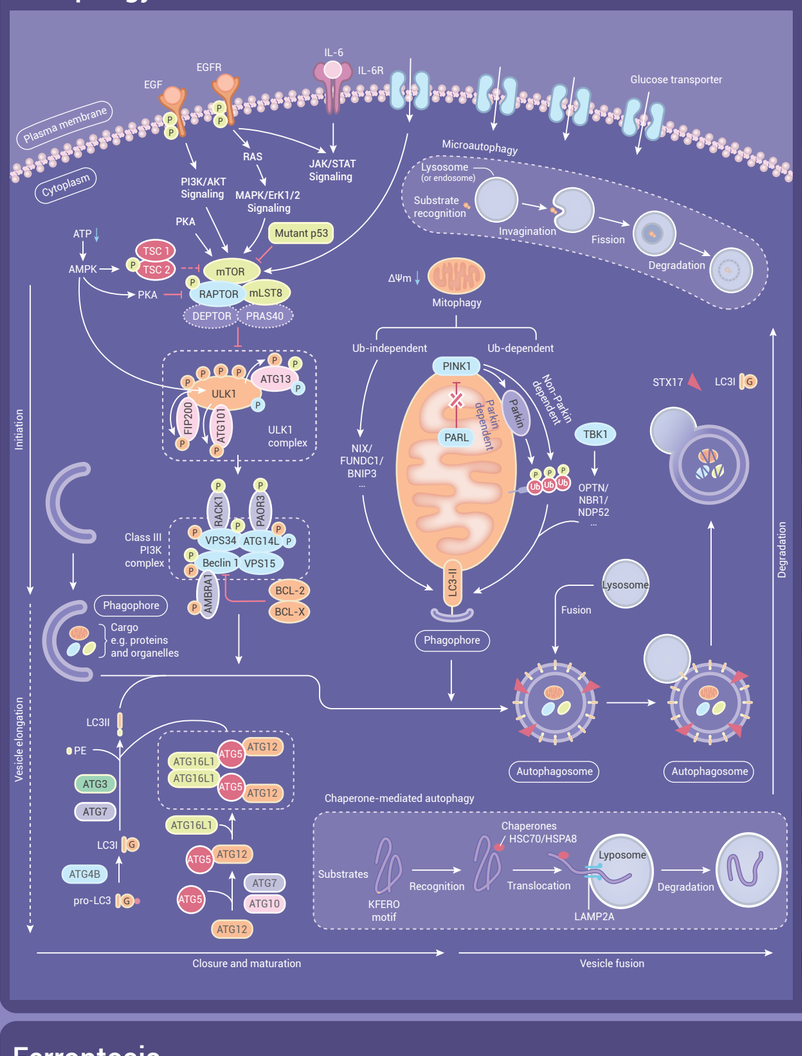
MedChemExpress Signaling Pathways --- Part Ib

Autophagy



Autophagy Inhibitors

Autophinib	HY-101920
GW406108X	HY-115570
SBP-7455	HY-137742
CA-5f	HY-112698
EACC	HY-129111

Autophagy Inducers

Rapamycin	HY-10219
MG-132	HY-13259
Adezmapimod	HY-10256
Olaparib	HY-10162

Key Regulators

mTOR
PI3K-related kinase family
RAPTOR
Regulatory protein associated with mTOR
ULK1
Unc51-like autophagy-activating kinase 1
VPS34
Components of the class III PI3K complex
Beclin 1
Autophagy-related protein
STX17
Autophagosome maturation
PARL
Mitochondrial rhomboid protease
PINK1/Parkin
Mitophagy signaling regulators
OPTN、BNIP3 etc.
Mitophagy receptors
HSC70/HSPA8
Chaperone proteins
LAMP2A
Lysosomal membrane protein

Introduction

Autophagy is the process of transporting damaged, denatured or aging proteins and organelles in cells to lysosomes for digestion, degradation and recycling. In mammalian cells, there are three main types of autophagy: microautophagy, macroautophagy, and chaperone-mediated autophagy (CMA). This article mainly focuses on autophagy, discusses its mechanism and the latest research progress.

