The Cell Death Census 2024

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Abstract

Cell death plays a pivotal role in many physiological processes, such as cell homeostasis, embryonic development, immune defence and in the pathophysiology of numerous diseases, such as cancer, infections and degenerative diseases. However, the lack of a comprehensive and up-to-date resource on cell death regulators poses a significant challenge to researchers in the field. Existing databases are often limited in scope, differ in content and are updated irregularly. This deficiency impedes progress in understanding the intricate molecular mechanisms governing cell death and hampers the development of targeted therapies. To address this, we have performed a census of the existing cell death databases as well as the cell death-associated entries in the UniProt and Gene Ontology databases. To ensure high quality, we have focused on manually curated entries rather than those created from automatic prediction tools. The results have been consolidated into a joint database of the known cell death regulators, including both proteins and non-coding RNAs. The Cell Death Census 2024 results and the associated python code for database parsing, cleaning and merging is publicly available at https://github.com/Aitslab/CellDeathCensus/.

Keywords

Cell death; apoptosis; necrosis; autophagic cell death; ferroptosis; lysosome-dependent cell death; database mining

Introduction

Cell death exists in accidental or regulated form (regulated cell death, RCD). Many forms of RCD, e.g. apoptosis, necroptosis, autophagic cell death, ferroptosis, have been described in the literature. In the past, these were thought of as distinct types of cell death but their tight interconnection has become increasingly obvious [1, 2, 3, 4, 5]. Thus RCD is better thought of as a single process, executed through a network of redundant pathways and feedback loops.

Regulated cell death (RCD) in a physiological setting, often referred to as programmed cell death (PCD), is crucial for many of the key processes of life such as tissue and colonial homeostasis, tissue remodeling, embryonal development and immune defense [6]. Consequently, both a lack of cell death where it is needed, or its aberrant activation contribute to a vast array of diseases in humans and other organisms. This makes cell death an important therapeutic target [7, 8, 9]. Alterations in cell death can be caused by numerous genetic or epigenetic changes, toxic substances, pathogens or other cell stressors.

Despite the importance of RCD, the exact molecular pathways regulating and executing it in all of these situations is typically not yet elucidated in full. Consequently, while many therapeutic efforts aim to modulate RCD, it is not yet possible to do so by specifically targeting the cell death machinery. One exception is venetoclax, which inhibits the BCL2 apoptosis regulator (BCL2) inhibitor and is used in leukemia treatment [10, 11], providing proof of concept for the usefulness of such targeted drugs.

To capture the current state of knowledge on RCD, a number of manually curated databases of cell death regulators have been created [12, 13, 14, 15, 16, 17, 18, 19, 20, 21]. In line with the traditional views on distinct cell death types, these are unfortunately typically limited in scope and most focus on apoptosis regulators. Even those with a broader scope, such as UniProt [22] and Gene Ontology [23] differ substantially in the listed cell death regulators. Furthermore, most of the databases are not updated regularly. To clear up this jungle of resources, we have performed a census of the existing databases and created a joint list over the known cell death-regulating proteins and non-coding RNAs. A similar effort has previously been made by the creators of the iPCD database [15], but unfortunately it has not been updated in several years and also left out some relevant databases. Our up-to-date census provides a clear overview over the state of knowledge in 2024, thereby facilitating further research on RCD.

Methods

Census procedure

Cell death databases were identified by Google search (search term “cell death database”) and from link lists in the websites of cell death-related organizations and databases. In addition, the GeneOntology and the UniProt database, which are widely used to look up functional associations with biological processes were included. To extract database content, bulk download files were used where they had been made available. Otherwise, database content was parsed from the database web site. Database entries not unambiguously related to cell death (e.g. autophagy regulators) or generated through automatic predictions (e.g. orthologue search) were excluded where possible. All data was downloaded on 2024-03-28 (ncRDeathDB V2 and FerrDb V2) or 2024-04-04 (all others).

