Apoptosis-related terms in the Gene Ontology (GO)

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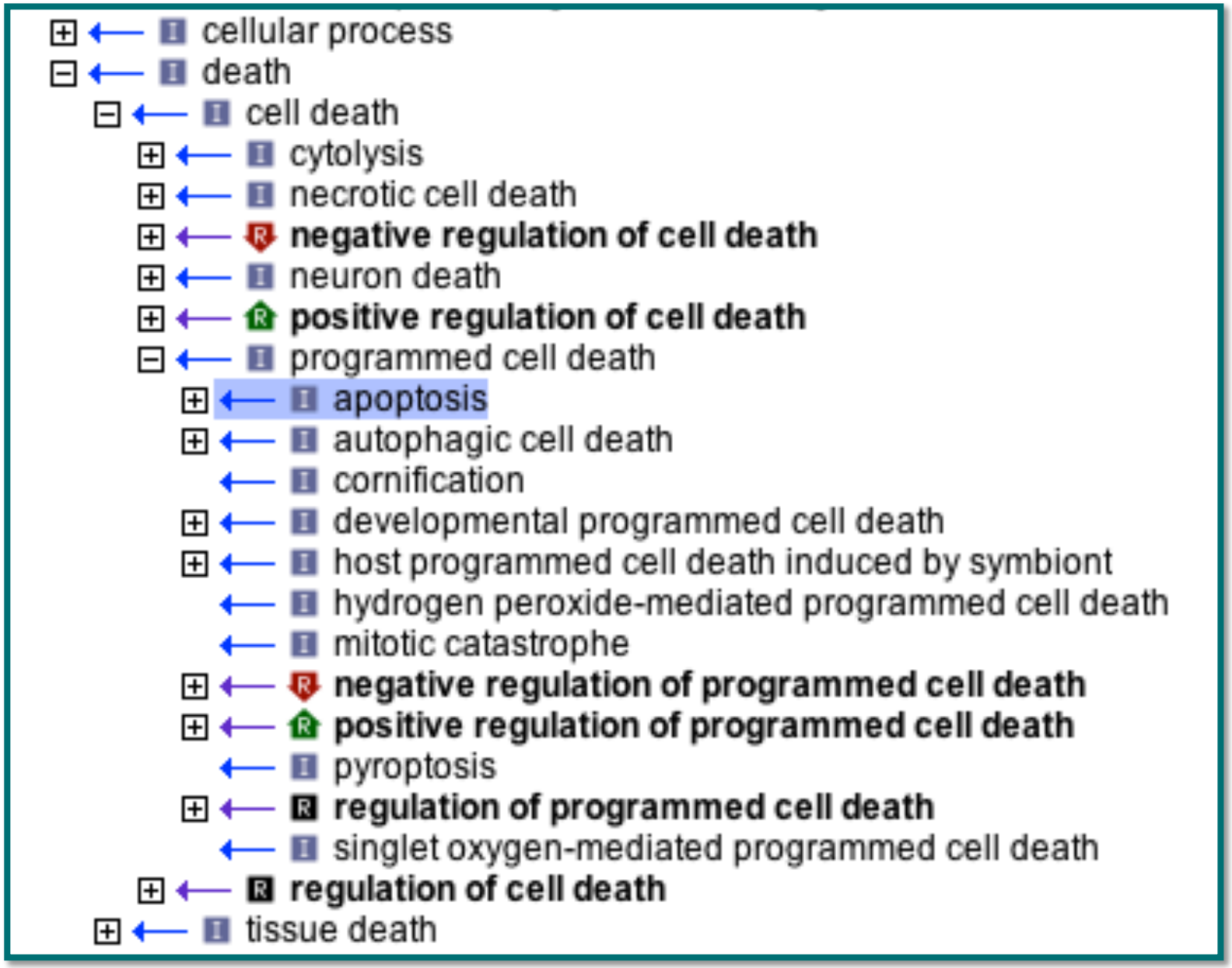
Apoptosis GO project call, 20/7/2011

Outline of the call

- Ask for your approval (or comments) on some apoptosis GO terms that were discussed during the content meeting held at EBI on June 1st. These are top-level terms in the apoptosis node and we need a final resolution on them.
- Ask for your advice on other apoptosis GO terms that could not be fully examined during the content meeting.

