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Programmed Cell Death and the Control of Cell Survival: Lessons from the Nervous System

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During the development of the vertebrate nervous system, up to 50 percent or more of many types of neurons normally die soon after they form synaptic connections with their target cells. This massive cell death is thought to reflect the failure of these neurons to obtain adequate amounts of specific neurotrophic factors that are produced by the target cells and that are required for the neurons to survive. This neurotrophic strategy for the regulation of neuronal numbers may be only one example of a general mechanism that helps to regulate the numbers of many other vertebrate cell types, which also require signals from other cells to survive. These survival signals seem to act by suppressing an intrinsic cell suicide program, the protein components of which are apparently expressed constitutively in most cell types.

Although the death of neurons (and other cell types) was first recognized as a regular feature of vertebrate development almost 70 years ago (*1*, *2*), it is only in the last 20 years that the scale and general importance of normal neuronal death have gradually become appreciated (*3*–*5*). The neurotrophic theory has provided a useful conceptual framework for an understanding of this massive cell death (*4*–*7*). The theory grew out of the pioneering studies of Levi-Montalcini, Hamburger, and Cohen on normal neuronal death, neuron–target-cell interactions, and the prototypic neurotrophic factor nerve growth factor (NGF), although it was many years after the discovery of NGF that its connection to normal neuronal death was recognized (*8*). The theory is based on two main suppositions: (i) The survival of developing vertebrate neurons depends on specific neurotrophic factors secreted by the target cells that the neurons innervate, and (ii) many types of neurons are produced in excess, so that only a proportion get enough neurotrophic support from their target cells to survive. This neurotrophic mechanism is thought to have at least three advantages for the nervous system, facilitating both its evolution and development (*4*–*7*). First, it ensures that neurons that project to an inappropriate target are automatically eliminated, because they fail to receive the neurotrophic factors they require for survival. Second, it increases the likelihood that all target cells become innervated. Third, it helps ensure that the number of neurons is appropriately matched to the number of target cells they innervate.

The strongest evidence for the neurotrophic theory has come from experiments on developing NGF-dependent sympathetic and sensory neurons, about half of which normally die during development. If perinatal animals are treated with exogenous NGF, this normal cell death is largely prevented (*9*), whereas if they are treated with neutralizing antibodies to NGF, almost all of these neurons die (*10*). Moreover, the target neurons produce NGF in small amounts that are correlated with the density of innervation (*11*); if a target tissue is removed, the developing neurons that should innervate it die (*3*, *12*). A similar dependence on target-derived survival factors is displayed by many types of vertebrate neurons (*4*–*7*). In addition, NGF is now known to be only one member of a family of homologous neurotrophic proteins called neurotrophins (*6*, *13*, *14*), which bind to complementary members of the Trk family of receptor tyrosine kinases (*14*, *15*). Like NGF, the other known neurotrophins—brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5)—have been shown to promote the survival of specific developing neurons in vitro (*6*, *13*, *14*) and (for BDNF) in vivo (*16*). Developing neurons, however, do not depend exclusively on signals from their targets for survival (*17*): Many require signals from the neurons that innervate them (*7*, *18*), some require specific hormones (*19*), and it seems likely that many require signals from neighboring glial cells. Thus, the control of neuronal survival

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is more complex than originally envisaged by the neurotrophic theory (*17*).

In this article we argue that a neurotrophic-like mechanism may operate for many types of vertebrate cells, possibly to eliminate misplaced cells and to help match the numbers of different cell types within a tissue or organ. We begin by reviewing the evidence that such a mechanism operates for developing oligodendrocytes in the central nervous system (CNS) and for at least some cells outside the nervous system. We then discuss experiments that suggest that extracellular survival signals act by suppressing an intrinsic cell suicide program that is constitutively expressed in cells and operates by default when a cell is deprived of such signals. Finally, we consider the possibility that survival factors may prove to be useful therapeutic agents.

Oligodendrocyte Survival in Culture

Oligodendrocytes make myelin in the CNS: Their processes wrap concentrically around nerve-cell axons to form an insulating myelin sheath. Like neurons, they are postmitotic cells that develop from rapidly dividing precursor cells (*20*). When either oligodendrocytes or their precursors are isolated from the developing rat optic nerve and are cultured in the absence of other cell types or exogenous signaling molecules, they rapidly die with the morphological features characteristic of cells dying by programmed cell death (apoptosis) (*21*) (Fig. 1). They can be saved by molecules released in culture by their normal neighbors (mainly astrocytes) isolated from the optic nerve (*21*). They can also be saved, although only for a few days, by individual growth factors or cytokines that are normally present in the developing optic nerve, including platelet-derived growth factor (PDGF), insulin-like growth factors (IGFs), ciliary neurotrophic factor (CNTF), and NT-3 (*21, 22*). Thus, oligodendrocytes and their precursors cannot survive alone in culture. They need signals from other cells, and their normal neighbors can provide such signals, at least in culture.