- **Macroautophagy:** By forming an autophagosome with a double-membrane structure to wrap intracellular substances, the autophagosome and lysosome finally fuse for degradation. The autophagy we often say is generally macroautophagy.
- **Organ-specific autophagy:** It is a selective autophagy pathway, such as mitophagy, pexophagy, reticulophagy, ribophagy, nucleophagy, lysophagy autophagy, etc. It can selectively eliminate organelles. The most widely studied selective autophagy pathway is mitophagy.
- **Microautophagy:** The process of cytoplasmic contents entering lysosomes through lysosomal membrane deformation, which is mainly divided into four steps: substrate recognition, membrane invagination, fusion, and degradation.
- **Chaperone-mediated autophagy (CMA):** With the help of HSP70 molecular chaperone, the protein with KEFRQ-like motif restores the protein from the folded state to the unfolded state, and then transports it through LAMP-2A transported to the lysosome for degradation.

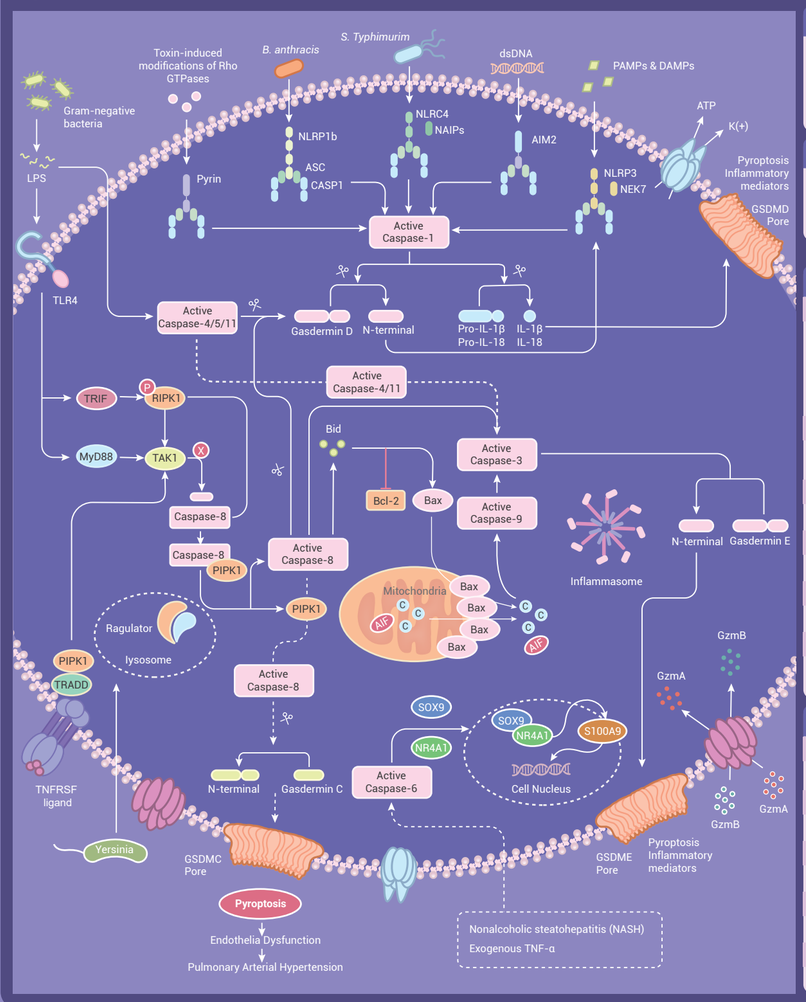
Morphological Features

Amorphous cytoplasm, Nuclear fragmentation and pyknosis,
Accumulation of autophagosomes,
Fusion of autophagosomes, lysosomes to degrade contents.

Biochemical Features

LC3 lipidation, Increased lysosomal activity.

