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# Modernized Divination into Ferroptosis

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***Abstract:*** ***Ferroptosis is sort of programmed necrobiosis characterized by the involvement of labile iron the buildup of super molecule peroxidation. Ferroptosis could also be provoke by aerophilic stresses or numerous chemical agents that inhibit with cellular protecting mechanism. The super molecule peroxidation from aerophilic stresses achieve by NADPH oxidase(s) (noxs) that's typically mended by peroxidase four (GPX4) victimization the glutathione as a co-factor. Therefore, Ferro ptosis are often lured by wipe-out of amino acid (limiting part for glutathione synthesis), restraint of GPX4, or activation of noxs. As an example, the canonical Ferro ptosis inducer, elastin, is an interception of aminoalkanoic acid-glutamate transporter (xct) that lower cysteine import and depletes glutathione1. The connectedness of Ferro ptosis human diseases, also as cancer, ischemia-reperfusion, neurodegeneration is currently inheritable attention. Inducing Ferro ptosis also can have therapeutic potential toward cancer. However, the biological progresses, the underlying mechanisms and regulators of Ferro ptosis stay unknown.***
***Keywords: Ferroptosis, NADPH oxidase[s] [noxs], [GPX4], iron, cysteine, lipid peroxidation, cell death, metabolism, chemical biology***

## I. INTRODUCTION

Death could be a law of common fate of all life, from organisms to cells. The understanding that death is regulated by molecular mechanisms and might yield physiological advantages and pathological consequences for cellular organisms emerged early within the Nineteen Sixties, with the thought of 'programmed cell death' [1–3]. It's currently established that such programmed death is vital for traditional development and homeostasis and, once deregulated, contributes to a variety of pathological conditions. Regulated death is written as a death technique that depends on dedicated molecular machinery, which may be modulated (delayed or accelerated) by specific drugs and genetic interventions. Programmed death refers to physiological instances of regulated death that occur among the context of development and tissue equilibrium, among the absence of any exogenous perturbations. Programmed death is therefore a bunch of regulated death. Regulated death is employed to elucidate death that originates from perturbations of the living thing or living thing microenvironment, dead by molecular mechanism once totally different adaptive responses are incapable of restoring cellular equilibrium [4]. Regulated necrobiosis is thus mechanistically distinct from classic, or unregulated cell death caused by stress, comparable to dramatic heat shock, use of detergents, pore forming reagents, or extremely reactive alkylating agent.

## II. EARLY OBSERVATIONS CONSISTENT WITH FERRO PTOSIS.

Ferroptosis has been discovered variety of times over the years before the ornate molecular understanding of this death technique, and thus the conception that it exists. Yet, till it had been termed in and of itself in 2012 reports describing what we tend to presently recognize as death with ferroptotic characteristics were attributed to different death mechanisms, or not recognized as being biologically vital. Maybe, metabolic dependencies resulting in cell death. At the centre of ferroptosis could be a method of fatal macromolecule peroxidation, which is that the aerobic addition of molecular chemical element (O2) to lipids, such as unsaturated fatty chemical group tails in phospholipids. The primary descriptions of such accelerator reactions were in 1955 by Peterson and colleagues' [5] and Rothberg and colleagues [6] independently; since then, macromolecule peroxidation by lipoxygenases' and alternative mechanisms for the peroxidation of lipids have received a good deal of attention in numerous biological contexts [7-8].The term ferroptosis was coined in 2012 [9], to elucidate this iron-dependent, non-apoptotic kind cell death elicited by erastin and RSL3. This discovery was within the center of the event of the first very little molecule ferroptosis substance, termed ferrostatin-1, and additionally the demonstration of glutamate-induced ferroptosis in organotypic rat brain slices, suggesting the potential operate of ferroptosis in neurodegeneration.

## III. BASIC MECHANISM OF FERROPTOSIS.

The role of aerophilic stress in death has been studied for a few time. Pioneering studies within the 1950's by Harry Eagle and colleagues examined the amino acids, vitamins and different nutrients needed to support the expansion and proliferation of class cells in culture [10].

Among those determined to be essential was aminoalkanoic acid (Cys2), the change variety of the thiol-containing aminoalkanoic acid amino acid (Cys) [10] among those determined to be essential was amino acid (Cys2), the change type of the thiol-containing organic compound aminoalkanoic acid (Cys) [10]. Cells empty Cys2 fail to grow unless refined at extraordinarily high densities [10-12]. Following up on these observations the depriving cultured human lung fibroblasts of $Cys_2$ resulted in rapid depletion of the Cys-containing antioxidant tripeptide GSH (γ-L-glutamyl-L-cysteinylglycine), and subsequent cell death [13]. Cell death was prevented, while not rescuing GSH levels, by growing cells within the presence of the oleophilic inhibitor α-tocopherol (vitamin E) [13]. These results inexplicit that Cys2 import was needed to sustain GSH levels, that death was triggered by a buildup of L-ROS. In resultant years, studies of Cys2 deprivation-induced death in human embryonic fibroblasts, cell somatic cell cells and rat oligodendrocytes confirmed the importance of GSH depletion in death, and unarguable that each lipophilic antioxidants and iron chelators could block this technique from occurring [14-17]. Collectively, these reports established that continuous Cys2 uptake and GSH synthesis are needed in many sorts of class cells to forestall the buildup of cytotoxic L-ROS and facilitate frame our understanding of however erastin and RSL3 trigger ferroptosis at the molecular level.

## IV. DIFFERENT STIMULI THAT MAY TRIGGER FERROPTOSIS.

Analysis of the erastin mechanism of action provided the first insights into proteins and pathways essential to forestall the onset of ferroptosis. Early chemoproteomic research exploitation erastin analogs conjugated to a stable aid matrix acknowledged the mitochondrial voltage established ion channel and three (VDAC2 and VDAC3) as direct erastin target [18]. Experiments using purified human VDAC2 reconstituted into artificial liposomes make sure that erastin will bind this target and modulate transport flux [19].