Several principles of cell survival control have been defined in these and other studies. First, some cytokines promote both cell survival and proliferation, whereas others promote only survival. For example, PDGF promotes both the survival (*21*) and the proliferation (*23, 24*) of oligodendrocyte precursor cells, whereas IGF-1 (*21*) or CNTF (*22, 25*) alone promotes only survival. Second, the survival requirements of cells can change as the cells develop: Whereas PDGF promotes the survival of newly formed oligodendrocytes and their precursors, it does not promote the survival of more mature oligodendrocytes (*21*), which no longer express PDGF receptors (26). Similarly, the neurotrophin dependence of developing trigeminal sensory neurons changes as development proceeds: Early in development they depend on NT-3 and BDNF, whereas later they depend on NGF (*27*). Third, multiple cytokines seem to be required for a cell to survive, at least in culture. The long-term survival of purified oligodendrocytes, for instance, requires at least three signaling molecules, all of which are made by astrocytes in culture: IGF-1 (or IGF-2 or a high concentration of insulin, both of which activate IGF-1 receptors), CNTF (or the related cytokines leukemia inhibitory factor or interleukin-6), and NT-3 (*22*). In similar experiments with embryonic chick motor neurons in culture, IGF-1, CNTF, and basic fibroblast growth factor (bFGF) act together to promote cell survival (*28*). Although it has not been shown that multiple cytokines are required for cell survival in vivo, in principle such combinatorial control would enable an animal to use a relatively small number of signaling molecules to control the survival of a large number of cell types in a cell-type–specific way; by this means each cell type would be confined to those locations in which the particular set of survival factors it requires is available.

Normal Oligodendrocyte Death in Development

Although the normal large-scale death of developing vertebrate neurons has been recognized for many years, the normal large-scale death of developing oligodendrocytes was recognized only recently, in studies of the developing rat optic nerve (*21*). The optic nerve contains the axons of retinal ganglion neurons that project from the eye to the brain. The axons are structurally and functionally supported by two major classes of glial cells: oligodendrocytes, which myelinate the axons, and astrocytes, which among other functions provide a structural framework for the nerve. Astrocytes first appear in the rat optic nerve about a week before birth and increase in number for about 3 weeks, whereas oligodendrocytes first appear at birth and increase in number for about 6 weeks (*29*).

When frozen sections of developing, postnatal rat optic nerves are stained with propidium iodide to label nuclear DNA, less than 0.3% of the nuclei are seen to be pyknotic (*21*), a morphology that is characteristic of normal cell death (*30*). If the sections are stained at the same time with cell-type–specific antibodies, 90% of the dead cells are found to be oligodendrocytes and the remaining 10% are oligodendrocyte precursor cells, suggesting that normal cell death in the postnatal nerve is confined to the oligodendrocyte lineage (*21*). The oligodendrocytes that die do so within 1 to 3 days of being produced from their dividing precursor cells, suggesting that this is a critical period of vulnerability for oligodendrocytes; most of those that survive this period probably live until the animal dies (*21*).

Why do newly formed oligodendrocytes die in the developing optic nerve? By analogy with developing neurons, it is possible that they require trophic factors to survive in vivo just as they do in vitro and that not all of them get enough. Consistent with this possibility, normal cell death in the developing nerve can be suppressed, at least temporarily, by treatment with a growth factor or cytokine that promotes the survival of newly formed oligodendrocytes in culture (*21*). In these experiments the amount of the survival factor is increased by the transplanting of cells into the brain that have been genetically engineered to secrete large amounts of the factor. In experiments where transfected COS cells secreting PDGF are transplanted into the brain, for example, cell death in the optic nerve is decreased by about 80% without any effect on cell proliferation. Over a 4-day period (between postnatal days 8 and 12), although there is no change in the number of astrocytes in the nerve, the number of oligodendrocytes is increased twofold, by about 40,000 cells, compared to the results in control animals. Each day, therefore, the excess PDGF saves about 10,000 newly formed oligodendrocytes that would nor-

