variety of physiological circumstances as well as pathological stress. Among these, improper iron metabolism and lipid peroxidation are significant causes of ferroptosis, and the main mechanism controlling it is the active state of System Xc and Glutathione peroxidase 4 (GPX4). Here, we provide a summary and further details about ferroptosis' regulating mechanism.

Iron metabolism

Because it plays a crucial role in the manufacture of numerous essential proteins and enzymes, iron, a fundamental element in living things, is necessary for all life processes. One of the crucial stages of ferroptosis is intracellular iron excess brought on by aberrant iron metabolism. Iron is mostly found as ferric ions (Fe3+) in in vivo circulation. When Fe3+ binds to transferrin, membrane transferrin receptor 1 specifically recognises it and transports it inside of cells (*TfR1*). The ferrous ion (Fe2+) is reduced by the six-transmembrane epithelial antigen of prostate 3 (*STEAP3*) and subsequently released into the cytoplasmic unstable iron pool with the aid of the divalent metal transporter 1 (*DMT1).* The iron pool can hold Fe2+ as well as ferric proteins produced by REDOX processes, such heme. To maintain the dynamic equilibrium of iron, ferroportin mediates intracellular iron output. Excess iron will remain intracellular as ferritin. To counteract cell damage brought on by an excess of iron, ferritin typically displays non-REDOX activity. However, too much iron can trigger Fenton and Haber-Weiss reactions, which build up ROS and cause cells to produce ferroportin. When H-RasV12 mutant fibrosarcoma cells are treated with erastin, TfR1 is upregulated, increasing iron absorption. Iron overload is also brought on by downregulation of the intracellular ferritin heavy-chain 1 (*Fth1*) and ferritin light-chain 1 (*Ftl1*) proteins. Inhibiting ferritin degradation and lowering free iron levels are achieved via low expression of the nuclear receptor coactivator 4 (*NCOA4*) or autophagy-related (*ATG*) genes, which in turn limits the oxidative damage brought on by ferroptosis. The crucial transcription factor nuclear factor erythroid 2-related factor 2 (*Nrf2*) is a key regulator of maintaining intracellular redox equilibrium as well as the cellular response to oxidative stress.

Lipid peroxidation

The presence of lipid peroxidation is a key indicator of ferroptosis. Overproduction of lipid peroxides can result in the lipid bilayer losing its integrity and the cell membrane rupturing. The degree of the lipid bilayer's unsaturation has an impact on how susceptible cells are to ferroptosis. Polyunsaturated Fatty Acids (PUFAs) are the ones that are most prone to peroxidation. The amount of intracellular lipid peroxidation is influenced by the location and composition of PUFAs, which in turn influences how severe ferroptosis is. The esterification process, which is carried out by acyl-coenzyme A (acyl-CoA), attaches PUFA to the sn-2 position of phospholipids.

Acyl-CoA synthase long-chain family member 4 (*ACSL4*) catalyses the formation of PUFA-CoA from the binding of long-chain PUFA (LC-PUFA) and adrenergic acid, which makes it easier for LC-PUFA to enter lipids and membranes. Lysophosphatidylcholine acyltransferase 3 (*LPCAT3*) then converts it into esterified anionic membrane phospholipids, which alters the remodelling of membrane phospholipids and impacts cell ferroptosis. Tammo et al. discovered that blocking *ACSL4* might lower phospholipid-PUFA levels and prevent ferroptosis brought on by *RSL3*.

Inducers and inhibitors

An essential type of cell death known as ferroptosis differs from other types of cell death in terms of appearance and biochemistry. Ferroptosis is caused by a complex network of signalling pathways and important variables. The creation and breakdown of several essential components can be controlled, which can alter how sensitive cells are to ferroptosis. To cure and improve tumours and CVDs, reasonable activation or inhibition of cell ferroptosis is useful. Ferroptosis has been discovered to be induced or inhibited by a number of medications or substances. Further research is still needed on the targets and possible uses of these inducers or inhibitors. Additionally, for some drugs having many targets, a better understanding of their processes, consideration of medication combinations, and creation of more focused inducers or inhibitors would improve the likelihood of their use in clinical therapy.