Content from different databases included identifiers, symbols, primary and alternate names, functional information, species information and other descriptive data. Column headers and species names were reviewed manually and unified where possible to enable database merging

(see Supplemental file 1 for column mapping). Names and symbols were pooled into a single synonym list as there was no consistent distinction between them in the databases. In addition, missing data that could be unambiguously identified from information on the database website, publication or other columns (e.g. species-related information, information about the cell death pathway and identifiers included in listed hyperlinks) was filled in.
For duplicate identification within individual databases, UniProt accession numbers (column 'UniProt_AC') were used where available. Alternatively, duplicates were assessed using gene symbols together with species information (columns 'Symbol' + 'Species' or 'NCBI_TaxID').
To ensure reproducibility and transparency, data extraction, cleaning and merging was performed using python code in a Colab notebook (Supplemental file 2). For the few exceptions where manual processing was needed, e.g. to download files, this is described in the notebook as well.

Included databases

ApoCanD: Database of Human Apoptotic Proteins in the context of cancer [12]
http://crdd.osdd.net/raghava/apocand/
This database contains 82 cancer-related genes involved in apoptosis.

DeathBase [13]
http://www.deathbase.org/
This database contains genes involved in different cell death processes. As the bulk files available for download were incomplete, database content was parsed from the "Proteins" overview web page (http://www.deathbase.org/proteins.php, accessed 2024-03-21) and the "Full view" page (http://www.deathbase.org/edit_view.php, accessed 2024-03-21). Only the manually curated part, which contains proteins from human, fly, mouse, worm and zebrafish, was extracted, whereas the data for other organisms, resulting from homology searches, was excluded. Entries for which the Pathway was only "IMMUNITY" were also excluded.

FerrDB V2 [14]
http://www.zhounan.org/ferrdb/current/
This database contains genes and compounds involved in ferroptosis. Database files for Driver, Suppressor, Marker, Unclassified sections were downloaded manually (http://www.zhounan.org/ferrdb/current/operations/download.html, accessed 20240325). The extended gene data from two more studies not yet included in the database [24, 25] was also downloaded from the FerrDB V2 website.

GO: Gene Ontology database [23]
https://geneontology.org/
This general database contains information on genes related to all kinds of biological processes. Cell death-related GO terms were identified by manually reviewing the term tree on AmiGO 2, the official web tool for accessing the database (https://amigo.geneontology.org/) (Table 1). The selected high-level terms included the subterms linked to the UniProt keywords used when extracting UniProt data (Table 2). To extract all genes associated with the GO terms from AmiGO 2 a download link was generated after performing a manual search for the first term and then selecting fields of interest (Figure 1). Links for the other GO terms were created by id substitution in the link.

Table 1. GO terms used in the census.

GO term	Process	Pathway

GO:0008219	cell death	
GO:0019835	cytolysis	
GO:0001906	cell killing	
GO:0097213	regulation of lysosomal membrane permeability	lysosomal_CD
GO:0046902	regulation of mitochondrial membrane permeability	
GO:0036337	Fas signaling pathway	
GO:0043293	apoptosome	Apoptosis
GO:0097136	Bcl-2 family protein complex	
GO:1990346	BID-BCL-xl complex	
GO:0005757	mitochondrial permeability transition pore complex	MPT

Figure 1. Fields extracted from the GO database

- Acc (id)
- Direct annotation (annotation_class_list)
- Direct annotation (annotation_class_list_label)
- Gene/product (bioentity_label)
- Gene/product name (bioentity_name)
- Synonyms (synonym)
- Organism (taxon)
- Organism (taxon_label)
- Type (type)
- Source (source)

iPCD: Integrated Annotations for Programmed Cell Death [15]
http://ipcd.biocuckoo.cn/
This database contains genes involved in a very large variety of cell death types. Only the "Reviewed" part was extracted whereas the data generated by orthologue search ("Unreviewed") was excluded. Entries only related to Autophagy were also excluded.

lncPCD [16]
http://spare4.hospital.studio:9000/lncPCD/
This database contains lncRNAs associated with apoptosis, autophagy, ferroptosis, necroptosis and pyroptosis and their disease associations. Entries only related to Autophagy were excluded.

