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Meeting Report

DATELINE: New York

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The Cell Death Society's 'Mechanisms of Cell Death',
Queens College of CUNY, Flushing, New York, 12 October, 1996

The newly formed Cell Death Society held a meeting at Queens College of CUNY on 12 October. Interest in the field has rocketed in the last few years, because abnormal programmed cell death or apoptosis is now considered to be a major force in AIDS, cancer, birth defects, and Alzheimer's Disease. Researchers reported that the signaling mechanisms were similar to those used by cells preparing for division, but that the response to the signals involved protein-digesting enzymes and reactive oxygen. Cells that are ready to respond to growth signals by having receptors for hormones on their surfaces are in a more precarious situation than cells that do not, for in the absence of appropriate signals cells with receptors are more likely to respond to other signals by dying. Many microorganisms exploit this sensitivity by inducing the cells that they are attacking to die. Scientists' understanding of the signaling mechanisms and of the relatively simple means that microorganisms use to cause cells to die point to new and accessible directions for therapy.

The newly formed Cell Death Society held its first national meeting, entitled 'Mechanisms of Cell Death', at Queens College of CUNY on Saturday, 12 October, 1996. Started and nicknamed 'The Death Poets' Society' by Zahra Zakeri of Queens College, Raymond Birge of Rockefeller University, Richard Lockshin of St. John's University, Richard Lang of New York University, and Michael Hengartner of Cold Spring Harbor Laboratories, the group has been holding monthly meetings for over one year at Rockefeller University and now has a web page. For the annual meeting, speakers included Samuil Umansky (LXR Corporation), Arturo Zychlinsky (NYU), Hengartner, Barbara Osborne (University of Massachusetts), Gabriel Nuñez (University of Michigan), David Vaux (Walter and Elisa Hall Institute, Melbourne, Australia), Dale Bredesen (La Jolla Cancer Research Foundation), Martin Tenniswood (W. Alton Jones Cell Science Center), and Mauro Piacentini (University of Rome 'Tor Vergata'). Approximately 170 scientists attended the meeting.

The field of programmed cell death or apoptosis has recently become one of major research interest since abnormalities of cell death are now known to underlie many diseases, ranging from birth defects through cancer, AIDS, and Alzheimer's Disease. Several cancers are known to arise from a failure of cells to kill themselves rather than from uncontrolled cell proliferation. As several of the speakers indicated, the number of papers on the subject has risen in the last ten years from a handful to over 7000 per year, with no sign that the growth has stopped. However, although the phenomenon is now well known, the application of the new knowledge to cure disease depends on scientists' understanding how it occurs and being able to turn it on or off at will. The scientists discussed how cell death is controlled and how the cells die.

Several major themes were emphasized. First, the mechanism of cell death appears to be common to all multicellular organisms. Hengartner and Vaux demonstrated that the genetic control of death is the same in primitive worms and humans, and that many of the enzymes are very similar. Hengartner further emphasized that cell death in the reproductive system followed the pattern of embryonic cells, linking these two types of cell death. Likewise, Nuñez has found a yeast gene that can interact with mammalian genes that protect the cell and thus kill a mammalian cell.

Second, cells seem to die by a common mechanism. Osborne pointed out that most cells can respond to damage caused by oxidation by dying, and Bredesen showed that, in the nervous system, cells contained receptors to respond to growth stimuli. If these receptors went unused, the cells could die. Tenniswood also indicated that basic cell processes such as attachment to substrate and absorption of secreted proteins could force cells to make the decision to die. To biologists, the preservation of a process throughout evolution indicates that the process is fundamental and too important to be modified.

A third theme, emphasized especially by Umansky, was that quiescent cells rarely die. These arguments underscore earlier observations that indicated that, in some instances, cell death was an active process requiring energy, protein synthesis, and the full participation of the cell. It now appears that this process is general and that cell death is as closely controlled as cell division.