However, it currently seems that the flexibility of erastin to trigger ferroptosis is decided primarily by inhibition of a unique target, the cystine/glutamate antiporter termed system x−cxc−.Using 'modulatory profiling' (see [20]) it absolutely was found that necrobiosis iatrogenic by erastin is comparable in several respects to cell death induced by sulfasalazine (SAS) [21], a known system x−cxc− inhibitor.

In addition to erastin and SAS, the FDA-authorized multi-kinase count sorafenib (trade name: Nexavar) will block machine operate, consume GSH and cause ferroptosis in somatic cellular lines derived from liver, kidney, bone, inner organ and alternative tissues. [22, 23, 24]. Related kinase inhibitors have no capability to block system x−cxc− feature or cause ferroptosis [22, 23], suggesting that the results of sorafenib might be due both to modulation of a completely unique kinase (that during turn modulates system activity) or to a direct effect on system x−cxc−activity).

This characteristic may additionally give an explanation for the capacity of sorafenib to cause caspase-independent mobile dying in certain cell kinds and enhance ROS accumulation in sorafenib-treated cancer patients [25,26]. However, the outcomes of this compound are definitely pleiotropic: in some cell lines sorafenib triggers apoptosis [27], or even in cellular lines wherein ferroptosis is located at low doses of sorafenib, apoptosis or some other form of cellular death is located at better doses [21]. Further have a look at is needed to disentangle the numerous consequences of sorafenib on the mobile and determine whether or not the consequences of this compound in sufferers are as a consequence of ferroptosis.

## V. GENETIC DETERMINANTS OF FERROPTOSIS

Many studies have known varied genetic determinants of ferroptosis and their associated communication pathways concerned within the glutathione/lipid metabolisms, oncogenic corporal mutations, and regulation of iron levels and processes of animal tissue mesenchyme transition. Ferroptosis was initial known by the mechanistic investigation of the necrobiosis induced by elastin. Erastin was discovered by a chemical screen to spot compounds that may by selection target cancer cells bearing RAS mutations [28]. Subsequent investigation found that the erastin changed into an effective inhibitor of xct, a transmembrane transporter that mediated the cystine import via the export of glutamate. Cystine enters cells to be reduced to cysteine that is the limiting aspect of glutathione (GSH). Cystine enters cells to be reduced to amino acid, that is that the limiting element of glutathione (GSH). Therefore, erastin treatment results in the depletion of GSH, the most cellular antioxidants and chemical compound for GPX4 needed to neutralize supermolecule peroxidation. Subsequently, the depletion of GSH leads to the extreme oxidative stresses and results in the giant lipid peroxidation mentioned inside the ferroptosis. Interestingly, a recent study cautioned that apart from GSH, the external cystine also fed into the de novo synthesis of Co-enzyme A (coa)[29] The depletion of coa synthesis [29,30] hypersensitised cells to erastin-induced ferroptosis. Reciprocally, coa addition was ready to shield cells from ferroptosis however the careful mechanisms stay to be investigated.

## VI. NON-GENETIC DETERMINANTS OF FERROPTOSIS

Ferroptosis can be a sort of regulated necrobiosis, which may even have therapeutic capacity closer to RCC; however, much stays unknown approximately the determinants of ferroptosis susceptibility. We located that ferroptosis susceptibility is awfully inspired by cellular density and confluency. Because cell density regulates the Hippo-YAP/TAZ pathway. Here, we identify that a non-genetic factor, cell density, regulates ferroptosis sensitivity [31, 32]. Cell density regulates ferroptosis in RCC; TAZ affects the degree of EMP1, NOX4, and ensuing lipoid peroxidation and ferroptosis. Therefore, TAZ activation might promote ferroptosis and predict of ferroptosis sensitivity. The Hippo pathway integrates a good type of non-genetic factors, reminiscent of mechanical properties and metabolic standing [33]. Therefore, our findings could recommend that these Hippo-sensitive, non-genetic factors might also regulate ferroptosis sensitivities.

## VII. ROLE OF AUTOPHAGY IN FERROPTOSIS

Autophagy could also be a regulated method within which the cell disassembles extra or dysfunctional organelles and proteins, thereby meeting the metabolic desires of the cell itself. [34, 35]. Autophagy gives an opposing, context-dependent position in cancer. The activation of autophagy suppresses the initiation of tumor growth within the first stages of cancer, while in installed tumors, the recycling capabilities of autophagy permit the survival and progression of tumors[36,37] Ferroptosis, the newly discovered kind of regulated necrobiosis, depends upon intracellular iron accumulation and subsequent lipid peroxidation[21]. Additionally to the induction of tissue injury and protective effects on neurodegenerative diseases [38, 39, 40], the activation of ferroptosis also exhibits anticancer activity [41]. Ferroptosis has currently been defined as an autophagic mobile loss of life process, and autophagy plays an important role inside the induction of ferroptosis by using regulating mobile iron homeostasis and ROS generation. Ferritin is that the main intracellular protein that stores iron. Reactive iron ($Fe^{2+}$) induces toxic Fenton-type oxidative reactions, whilst the unreactive state ($Fe^{3+}$) saved in ferritin is a smaller amount harmful [42]. Under ferroptosis-inducing conditions, including erastin treatment, autophagy is activated, as confirmed by using the conversion of LC3I to LC3II and GFP-LC3 puncta formation [43]. Autophagy promotes protein degradation and thus finishes up within the discharge of chelate iron in ferritin, a way called ferritinophagy. An increase within the cellular labile iron pool induces aerophilous stress and eventually leads the prevalence of ferroptosis [43]. Knockout or knockdown of Atg5 suppresses erastin-triggered ferroptosis by decreasing intracellular ferric iron levels, indicating that autophagy is important for protein degradation and ferroptosis induction [42]. Ferroptosis and autophagy had been currently shown to set off loss of life severally and at totally different instances once siramesine and lapatinib remedy in carcinoma cells [44].However, researchers do observe enhanced protein degradation promoted by autophagy. Studies are required to raised illustrate the cooperation between ferroptosis and autophagy in inducement death.