MCDB: Mitotic Catastrophe Database [17]
http://www.combio-lezhang.online/MCDB/index_html/
This database contains genes and compounds related to mitotic catastrophe.

ncRDeathDB, Release 2.0 [18]
http://www.rna-society.org/ncrdeathdb/

This database contains miRNAs, lncRNAs and snoRNAs related to apoptosis, necrosis and autophagy and their target genes. Both non-coding RNAs and target genes were extracted. Autophagy-related entries were excluded.

RCDMap: Comprehensive Map of the Regulated Cell Death Signaling Network [19]
https://navicell.vincent-noel.fr/pages/maps_rcd.html
As the data was no longer accessible on the main website, the version deposited in Minerva was downloaded by manual export (https://acsn-curie.lcsb.uni.lu/minerva/index.xhtml?id=Regulated_Cell_Death, accessed 20240404).

UniProt, Release 2024-02 [22]
https://www.uniprot.org/
This general database contains information on proteins related to all kinds of biological processes. All UniProt keywords were downloaded and manually reviewed to identify those linked to cell death. For each keyword all "Reviewed" entries, corresponding to the SwissProt part of UniProt, were extracted. Species names were typically in the format Latin name (Common name). For the most frequent species, common names were removed to enable merging with other databases.

Table 2. UniProt keywords used in the census.

Keyword ID	Process	Pathway	Related GO terms
KW-0053	Apoptosis	Apoptosis	GO:0006915:apoptotic process
KW-0381	Hypersensitive response		GO:0009626:plant-type hypersensitive response
KW-0928	Hypersensitive response elicitation		GO:0034053: symbiont-mediated perturbation of host defense-related programmed cell death
KW-0959	Myotoxin		
KW-1061	Dermonecrotic toxin		
KW-1073	Activation of host caspases by virus	Apoptosis	GO:0019051:induction by virus of host apoptotic process
KW-1081	Inhibition of host apoptosis by viral BCL2-like protein	Apoptosis	GO:0019050:suppression by virus of host apoptotic process
KW-1082	Inhibition of host apoptosis by viral FLIP-like protein	Apoptosis	GO:0019050:suppression by virus of host apoptotic process
KW-1085	Inhibition of host caspases by virus	Apoptosis	GO:0019050:suppression by virus of host apoptotic process
KW-1119	Modulation of host cell apoptosis by virus	Apoptosis	GO:0039526:perturbation by virus of host apoptosis
KW-1210	Necrosis	Necrosis	GO:0012501:programmed cell death

yApoptosis [20]
http://www.ycelldeath.com/yapoptosis/
This database contains genes related to apoptosis in yeast.

XDeathDB [21]
https://pcm2019.shinyapps.io/XDeathDB/
This database contains human genes related to 12 modes of cell death and information on associated diseases and drugs. After searching in the Cell Death Engine section for cell death modes "All" and disease types "All" the csv file with all entries was downloaded manually. Entries displaying "Autophagy", "Proliferation" or no value as cell death mode were excluded.

Excluded databases

Apoptosis DB [26]
http://www.apoptosis-db.org
This database contained proteins related to apoptosis. It is no longer publicly accessible.

BCL2DB: BCL2 DataBase [27]
https://bcl2db.lyon.inserm.fr/
This database was not available for bulk download and undergoing a major revision at the time of the census (personal communication with the developer Christophe Combet, 20240321).

CASBAH : The CAspase Substrate dataBAse Homepage [28]
https://bioinf.gen.tcd.ie/casbah/
This database contained caspases and their substrates. It is no longer publicly accessible.

CASBASE: The Database for Caspases & Substrates
http://origin.bic.nus.edu.sg/casbase/
This database contained caspases and their substrates. It is no longer publicly accessible.

