Social controls on cell survival and cell death

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Programmed cell death occurs in most animal tissues at some stage of their development, but the molecular mechanism by which it is executed is unknown. For some mammalian cells, programmed death seems to occur by default unless suppressed by signals from other cells. Such dependence on specific survival signals provides a simple way to eliminate misplaced cells, for regulating cell numbers and, perhaps, for selecting the fittest cells. But how general is this dependence on survival signals?

AFTER many years of neglect, normal (or programmed) cell death is at last coming alive. It has long been known to be a fundamental feature of animal development[1-3] and to occur in many adult tissues[4-6], but only very recently has it become a fashionable subject of general biological interest. Although the molecular mechanisms are unknown, it is thought that the cells that die usually kill themselves by activating a suicide programme[7-10]. Many studies of normal cell death have focused on what seem to be special cases: cells dying at metamorphosis, neurons dying during synaptogenesis, lymphocytes dying during receptor repertoire selection, and so on, and cell suicide has not been thought to be a part of the repertoire of cells in general. But there is increasing evidence to suggest that most animal cells are capable of killing themselves and that these ubiquitous cell suicide programmes can be activated or suppressed by signals from other cells[10]. It seems that cell survival and cell death are subject to the same kinds of social controls that operate on cell proliferation; yet compared with the control of cell proliferation, relatively little is known about the control of cell survival.

Cell suicide provides an efficient mechanism for eliminating unwanted cells[8]. These are usually normal cells that are unwanted for any one of a number of reasons[9]. They may have been produced in excess, as is the case for many vertebrate neurons[11-13]. They may have served a function at some time during evolution or development but are no longer needed, as in the tadpole tail at metamorphosis[14,15]. Some cells are needed in one sex but not in the other, as in the mammalian Müllerian duct, which is needed in females but not males[16]. Others have to be sacrificed in the process of sculpting the body[1,2], as in the regions between developing digits in amniotes[17]. Cells that migrate to an abnormal location may be eliminated by cell suicide, as may lymphocytes that have either failed to produce functional antigen-specific receptors and therefore are of no use, or have produced high-affinity self-reactive receptors and therefore are potentially harmful to the animal[18,19]. In each of these cases, it is easy to see the advantage of a cell suicide programme that can be regulated by interactions with other cells.

Cell suicide by default

An extreme view is that, in higher animals at least, just as a cell seems to need signals from other cells in order to proliferate[20-22], so it needs signals from other cells in order to survive; in their absence, the cell kills itself by activating an intrinsic suicide programme. The view is extreme because it implies that cells are programmed to kill themselves unless they are continuously signalled by other cells not to do so, and because it suggests that this precarious state is shared by most cells in both developing and mature higher animals.

Evidence for cell suicide

The evidence that normal cell deaths occur by suicide is indirect. In some cases, an increase in the synthesis of specific messenger RNAs has been shown to precede the cell deaths[23-26], although it has yet to be shown that any of the proteins encoded by these mRNAs contributes to cell death. Death can sometimes be suppressed by the inhibition of RNA or protein synthesis in the cells that should die[27-29], suggesting that gene transcription and RNA translation are required in these cells for the deaths to occur.

As originally pointed out by Kerr, Wyllie and Currie[30], the cytological characteristics of normal cell deaths are generally different from those seen in acute pathological cell deaths. In acute pathological cell deaths, which result from cell injury, the cells tend to swell and lyse—a process called necrosis[7,30,31]—and the cell's contents spill into the extracellular space, inducing an inflammatory response. In normal cell deaths, by contrast, the nucleus and cytoplasm shrink and often fragment, and the cells or fragments are rapidly phagocytosed by their neighbours or by macrophages—a process called apoptosis[7,30,31] (Fig. 1); as the contents of the cell do not leak into the extracellular space, there is no inflammation. Because the dead cells are rapidly removed without inflammation, even large-scale normal cell death is often histologically inconspicuous and therefore ignored, which is one important reason why it has received less attention than it deserves. Normal cell deaths can vary in their features, however, even in the same organism[9,32,33]; in some cases, for example, the nuclear DNA is degraded into oligomers of oligonucleosome-sized fragments[8,33-35], whereas in others it apparently is not[33]. It is uncertain whether the variability reflects differences in the mechanism of cell death, although this seems likely[33].