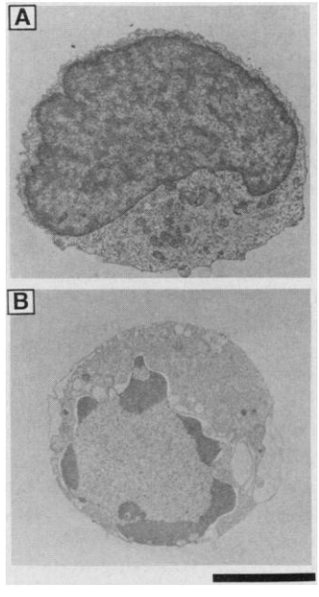

Fig. 1. Electron micrographs of (**A**) a normal and (**B**) an apoptotic oligodendrocyte precursor cell in culture. Purified precursor cells were cultured (A) with or (B) without survival factors for 15 hours. The apoptotic cell is shrunken, the chromatin has condensed around the margin of the nucleus, and the cytoplasm contains large vesicles—all changes that are typical of apoptosis. Scale bar, 4 μm. [Adapted from (*21*)]

mally have died if the PDGF concentration had not been artificially increased (*21*). Thus, at least 10,000 newly formed oligodendrocytes apparently normally die in the optic nerve each day during this period, which is about half of the oligodendrocytes that are generated each day (*21*). Approximately the same proportion of newly formed oligodendrocytes seem to die in the nerve each day throughout the 6-week period of oligodendrocyte production (*21*).

One reason that this massive oligodendrocyte death was initially missed is that, although 10,000 oligodendrocytes apparently die each day in the optic nerve during the second postnatal week, one sees only about 400 dead cells in the nerve at this time (*21*). This low number means that the time from which a cell dies to the time that it is phagocytized and degraded (so that it can no longer be recognized in a light microscope) is about 1 hour, which is the clearance time that has been directly observed for cells dying during normal development in the nematode *Caenorhabditis elegans* (*31*). This remarkably rapid clearance of apoptotic cells is presumably the main reason that normal cell death was unrecognized for so long (*3, 4*) and why it is still probably greatly underestimated.

Similar results are obtained if other factors that promote oligodendrocyte survival in vitro are delivered instead of PDGF: When transfected cells secreting IGF-1 (*32*), NT-3 (*33*), or CNTF (*32*) are transplanted into the postnatal rat brain, there is a striking reduction in the normal death of newly formed oligodendrocytes. Thus, the factors that promote the survival of newly formed oligodendrocytes in vitro also do so in vivo. It has yet to be shown, however, that reducing the amount of any of these factors in vivo increases oligodendrocyte death. Thus, it is not clear whether any of these factors are normally required for oligodendrocyte survival, although it seems likely that at least some of them are.

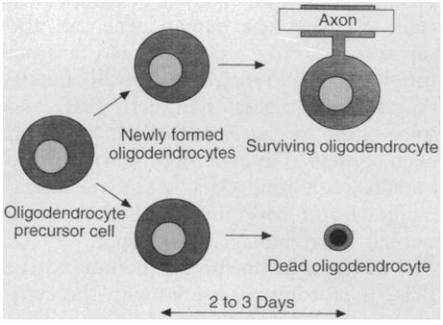

Fig. 2. A model for how axon-derived survival signals may help match the number of oligodendrocytes to the number and length of axons to be myelinated. Once a precursor cell stops dividing and differentiates into an oligodendrocyte, it has 2 to 3 days to contact a nonmyelinated region of an axon, which provides signals required for continued oligodendrocyte survival. About half of the newly formed oligodendrocytes fail to contact an axon and consequently die. [Adapted from (*32*)]

Axon Dependence of Oligodendrocyte Survival

What might be the purpose of the large-scale death of oligodendrocytes in the developing optic nerve (and presumably elsewhere in the CNS)? By analogy with normal neuronal death, it is possible that normal oligodendrocyte death helps to adjust the number of oligodendrocytes to the number (and length) of axons that need to be myelinated. If so, then axons should play a crucial part in controlling oligodendrocyte survival, which seems to be the case: If the postnatal rat optic nerve is cut just behind the eye so that all of the axons in the nerve rapidly degenerate, most of the oligodendrocytes in the nerve selectively die, which suggests that they normally depend on the axons for their survival (*32*).

