FERROPTOSIS: ITS MECHANISM AND ROLE IN VARIOUS CLINICAL CONDITIONS

Abstract:

Ferroptosis is basically a distinctive type of iron-dependent and non-apoptotic cellular death which is specificallycoaxed by oncogenic RAS-selective fatal small chemical erastin. Ferroptosis is a total different type of cell death; which differs from other types of cell deaths such as, programmed cell death (apoptosis), mortification(necrosis), and self-degradation (autophagy) with variety of differences in the terms of structures, biochemistry, and heredity. It is totally depended on the intracellular iron and not on other metals.Nonapoptotic cell death mechanisms may help to selectively eliminate some tumor cells or may be induced in particular clinical conditions So, Preventing ferroptosis can defend organisms against neurodegeneration while activating it causes the nonapoptotic death of certain malignant cells.[1]

Keywords: ferroptosis, non-programmed cell death, iron induced cell death.

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I. INTRODUCTION

The iron- contingent death of cell is referred to as ferroptosis, it is distinctive from various types of cell death, especially apoptosis and necrosis. The program incorporates three main metabolic processes involving thiol, lipid, and iron, that cause lipid peroxidation which is iron-dependent and eventually, leads to cell death. The enzyme known as Glutathione peroxidase 4 (GPx4), which triggers the reduction process of lipid peroxides in a reaction that is specifically glutathione-dependent, and the recently observed molecule known asferroptosis suppressor protein (FSP1), which causes the regeneration of ubiquinones (Coenzyme Q10, CoQ10), that serves as a lipid peroxyl radical trap, are two of the major antioxidant systems that can prevent ferroptosis.[1,2]Iron chelators (such as deferiprone and deferoxamine) and few of the minute lipophilic antioxidants (such as ferrostatin and liproxstatin) can prevent the boost up of fatal lipid species that results from lipid peroxidation, which is the reason for ferroptotictype of cell death.[3]Ferroptotic cell death may be individualized from other kinds of cell death through a variety of alterations in the shape of cells, metabolism, and protein expression. At the cellular and subcellular levels, ferroptotic cells takes on an unusual rounded shape prior to their death, that shape is typically similar to necrotic cells, the only difference is that; there is no enlargement of the cytoplasm and other cellular organels, and there is no injury to the plasma membrane.[1,4]Ferroptotic cells' nuclei maintain their structural integrity without the process of condensation, chromatin margination, vesication of the plasma membrane, or the production of bodies responsible for apoptosis[1],the changes defines the characteristics of apoptosis.[5]In addition, the structural characteristics includes attributes like a bi-membrane encapsulated vesicles from autophagic cells, delayed blebbing, and plasma losses the membrane integrity, the typical change shown in pyroptosis isn't observed in ferroptotic cells.[6]The sole characteristic morphological feature observed in the ferroptosis is mitochondria with smaller than usual size and enhanced membrane thickness.[1]

This chapter summarizes the ferroptosis brief introduction, history surrounding its discovery, significant research on the phenomena, its mechanism, as well as its future implications and potential study areas.

II. DISCOVERY OF FERROPTOSIS

Despite the fact that, the relationship between iron and lipid peroxidation has been well developed for a long period of time,[7] it wasn't until Brent Stockwell and Scott J. Dixon established the total terminology aboutferroptosis in 2012 and they explained few of its key characteristics,[1] even though Pamela Maher and David Schubert first identified the differential type of cell death process in 2001 under the name oxytosis. Despite the fact that iron was not mentioned in their findings, oxytosis and ferroptosis are now regarded two different terminologies for the same cell death process.[8,9]

The table below displays the overall amount of progress and research made about the phenomenon:[10]

