

Molecular Animation of Cell Death Mediated by the Fas Pathway

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This Teaching Resource includes a description and movie of the molecular events associated with apoptosis induced by the prototypic death receptor Fas. The molecules and macromolecular complexes are represented using the published structures. The movie follows the formation of the death receptor complex that causes the initial caspase activation, the release of cytochrome c from the mitochondria, and the formation of the apoptosome, and finally shows the destruction of the cytoskeleton leading to membrane blebbing. Death is initiated in a diseased cell by ligation of the Fas receptor by a killer T cell.

Description

Programmed cell death, which is also known as apoptosis, occurs during development and throughout the life of a multicellular organism to eliminate excess or diseased cells. This movie (<http://stke.sciencemag.org/cgi/content/full/2007/380/tr1/DC1>) follows the molecular interactions that occur when a diseased cell is recognized by a killer T cell. Killer T cells are specialized cells of the immune system that can trigger the death of an infected or diseased cell. One mechanism by which killer T cells cause target cell death is through the activation of “death” receptors, in this case Fas, on the surface of the target cell. (The other, which is not shown in the movie, is by perforin-granule exocytosis mechanism.)

Activation of Fas involves the formation of multimeric complexes of the receptors on the surface of the target cell. For simplicity, the movie shows the activation of a single trimeric receptor complex. Once the trimeric receptors oligomerize, adaptor proteins interacting with the intracellular portion of the receptors recruit an inactive form of an aspartic acid protease pro-caspase 8, which is then cleaved and activated at the receptor complex. Caspase 8 acts as an initiator caspase and cleaves another proenzyme, caspase 3, activating it. Caspase 3 then begins to cleave a various intracellular proteins. Caspase 8 also cleaves BID, which is a BH3 domain-containing proapoptotic protein (not shown in the movie). Cleaved BID contributes to the release of cytochrome c from mitochondria. Caspase 3 begins to cleave a various intracellular proteins, amplifying the signal. In response to this cascade of activated caspase 3 and cleaved BID, the mitochondria undergo a permeability transition that results in the release of cytochrome c, which is normally present in the intermembrane space. Cytochrome c acts as a catalyst activating apoptosis protease activating factor 1 (Apaf-1), which complexes with cytochrome c and caspase 9 to form the apoptosome, which activates more caspase 3. As the abundance of activated caspase 3 grows, critical intracellular proteins and structures begin to be cleaved, including the actin cytoskeleton. Ultimately, the cell’s membrane begins to bleb and the DNA becomes fragmented, leading to cell death. The

apoptotic cell is engulfed by macrophages or neighboring cells (typically prior to the fragmentation of the cell’s membrane) and eliminated (not shown in the movie).

Educational Details

Learning Resource Type: Movie

Context: Undergraduate upper division, graduate, professional (degree program)

Intended Users: Teacher, learner

Intended Educational Use: Teach, learn

Discipline: Biochemistry, cell biology, developmental biology, immunology

Keywords: Apoptosis, death receptor, caspase, apoptosome

Related Resources

Reviews

- J. C. Reed, K. S. Doctor, A. Godzik, The domains of apoptosis: A genomics perspective. *Sci. STKE* **2004**, re9 (2004).

Teaching Resources

- S. Wilk, Apoptosis. *Sci. STKE* **2005**, tr16 (2005).

Database of Cell Signaling

- M. Saleh, C. Bender, J. Chipuk, G. McStay, D. C. J. Spierings, U. Maurer, D. R. Green, Mitochondrial pathway of apoptosis: Caspases. *Sci. STKE* (Connections Map in the Database of Cell Signaling, as seen April 2007), http://stke.sciencemag.org/cgi/cm/stkem;CMP_18019.
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Forums

- Ligation of Fas and cell death. *Sci. STKE* (Forum, as seen April 2007), http://stke.sciencemag.org/cgi/forum-display/stkeforum;1?FORUM_ID=stkeforum;1.

Suggested Reading

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