Cell Death Proteomics (CDP) database [29]
http://celldeathproteomics.uio.no/
This database contained proteins related to cell death. It is no longer publicly accessible.

Results

Cell death-related databases greatly vary in scope, size and update frequency

Seven cell death-specific and two general gene/protein annotation databases were included in the census (Table 3). The Bcl2DB database was excluded as it is currently undergoing a major revision and lacks bulk download options. This will hopefully be completed in time for the next census update. In addition, four databases reported in the literature were found to be no longer accessible: Apoptosis DB, CASBAH, CASBASE and Cell Death Proteomics database.

When examining the content of the available cell death-related databases, large variations were observed regarding the types of cell death, species, size and update frequency. While the large general databases UniProt and GO were not limited to a specific cell death type, only one of the specialized cell death databases, iPCD had a similarly broad scope. A similar limitation in scope was seen on the species level. Both the iPCD and the DeathBase also have a section with many additional species and entries, generated by orthologue prediction but as we wanted to focus on high quality manually reviewed data this data was not included. The number of entries in each database, after removal of duplicates ranged from 51 (yApoptosis) to 10870 (GO). However, a large part of the GO database is not manually curated. As it was not immediately obvious which entries in GO stemmed from automated annotation, these were not excluded for this database.

Of the databases which reported their last update on the website, which several did not, only UniProt and GO were updated regularly. iPCD, the only other database comparable to our efforts, was last updated in 2021, highlighting the need for this new census.

Table 3. Overview over the databases in the Cell Death Census 2024

Database	**Entry count**	**Species**	**Source**	**Link**	**Last update**
DeathBase	207	human, fly, worm, mouse, zebrafish	Manual curation	http://www.deathbase.org/	unclear
ApoCanD	82	human	Manual, subset of DeathBase	http://crdd.osdd.net/raghava/apocand/	unclear
Mitotic Catastrophe Database (MCDB)	1214		Manual curation	http://www.combio-lezhang.online/MCDB/	unclear
ncRDeathDB, release 2.0	614 RNAs + 746 target genes	multiple	Manual curation	http://www.rna-society.org/ncrdeathdb/	unclear
FerrDb V2	724 + 30*	human, mouse, rat, pig, fly	Manual curation	http://www.zhounan.org/ferrdb/current/	2022-09-09
yApoptosis	51	yeast	Manual curation	http://www.ycelldeath.com/yapoptosis/	2013-10-01
GO (AmiGO 2 version: 2.5.17)	10870	multiple	Manual and automated curation	https://amigo.geneontology.org/	2024-01-19
UniProt, Release 2024_02	3848	multiple	Manual curation	https://www.uniprot.org/	2024-02
iPCD	4399	multiple	Manual curation	http://ipcd.biocuckoo.cn/	2021-06-25
XDeathDB	6779	human	Manual curation	https://pcm2019.shinyapps.io/XDeathDB/	unclear
lncPCD	1176	human, mouse, rat	Manual curation	http://spare4.hospital.studio:9000/lncPCD/	unclear
RCDMap	1146	human#	Manual curation	https://acsn-curie.lcsb.uni.lu/minerva/index.xhtml?id=Regulated_Cell_Death	unclear

* This database consisted of the main database and extended data. Both were included.

This database was assumed to contain only human data as all entries with UniProt_AC came from this organism.

The Cell Death Census 2024 gathers a large number of cell death regulators but species coverage is very uneven

To merge the data obtained from the different databases, column names were manually reviewed and unified where suitable. Missing data was filled in where unambiguously possible. For example, we added species information listed on the website and extracted identifiers contained in hyperlinks. In total, we obtained 49544 records from the census (Supplemental file 1). This included a large number of partially duplicate records. As the naming was inconsistent between databases it was impossible to fully merge the duplicates without extensive manual review. It was therefore not attempted.

