CONFERENCE

Cell death according to plan

If a cell does not differentiate normally or is unable to assume its proper physiological role, it must die, lest malformations, neoplasms, or autoimmune diseases develop. How unwanted cells are eliminated was discussed at the Programmed Cell Death conference at the US National Institutes of Health, Aug 31–Sept 2. The term programmed cell death in vertebrates is usually synonymous with apoptosis. During apoptosis the cell shrinks, the chromatin condenses at the margins of the nucleus, the nuclear envelope disintegrates, and the cell fragments into membrane-bound apoptotic bodies; the DNA is typically degraded into fragments that are multiples of 180 bp (the internucleosomal distance). Surface signals from apoptotic bodies encourage rapid phagocytosis by other cells. Apoptotic cells die tidily, whereas with "necrosis" osmotic control is lost, the cell contents spill out, and inflammation is triggered. Blockage of apoptosis by inhibitors of protein or RNA synthesis indicate the active nature of the process, whereas necrosis results from damage so great that the cell is rendered completely passive.

Apoptosis can be induced via stimulation of the cell-surface Fas protein by the Fas ligand (Fas L). Fas L and Fas are homologous to tumour necrosis factor and its receptor. (By the definitions used here, tumour necrosis factor is a misnomer, because TNF causes apoptosis, not necrosis.) Fas is expressed on a variety of lymphocytes, and Fas L on cytotoxic T lymphocytes (CTLs). Mutant mice with non-functional Fas or Fas L (*lpr* or *gld* mice) develop lymphadenopathy and an autoimmune disease resembling systemic lupus erythematosus, suggesting that Fas-based killing is important in the elimination of self-reactive lymphocytes (Shikekazu Nagata, Osaka). The two fast-acting weapons carried by CTLs seem to be Fas L and perforin (also called cytolysin), with which CTLs murder self-reactive lymphocytes (Pierre Golstein, Marseille). There is evidence that activated T cells can commit suicide by expressing both Fas and Fas L, as a means of limiting the extent of the normal immune response (John H Russell, St Louis).

CTLs carry perforin and proteases called granzymes in secretory granules. When the granules are exocytosed onto a target cell, perforin punctures the membrane, the granzymes enter, and apoptosis is triggered. The efficiency of killing correlates with the amount of granzymes released, not the amount of perforin (Pierre Henkart, Bethesda). Erythrocytes are killed efficiently by perforin alone, probably because they cannot repair membrane damage as other cells can.

Immature thymocytes die if stimulated via their T-cell receptor (TcR), or if they encounter glucocorticoids, but the two stimuli together are not fatal. Jonathan D Ashwell (Bethesda) believes that the balance between the signal transduced by the glucocorticoid receptor on the one hand and the TcR on the other controls positive and negative selection of T cells in the thymus.

Mature T cells activated via the TcR will die unless they also are stimulated by the CD28 molecule on an antigen-presenting cell (Lawrence H Boise, Bethesda). Similarly, to survive, B cells activated via the B-cell receptor require co-stimulation by T-helper cells via the CD40 molecules (Tasuku Honjo, Kyoto).

A candidate for a protein necessary to turn on the internal cell death pathway is reaper, discovered by genetic analysis in *Drosophila.* Fly embryos lacking reaper retain excess cells in their nervous systems, whereas flies transgenic for reaper driven by a retina-specific promoter have no eyes at all (Hermann Steller, Cambridge Mass). In mice, TcR-mediated apoptosis in immature thymic T cells requires the expression of *nur 77* (an orphan steroid receptor—ie, resembling a steroid receptor, but its ligand is unknown), and *apt 4* is required for apoptosis induced via the TcR or glucocorticoids, whereas the tumour-suppressor gene *p53* is required only for radiation-induced killing of these cells (Barbara A Osborne, Amherst, Mass). The role of *p53* in radiation-induced cell death includes the turning on of the gadd (growth arrest and DNA damage-inducible) genes (Albert J Fornace, Bethesda).

A much-studied gene that antagonises apoptosis is *bcl-2*. Its overexpression in tumours predicts poor response to therapy (John C Reed, La Jolla). In the mouse immune system, *bcl-2* is required for normal survival of peripheral lymphocytes (Dennis Y Loh, St Louis).

For viruses to hijack the cellular replication machinery, they must overcome the cell's tendency to commit suicide whenever the cell cycle has gone awry. Adenovirus E1A gene expression induces proliferation, but also leads to apoptosis, unless it is accompanied by expression of the E1B gene, which resembles *bcl-2* and blocks apoptosis (Eileen White, Piscataway, New Jersey). Cowpox virus encodes a protease inhibitor, crmA, which blocks several of the proteases involved in apoptosis (Junying Yuan, Boston, Mass). Apoptosis may also be activated in infections by viruses such as HIV (David I Cohen, Bethesda).

Meeting participants were enthusiastic, not only because a relatively new area of basic cell biology is opening up, but also because the new knowledge will eventually improve our ability to kill unwanted cells, as in cancer, and our ability to coax salvageable cells to live, as in AIDS.

Paul M Rowe

Private health insurance in Australia

Federal Cabinet has approved proposals from the Minister for Health, Dr Carmen Lawrence, for slight reform of private health insurance. The proposals will allow a system of single billing whereby health funds negotiate a package with doctors and private hospitals. It seems the bill will be set in advance of admission to hospital, wherever that is possible. Lawrence hopes that the funds will be able to use their substantial market power to drive down some doctors' and hospitals' fees. Community rating—the principle under which all members of a particular scheme pay the same irrespective of age, sex, or health status—remains.

Details of the proposals are scant and groups such as the Australian Medical Association have found it difficult to comment. Some have wondered whether this will be the start of a trend towards US-style preferred-provider organisations.

Mark Ragg