The most direct evidence that normal cell death in animals is caused by the activation of a suicide programme comes from studies in the nematode *Caenorhabditis elegans*[9]. Of the 1,090 somatic cells formed during the development of an adult hermaphrodite, 131 die, each with morphological features resembling apoptosis[9]. Genetic analyses have identified two genes, *ced-3* and *ced-4* (ref. 36), that must function in the dying cells or their close ancestors for these cells to die[37]; if either gene is inactivated by mutation, the deaths fail to occur. These mutant worms are superficially normal[36] and die at the usual age of several weeks[9], indicating that although the cell deaths that occur in normal development involve a *ced-3*- and *ced-4*-dependent death programme, senescence does not. The DNA sequences of both genes have been determined; *ced-3* encodes a novel protein with many potential phosphorylation sites, whereas *ced-4* encodes a novel protein with two potential Ca^{2+}-binding domains[9], but it is not known how either protein participates in cell death.

From the perspective of the extreme view, another *C. elegans* gene, *ced-9*, is of special interest as it seems to act as a brake on the suicide programme[38]. If its function is abnormally activated by mutation, the cell deaths do not occur; if its function is inactivated by mutation, many cells that normally survive now die and the animal dies early in development. If *ced-3* and *ced-9* are both inactivated, neither the normal nor extra cell deaths occur and the animal survives[38]. These results suggest that many more cells than the 131 that normally die during nematode development have the *ced-3* and *ced-4*-dependent suicide programme ready to run, but it is normally suppressed in these cells by *ced-9*-dependent mechanism. The extreme view that

cells need continuous signalling from other cells to avoid killing themselves would gain support if the activity of *ced-9* were found to depend on signals from other cells, but this possibility has not been tested. In one respect the mammalian gene *bcl-2* resembles *ced-9*; when overexpressed in some cells, such as lymphocytes, it can protect them from programmed cell death[39–41]; in the case of B lymphocytes isolated from germinal centres, both the expression of *bcl-2* and cell survival are stimulated by ligand binding to antigen-specific receptors on these cells[42]. The finding that the BCL-2 protein is mainly localized in the inner mitochondrial membrane[43] raises the possibility that mitochondria may play an important part in at least some forms of programmed cell death.

The death programme in animal cells can clearly be activated by signals from other cells. Cells in the tadpole tail, for example, are induced to die by thyroid hormone secreted by the thyroid gland at metamorphosis[27,44], and lymphocytes in the mammalian thymus are induced to die by corticosteroid hormones secreted by the adrenal gland[18]; in both cases, the deaths have the characteristic features of programmed cell death, in that they occur by apoptosis[14,35] and can be suppressed by inhibitors of RNA or protein synthesis[27,45]. Both cytotoxic lymphocytes and tumour necrosis factor, which is secreted mainly by lymphocytes and macrophages, are able to stimulate many cell types to undergo apoptosis, although these deaths are not suppressed by RNA or protein synthesis inhibitors[18,19]. Interestingly, the binding of antibodies to either the Apo-1 (ref. 46) or the Fas (ref. 47) protein on the surface of lymphocytes or other cells can also induce programmed cell death, and mutations in the gene encoding the Fas protein are associated with a defect in the elimination of self-reactive T lymphocytes in the thymus and, consequently, with autoimmune disease[48]. More important for the extreme view, however, is the evidence that the survival of some cells depends on the continuous suppression of the death programme by signals produced by other cells.