Pyroptosis



Inhibitors

Disulfiram	HY-B0240
LDC7559	HY-111674
Morroniside	HY-N0532
Ac-FLTD-CMK	HY-111675

Activators

ICy OH	HY-150970
ICy-Q	HY-150971
8αTGH	HY-138071

Key Regulators

Caspase Family
Caspase 1 Caspase 3 Caspase 4/5/11 Caspase 6 Caspase 8 Caspase 9
NOD-like Receptor (NLR)
NLRC4 NLRP3
NLRP1 Ptorein
NLRP1b
AIM2
Absent in melanoma 2
Toll-like Receptor (TLR)
TLR4
Interleukin Related
IL-1β IL-18

Represented Complexes

Pyrin
ASC-CASP1
NLRP1b
ASC-CASP1
NLRC4
ASC-CASP1+NAIPs
AIM2
ASC-CASP1
NLRP3
ASC-CASP1+NEK7

Introduction

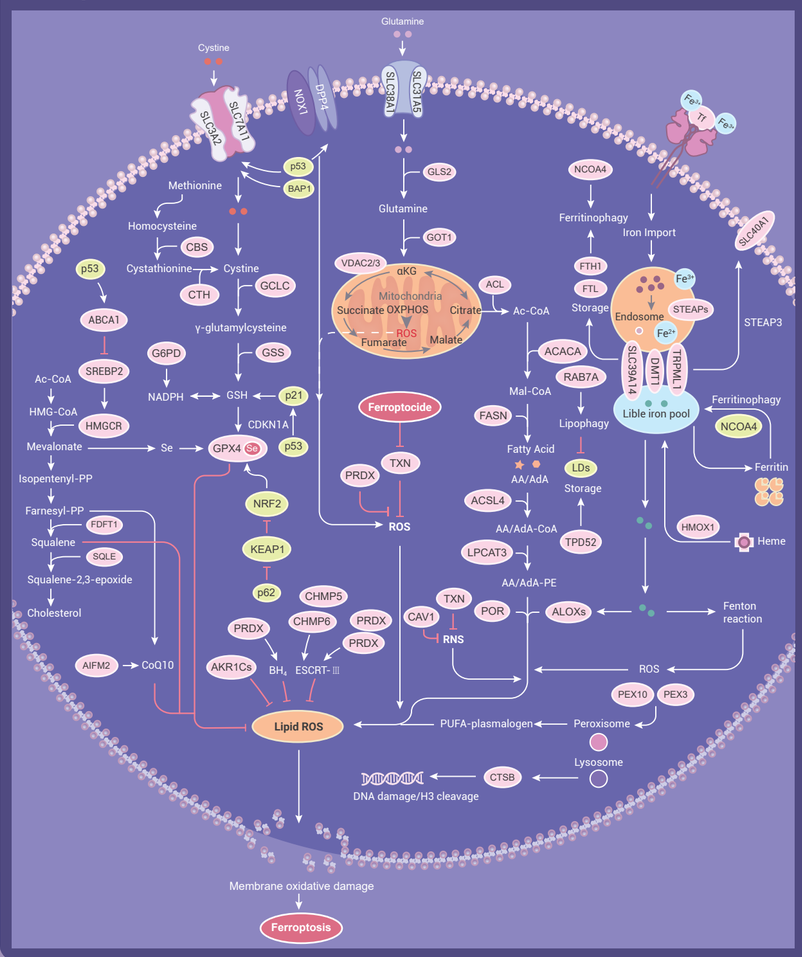
Pyroptosis, also known as pyroptosis programmed cell death. Pyroptosis, distinct from apoptosis and necroptosis, is caused by the activation of inflammasomes and inflammatory caspases.

1. Pyroptosis is the Gasdermin-mediated programmed cell death. Gasdermin proteins have membrane pore-forming activity, thus Gasdermin cleavage causes membrane perforation and leakage of cell contents.
2. Pyroptosis mainly occurs through Caspase1-dependent and independent pathways in response to certain bacterial damage disease, and immune responses. It causes cell swelling, cell membrane blistering and other cell lysis phenomena.
3. The process of pyroptosis includes pathogen infection, inflammasome formation, Caspase protein activation, Gasdermins cleavage, and cell membrane rupture. Cellular debris formed by pyroptosis is cleared by surrounding macrophages.

