Apoptosis terms in the Gene Ontology (GO)

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Aim of the Apoptosis project

• (From the wiki page) The aim of this project is to overhaul all the terms related to apoptosis in GO, mainly processes. Term phrasing and tree structures will be standardized, and new terms will be added with the aim of giving a broad coverage for all applicable species.
Aim of this call: get ready for the Apoptosis workshop (June 1st at EBI)

• We’d need the experts to:
  • Identify problematic terms and issues
  • Start thinking about:
    • correct placement of terms
    • names and definitions
    • references

• Why is this important

• In order to do this, we first need to show you how the Gene Ontology works in general, and what is the current “look” of apoptosis terms.
Background: the Gene Ontology (GO)

• The Gene Ontology (GO) project aims at standardizing the representation of gene and gene product attributes across species and databases. GO provides a controlled vocabulary of terms to describe gene product characteristics:
  • Biological Process (e.g. GO:0006915 apoptosis)
  • Molecular Function (e.g. GO:0043028 caspase regulator activity)
  • Cellular Component (e.g. GO:0043293 apoptosome)
    • Relationships exist to link these classes when necessary
• http://www.geneontology.org/
Background: the Gene Ontology (GO)

• GO covers normal, natural processes
  • NO pathological processes or disease states; e.g. “oncogenesis” is not a valid GO term because causing cancer is not the normal function of any gene.
  • NO experimental conditions (e.g. in vitro assays)

• GO terms must be species-independent
  • Taxon restrictions can be introduced when needed; e.g. “salivary gland cell autophagic cell death” is restricted to Arthropoda

• GO terms represent characteristics of gene products
  • NOT gene products themselves; e.g. we obsoleted all “caspase activity” GO terms because they represent gene products, while “caspase regulator activity” is fine
  • GO is NOT a nomenclature system
GO terms must have:

- At least one parent term:
  - apoptosis is_a programmed cell death
- A term name:
  - lowercase
    - apoptosis, not Apoptosis
  - singular
    - mitochondrion, not mitochondria
  - expanded, not abbreviated
    - epidermal growth factor receptor binding, not EGF receptor binding
  - as precise as possible
    - cleavage of cytoskeletal proteins involved in apoptosis
GO terms must have:

• A definition:
  • Unambiguous
  • For processes, beginning and end should be defined
    • These are necessary for annotators, when deciding between ‘x process’ and ‘regulation of x process’ terms
  • Many definitions don’t conform at the moment
• apoptosis: “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 terms must have:

- At least one reference to support the definition:
  - PMID
  - ISBN
  - Wikipedia
  - Reactome
  - GOC:pr, GOC:go_curators, GOC:BHF
  - Other OBO ontologies (cell ontology, anatomy ontologies)
GO terms may have (optional):

• **Synonym(s):**
  • apoptosis: apoptotic cell death, apoptotic program, apoptotic programmed cell death, programmed cell death by apoptosis, signaling (initiator) caspase activity, type I programmed cell death

• **A comment to clarify meaning of term:**
  • This term is intended for ......
  • This term should not be used to annotate .....
  • Consider also annotating to the term ....
  • This term does not have x parent because ....
Background: the Gene Ontology (GO)

- Ways exist in GO to link the 3 classes (BP, MF, CC). Here are some relevant to this project:
  - process-function links: “part_of” relationship
  - “regulates” relationship
Process-Function Links in GO: part_of

- **Process**: protein transport
- **Function**: substrate-specific transporter activity
- **Function**: protein transporter activity
New relationship in GO: regulates

The new relationships and new links between ontologies serve several purposes for the user. First, with links between ontologies, annotations can now be propagated from one ontology to another. The most obvious example of this is the propagation of gene-product annotations from a MF term to a BP term when the molecular function has a part_of relationship to a biological process. It is our hope that our users will go beyond this very basic benefit of the cross-ontology links and begin to ask more hypothetical questions using the ontology and annotations to the ontology. For example, a user could now ask what gene products might be involved in regulating a specific metabolic process if they know a regulatory process that controls the metabolic process and they know the types of molecular functions that play roles in the regulatory process.