Dependence on survival signals

Although the notion that cells in higher animals depend on signals from other cells to avoid killing themselves is extreme, at least some cells seem to operate in this way. The survival of many developing vertebrate neurons depends on neurotrophic factors that are secreted by the target cells they innervate[11–13,49,50]; those that fail to get enough die, apparently by active suicide as, in some cases at least, their death can be prevented for days by drugs that inhibit RNA or protein synthesis[29]. Dependence on signals from other cells for survival is not confined to neurons or to developing cells: in adult rats, for example, the survival of epithelial cells in the ventral prostate depends on testosterone secreted by the testes[51,52], whereas the survival of cells in the adrenal cortex depends on adrenocorticotropic hormone (ACTH) secreted by the pituitary[5,7]; if testosterone or ACTH levels are experimentally decreased, the respective cells die with the characteristic features of programmed cell death[5,7,51,52]. Among non-neural tissues, it is not only endocrine-dependent cells that require specific signalling molecules to survive: in culture at least, haemopoietic progenitor cells require one or more colony-stimulating factors[53–55], T lymphoblasts require interleukin-2 (ref. 28), and endothelial cells require growth factors such as fibroblast growth factor[56]; in all of these cases, cells deprived of survival signals die by typical programmed cell death.

Thus the idea that cells require signals from other cells to avoid killing themselves is not new. What is novel is the suggestion that these cases are only examples of a general mechanism that may operate in most cells, at least in higher animals. The simplest way to test whether a cell depends on survival signals produced by other cells is to determine whether it can survive on its own in culture without added signalling molecules. It is important to test highly purified cells in order to avoid signalling between cell types: studying single cells is the ultimate test as it also excludes signalling between cells of the same type. It will be important to determine which types of normal animal cells, other than blastomeres[57], can survive under these conditions. Chondrocytes from embryonic chick cartilage have been shown to survive in serum-free cultures at low density without added signalling molecules, but single cells were not tested[58]. My colleagues and I recently tested newly formed oligodendrocytes (the cells that make myelin in the vertebrate central nervous system) and their precursors, both as purified populations and as single cells, isolated from the rat optic nerve[59]. We found that they died rapidly, with the characteristics of programmed cell death, when cultured in the absence of serum and exogenous signalling molecules. They could be saved for at least a few days by molecules secreted in culture by their normal neighbours isolated from the developing optic nerve, or by recombinant platelet-derived growth factor or insulin-like growth factor-1, both of which are present in the developing optic nerve.

Tissue-specific survival signals

What might be the advantages of having a cell's survival depend on signals produced by other cells? One is that it could provide a simple mechanism for eliminating cells that end up in an abnormal location: as different vertebrate tissues would be expected to produce different sets of survival signals, a misplaced cell may be deprived of the specific signals required for its survival. Nerve cells (or their processes[60]) that project to an abnormal target that cannot provide the necessary neurotrophic factors, for example, will be automatically eliminated[12]. Primordial germ cells may be another example. They migrate early in vertebrate development from the hindgut to the genital ridges, where they ultimately differentiate into gametes[61]. Some fail to reach the genital ridges and are eventually eliminated[62]. It has been suggested that at least some of these misplaced cells in mice might die because they are deprived of an extracellular signalling protein encoded by the *Steel* (*Sl*) gene, which may be required for germ-cell survival[63]. Several lines of evidence

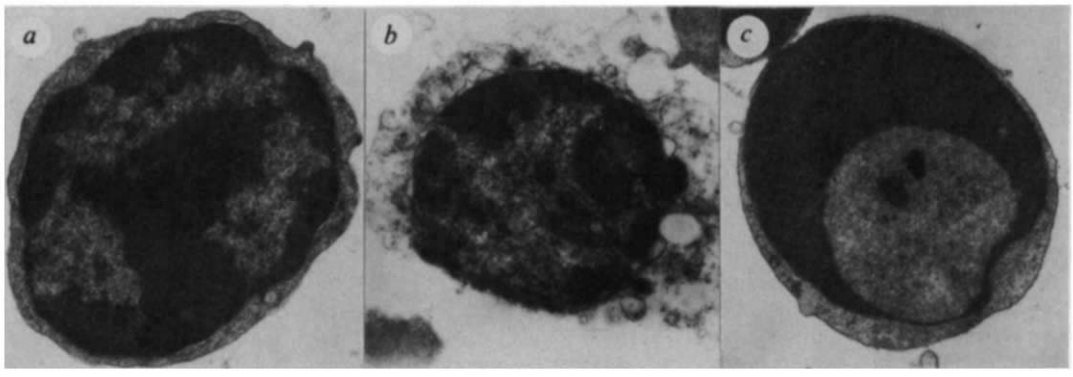

FIG. 1 Electron micrographs of a normal thymocyte (*a*), a necrotic thymocyte (*b*) that died after exposure to polyethyleneglycol, and an apoptotic thymocyte (*c*) that died after exposure to glucocorticoid. Magnifications are ×15,000 in *a*, ×12,000 in *b*, and ×24,000 in *c*. (Kindly provided by A. Wyllie from *J. Path.* **142**, 67–77, 1984.)