Main Participants

1. Caspase-1: Mediated the cleavage of the substrate GSDMD and pro-inflammatory cytokines (such as pro-IL-1β and pro-IL-18). Inflammasome complex: NLRP3, AIM2, and Pyrin bound ASC, thereby recruiting Caspase-1; or NLRC4 and NLRP1b directly bound Caspase-1.
2. Caspase-4/5/11: Combined with LPS, directly cut Gasdermin D and led to cell membrane perforation. Activated Caspase-4/11 cleavage, thereby activated Caspase-3, which further cleaved GSDME.
3. Caspase-3: Related to apoptosis and pyroptosis. Activated and indirectly drove the cleavage of GSDME during viral infection.
4. Caspase-6: Controled NR4A1-SOX9 interaction to drive liver inflammation. Specifically, SOX9 served as a coactivator of NR4A1 targeting the downstream gene S100A9, led to NEK7/NLRP3 inflammasome activation and pyroptosis.
5. Caspase-8: Mediated GSDMD-dependent pyroptosis. Regulated the RIPK3/MLKL signaling pathway and may cross-communicate with necroptosis.

Ferroptosis



Ferroptosis Inducers

RSL3	HY-100218A
Erastin	HY-15763
Sorafenib	HY-10201
FIN56	HY-103087
Sulfasalazine	HY-14655

Ferroptosis Inhibitors

Ferrostatin-1	HY-100579
Liproxstatin-1	HY-12726
YL-939	HY-152093
Rosiglitazone	HY-17386
ML162	HY-100002
ML210	HY-100003

Key Regulators

SLC7A11
Cystine/glutamate transporter
SLC38A1
Glutamine transpoter
HSPB1
Heat Shock protein
TFRC
Iron importer
VDAC2/3
Mitochondrial porins
ACSL4
Lipid biosynthesis
NCOA4
Ferritinophagy
ALOXs
Lipoxygenase
Hemoglobin Hemin
Iron containing protein
BAP1
Epigenetic regulation
CTSB
Lysosomal cell death
AIFM2
CoQ10 production
Cyst(e)inase
Cysteine depletion
CHMP5/6
ESCRT-III membrane repair
PEX10/3
Peroxisome
NRF2 (NFE2L2)
Transcription factor

Introduction

Ferroptosis is a new type of RCD that depends on iron and characterized by the accumulation of lipid peroxides, and is genetically and biochemically distinct from other forms of regulated cell death such as apoptosis. This article mainly focuses on ferroptosis and discusses its mechanism and the latest research progress.

1. Ferroptosis is a regulated cell death that depends on iron-mediated oxidative damage.

2. Ferroptosis can occur through two main pathways: the exogenous (transporter-dependent) pathway and the endogenous (enzyme-regulated) pathway.

3. Increased iron accumulation, production of free radicals, fatty acid supply and increased lipid peroxides are the keys to induce ferroptosis.