## VIII. NEURO-DEGENERATIVE DISEASES THAT INVOLVE FERROPTOSIS

Neurodegenerative diseases, consisting of Alzheimer's disease (AD) and Parkinson's disease (PD), are recognized to be associated with dysregulation of iron homeostasis and excessive ROS inside the brain. Before the idea of ferroptosis, neurodegenerative diseases were thought to be due to apoptosis [45]. With the definition of ferroptosis in 2012 and iron structured oxidative strain as a large marker of mobile ferroptosis, there is an increasing amount of research supporting the idea that ferroptosis is inextricably connected to neurodegenerative diseases. Ferroptosis is characterized with the aid of an accumulation of lipid peroxidation and dysregulation of iron, which are exactly the hallmarks of Alzheimer's disease [46].Therefore, regulating ferroptosis has turn out to be a new path for the potential remedy of Alzheimer's disease. Therefore, regulating ferroptosis has grow to be a new direction for the potential treatment of Alzheimer's disease. Iron chelators also prevent the improvement of AD by keeping tiers of hypoxia inducible factor-1 alpha (HIF-1α) within the nerve and inhibiting neuronal death, which provides a unique neuroprotective mechanism in opposition to AD [47].According to our understanding, the radical-trapping antioxidant α-tocopherol and the iron chelators DFO entered clinical trying out to treat AD earlier than they were discovered as inhibitors of ferroptosis [48]. Parkinson's disease is the most common neurodegenerative disease and it's characterized through the lack of dopaminergic neurons inside the substantia nigra and the formation of cytoplasmic eosinophilic inclusion bodies [49]. It is presently believed that lipoid peroxidation of dopaminergic neurons within the neural structure pars compacta is very important in the pathologic process of PD [50]. Some pathological functions observed in PD patients are increased ranges of loose iron inside the substantia nigra neurons, lipid peroxide production, and accumulation of ROS, are closely related to ferroptosis. Recently, Huntington's disorder (HD), a hereditary neurodegenerative disorder, has additionally been shown to be inextricably linked to ferroptosis. Similar to Alzheimer's and Parkinson's diseases, Huntington's disease also buddies with ordinary degrees in lipid peroxidation, GSH metabolism, and iron accumulation [51].

Increasing lipid peroxidation was detected in cortical striatal mind sections [52] and cerebrospinal fluid [53] of the mn90q73 HD mouse model. 3-nitropropionic acid (3-NP)-brought about HD mice show a decrease in GSH and GSH-S-transferase inside the striatum, cortex, and hippocampus [54] Moreover, increasing iron supplementation reduces the striatum extent and contributes to neurodegeneration [55]. In conclusion, current research on the position of ferroptosis in neurodegenerative diseases specifically listen on analyzing whether ferroptosis inhibitors could slow disorder progression, and generally use animal models. Most of the experimental research in animals have proven that effective inhibition of ferroptosis provided potential treatment. However, most clinical trials on administering iron chelators and antioxidants showed handiest moderate treatment effect. These outcomes lead us to assume that iron chelators and antioxidants are not enough to offer powerful remedy. Potential molecules that adjust ferroptosis through different signalling pathways have not begun to be similarly explored for their potential to deal with neurodegenerative diseases and could provide better remedy.

## IX. PHYSIOLOGICAL ROLE OF FERROPTOSIS

Ferroptosis is morphologically, biochemically and genetically distinct from distinct pathways for RCD, together with necroptosis, apoptosis and autophagy [56]. Aminoalkanoic acid, iron and lipid metabolism are concerned within the manner of ferroptosis.During ordinary physiological function, extracellular glutamate induces ferroptosis. Lipid metabolism might have an effect on the sensitivity of cells to ferroptosis. Unsaturated fatty acids are prone to lipoid peroxidation and are needed for ferroptosis [57]. Iron is concerned at intervals the buildup of lipoid peroxides and ferroptosis. Many molecules, like voltage dependent ion channel (VDAC) 2/3, glutathione oxidase four (GPX4), heat shock macromolecule β-1, nuclear factor E2-related issue a pair of (NRF2), NADPH enzyme, the growth suppressor p53 (TP53) and substance carrier circle of relatives seven member one (SLC7A1), alter ferroptosis via the direct or indirect objectives of iron metabolism to boot to lipoid peroxidation [56]. Physiological function for ferroptosis in the form of cell death has not been established. However, ferroptosis has varied connections to pathological cell death. A complicated set of processes, represented below, will power or suppress fatal lipoid peroxidation, suggesting that Nature regulates this vulnerability in varied contexts. Maybe, some chronic pathologies seem as if thanks to overwhelming the capability to revive peroxidised lipids, resulting in cellular death; rising proof conjointly indicates that ferroptosis would possibly serve a tumour suppressor feature in adjourning cells that lack get entry to essential nutrients of their surroundings, or that are compromised by contamination or environmental stress. The bulk of research to the present point propose that ferroptosis is precipitated through degenerative methods or could also be prompted therapeutically during a few cancers, but few studies have explored its natural functions. It's conceivable, however not but demonstrated, that ferroptosis are often brought on during development or ordinary homeostatic tissue turnover by means of the buildup of glutamate, iron, or PUFA-phospholipids, or through depletion of endogenous inhibitors of ferroptosis, which incorporates GSH, NADPH, GPX4 or vitamin E. Examining such prospects are going to be a very important space of investigation within the future to see whether or not ferroptosis is genetically programmed to occur, or is primarily a vulnerability caused by pathologies and exploited by potential medicine.