Table:1

Year	Findings	Name of the Researcher
2003	• Erastin (mutant RAS selective compound)	B.Stockwell
2007	• VDAC2/3 (mitochondrial porins) Mutated RAS Oncogene) Vitamin E (Antioxidant)	B.Stockwell
2008	• TFRC(Iron importer) • RSL 3,RSL 5 (Mutant RAS Selective compounds) DFO (Iron chelator)	B.Stockwell
2010	• ML 162, ML210 (Mutant RAS Selective compounds)	S.Schreiber
2012	• SLC7A11(Cystine/glutamate transporter; coins the term ferroptosis) • Ferrostatin-1(Ferroptosis inhibitor) Sufasalazine(SLCA11 inhibitor) • DPI GKT137831(NOX inhibitor)	B.Stockwell
2014	• GPX (Phospholipid hydroperoxidase) • Sorafenib (SLC7A11 inhibitor)	B.Stockwell
2014	• Liprox-statin-1(Ferroptosis inhibitor) • Zileuton (ALOX inhibitor)	M.Conrad
2015	• SLC38A1(Glutamine transporter)	X.Jiang
2015	• HSPB1(Heat shock protein)	D.Tang
2015	• TP53(Transcription factor)	W.Gu
2015	• Artesunate (Antimalarial agent)	N.Brady
2015	• IKE(SLC7A11 inhibitor)	B.Stockwell
2016	• ACSL4 (Lipidbiosynthesis)	D.Tang,M.Conrad, V.Kagan
2016	• NEF2L2(Transcription factor)	D.Tang
2016	• NCOA4 (Ferritinophagy)	D.Tang,X.Jiang
2016	• ALOXs (Lipoxygenase), FIN56(GPX4 and CoQ10 inhibitor), Statins (HMG-CoA reductase)	B.Stockwell
2016	• $FINO_2$ (GPX4 inactivation and iron oxidation)	K.Woerpel
2017	• BID (BCL2 family)	C.Culmsee
2017	• ZEB1(EMT-activator)	S.Schreiber
2017	• ITGA6, ITGB4 (Cell adhesion)	A.Mercurio
2017	• Hemoglobin Hemin (Iron containing protein)	R.Ratan
2017	• Rosiglitazone (ACSL4 inhibitor)	M.Conrad
2018	• BAP1 (Epigenetic regulation)	B.Gan
2018	• NECTIN4 (Cell clustering)	A.Mercurio
2018	• CTSB (Lysosomal cell death)	D.Tang
2018	• Withaferin A (Increase Iron), LOX-Block-1 (ALOX inibitor)	T.VandenBerghe
2019	• YAP,NF2,WWTR1(Cell contact)	X.Jiang, J.Chi
2019	• AIFM2 (CoQ10 Production)	M.Conrad, J.Olzmann

2019	• Cyst(e)inase (Cysteine depletion)	W.Zou
2019	• Ferroptocide (Thioredoxin inhibitor)	P.Hergenrother
2019	• iFSP (AIFM2 inhibitor)	M.Conrad
2020	• PEX10, PEX3 (Peroxisome)	S.Schreiber
2020	• GCH1 (BH_4 production)	J.Schick
2020	• CHMP5, CHMP6 (ESCRT-III membrane repair)	D.Tang
2020	• POR (Phospholipid peroxidation)	S.Schreiber
2020	• Zalcitabine (Antiretroviral agent)	D.Tang
2020	• Quercetin (Antioxidant agent)	D.Chen

III. MECHANISM OF FERROPTOSIS

The excessive production and storage of iron dependent andoxidatively damaged phospholipids (also known as lipid peroxides) is one of the distinguishing characteristics for the termoxytosis/ferroptosis. Sequestering iron in lysosomes can take advantage of a Fenton chemistry property that is indispensable for the production of reactive oxygen species.[11] When electrons are removed from a lipid molecule due to free redicals (which is usually affecting polyunsaturated fatty acids), they can inspire the oxidation of phospholipids. Glutathione peroxidase 4 (GPX4),which is a glutathione-dependent hydroperoxidase class enzyme that transforms harmful lipid peroxides into a non-toxic(non harmful) lipid alcohols, mediates the main cellular defenseagainstoxytosis/ferroptosis.[12]Recently two laboratories identified a second parallel protactive route involving the oxidoreductase FSP1which is also known as AIFM2. According to their research,FSP1 degrades non-mitochondrial enzyme Q10 enzymetically to produce a powerful lipophilic antioxidant that is responsible for the inhibition of the growth of lipid peroxides[13,14] Tetrahydrobiopterin (BH4), that is a byproduct of the rate-limiting enzyme GCH1, was also shown to have a mechanism that is believed to be much same for a cofactoracringas a diffusable antioxidant, proven in the same year.[15,16] Small compounds that induce oxytosis/ferroptosis, such as, sulfasalazine,erastinsorafenib, (1S, 3R)-RSL3, ML210, and ML162 are investigated and found to suppress the proliferation of tumor cells. These substances do not promote the events like margination of chromatinmolecules orcleavage of poly (ADP-ribose) polymerase (PARP) because they do not cause apoptosis. Instead, oxytosis/ferroptosis alters the phenotype of the mitochondria. The initiation of oxytosis/ferroptosis for small-molecules also requires iron, so it is understood thatiron chelator molecules can easily block these substances. Erastin works by preventing the cystine/glutamate transporter, which results in lower intracellular glutathione (GSH) concentrations.[1] Because GPX4 depends on GSH for proper operation, its loss might cause cell death of the cells based on ferroptosis mechanism.[17]Inhibition of GPX4can also be induce the process of Oxytosis/ferroptosis, as it is the mechanism of its action which is typically based on molecular mechanism of RSL3, ML162, and ML210.[16] In some of the cells, the loss of GPX4 activity can be compensated by FSP1 molecule, and for the induction of oxytosis or ferroptosis process bothFSP1 and GPX4must be inhibited at the same point of time.[18]