A primary means by which cells die is the activation of protein-digesting enzymes. Several types of proteases are important in cell death. One, called interleukin-converting enzyme, is conserved from worms to man, but at least two other major classes of proteases have been demonstrated to be critical. In the immune system, Osborne showed that proteasomes-small intracellular bodies that are responsible

for the digestion of many proteins-appear to initiate the cell death process, while Vaux indicated that enzymes previously known to be involved in cells' killing other cells could function in cell suicide, and Tenniswood showed that proteases secreted from cells could free them from their attachments. These cells would then normally die but if death is blocked – an early stage of cancer – the cells would be freed to migrate (metastasize).

The role of oxidation intermediates became a theme. It is well known that intermediates in the consumption of oxygen-free radicals can damage cell membranes and DNA. Osborne and Bredesen argued that the same process can regulate cell death. Osborne showed that cells in the immune system were resistant to death in the absence of oxygen, and Bredesen showed that mutations in an enzyme used to help eliminate free radicals could cause diseases such as Lou Gehrig's Disease (Amyotrophic Lateral Sclerosis, ALS). Similarly, Tenniswood emphasized that a cell's attachment to a substrate was communicated throughout the cell by the cytoskeleton, which collapsed rapidly in a dying cell, and Piacentini showed that cross-linking of proteins was a major means of shrinking cells. These latter processes are heavily influenced by oxidation. Piacentini noted that the cross-linking was identifiable in lymphocytes before AIDS became symptomatic. Increasing the crosslinking enzyme (transglutaminase) rendered cells more sensitive to apoptotic stimuli, as Piacentini emphasized, and inhibiting it rendered them resistant to death.

Everyone is starting to envisage cell death as following a signal transduction pathway similar to those seen in growth and differentiation. An important concept that is emerging is that cell death is engaged by a series of intracellular signals, with a regulation similar to that of cell growth and differentiation. Hengartner, Osborne, Nuñez, Bredesen, and Tenniswood provide examples where cell death signals, initiated at the plasma membrane via specific receptors, acted on intracellular targets to propagate signals to death effectors such as proteases. Where cell death differs from other pathways is that a new and different set of players, such as reactive oxygen and proteases, propagate the signals. As we gain knowledge of how these effectors propagate signals, then rational approaches to the treatment of diseases involving cell death can be realized.

There are several other therapeutic implications. Controlling production of free radicals and reactive oxygen species is at least theoretically conceivable today and, in the interpretation of these researchers, might be used to control cell death in AIDS (Osborne) and neurological diseases (Bredesen). If one could reduce the number of deaths of lymphocytes in AIDS by less than 0.1% one might stabilize the immune system; a similar reduction might block progression of ALS or Alzheimer's Disease.

In another direction, Tenniswood argues that, according to his results, current treatment of hormone-dependent cancers may kill the wrong cells and select for cells resistant to killing. The idea that unloaded hormone receptors are dangerous for cells, as suggested by Tenniswood and Bredesen, is gaining credence in other laboratories. (See NY Times 'Science Times' 15 October, 1996, article by Jane Brody on publication by Shutsung Liao in latest Proc. National Acad. Sci., stating that hormone-independent prostatic cancer cells acquire hormone receptors and then can be killed by small amounts of hormone). Finally, Zychlinsky reported a surprising finding that the organism that causes dysentery achieves its invasion of the intestine by deliberately provoking cells to kill themselves. This also suggests new therapeutic approaches, here by attempting to prevent cell suicide.

Perhaps the most important lesson that the scientists took from the meeting was that many organisms such as bacteria and viruses have learned through relatively simple tricks to exploit the highly conserved cell death mechanisms present in all cells. Since cell death is so conserved, these natural examples should contain the secrets of how death is regulated and carried out. Once we know this, therapeutic means of protecting cells in diseases such as AIDS, Alzheimer's Disease, and amyotrophic lateral sclerosis; or of destroying dangerous cells, in cancer and autoimmune diseases such as lupus, will be on the horizon.

The meetings will be continued on an annual basis, and the society is considering incorporation.