## X. THE ROLE OF FERROPTOSIS IN VARIOUS HUMAN DISEASES

Ferroptosis inhibitors had been used to treat quite some kidney injuries, including ischemia-reperfusion and oxalic acid-brought about kidney damage [58], rhabdomyolysis [59], and acute renal failure (ARF) [59]. Ferroptosis inhibitor Fer-1 prevents cellular dying in an in vitro version of rhabdomyolysis-prompted acute kidney injury. Ferroptosis inhibitor Fer-1 prevents cell death in an in vitro model of rhabdomyolysis-induced acute kidney injury [60]. In a vivo model of renal ischemia-reperfusion injury, SRS16-86, a third era ferrostatin with improved plasma and metabolic stability, covered renal characteristic and prolonged survival after ischemia-reperfusion injury [61]. Ferroptosis inhibitor Lip-1 can rescue acute renal failure and prolong life in mice because of GPX4 deletion [62]. In addition, thiazolidinedione's (tzds) inhibit acyl-coa synthase four and partially reduce the mortality of triggered GPX4 knockout mice [63]. These consequences give a boost to the sensitivity of kidney tissue to ferroptosis and show the price of ferroptosis inhibitors in the remedy of renal damage [64].Excessive accumulation of iron ions reasons lipid peroxidation and tissue damage, main to atherosclerosis and diabetes [65]. Studies have proven that iron overload within the heart brought on myocardial dysfunction and metabolic harm that ultimately led to heart disease [21]. In GPX4-deficient T cells, the mobile membrane rapidly accumulates lipid peroxides, which induces ferroptosis. Instead, inhibiting ferroptosis promotes the survival and enlargement of T cells and protects the immune characteristic of T cells [66]. Research also indicates that ferroptosis participates in keratinocyte death because of GSH loss, and excessive doses of nutrition E can inhibit ferroptosis of pores and skin keratinocytes and reduce skin damage [65].

Recent studies display that the reduced expression of frataxin, a key protein of Friedreich's ataxia (FRDA), characterized with the aid of puberty onset, lack of tendon reflexes, and deep sensory loss, is related to mitochondrial dysfunction, mitochondrial iron accumulation,and improved oxidative stress. Ferroptosis inhibitor SRS11-ninety two reduces cellular death caused by FRDA [67]. The survival of cells is an important a part of the body's regular metabolism. It is apparent that ferroptosis has an intimate relationship with pathological mobile death. Effective remedy or prevention of the development of the disorder or the clinical symptoms in mice or rat models can be finished with the aid of administering ferroptosis inhibitors or inducers. Emerging evidence also shows that ferroptosis initiation has an ability tumor inhibitory function that may clear tumor cells that lack key nutrients inside the environment and cells which can be broken via infection [68]. In-depth look at and explanation of the pathophysiological mechanism of ferroptosis in associated sicknesses will offer new ideas for coming across potential drug targets and clinical prevention methods

## XI. CONCLUSION & PERSPECTIVE

Collectively, ferroptosis has taken a full expectation to produce a replacement approach in anti-tumor therapies. Current researches have principally centered on the eradication of residual or resistant cancer cells, wherever ferroptotic death emerges to be a replacement cell death for this purpose. Conspicuously, getting a mesenchymal cell kingdom (e.g., epithelial-mesenchymal transition (EMT) or cancer stem cells) has been cautioned to form a call metastatic dissemination and chemo-resistance. A lot of recently, the foremost cancers cells with the high-mesenchymal country have arisen as a vital mechanism of each received and DE novo resistance to centered therapies. This resistant mesenchymal most cancers cells have bred a state of non-oncogene addition to GPX4, that inhibition can intuitively cause ferroptosis. Systematically, chronic most cancers cells that are appointed to escape from conventional cytotoxic treatment via a dormant kingdom growth showed AN identically selective dependency at the GPX4 pathway. Therefore, ferroptosis may be considered a feasible therapeutic method to reverse therapy-resistance in cancer approach. Ferroptosis may be a sort of programmed necrosis, which is frequent to be greater immunogenic than apoptosis. By delivering chemoattractant signals, ferroptosis hold the capacity to recruit and depart immune cells at tumor sites, which give the opportunity of ferroptosis inducer as an appropriate enhancer for anti-tumour immunotherapy treatment like checkpoint-inhibitor .Although it turned into promising from the benefits of ferroptosis in most cancers remedial, ferroptosis remains waiting for formal addressing in a pre-clinical placing and clinical achievability, partially due to the complexity of it observed in special contexts along with P53 or Ras-mutant most cancers cells. Another project is that ferroptosis induction which include GPX4 inhibitor impacts the development and characteristic of nervous machine and kidney, via inflicting GPX4 gene which is essential for embryonic development and some person tissue homeostasis in mice. In addition, every other noticeable issue is that the prevalence of ferroptotic resistance, which become originally observed in the Hela cells with the erastin treatment. The resistance mechanism turned into the HSP27 overactivation through suppressing cytoskeleton-mediated iron absorption

## REFERENCES

[1] J.F.R. Kerr, A histochemical study of hypertrophy and ischaemic injury of rat liver with special reference to changes in lysosomes. J. Pathol. Bacteriol 1965; 90: 419–435.