For your reference: current tree-view



GO:0008219 cell death

- The definition of GO:0008219 cell death should include all types of cell death, so we can refer to it when we define the apoptotic process.
- Current definition: A biological process that results in permanent cessation of all vital functions of a cell.

Proposal for definition of GO:0008219 cell death

- Based on recommendations of Nomenclature Committee on Cell Death 2009 (PMID:18846107):
- Any biological process that results in permanent cessation of all vital functions of a cell. A cell should be considered dead when any one of the following molecular or morphological criteria is met: (1) the cell has lost the integrity of its plasma membrane; (2) the cell, including its nucleus, has undergone complete fragmentation into discrete bodies (frequently referred to as 'apoptotic bodies'); and/or (3) its corpse (or its fragments) has been engulfed by an adjacent cell *in vivo*.

- **This will be implemented unless you have serious concerns.**

New GO term: apoptotic body

- Apoptotic bodies are always present in apoptotic process.
- Currently, they're not referred to in GO at all.
- Proposed definition: A fragment containing parts of a dying cell. Apoptotic bodies can be formed during the execution phase of the apoptotic process, when the cell's cytoskeleton breaks up and causes the membrane to bulge outward. These bulges may separate from the cell, taking a portion of cytoplasm with them, to become known as apoptotic bodies. These are then engulfed by phagocytic cells, and their components recycled.

- **This will be implemented unless you have serious concerns.**

GO:0012501 programmed cell death

- The definition of GO:0012501 programmed cell death should include all types of programmed cell death.
- Current definition: A process which begins when a cell receives an internal or external signal and activates a series of biochemical events (signaling pathways). The process ends with the death of the cell.
- Experts highlighted that in non-programmed cell death there is no signaling, so we should keep that in the definition.

- Not sure how we could make that definition better;
- We could write it in a comment to the GO term that in non-programmed cell death there is no signaling;
- **Do you have any other suggestions?**
- **Or should we leave it as is?**

Caspase-independent cell death

- Nomenclature Committee on Cell Death 2009:
- "Caspase-independent cell death can exhibit some of the morphological signs of apoptosis, autophagy or necrosis."
- Consensus: it is not apoptosis, but rather an apoptosis-like "programmed" cell death.

- **What is the *in vivo* nature of the caspase-independent cell death process?**
- **Should we add this term?**
- **If so, where should we place it?**
  - **Generically under "cell death", as it can sometimes develop into necrosis?**
  - **Or as a type of programmed cell death?**
- **And how should we name it?**
  - **Caspase-independent cell death?**
  - **Caspase-independent apoptosis-like process? (This could be a synonym)**
- **What genes should be annotated to this term?**
- **Can you suggest references (*e.g.* papers) to support such annotations?**

GO:0070270 mitotic catastrophe - 1

- At the content meeting it was suggested that we should remove this term from GO because it's a pre-phase or pre-stage, not a type of cell death.
- It's currently placed under "programmed cell death".
- Definition: A type of programmed cell death that occurs during or shortly after a dysregulated or failed mitosis and can be accompanied by morphological alterations including micronucleation and multinucleation.
- Currently, no gene products are annotated to this term.
- But it seems to be widely used in the literature…

GO:0070270 mitotic catastrophe - 2

- Nomenclature Committee on Cell Death 2009:
- "Mitotic catastrophe is a cell death mode occurring either during or shortly after a dysregulated/failed mitosis and can be accompanied by morphological alterations including micronucleation (which often results from chromosomes and/or chromosome fragments that have not been distributed evenly between daughter nuclei) and multinucleation (the presence of two or more nuclei with similar or heterogeneous sizes, deriving from a deficient separation during cytokinesis). However, there is no broad consensus on the use of this term, and mitotic catastrophe can lead either to an apoptotic morphology or to necrosis. As a result, the NCDD recommends the use of expressions such as 'cell death preceded by multinucleation' or 'cell death occurring during metaphase', which are more precise and more informative."