are consistent with this suggestion: (1) if either the *Sl* gene, which encodes the signal, or the c-*kit* gene, which encodes its receptor, is inactivated by mutation, the mouse is deficient in germ cells (as well as in erythrocytes and melanocytes)[64,65]; (2) the *Sl* gene is expressed in the genital ridges and along the migratory pathway followed by primordial germ cells[66,67], whereas the c-*kit* gene is expressed in primordial germ cells[68]; and (3) the *Sl* factor promotes the survival, but not the proliferation, of primordial germ cells in serum-free cultures[63,69]. The *Sl* factor illustrates two important principles. First, whereas many signalling molecules that promote the survival of a cell also stimulate its proliferation, this is not always the case. Second, the *Sl* factor is produced in both soluble and plasma membrane-bound forms, and the membrane-bound form is much more effective both *in vivo*[70] and *in vitro*[69], indicating that cell-bound signals, as well as soluble ones, can promote cell survival.

Adult animals also need to be able to eliminate misplaced cells. When the skin is cut, for example, epidermal cells are displaced into the hypodermis and subcutaneous tissue, where they could cause trouble if they survived and proliferated; dependence on tissue-specific survival signals could, in principle, eliminate the problem by ensuring that the displaced cells die. The same mechanism may prevent cancer cells from establishing metastases; the protection would fail, however, once cancer cells, through mutation, became able to produce autonomously either their own survival factors, the intracellular signals stimulated by such factors, or other proteins, such as BCL-2 (refs 39–41), that can protect the cell from programmed cell death.

Competition for survival signals

Dependence on survival signals can also be useful in the control of cell numbers in higher animals, especially if cells are forced to compete with one another for limiting amounts of such signals. Developing sympathetic neurons provide an informative example. They are produced in larger numbers than are needed and then apparently compete with one another for limiting amounts of nerve growth factor released by the target cells they innervate[72]; only some of the neurons get enough nerve growth factor to survive, while the others die[11–13,49,50,73]. In this way the number of sympathetic neurons innervating a population of target cells is automatically adjusted to match the number of target cells. A similar competition for target-cell-derived survival signals (neurotrophic factors) seems to operate widely in the developing vertebrate peripheral and central nervous systems, where it is thought to play an important part in matching the numbers of presynaptic and postsynaptic cells during both evolution[13] and development[11–13,49,50].

It seems unlikely that such a simple and effective mechanism for controlling cell number is confined to neurons. In addition to providing a mechanism for matching the numbers of different types of cells in a tissue or organ, competition for survival signals would be a simple way to ensure that cell turnover in adult tissues is balanced (as it must be if the tissue is neither growing nor shrinking) so that the number of cells produced by division is exactly matched by the number that die: if a given level of survival factor supports a certain number of cells of a particular type, any increase of these cells above this number would stiffen the competition and thereby tend to cause enough cells to die to return the cell number to its original value; a fall in cell number would have the reverse effect. This mechanism could explain the rapid regression of experimentally induced hyperplasia that has been observed to occur in various mammalian organs, such as the adrenal cortex, liver, kidney and pancreas; the regression occurs much too rapidly to be explained solely by a decrease in cell proliferation, and in several cases it has been shown to result from a large increase in apoptotic cell death[7,74–77]. Although the regulation of cell numbers is usually considered mainly in terms of the control of cell proliferation, these observations suggest that, even in mature animals, control of cell survival can also play an important part. It is possible that growth hormone and insulin-like growth factors stimulate vertebrate growth at least partly in this way: for some types of cells in culture, insulin-like growth factors promote cell survival rather than cell proliferation[59,78–80].