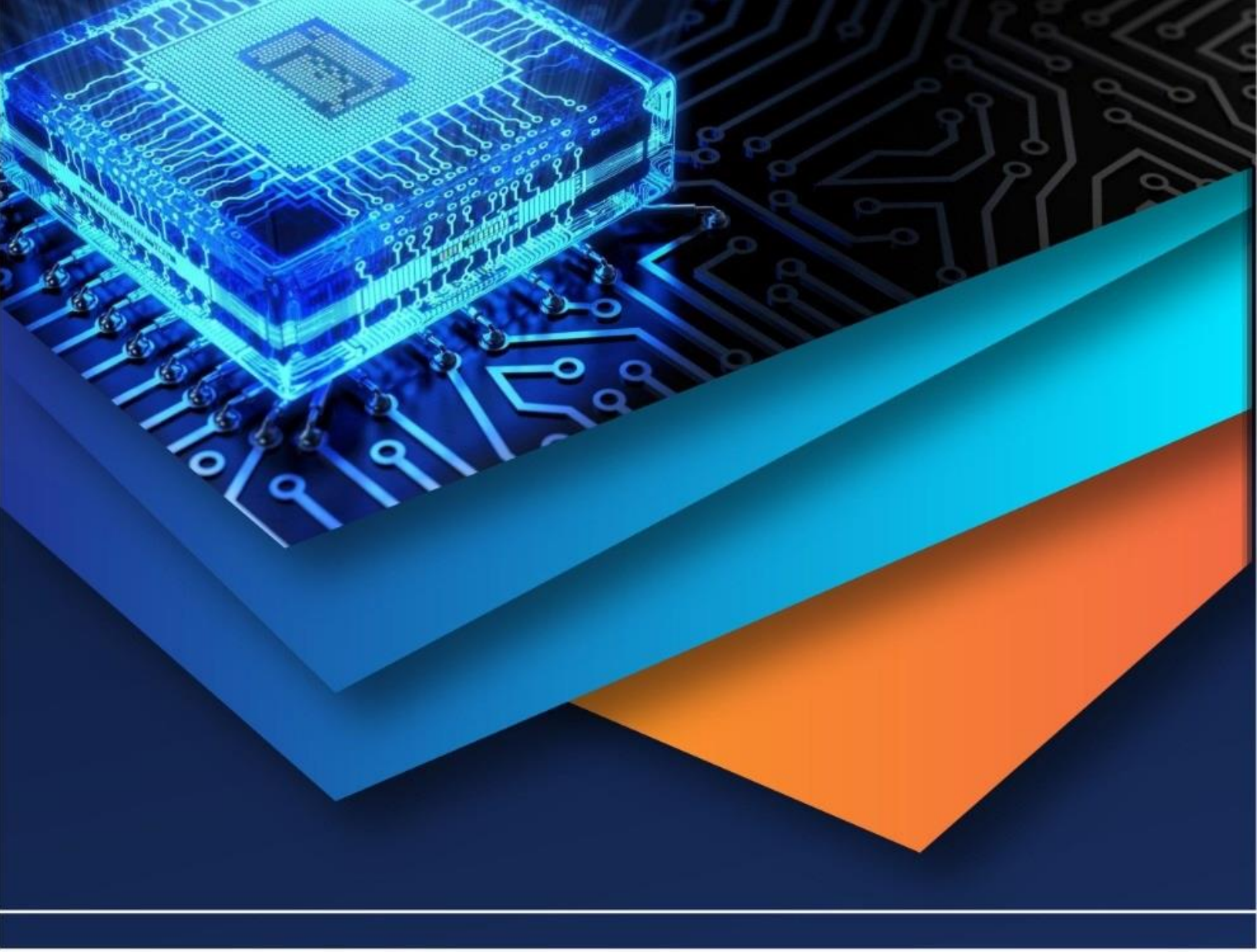
[2] R.A. Lockshin, C.M. Williams, Programmed cell death—II. Endocrine potentiation of the breakdown of the intersegmental muscles of silk moths. J. Insect Physiol 1964; 10: 643–649.

[3] R.A. Lockshin, C.M. Williams, Programmed cell death—I. Cytology of degeneration in the intersegmental muscles of the Pernyi silkmoth, J. Insect Physiol 1965; 11: 123–133.

[4] 8L. Galluzzi, I. Vitale, S.A. Aaronson, J.M. Abrams, D. Adam, P. Agostinis, E.S. Alnemri, L. Altucci, I. Amelio, D.W. Andrews, M. Annicchiarico-Petruzzelli, A.V. Antonov, E. Arama, E.H. Baehrecke, N.A. Barlev, N.G. Bazan, F. Bernassola, M.J.M. Bertrand, K. Bianchi, M.V. Blagosklonny, K. Blomgren, C. Borner, P. Boya,C. Brenner, M. Campanella, E. Candi, D. Carmona-Gutierrez, F. Cecconi, F.K.-M. Chan, N.S. Chandel, E.H. Cheng, J.E. Chipuk, J.A. Cidlowski, A. Ciechanover, G.M. Cohen, M. Conrad, J.R. Cubillos-Ruiz, P.E. Czabotar, V. D'Angiolella, T.M. Dawson, V.L. Dawson, V. De Laurenzi, R. De Maria, K.-M. Debatin, R.J. deberardinis, M. Deshmukh, N. Di Daniele, F. Di Virgilio, V.M. Dixit, S.J. Dixon, C.S. Duckett, B.D. Dynlacht, W.S. El-Deiry, J.W. Elrod, G.M. Fimia, S. Fulda, A.J. García-Sáez, A.D. Garg, C. Garrido, E. Gavathiotis, P. Golstein, E. Gottlieb, D.R. Green, L.A. Greene, H. Gronemeyer, A. Gross, G. Hajnoczky, J.M. Hardwick, I.S. Harris, M.O. Hengartner, C. Hetz, H. Ichijo, M. Jäättelä, B. Joseph, P.J. Jost, P.P. Juin, W.J. Kaiser, M. Karin, T. Kaufmann, O. Kepp, A. Kimchi, R.N. Kitsis, D.J. Klionsky, R.A. Knight, S. Kumar, S.W. Lee, J.J. Lemasters, B. Levine, A. Linkermann, S.A. Lipton, R.A. Lockshin, C. Lópezotín, S.W. Lowe, T. Luedde, E. Lugli, M. Macfarlane, F. Madeo, M. Malewicz, W. Malorni, G. Manic, J.-C. Marine, S.J. Martin, J.-C. Martinou, J.P. Medema, P. Mehlen, P. Meier, S. Melino, E.A. Miao, J.D. Molkentin, U.M. Moll, C. Muñozpinedo, S. Nagata, G. Nuñez, A. Oberst, M. Oren, M. Overholtzer, M. Pagano, T. Panaretakis, M. Pasparakis, J.M. Penninger, D.M. Pereira, S. Pervaiz, M.E. Peter,M. Piacentini, P. Pinton, J.H.M. Prehn, H. Puthalakath, G.A. Rabinovich, M. Rehm, R. Rizzuto, C.M.P. Rodrigues, D.C. Rubinsztein, T. Rudel, K.M. Ryan, E. Sayan,L. Scorrano, F. Shao, Y. Shi, J. Silke, H.-U. Simon, A. Sistigu, B.R. Stockwell, A. Strasser, G. Szabadkai, S.W.G. Tait, D. Tang, N. Tavernarakis, A. Thorburn, Y. Tsujimoto, B. Turk, T. Vanden Berghe, P. Vandenabeele, M.G. Vander Heiden, A. Villunger, H.W. Virgin, K.H. Vousden, D. Vucic, E.F. Wagner, H. Walczak, D. Wallach, Y. Wang, J.A. Wells, W. Wood, J. Yuan, Z. Zakeri, B. Zhivotovsky, L. Zitvogel, G. Melino, G. Kroemer, Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018, Cell Death Differ 2018; 25: 486–541.