GO:0070270 mitotic catastrophe - 3

- It seems that we have two options here:
- a) Remove the term from GO altogether
- b) Keep it, take “programmed” out of its definition, and move it under “cell death”

- **What would you recommend?**
- **If we removed it, do you feel that we’d lose information?**
- **If we kept it, could you suggest genes that should be annotated to this term, and references (*e.g.* papers) to support such annotations?**

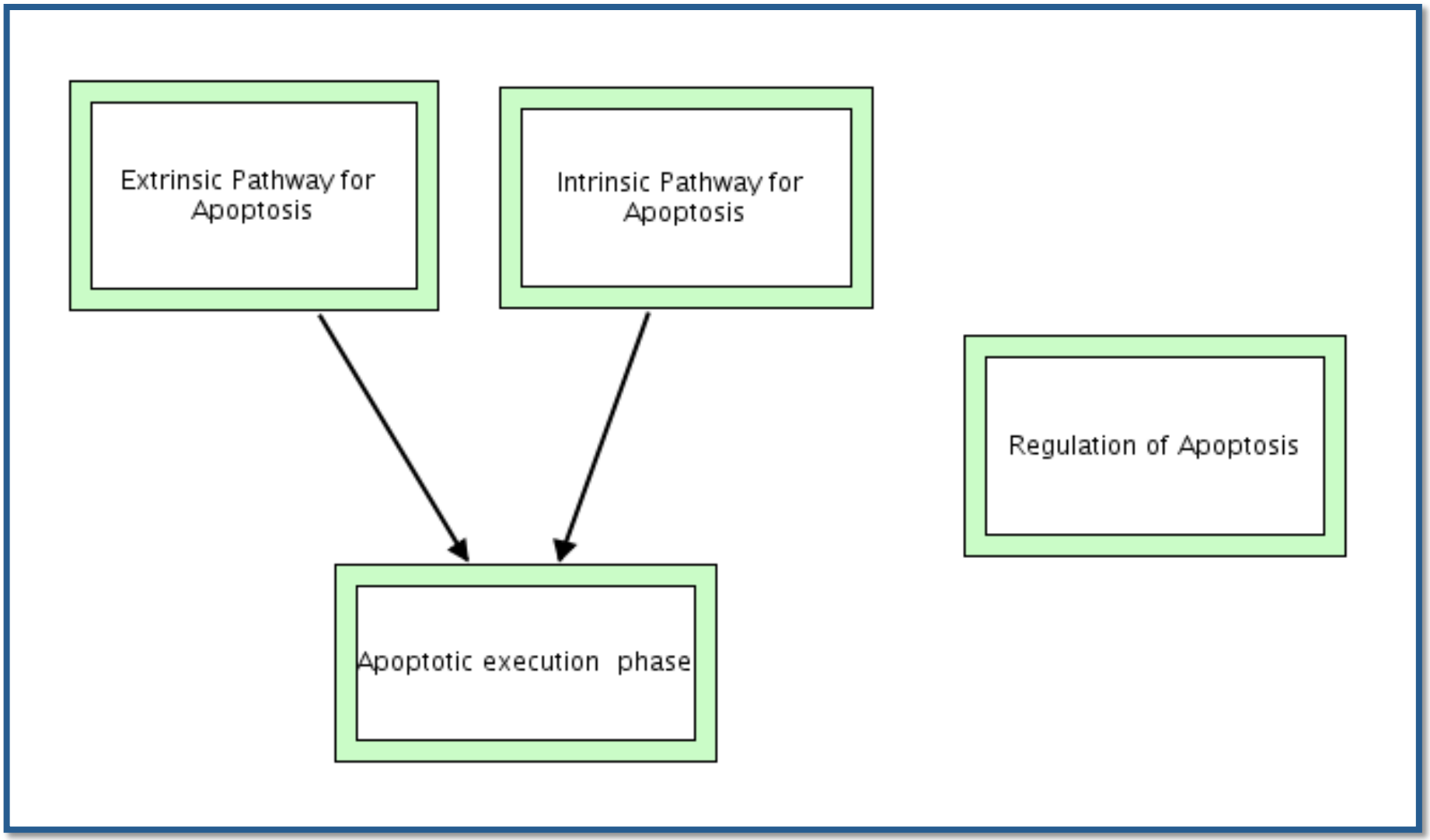
GO:0006915 apoptosis - 1

- Currently defined as:
- A form of programmed cell death that begins when a cell receives internal or external signals that trigger the activity of proteolytic caspases, proceeds through a series of characteristic stages typically including rounding-up of the cell, retraction of pseudopodes, reduction of cellular volume (pyknosis), chromatin condensation, nuclear fragmentation (karyorrhexis), and plasma membrane blebbing (but maintenance of its integrity until the final stages of the process), and ends with the death of the cell.