Ferroptosis with CVDs

The pathogenic mechanism of CVDs is complicated and involves numerous types of cell death. Ferroptosis has recently been demonstrated to be a significant factor in CVDs in ongoing studies. By controlling crucial ferroptosis-related variables and modifying the sensitivity of cells to ferroptosis, researchers often determine the effect of ferroptosis in relevant CVDs. Here, we provide a summary of the relationships between major CVDs, including MI, reperfusion injury, AS, hypertension, cardiac hypertrophy, HF, DCM, and DIC, and ferroptosis. The term MI describes damage to the coronary artery brought on by acute and/or ongoing ischaemia and hypoxia. Currently, MI has steadily risen to the top of the list of killers of CVD patients globally. According to earlier studies, the main negative effects of MI are cardiomyocyte apoptosis, necrosis, and autophagy. Recent research, however, indicates that the expression of *GPX4* is markedly reduced in the early and middle phases of MI, which raises the possibility that MI can result in ferroptosis in cardiac cells. Since *BACH1* / animals are more resistant to MI than wild-type mice, it is believed that these transcription factors BTB and CNC homology 1 (*BACH1*) induce ferroptosis at the transcriptional level. Ferroptosis also frequently causes inflammation, which aggravates cardiac dysfunction and results in inadequate myocardial remodelling following MI. Therefore, preventing cardiomyocyte ferroptosis may be an unique approach to treating MI and enhancing cardiac function.

Discussion

Human health and quality of life are threatened by CVDs. Formulating heart protection methods requires an understanding of how cardiomyocyte injury contributes to the pathological process of heart-related disorders. The pathogenic function of iron excess in cardiotoxicity has received a lot of attention recently. Ferroptosis is an iron-dependent programmed cell death with two obvious biochemical characteristics: intracellular iron buildup and lipid peroxidation, in contrast to the previously identified kinds of cell death, such as apoptosis, necrosis, autophagy, and pyroptosis. System Xc, *GPX4*, lipid peroxidation, and iron metabolism all play significant roles in the control of pathways relevant to ferroptosis. Intracellular iron excess is mostly caused by abnormal iron metabolism, and lipid peroxidation is a key indicator of ferroptosis. Another crucial indicator of ferroptosis is *GPX4*, a crucial component of System Xc, which forms the metabolic pathway for ferroptosis. The research of ferroptosis, a novel kind of programmed cell death, includes disorders of the neurological system, kidney-related disorders, tumours, and cardiovascular disorders. Numerous substances reduce iron buildup, control oxidative stress, and prevent lipid peroxidation to alleviate ferroptosis in cardiomyocytes and cardiac dysfunction in CVDs. However, the precise microscopic response targets of these ferroptosis inhibitors are unclear, and it is still unknown whether they may be hazardous to other organs, which restricts their therapeutic use in the management of CVDs. Studies on ferroptosis currently largely use cell and animal models, and there is still a dearth of experimental validation in vivo. ROS signals frequently become unbalanced or abnormally elevated during ferroptosis, which has an impact on inflammatory signal transmission and cell metabolism.

However, a thorough explanation of the precise chemical mechanism by which ROS produce ferroptosis is lacking. ROS levels, iron levels, cell viability, and certain associated marker proteins were employed in assays to assess ferroptosis. The proper monitoring of ferroptosis progression in vivo is still lacking. It will benefit the prevention and treatment of CVDs if a specialised probe or ferroptosis-related kit can be developed. Additionally, more ferroptosis-related molecular pathways need to be uncovered. Research on the mechanism of ferroptosis is made more difficult by Gu et aldiscovery .'s that p53 participates in the nonclassical pathway of ferroptosis regulation. Ferroptosis is implicated in the pathophysiology of CVDs, indicating that it may provide a new target for pharmacological therapy. However, more work needs to be done before its practical use may be realised.

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