[5] H.S. Mason, W.L. Fowlks, E. Peterson, Oxygen transfer and electron transport by the phenolase complex1, J. Am. Chem. Soc 1955; 77: 2914–2915.
[6] O. Hayaishi, M. Katagiri, S. Rothberg, Mechanism of the pyrocatechase reaction, J.Am. Chem. Soc 1955; 77: 5450–5451.
[7] G. Barrera, S. Pizzimenti, M.U. Dianzani, Lipid peroxidation: control of cell proliferation, cell differentiation and cell death, Mol. Asp. Med 2008; 29: 1–8.
[8] E. Niki, Y. Yoshida, Y. Saito, N. Noguchi, Lipid peroxidation: mechanisms, inhibition, and biological effects, Biochem. Biophys. Res. Commun 2005; 338: 668–676.
[9] S.J. Dixon, K.M. Lemberg, M.R. Lamprecht, R. Skouta, E.M. Zaitsev, C.E. Gleason, D.N. Patel, A.J. Bauer, A.M. Cantley, W.S. Yang, B. Morrison, B.R. Stockwell,Ferroptosis: an iron-dependent form of nonapoptotic cell death, Cell 2012; 149: 1060–1072.
[10] Eagle H. Nutrition needs of mammalian cells in tissue culture. Science 1955; 122: 501- 514. Doi: 10.1126/science.122.3168.501.
[11] Eagle H. Amino acid metabolism in mammalian cell cultures. Science 1959; 130: 432–437. Doi: 10.1126/science.130.3373.432.
[12] Eagle H, Piez KA, Oyama VI. The biosynthesis of cystine in human cell cultures. J Biol Chem 1961; 236: 1425–1428.
[13] Bannai S, Tsukeda H, Okumura H. Effect of antioxidants on cultured human diploid fibroblasts exposed to cystine-free medium. Biochem Biophys Res Commun 1977; 74:1582–1588. Doi: 10.1016/0006-291X (77)90623-4.
[14] Yonezawa M, Back SA, Gan X, et al. Cystine deprivation induces oligodendroglial death: rescue by free radical scavengers and by a diffusible glial factor. J Neurochem 1996; 67: 566–573. Doi: 10.1046/j.1471-4159.1996.67020566.x.
[15] De Brabander M, Van Belle H, Aerts F, et al. Protective effect of levamisole and its sulfhydryl metabolite OMPI against cell death induced by glutathione depletion. Int J Immunopharmacol 1979; 1: 93–100. Doi: 10.1016/0192-0561(79)90011-0.
[16] Murphy TH, Miyamoto M, Sastre A, et al. Glutamate toxicity in a neuronal cell line involves inhibition of cystine transport leading to oxidative stress 1989; 2: 1547- 1558.
[17] Murphy TH, Schnaar RL, Coyle JT. Immature cortical neurons are uniquely sensitive to glutamate toxicity by inhibition of cystine uptake. FASEB J 1990; 4: 1624–1633.
[18] Yagoda N, von Rechenberg M, Zaganjor E, et al. RAS-RAF-MEK-dependent oxidative cell death involving voltage-dependent anion channels. Nature 2007; 447: 864–868. Doi: 10.1038/nature05859.
[19] Bauer AJ, Gieschler S, Lemberg KM, et al. Functional model of metabolite gating by human voltage-dependent anion channel 2. Biochemistry 2011; 50: 3408–3410. Doi: 10.1021/bi2003247.
[20] Wolpaw AJ, Shimada K, Skouta R, et al. Modulatory profiling identifies mechanisms of small molecule-induced cell death. Proc Natl Acad Sci USA 2011; 108: E771–E780, Doi: 10.1073/pnas.1106149108.
[21] Dixon SJ, Lemberg KM, Lamprecht MR, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell 2012; 149: 1060–1072. Doi: 10.1016/j.cell.2012.03.042.
[22] Dixon SJ, Patel DN, Welsch M, et al. Pharmacological inhibition of cystine-glutamate exchange induces endoplasmic reticulum stress and ferroptosis. Elife 2014; 3: e02523.