GO:0006915 apoptosis - 2

- At the content meeting, it was agreed that we need to
  - clarify better what this term encompasses,
  - divide it into component parts,
  - add the missing parts in GO.
- A helpful starting point was the way that Reactome represents apoptosis:

Reactome view of apoptosis



Proposal for overall re-organization of the apoptosis node in GO:

- apoptotic process [was: apoptosis]
  - (P) apoptotic signaling pathway
    - (I) extrinsic apoptotic signaling pathway
    - (I) intrinsic apoptotic signaling pathway
  - (P) execution phase of apoptosis

[(P) means the process *is part of* its parent process;
(I) means the process *is a type* (or *child*) *of* its parent process.]

- This is in line with on-going revision of signaling terms in GO.
- **This will be implemented unless you have serious concerns.**

GO:0006915 apoptotic process (was: apoptosis)

- Proposed definition: A programmed cell death process which begins when a cell receives an internal (*e.g.* DNA damage) or external signal (*e.g.* an extracellular death ligand), and proceeds through a series of biochemical events (signaling pathways) which typically lead to rounding-up of the cell, retraction of pseudopodes, reduction of cellular volume (pyknosis), chromatin condensation, nuclear fragmentation (karyorrhexis), plasma membrane blebbing and fragmentation of the cell into apoptotic bodies. The process ends when the cell has died. The process is divided into a signaling pathway phase and into an execution phase, which is triggered by the former.

- **This will be implemented unless you have serious concerns.**

GO:0039101
apoptotic signaling pathway

- Proposed definition: A series of molecular signals which triggers the apoptotic death of a cell. The pathway starts with reception of a signal, and ends when the execution phase of apoptosis is triggered.

- **Would you suggest any changes to this proposed definition?**

GO:0039102
extrinsic apoptotic signaling pathway

- Proposed definition: A series of molecular signals which triggers the apoptotic death of a cell. The pathway starts with reception of an extracellular signal by a death receptor, and ends when the execution phase of apoptosis is triggered.

- **Would you suggest any changes to this proposed definition?**

GO:0039103
intrinsic apoptotic signaling pathway

- Proposed definition: A series of molecular signals which triggers the apoptotic death of a cell. The pathway starts with reception of an intracellular signal (*e.g.* DNA damage, growth factor withdrawal, endoplasmic reticulum stress, oxidative stress etc.), and ends when the execution phase of apoptosis is triggered.

- **Would you suggest any changes to this proposed definition?**

Issue: cross-talk between extrinsic and intrinsic apoptotic signaling pathways

- Experts pointed out that this starts when caspase-8 cleaves Bid and truncated Bid interacts with mitochondria. From this point, there is no difference between the two pathways. Any event downstream of this point will be considered generic “apoptotic signaling pathway”.

- **This will be implemented unless you have serious concerns.**

GO:0039112
execution phase of apoptosis

- Proposed definition: A stage of the apoptotic process that starts with the controlled breakdown of the cell through the action of effector caspases or other effector molecules (*e.g.* cathepsins, calpains etc.), and ends when the cell has died. Key steps of the execution phase are rounding-up of the cell, retraction of pseudopodes, reduction of cellular volume (pyknosis), chromatin condensation, nuclear fragmentation (karyorrhexis), plasma membrane blebbing and fragmentation of the cell into apoptotic bodies.

- **This will be implemented unless you have serious concerns.**

Proposal for overall re-organization of the apoptosis node in GO (more granular - 1):

- apoptotic process
  - (P) apoptotic signaling pathway
    - (I) extrinsic apoptotic signaling pathway
    - (I) intrinsic apoptotic signaling pathway
      - intrinsic apoptotic signaling pathway in response to oxidative stress, etc.
  - (P) execution phase of apoptosis

- Given the definition of intrinsic apoptotic signaling pathway, we would have children GO terms to indicate what causes it to start (*e.g.* oxidative stress). Also based on this, we would make the following changes in GO:

We currently have:

- induction of apoptosis by extracellular signals
  - induction of apoptosis by granzyme
  - induction of apoptosis by hormones
  - induction of apoptosis in response to chemical stimulus
  - induction of apoptosis via death domain receptors

Proposal to change these into:

- ~~induction of apoptosis by extracellular signals~~
  - induction of apoptosis by granzyme
  - induction of apoptosis by hormones
  - induction of apoptosis in response to chemical stimulus
  - induction of apoptosis via death domain receptors