Nevertheless, we tried to obtain an estimate of the unique number of regulators in the census dataset. For this purpose, we first examined the presence of commonly used identifiers (Table 4) that could be used for merging. Despite the ambiguity, symbols (column 'Symbol') were the most frequent identifiers, followed by UniProt accession number (column 'UniProt_AC'), which covers only proteins. When merging the Census results on UniProt_AC, we obtained 14746 unique records (Supplemental file 4).

Table 4. Frequency of common identifiers in the Cell Death Census (45012 records)

Identifier	Records (with duplicates)
Symbol	48690
UniProt_AC	23594
Ensembl	13143
NCBI_GeneID	7662
HGNC_ID	3807
miRBase_ID	2119

An alternative strategy to merge duplicates is to merge on symbol and species information combined, thereby reducing ambiguity. For this, we first filled in missing values for Species and NCBI_TaxID based on the existing pairs in the dataset. When counting the occurrence of each species, it was clear that most records represent human data (Table 5). After merging on the combined Symbol and Species, we obtained 25555 unique records (Supplemental file 5). Similar results were seen after merging on Symbol and NCBI_TaxID which resulted in 25329 unique records (Supplemental file 6.

Table 5. Frequency of the most common species terms in the Cell Death Census

Species	Count
homo sapiens	25594
mus musculus	5485
rattus norvegicus	2426
bos taurus	932
canis lupus familiaris	882
sus scrofa	839
danio rerio	596
strongylocentrotus purpuratus	558

gallus gallus	542
drosophila melanogaster	471
xenopus laevis	330
caenorhabditis elegans	319
xenopus tropicalis	318
oryzias latipes	258
arabidopsis thaliana	237
macaca mulatta	212
pan troglodytes	207
equus caballus	205
felis catus	204
gorilla gorilla gorilla	203
branchiostoma floridae	183
lepisosteus oculatus	180
daphnia pulex	178
monodelphis domestica	157
ornithorhynchus anatinus	142
triticum aestivum	140
saccharomyces cerevisiae s288c	132
pongo abelii	128
saccharomyces cerevisiae	125
anolis carolinensis	115
candida albicans sc5314	112
nakaseomyces glabratus cbs 138	109
candida dubliniensis cd36	102
candida parapsilosis cdc317	102
anopheles gambiae	97
nematostella vectensis	95
helobdella robusta	95
[candida] auris	91
caenorhabditis briggsae	90
tribolium castaneum	86
arabidopsis thaliana (mouse-ear cress)	82
brassica napus	77
pristionchus pacificus	73
dictyostelium discoideum	66
nicotiana tabacum	61
ciona intestinalis	60
gossypium hirsutum	58
capsicum annuum	55
glycine max	52
ixodes scapularis	49

Existing cell death databases are strongly biased towards apoptosis

We next examined the frequency of different cell death types. A strong bias towards apoptosis was observed. One notably absent term was “autophagic cell death”. Several databases had included autophagy regulators, but these were excluded as the databases did not distinguish between autophagic cell death regulators and pro-survival autophagy regulators.

Table 6. Frequency of cell death terms in the Cell Death Census

Term	Count
Apoptosis	17823
Immunogenic or immunogenic cell death	3458
Mitotic catastrophe or mitotic_CD	3019
Autosis	1833
Ferroptosis	1658
Anoikis	742
Pyroptosis	718
Lysosomal cell death or lysosomal_CD	645
Necroptosis	365
Parthanatos	306
Hypersensitive response	253
MPT	204
Necrosis	119
Efferocytosis	30
Disulfidptosis	22
Heterokaryon incompatibility	18
Cuproptosis	17
Entosis	15
NETosis	11
Excitotoxicity	10
Alkaliptosis	8
Paraptosis	7
Phagoptosis	5
Cornification	3
Wallerian degeneration	3
Oncosis	2
PANoptosis	1
Phenoptosis	1

