Web alert

Apoptosis

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Apoptosis, also known as programmed cell death, is essential for the normal development and homeostasis of multicellular organisms. Apoptosis is the physiological mechanism by which the body deliberately eliminates autoreactive cells and counterbalances cell division (for background information see http://www.ultranet.com/~jkimball/BiologyPages/A/Apoptosis.html). The conservation of apoptosis throughout evolution underscores its fundamental importance. Dysregulation of programmed cell death may contribute to the pathogenesis of diseases in which there is insufficient apoptosis, such as cancer, or excessive apoptosis, such as Alzheimer's disease. Apoptosis was first characterized microscopically by morphological cellular changes during tissue remodeling, and many of the underlying biochemical components have been discovered in recent years.

The Entrez medline literature search (http://www4.ncbi.nlm.nih.gov/Entrez/) is a powerful online resource, but the number of articles on apoptosis is overwhelming (currently over 29,000 on medline). There are many websites specifically devoted to apoptosis that can distill the important components of apoptosis and help to organise all this information. This month's Web alert provides a few starting points.

Hallmarks of apoptosis

Apoptosis is characterized by morphological changes that take place within the cell (see the Apoptosis Dance of Death at http://lbfa.ujf-grenoble.fr/sites1/www.cellsalive.com/apop.htm). Unlike 'accidental' cell death or necrosis that results in cellular swelling, loss of membrane integrity, and inflammation, apoptosis is characterized by the methodical disassembly of the cell indicated by cytoplasmic shrinkage and membrane blebbing. The wave of death progresses from the cytoplasm to the nucleus, leading to chromatin condensation and DNA fragmentation. The last step of apoptosis is the breakdown of the cell into apoptotic bodies that are consequently engulfed by surrounding cells, quietly eliminating the cell.

Executioners and inhibitors of apoptosis

Although the stimuli leading to programmed cell death are extremely diverse, they lead to a common effector pathway. The core components of cellular suicide were originally discovered using *Caenorhabditis elegans* as a model system. Genetic studies identified two genes that are essential for the promotion of apoptosis, *ced-3* and *ced-4*, and one gene that is essential for the inhibition of apoptosis, *ced-9*. A slide show of apoptosis in *C. elegans* can be found at http://www.ed.ac.uk/%7Emig/apopt/migapo.html. Counterparts of these genes have been discovered in higher organisms and they constitute gene families important for cell death. CED-3 homologs form the caspase family, CED-4 is represented by Apaf-1 and CED-9 homologs form the Bcl-2 family. Comprehensive lists of proteins involved in apoptosis can be found in the Apoptosis Glossary (http://www.biosource.com/content/apop/glossary.html) and in an alphabetical index of apoptosis proteins (http://www-personal.umich.edu/~ino/List/alphabet.html).

Caspases

To date, 14 mammalian homologs of CED-3 make up a family of aspartate-specific cysteine proteases termed caspases. Caspases are synthesized as zymogens, which have low intrinsic enzymatic activity. After receiving a death stimulus, the caspases are proteolytically processed to their fully active heterotetrameric forms composed of two identical subunits of ~20 kDa plus two identical subunits of ~10 kDa. The crystal structure of active caspase 1 and 3 can be seen at the ICE family of cysteine proteases web page (http://www.enzim.hu/~gaspar/caspase/index.htm) and the Caspase website (http://pps97.cryst.bbk.ac.uk/assignments/projects/criekinge/). Active caspases ignite a proteolytic cascade that leads to the cleavage of cellular substrates necessary for normal structural integrity and survival. Knockout studies of many caspases have revealed their absolute importance in normal development (see BioMedNet's Mouse Knockout and Mutation Database at http://www.biomednet.com/db/mkmd). The Caspases website (see above) includes a list of useful references and the alphabetical index of apoptotic proteins also contains a list of recent reviews.

Apaf-1

The mammalian homolog of CED-4 is Apaf-1, a molecule required for activation of caspase-9. Apaf-1 can directly interact with caspase-9, as well as with the inhibitors of cell death, Bcl-2 and Bcl-xL. These core components seem to play a role by integrating a non-receptor mediated death stimulus. Apaf-1 deficiency leads to embryonic death caused by severe neuronal hyperplasia. For knockouts pertaining to apoptosis see the Mouse Knockout and Mutation Database.

Bcl-2 family

The mammalian Bcl-2 family of proteins consists of both activators and inhibitors of cell death. One of the inhibitors, Bcl-2, is most closely related to the *C. elegans* anti-apoptotic protein CED-9. The pro-apoptotic

Bcl-2 relatives also have a *C. elegans* homolog, termed EGL-1. The pro-apoptotic members act by binding and inhibiting the anti-apoptotic Bcl-2 family members. Inactivation of the prosurvival genes *bcl-2* or *bcl-xL* leads to inappropriate cell suicide. The Bcl-2 family and links to important papers and reviews can be found at the alphabetical index mentioned above.

Death receptors

One important component of mammalian apoptosis that appears to have evolved in higher organisms is the family of tumor necrosis factor (TNF) receptors. A subset of this family, known as death receptors, act to receive external cues for cell death. Upon engagement of the cell-surface receptor by a cognate death ligand, the receptor can transmit its signal to the intracellular effector machinery of apoptosis via adaptor proteins. This is especially important in homeostasis of the immune system. The growing family of TNF receptors and their cognate ligands can be seen at the New TNF Nomenclature web page (http://www.hugo-international.org/users/hester/tnftop.html), the Apoptosis Special Interest Site (http://biochem.boehringer-mannheim.com/techserv/apoptosis/) and the alphabetical index referenced earlier.

Adaptor molecules

The adaptor proteins link the death receptors or other apoptosis regulators to the caspases. In general, these molecules have at least two motifs that characterize them as adaptor molecules. The motifs can be a death domain (DD), a death effector domain (DED) or a caspase activation and recruitment domain (CARD). The Fas death receptor is the prototypic example of a protein that utilizes adaptor molecules to transmit the death signal. After Fas ligand binding, the DD-containing Fas receptor recruits the DD-containing adaptor molecule FADD via a DD homotypic interaction. FADD also contains a DED, which in turn recruits caspase-8 via the enzyme's own DED regions. Caspase-8 aggregation leads to its activation, thus initiating the proteolytic caspase cascade that results in cell death. Numerous other adaptor molecules grouped by their functional domains can be seen at the Death Domain site (http://www.isrec.isb-sib.ch/domains/dd/) and the alphabetical index described above.

Other inhibitors

To keep the activation of apoptosis in check, there are many inhibitors acting at all levels of the death pathway. In general, inhibitors of the death pathway act either to prevent molecules from binding to their activator or by forming a complex with an active protease to render it inactive. Viruses have also exploited inhibitors of cell death to promote their own replication. A list of cell death inhibitors can be found at http://www-personal.umich.edu/~ino/List/alphabet.html under Bcl-2, BIR-containing proteins and viral inhibitors.

Apoptosis community

The field of apoptosis is growing at a fervent pace, as are is the number of people who need to keep up with the current news, discussions and meetings. To tap into the community and its activities, go to the Cell Death Society's home page (http://www.celldeath-apoptosis.org/) or Apoptosis Online (http://www.apopnet.com/).

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Eric W Humke, Department of Molecular Oncology, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA; ehumke@gene.com