- Remove this term, and move its children terms under more appropriate terms such as “intrinsic apoptotic signaling pathway”

Proposal to change these into:

- ~~induction of apoptosis by extracellular signals~~
  - induction of apoptosis by granzyme
  - induction of apoptosis by hormones
  - induction of apoptosis in response to chemical stimulus
  - induction of apoptosis via death domain receptors

- Change this term to “granzyme-mediated apoptotic signaling pathway”, and place it under “extrinsic apoptotic signaling pathway”

- **Would you have any objections to that?**

Proposal to change these into:

- ~~induction of apoptosis by extracellular signals~~
  - induction of apoptosis by granzyme
  - induction of apoptosis by hormones
  - induction of apoptosis in response to chemical stimulus
  - induction of apoptosis via death domain receptors

- We could change this term to “hormone-mediated apoptotic signaling pathway”;

- **Should it be under “extrinsic” or “intrinsic apoptotic signaling pathway”?**

Proposal to change these into:

- ~~induction of apoptosis by extracellular signals~~
  - induction of apoptosis by granzyme
  - induction of apoptosis by hormones
  - induction of apoptosis in response to chemical stimulus
  - induction of apoptosis via death domain receptors

- Change this term to “intrinsic apoptotic signaling pathway in response to chemical stimulus”

- **This will be implemented unless you have serious concerns.**

Proposal to change these into:

- ~~induction of apoptosis by extracellular signals~~
  - induction of apoptosis by granzyme
  - induction of apoptosis by hormones
  - induction of apoptosis in response to chemical stimulus
  - induction of apoptosis via death domain receptors

- Change this term to “death domain receptor apoptotic signaling pathway”

- **This will be implemented unless you have serious concerns.**

Proposal for overall re-organization of the apoptosis node in GO (more granular - 2):

- apoptotic process
  - (P) apoptotic signaling pathway
    - (I) extrinsic apoptotic signaling pathway
      - extrinsic apoptotic signaling pathway via apoptotic mitochondrial changes
      - extrinsic apoptotic signaling pathway via direct activation of effector caspases
    - (I) intrinsic apoptotic signaling pathway
  - (P) execution phase of apoptosis

- This is in line with on-going revision of signaling terms in GO.
- **This will be implemented unless you have serious concerns.**

Role of caspases

- Specific terms for “caspases” are outside the scope of GO, so:
- We created a term “effector caspase activation”. We need to work on how to name and define this term to distinguish it from the initiator caspases, without actually referring to effector caspase vs. initiator caspase.

- **Would you have any suggestions?**

GO:0070782 phosphatidylserine exposure on apoptotic cell surface

- Currently defined as: A phospholipid scrambling process that results in the appearance of phosphatidylserine on the outer leaflet of the plasma membrane of an apoptotic cell, which acts as an "eat-me" signal for engulfing cells. Phosphatidylserine is exposed on the apoptotic cell surface by a phospholipid scramblase activity.

- We suggest that this process should be a part of “execution phase of apoptosis”.

- **Is phosphatidylserine exposure on apoptotic cell surface a terminal event or can a cell subsequently recover?**

GO:0043653 mitochondrial fragmentation involved in apoptosis

- Definition: The change in the morphology of the mitochondria in an apoptotic cell from a highly branched network to a fragmented vesicular form.
- Currently is part of the apoptotic process, and this placement may be too generic.

- **Should this be regarded as part of the execution phase of apoptosis, along with other identified components of the cell breakdown?**
- **Or is it rather an earlier sub-process of apoptotic signaling pathway?**

Apoptosis GO project

- Apoptosis GO wiki page: http://wiki.geneontology.org/index.php/Apoptosis

- Action items resulting from the content meeting held at EBI on June 1st 2011:

http://gocwiki.geneontology.org/index.php/Apoptosis#Summary_of_Action_Items_from_Apoptosis_Content_Meeting

Follow-ups

- Please email your suggestions to
  - Paola Roncaglia paola@ebi.ac.uk or
  - Emily Dimmer edimmer@ebi.ac.uk

- Apoptosis curator will start work at EBI on August 1st and will annotate gene products to the newly created apoptosis GO terms
- There will be an APO-SYS meeting in Stockholm on September 13th, and the apoptosis curator will likely participate.