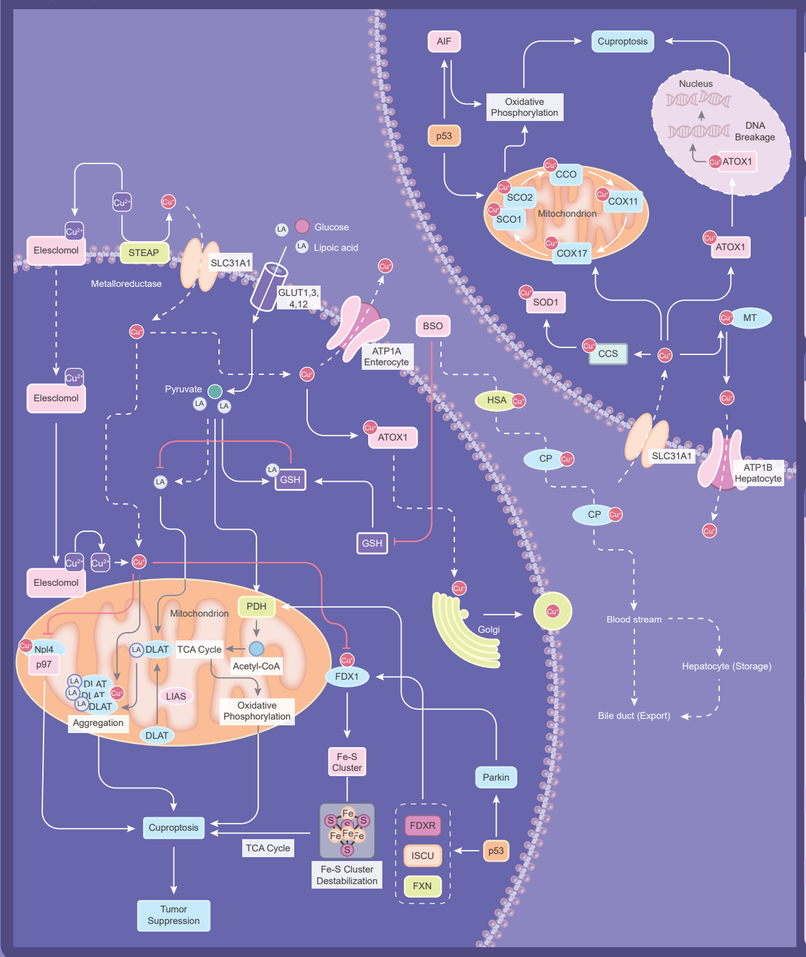
Morphological features

- Increased Mitochondrial membrane density,
- Reduced Mitochondrial cristae,
- Ruptured mitochondrial outer membrane, but the nucleus is normal

Biochemical features

- Iron accumulation and lipid peroxidation,
- Inhibition of System xc- , Downregulation of GSH level, GPX4 inhibition

Cuproptosis



Inhibitors/ Copper Chelators

Tetrathiomolybdate	HY-128530
Salpyran	HY-132927
Penicillamine	HY-B0300
Ammonium tetrathiomolybdate (VI)	HY-W076067

Inducers/ Copper Ionophores

Zinc Pyrithione	HY-B0572
Elesclomol (STA-4783)	HY-12040
Disulfiram	HY-B0240
Cu(II)GTSM	HY-139324
Clioquinol	HY-14603

Others

Cuproptosis Compound Library HY-L133

Key Regulators

Membrane Transporters
SLC31A1 ATP1A/B
Cytoplasmic Transporters
FDX1 ATOX1 MT
Mitochondrial Transporters
SCO1/2 CCO COX11 COX17
Plasma transporters
HSA CP
Protein Complexes
Fe-S Cluster Npl4-p97 DLAT

Introduction

Cuproptosis is a form of cell death induced by copper-targeted TCA cycle fatty acylated proteins. Unlike other known programmed cell deaths (apoptosis, pyroptosis, necrosis, ferroptosis), it is highly related to mitochondrial respiration and lipoic acid (LA) pathways. Cuproptosis can be inhibited by copper chelators, but can not be inhibited by ferroptosis inhibitors, necrosis inhibitors, or oxidative stress inhibitors.

1. Normally, copper is transported through the blood system to maintain dynamic balance. It has extremely low levels in the internal environment. Dysregulation of copper homeostasis can lead to cellular metabolic disorders.

2. Cuproptosis, due to copper ions combine with lipoylated TCA cycle proteins to promote the aggregation and functional loss of lipoylated proteins. The process triggers the instability of iron-sulfur cluster proteins, and ultimately induce proteotoxic stress and cell death.

3. The hallmark of cuproptosis, is protein thioctylation of the tricarboxylic acid (TCA) cycle in the mitochondrial respiratory chain.

4. The main cell morphological manifestations of cuproptosis, are mitochondrial shrinkage, cell membrane rupture, endoplasmic reticulum damage, and chromatin rupture.

Main Participants

- FDX1: Ferredoxin 1, a small molecule protein containing iron-sulfur clusters, with electron transport function;
- LIPT1: Lipoate transferase, which catalyzes the binding of fatty acids to the mitochondrial 2-keto dehydrogenase complex and glycine cleavage system through covalent linkage;
- LIAS: Lipoic Acid Synthetase, involved in the biosynthesis process of alpha-lipoic acid in organisms;
- DLAT: Dihydrolipoamide Acetyltransferase, in glucose metabolism, decomposes gluconic acid (pyruvate) into acetyl coenzyme A (acetyl-CoA).