IV. FUTURE ASPECTS OF FERROPTOSIS

With advances in the field of experimentation, the term ferroptosis has been discovered in the pathophysiological mechanisms of an increasing number of illnesses, and it

offers a novel therapeutic approach.Additionally, ferroptosis, an independent method for causing death of a cell, that can contribute to illnesses in conjunction with other types of mechanisms responsible for death of cell, opening the door for the collaborative use of current treatment plans and assisting in the resolution of drug resistance difficulties in specific diseases. Ferroptosis research, however, is still in its infancy, and there are still many of issues to be resolved.[1]Ferroptosis inducers or inhibitors are effective treatments for a variety of illnesses. Tumors, neurological disorders, organ damage, etc. have all been treated by ferroptosis. Several investigations have presented proof that ferroptosis can stop tumor development. It has been shown that ferroptosis inducers are cytotoxic to a variety of cancerous cells both inside the living system and in experimental tubes.[1,19,20] It is proved that activators of ferroptosiscan also be transported by some specific carriers as an alternative to direct administration of ferroptosis agents, which revealed improved anticancer results.[21,22] Since certain nanoparticles, like C' dots, may cause ferroptosis, implication of the same nanoparticles is an another efficient technique to cause ferroptosis particularly in neoplastic tissues. an example is, the study in which different-sized Fe3O4 nanoparticles have demonstrated variable capacities to cause ferroptosis.[23] Additionally, one strategy to improve the effectiveness of tumor immunotherapy is to control the immune cells' susceptibility to ferroptosis.[24]Ferroptosis is also linked to a few neurological conditions. According to a recent research, the glycoprotein molecule used for transport of lipids, known as apolipoprotein E (ApoE),which is a key protein found in Alzheimer's disease**.**[25] can shield cells against substances that cause ferroptosis, such as erastin and SAS. By loweringthe release of iron from ferritin by means of activating the PI3K/AKT pathway, apoE prevents ferroptosis[26]Ferroptosis inhibitors can improve these symptoms since the Alzheimer's mice model had down-regulated ferroportin1, a nonheme iron exporter that triggers ferroptosis, neuronal death, and memory impairment**.**[27] A stroke sub-type associated with ferroptosis is intracerebral hemorrhage. In intracerebral hemorrhage, blocking ferroptosis has a therapeutic impact,[28] also the emergence and development of a few other neurological conditions that are linked to ferroptosis, such as Parkinson's disease,Huntington's disease, and amyotrophic lateral sclerosis.[20] One of the causes of glaucoma, as recently found by Yao et al., is ferroptosis of ganglion cells of retina, caused by high intraocular pressure.[29]Ferroptosis has a role in controlling varioustypes of illnesses including TB and autoimmune disorders other than cancer and neurological disorders. Mycobacterium tuberculosis (Mtb) is the cause of TB. Ferroptosis has been demonstrated to be one of the processes by which Mtb infection results in necrosis of host cells**.**[30] Neutrophils from people with systemic lupus erythematosus exhibit ferroptosis, according to a recent research. The expression of GPX4 was suppressed in the neutrophils of patients**.**[31]Ferroptosis' mechanism and pertinent metabolic route still require investigation. New questions also emerge as research is continually advanced. For instance, the propagation of waves in ferroptosis is a rare phenomenon.[32] The mechanism behind GPX4's apparent requirement for propagation is currently unknown.[33] With the investigation of the ferroptosis mechanism, various possible inducers and inhibitors are also presented. For instance, the activity of mTOR, a key regulator responsible for growth and proliferation of cells, can be inhibited by torin 1. Under conditions of low glucose, Torin 1 is proved and demonstrated to protect cells by lowering the activity of System Xc.[34] More research is required to determine whether the activity of Torin 1 can be used as an inducer of ferroptosis. Furthermore, certain substances may have many roles. A proteasome inhibitor is MG132. Since the deubiquitinaseclass of enzyme known as OTUB1 may maintain the System Xc in a mannerdependent on proteasomes, treatment with the potent inhibitor proteasome known as MG132 enhanced the expression of System Xc.[34,35] In

this sense, MG132 can become a potential inhibitor of ferroptosis.Fortunately a different investigation found that ferroptosis inducers prevented the proteasome from being expressed. Thus, encouraging proteasome expression is advantageous for cells undergoing ferroptosis.[36]

V. CONCLUSION

It can be concluded that, the uncovering of ferroptosis has opened a new platform, which provided a totally new angle for the study of various diseases, in addition to that; its importance and clinical co-relation in the commencement, development as well as the management of illnesses has slowly become apparent. As the research and exploration of ferroptosis is still in its early stages at the moment, exploring the mechanism responsible for ferroptosis and its impact in many illnesses and its suggesting efficient and strongly focused therapeutics have significant scientific and practical utility. Ferroptosis research will continue in this manner in the future. The developmental study and proof of inducers and inhibitors of ferroptosis is a crucial research, and the ongoing discoveries of new target molecules of ferroptosis and its mechanisms can probably leads to development of various new therapeutic drugs and methods for several types of diseases. In conclusion, ferroptosis is a recently defined form of programmed cell death that is having high application prospects in various clinical conditions but still needs to be studied more for further advance ment in the area of treatment in different types of clinical conditions.

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