[23] Lachaier E, Louandre C, Godin C, et al. Sorafenib induces ferroptosis in human cancer cell lines originating from different solid tumors. Anticancer Res 2014; 34: 6417–6422.
[24] Louandre C, Ezzoukhry Z, Godin C, et al. Iron-dependent cell death of hepatocellular carcinoma cells exposed to sorafenib. Int J Cancer 2013; 133: 1732–1742. Doi: 10.1002/ijc.28159.
[25] Panka DJ, Wang W, Atkins MB, Mier JW. The Raf inhibitor BAY 43-9006 (Sorafenib) induces caspase-independent apoptosis in melanoma cells. Cancer Res 2006; 66: 1611-1619. Doi: 10.1158/0008-5472.CAN-05-0808.
[26] Coriat R, Nicco C, Chéreau C, et al. Sorafenib-induced hepatocellular carcinoma cell death depends on reactive oxygen species production in vitro and in vivo. Mol Cancer Ther 2012; 11: 2284–2293. Doi: 10.1158/1535-7163.MCT-12-0093.
[27] Liu L, Cao Y, Chen C, et al. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. Cancer Res 2006; 66: 11851–11858. Doi: 10.1158/0008-5472.CAN-06-1377.
[28] S. Dolma, S.L. Lessnick, W.C. Hahn, et al.Identification of genotype-selective antitumor agents using synthetic lethal chemical screening in engineered human tumor cells Canc Cell 2003; 3(3): 285-296
[29] M.A. Badgley, D.M. Kremer, H.C. Maurer, et al.Cysteine depletion induces pancreatic tumor ferroptosis in mice Science 2020; 368(6486): 85-89
[30] C.C. Lin, M. Kitagawa, X. Tang, et al.coa synthase regulates mitotic fidelity via CBP-mediated acetylation Nat Commun 2018; 9(1): 1039
[31] Chen, P.-H., Wu, J., Ding, C.C., Lin, C.-C., Pan, S., Bossa, N., Xu, Y., Yang, W.-H., Mathey-Prevot, B., and Chi, J.-T. (2019). Kinome screen of ferroptosis reveals a novel role of ATM in regulating iron metabolism. Cell Death Differ. Published online July 18, 2019.
[32] Ding, C.-K.C., Rose, J., Wu, J., Sun, T., Chen, K.-Y., Chen, P.-H., Xu, E., Tian, S., Akinwuntan, J., Guan, Z., et al. Mammalian stringent-like response mediated by the cytosolic NADPH phosphatase. MESH1 2018
[33] Zanconato, F., Cordenonsi, M., and Piccolo, S.YAP/TAZ at the Roots of Cancer. Cancer Cell 2016; 29: 783–803.
[34] Kolinsky DJ, Emr SD Autophagy as a regulated pathway of cellular degradation. Science 2000; 290: 1717–21. Doi: 10.1126/science.290.5497.1717.
[35] Kuma A, Hatano M, Matsui M, Yamamoto A, Nakaya H, Yoshimori T, et al The role of autophagy during the early neonatal starvation period. Nature 2004; 432: 1032–6. Doi: 10.1038/nature03029.
[36] Chude CI, Amaravadi RK Targeting autophagy in cancer: Update on clinical trials and novel inhibitors. Int J Mol Sci 2017; 18: E1279. Doi: 10.3390/ijms18061279.
[37] Ozpolat B, Benbrook DM Targeting autophagy in cancer management-strategies and developments. Cancer Manag Res 2015; 7: 291–9.
[38] Linkermann A, Skouta R, Himmerkus N, Mulay SR, Dewitz C, De Zen F, et al Synchronized renal tubular cell death involves ferroptosis. Proc Natl Acad Sci USA 2014; 111: 16836–41. Doi: 10.1073/pnas.1415518111.
[39] Xie BS, Wang YQ, Lin Y, Mao Q, Feng JF, Gao GY, et al Inhibition of ferroptosis attenuates tissue damage and improves long-term outcomes after traumatic brain injury in mice. CNS Neurosci Ther 2019; 25: 465–75. Doi: 10.1111/cns.2019.25.issue-4.