In addition to contributing to the control of cell numbers in a tissue or organ, competition for limiting amounts of survival factors could have the added advantage of continually selecting for the most competitive cells—a form of survival of the fittest. The most competitive cells might be those with most receptors for survival signals, those with the most efficient signal transduction pathways, and so on. The same type of selection process may also operate at the level of cell proliferation, with cells competing for limiting amounts of growth factors[81,82], but on its own this would not eliminate the less competitive cells as effectively as competition for survival factors. Intercellular competition comes at a price, however: it contributes to tumour progression[83] and is thus partly why one in five of us will die of cancer.

The way ahead

If many types of animal cells require signals from other cells to survive, then there is much work to be done: compared with the great amount of attention given to the control of cell proliferation, remarkably little attention has been given to the control of cell survival, other than in a small number of special cases, many of which I have mentioned. In addition to defining the molecular mechanisms of normal cell death, one will need to determine (1) the survival factors for each cell type: (2) the receptors for these factors; (3) the intracellular signalling pathways activated by the receptors; (4) how these pathways suppress cell death (is it always by suppressing cell suicide, for example?); and (5) how the amount of each survival factor is controlled. In short, much of what has been, and is being, done for cell proliferation control will need to be done for cell survival control. □

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Palaeomagnetic constraints on the geometry of the geomagnetic field during reversals

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Palaeomagnetic records of the path of the pole during reversals of the Earth's magnetic field provide a test of the hypothesis that dipolar or low-order axisymmetric components of the field dominate during reversals. Multiple records of reversals during the past 12 Myr show no simple or consistent geographical pattern. Although a more robust analysis of the transitional field awaits a greater number of well-distributed sampling sites, the present data are not inconsistent with the simplest models, in which a field reminiscent of the non-dipole component of the present-day field becomes dominant.

SINCE the first palaeomagnetic records of geomagnetic reversals were published 30 years ago, there has been hope that detailed knowledge of field behaviour during transitions between the two polarity states would reveal key aspects of the geodynamo. The first results[1,2] indicated that the directional changes occur over a short period (between 2,000 and 15,000 yr) and are systematically accompanied by a large drop (almost an order of magnitude) in the field intensity. A first attempt to compare the virtual geomagnetic pole (VGP) paths of the last reversal as seen from Japan and California[3] led to the conclusion that the field was predominantly non-dipolar, a view which was later reinforced by additional data from the same transition.

Basically, three types of model were proposed to account for the non-dipolar structure of the reversing field. The first approach (referred to as the flooding model[4-6]) involves time-dependent low-order zonal harmonics (that is, those symmetrical about the Earth's rotation axis), produced by coexisting dipolar axial sources in the core. At some point of the reversal the transitional field will become vertical (upward or downward) at any site of observation; the VGP paths should thus pass near the site of observation or its antipode[5].

The second approach (initially called 'the standing field model'[3]) suggests that a persistent component would dominate after collapse of the axial dipolar structure and is observed through successive reversals. Further developments of this model have been proposed recently by several authors[7-9] who noticed a preferential grouping of VGP paths from different reversals over the Americas and to a lesser extent their antipode. After a first interpretation involving a dipolar transitional component, very recent work[10] claims that a particular octupole component (h_3^1) could account for this characteristic. If so the VGP paths of multiple records relative to the same reversals from different sites should lie systematically within these two sectors of longitude.

Although many data obtained from sediments appear as longitudinally confined VGP paths, complex features such as large and rapid directional changes and rebounds of the directional vector to a previous direction are present in other records. Following early conclusions reached by Dagley and Lawley[11] from a review of volcanic data from Iceland, the diversity of these pole paths has led several authors to support a third kind of model in which the non-dipole field becomes dominant during the transition[12,13]. This conclusion was reached independently from a statistical analysis of the present geomagnetic field[14].

The large variety of models for geomagnetic reversals reflects the difficulty in using palaeomagnetic observations to constrain the geometry of the transitional field. Even more vexing is the fact that the fundamental question of dipole versus non-dipole dominance is not yet answered. It is often argued that there are currently too few transition studies to assess the validity of these