Discussion

It is important for researchers to be aware of the state of the current knowledge in their field. Therefore, many bioinformatics databases have been produced to list genes, proteins and/or

non-coding RNAs linked to specific processes. These databases can be populated by manual curation or algorithms. Such databases are for example used when estimating changes in specific pathways in omics experiments or when trying to piece together signaling pathways. Within the field of cell death research, several such databases have been compiled with manually curated data. These vary greatly in species, cell death processes, gene types, number of entries and other aspects. The scatteredness of this information makes it difficult for researchers to make use of it in full. There has previously been an effort by the iPCD database to combine some of this data but unfortunately general databases that are widely used in pathway analysis were left out. The database has also not been updated since 2021. To unite the existing information on cell death regulators we therefore conducted a census of the available databases, also including GO and UniProt, two of the most widely used general databases with functional annotations. All results as well as two Colab notebooks (Supplemental file 1-3) to repeat the analysis are made publicly available. The latter enables cell death researchers to repeat the census in an almost fully automated manner. Frequent updates of the census do not seem to be necessary, however, as most of the surveyed databases had not been updated in years.

The Census revealed a large number of reported cell death regulators. However, there was a strong bias towards human apoptosis-related protein-coding genes. Future curation efforts should therefore aim to include genes from a broader range of species and alterative cell death types as well as non-coding RNAs.

One of the largest problems encountered in the data analysis was the inconsistent use of unique identifiers. Indeed, many entries were only listed with the highly ambiguous gene symbol. This makes it impossible to fully merge the content of different databases without extensive manual work. We strongly recommend that database designers list several common identifiers for each entry, e.g. UniProt_AC, HGNC_ID and NCBI_GeneID. Likewise, species should be unambiguously identified with the widely used NCBI_TaxID.

Another problem was that several databases were no longer accessible or lacked bulk download options. Database developers should consider uploading a copy of their database and all updates to a general research data repository. This would ensure that manual curation efforts are not lost when database developers can no longer maintain the online presence of their database. At the same time, deposited datasets will also receive a DOI and version number, making it easier for other researchers to cite the data in a clear manner.

A full list of recommendations for database developers based on our experience with the Census can be found in Box 1.

Box 1. Recommendations for database development and maintenance

1. At the time of release and with every update, a copy of the database should be deposited in a general research repository (e.g. zenodo) where it will receive a DOI and version number. This DOI should be included in the research article describing the database.
2. A clear description of the database scope (e.g. gene type, species, cell death type), curation procedure, manual annotation guidelines, external sources, files and column headings should be published on the database page and deposited in a general research repository together with the database content. For automated content collection, e.g. by orthologue search or import from other databases, a clear description of the procedure and all settings, and/or the code used in the process, should be provided.

3. The date of the last update and database version should be highlighted on the landing page of the database.
4. An option for automated bulk download of the database content should be provided.
5. Genes should be identified unambiguously with several general identifiers, e.g. UniProt_AC + HGNC_ID + NCBI_GeneID. Ensure that the identifiers are still active at the time of database release and update with each release.
6. Species should be identified unambiguously with NCBI_TaxID + Linnean name.
7. PMIDs should be provided so end users can review the evidence used during manual curation.
8. Delimiters used to separate content within a column and between columns should be different and used consistently.
9. Empty values should be indicated clearly and consistently.

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Competing Interests Statement

The authors have no competing interests in relation to this article.

Supplemental data

Supplemental files are available on
https://github.com/Aitslab/CellDeathCensus/SupplementalData

Supplemental file 1. Cell Death Census 2024 – zip file with all merged data
Supplemental file 2. Cell Death Census 2024 – Data collection colab notebook
Supplemental file 3. Cell Death Census 2024 – Data analysis colab notebook
Supplemental file 4. Cell Death Census 2024 – unique entries merged on UniProt_AC
Supplemental file 5. Cell Death Census 2024 – unique entries merged on Symbol + Species
Supplemental file 5. Cell Death Census 2024 – unique entries merged on Symbol + NCBI_TaxID

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