[40] Masaldan S, Bush AI, Devos D, Rolland AS, and Moreau C Striking while the iron is hot: Iron metabolism and Ferroptosis in neurodegeneration. Free Radic Biol Med 2019; 133: 221–33. Doi: 10.1016/j.freeradbiomed.2018.09.033.
[41] Lu B, Chen XB, Ying MD, He QJ, Cao J, Yang B The role of ferroptosis in cancer development and treatment response. Front Pharmacol 2018; 8: 992. Doi: 10.3389/fphar.2017.00992.
[42] Torti FM, Torti S V Regulation of ferritin genes and protein. Blood 2002; 99: 3505–16. Doi: 10.1182/blood.V99.10.3505.
[43] Gao MH, Monian P, Pan QH, Zhang W, Xiang J, Jiang XJ Ferroptosis is an autophagic cell death process. Cell Res 2016; 26: 1021–32. Doi:10.1038/cr.2016.95.
[44] Ma S, Dielschneider RF, Henson ES, Xiao W, Choquette TR, Blankstein AR, et al Ferroptosis and autophagy induced cell death occur independently after siramesine and lapatinib treatment in breast cancer cells. Plos One 2017; 12: e0182921. Doi: 10.1371/journal.pone.0182921.
[45] Ward R. J., Zucca F. A., Duyn J. H., Crichton R. R., Zecca L. (2014). The role of iron in brain ageing and neurodegenerative disorders. Lancet Neurol 13, 1045–1060. 10.1016/s1474-4422(14)70117-6
[46] Castellani R. J., Moreira P. I., Liu G., Dobson J., Perry G., Smith M. A., et al. Iron: the redox-active center of oxidative stress in Alzheimer disease. Neurochem. Res 2007; 32: 1640–1645. 10.1007/s11064-007-9360-7
[47] .Ashok B. S., Ajith T. A., Sivanesan S.Hypoxia-inducible factors as neuroprotective agent in Alzheimer's disease. Clin. Exp. Pharmacol. Physiol 2017; 44: 327–334. 10.1111/1440-1681.12717
[48] Dysken M. W., Sano M., Asthana S., Vertrees J. E., Pallaki M., Llorente M., et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. JAMA 2014; 311: 33-10.1001/jama.2013.282834
[49] Hornykiewicz O. Basic research on dopamine in Parkinson's disease and the discovery of the nigrostriatal dopamine pathway: the view of an eyewitness. Neurodegener. Dis 2008; 5: 114–117. 10.1159/000113678
[50] Burbulla L. F., Song P. P., Mazzulli J. R., Zampese E., Wong Y. C., Jeon S., et al. Dopamine oxidation mediates mitochondrial and lysosomal dysfunction in Parkinson's disease. Science 2017; 357: 1255–1261. 10.1126/science.aam9080
[51] Paul B. D., Sbodio J. I., Xu R., Vandiver M. S., Cha J. Y., Snowman A. M., et al. Cystathionine gamma-lyase deficiency mediates neurodegeneration in Huntington's disease. Nature 2014; 509: 96–100. 10.1038/nature13136
[52] Skouta R., Dixon S. J., Wang J., Dunn D. E., Orman M., Shimada K., et al. Ferrostatins inhibit oxidative lipid damage and cell death in diverse disease models. J. Am. Chem. Soc 2014; 136: 4551–4556. 10.1021/ja411006a
[53] Reddy P. H., Shirendeb U. P. (2012). Mutant huntingtin, abnormal mitochondrial dynamics, defective axonal transport of mitochondria, and selective synaptic degeneration in Huntington's disease. Biochim. Biophys. Acta 2012: 101–110.
[54] Kumar P., Kalonia H., Kumar A. Nitric oxide mechanism in the protective effect of antidepressants against 3-nitropropionic acid-induced cognitive deficit, glutathione and mitochondrial alterations in animal model of Huntington's disease. Behav. Pharmacol 2010; 21: 217–230.
[55] Van Bergen J. M., Hua J., Unschuld P. G., Lim I. A., Jones C. K., Margolis R. L., et al. Quantitative susceptibility mapping suggests altered brain iron in premanifest Huntington disease. AJNR Am. J. Neuroradiology 2016; 37: 789-796.
[56] Xie Y, Hou W, Song X, Yu Y, Huang J, Sun X, Kang R and Tang D: Ferroptosis: Process and function. Cell death Differ 23: 369-379, 2016.
[57] Yang WS and Stockwell BR: Ferroptosis: Death by lipid peroxidation. Trends Cell Biol 2016; 26: 165-176
[58] Griesser, M., Shah, R., Van Kessel, A. T., Zilka, O., Haidasz, E. A., Pratt, D. A. The catalytic reaction of nitroxides with peroxyl radicals and its relevance to their cytoprotective properties. J. Am. Chem. Soc 2018; 140: 3798–3808.
[59] Bosch, X., Poch, E., Grau, J. Current concepts: Rhabdomyolysis and acute kidney injury. N Engl. J. Med 2009; 361: 62–72.
[60] Skouta, R., Dixon, S. J., Wang, J., Dunn, D. E., Orman, M., Shimada, K., et al. (2014). Ferrostatins inhibit oxidative lipid damage and cell death in diverse disease models. J. Am. Chem. Soc 136, 4551–4556. Doi: 10.1021/ja411006a
[61] Linkermann, A., Skouta, R., Himmerkus, N., Mulay, S. R., Dewitz, C., De Zen, F., et al. (2014). Synchronized renal tubular cell death involves ferroptosis. Proc. Natl. Acad. Sci. U. S. A 2014; 111: 16836–16841. Doi: 10.1073/pnas.1415518111
[62] Friedmann Angeli, J. P., Schneider, M., Proneth, B., Tyurina, Y. Y., Tyurin, V. A., Hammond, V. J., et al. Inactivation of the ferroptosis regulator GPX4 triggers acute renal failure in mice. Nat. Cell Biol 2014; 16: 1180–1191. Doi: 10.1038/ncb3064
[63] Doll, S., Proneth, B., Tyurina, Y., Panzilius, E., Kobayashi, S., Ingoid, I., et al. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. Nat. Chem. Biol 2017; 13: 91–98. Doi: 10.1038/NCHEMBIO.2239
[64] Sancho-Martinez, S. M., Lopez-Novoa, J. M., Lopez-Hernandez, F. J. Pathophysiological role of different tubular epithelial cell death modes in acute kidney injury. Clin. Kidney J 2015; 8: 548–559. Doi: 10.1093/ckj/sfv069
[65] Wu, D., Chen, L.Ferroptosis: a novel cell death form will be a promising therapy target for diseases. Acta Biochim. Biophys. Sin. (Shanghai) 2015; 47: 857–859.
[66] Matsushita, M., Freigang, S., Schneider, C., Conrad, M., Bornkamm, G. W., Kopf, M. (). T cell lipid peroxidation induces ferroptosis and prevents immunity to infection. J. Exp. Med 2015; 212: 555–568. Doi: 10.1084/jem.20140857
[67] Cotticelli, M. G., Xia, S., Lin, D., Lee, T., Terrab, L., Wipf, P., et al. Ferroptosis as a novel therapeutic target for friedreich's ataxia. J. Pharmacol. Exp. Ther 2019; 369: 47–54.
[68] Yang, W. S., Sriramaratnam, R., Welsch, M. E., Shimada, K., Skouta, R., Viswanathan, V. S., et al. (2014). Regulation of ferroptotic cancer cell death by GPX4. Cell 2014; 156: 317–331. Doi: 10.1016/j.cell.2013.12.010



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