New ontology files

GO is edited and released on a daily basis. Several versions of GO are available for download (Table 2). An extended version, in OBO 1.2 format, includes the regulates links, the has_part links and the intra-ontology part_of links discussed above and information on when, and by whom, a term was created. Other versions without this additional information are made available to accommodate existing software tools. There are several ways to convert the OBO-format file into the Web Ontology Language (OWL) format (http://www.bioontology.org/wiki/index.php/OboInOwl:Main_Page). These multiple formats allow users to use GO in the ways that they always
Background: the Gene Ontology (GO)

- Biological process terms can be at 3 different levels:
  - cellular process
  - multicellular organismal process
  - multi-organism process

- Note that some terms don’t fall under any of these levels
Apoptosis: issues and questions

- We need to pinpoint what’s wrong with apoptosis in GO at the moment
- How are apoptosis-related terms currently represented?
- Apoptosis wiki page:
GO:0006915 apoptosis (top view)
GO:0006915 apoptosis

cellular process
  death
    cell death
      cytolysis
      necrotic cell death
      negative regulation of cell death
      neuron death
      positive regulation of cell death
      programmed cell death
        apoptosis
        autophagic cell death
        cornification
        developmental programmed cell death
        host programmed cell death induced by symbiont
        hydrogen peroxide-mediated programmed cell death
        mitotic catastrophe
        negative regulation of programmed cell death
        positive regulation of programmed cell death
        pyroptosis
        regulation of programmed cell death
        singlet oxygen-mediated programmed cell death
        regulation of cell death
        tissue death
GO:0006915 apoptosis

- Definition:
  - 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.
Extrinsic apoptosis pathway (e.g. TNF, FAS & TRAIL)

Intrinsic apoptosis pathway (e.g. DNA damage, ROS)

Caspase-independent apoptosis pathway

Chromatin Condensation
Nuclear Fragmentation
Membrane Blebbing
Cytoskeletal Rearrangement

• What exactly should we define as apoptosis?
  • where does apoptosis begin?
  • where does it end?
  • what regulates apoptosis, but is not apoptosis itself?
  • Should we consider apoptosis as a signaling pathway in itself, separate from the downstream morphological changes that lead to cell death?
Reactome view of apoptosis

http://www.reactome.org/
• What exactly should we define as apoptosis?
  • where does apoptosis begin?
  • where does it end?
  • what regulates apoptosis, but is not apoptosis itself?
  • Should we consider apoptosis as a signaling pathway in itself, separate from the downstream morphological changes that lead to cell death?
  • Or should apoptosis be limited to those downstream cellular processes, and be broken into e.g. DNA cleavage, mitochondrial and cytoskeleton changes, and so on?
GO term: *regulation of glycogen synthesis by insulin receptor signaling pathway*
A signaling pathway REGULATES a DOWNSTREAM CELLULAR PROCESS (e.g. transcription, apoptosis, protein synthesis).

GO term: regulation of glycogen synthesis by insulin receptor signaling pathway
GO term: regulation of glycogen synthesis by insulin receptor signaling pathway

The CELLULAR PROCESS can be involved in MULTICELLULAR processes (e.g. heart development, wound healing, pattern formation).
GO term: regulation of glycogen synthesis by insulin receptor signaling pathway

If a protein is part of a downstream cellular process (e.g. glycogen synthase is involved in glycogen synthesis), it’s NOT part of the signaling pathway itself.
• What exactly should we define as apoptosis?
  • What role should key players such as caspases or Bcl2 have:
    • Should they be annotated as “apoptosis”,
    • Or as regulators of apoptosis?
    • Or as interacting with regulators of apoptosis?
    • Should we have e.g. a “caspase cascade” term?
GO:0006915 apoptosis (bottom view)
GO:0006915 apoptosis (bottom view)
GO:0060561 apoptosis involved in morphogenesis
GO:0006915 apoptosis (bottom view)
Negative regulation of apoptosis vs. anti-apoptosis

We have:
• negative regulation of apoptosis; GO:0043066
• anti-apoptosis; GO:0006916
• negative regulation of anti-apoptosis; GO:0019987

GO:0019987 is particularly confusing, because it is akin to 'positive regulation of apoptosis'. Can we improve the definition for 'anti-apoptosis' to distinguish it from its parent: GO:0043066, or is the term needed at all?
Apoptosis in different organisms

Re-cap of this call’s aims

• Get ready for the Apoptosis workshop (June 1st at EBI)
• Identify problematic areas and terms
Re-cap of this call’s aims

• Get ready for the Apoptosis workshop (June 1\textsuperscript{st} at EBI)
• Identify problematic areas and terms

• Recap of main issues we identified:
  • How should apoptosis be represented? It now includes downstream events (cellular modifications) leading to cell death
  • Apoptosis involved in morphogenesis
  • Negative regulation of apoptosis vs. anti-apoptosis
  • Apoptosis in different species

• Other issues?
Re-cap of this call’s aims

- Get ready for the Apoptosis workshop (June 1\textsuperscript{st} at EBI)
- Identify problematic areas and terms
- Start thinking about:
  - correct placement of terms
  - names and definitions
  - references (including any review or paper you’d recommend us)
- All according to GO rules (esp., terms should work across species, and must not correspond to gene products)
- Also, how would you suggest approaching this?
  - Starting from the top-level apoptosis terms, and working down?
- Anyone else we may contact individually?
- Follow-up by email/call before June 1\textsuperscript{st}
Wiki page for the Apoptosis project:

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

THANK YOU