It is not clear how axons promote oligodendrocyte survival. It is possible that they act indirectly by stimulating astrocytes either to make survival factors, secrete them, or both. However, they seem able to act directly, at least in vitro, as purified sensory neurons can promote the survival of purified oligodendrocytes (*32*). We proposed a tentative model for how the survival of newly formed oligodendrocytes may be regulated by axons (*32*). When oligodendrocyte precursor cells stop dividing and begin to differentiate into oligodendrocytes, their survival requirements change: They become insensitive to PDGF, for example (*21*), and become dependent on axon-derived signals. They have only 2 to 3 days in which to contact a myelin-free region of axon, which only about 50% of the cells manage to do, while the others undergo programmed cell death (Fig. 2). The limited availability of the axon-derived survival signals would ensure that the number of oligodendrocytes is automatically adjusted to the number and length of axons requiring myelination, just as the limited availability of neurotrophic factors derived from target cells is thought to ensure that the number of neurons is automatically adjusted to the number of target cells requiring innervation. The putative axon-derived survival signals have not been identified.

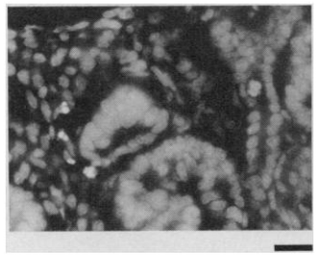

Fig. 3. Immunofluorescence micrograph of a frozen section of the nephrogenic zone of a newborn rat kidney stained with propidium iodide to reveal the nuclei. Note the four brightly stained apoptotic nuclei, which lie close to a developing nephron. Scale bar, 22 μm. [Adapted from (*35*)]

Normal Cell Death in the Developing Kidney

Normal cell death is not confined to the nervous system. It probably occurs in all of our tissues, at least at some stage of their development (*2, 34*), and in many tissues it continues throughout life. Because the dead cells are phagocytized and degraded so quickly and there is no inflammation associated with the process, even large-scale normal cell death can be histologically inconspicuous and therefore go unrecognized (*30*). This is the case for oligodendrocyte death in the developing optic nerve (*21*). The developing kidney provides another example. Until very recently, cell death was not thought to be a feature of mammalian kidney development. Yet, when frozen sections of perinatal rat kidney are stained with propidium iodide, the proportion of dead cells seen in some regions is more than fivefold higher than in the developing optic nerve (Fig. 3), and the number of dead cells has been estimated to be comparable to that in the developing nervous system (*35*).

If newborn rats are treated with exogenous epidermal growth factor (EGF) (*35*) or IGF-1 (*36*), the number of dead cells in the kidney rapidly decreases, suggesting that the normal cell death in the developing kidney, as in the developing nervous system, may reflect the failure of many of the cells to receive the signals they need to survive. During kidney development, metanephric mesenchymal cells are normally induced by cells of the invading ureteric bud to differentiate into epithelial cells that form nephrons (*37*). If the mesenchymal cells are deprived of such inducing signals in explant cultures, they undergo programmed cell death, although many of them can be rescued if EGF is added to the culture medium (*38*). Thus, some of the cells that die in the normal developing kidney may be metanephric mesenchymal cells that fail to receive adequate signals from ureteric bud cells. It is possible that many of the other normal cell deaths in developing animals occur because the cells fail to get sufficient survival signals, either because the signals are available in only limiting amounts or because the cells are not well placed to receive the signals or are insensitive to them.

Do All Cells Need Survival Signals?

There is increasing evidence that many types of mammalian cells require signals from other cells to survive (*39*). Experiments in vivo indicate that many endocrine-dependent cells die if deprived of their specific hormones. In adult rats, for example, epithelial cells in the ventral prostate die if deprived of testosterone secreted by the testes (*40*), while cells in the adrenal cortex die if deprived of adrenocorticotropic hormone (ACTH) secreted by the pituitary (*30*). Experiments in vitro indicate that many non–endocrine-dependent cells also require survival signals, at least in culture. For example, developing neurons and oligodendrocytes require neurotrophic factors and cytokines, hemopoietic cells require one or more colony-stimulating factors (*41*), T lymphoblasts require interleukin-2 (*42*) and endothelial cells require growth factors such as bFGF (*43*).

Do all mammalian cells need signals from other cells to survive? Blastomeres apparently do not. They can survive and divide in culture in the absence of exogenous signaling molecules (*44*). This survival is perhaps not surprising, because blastomeres are the only cell type in the embryo at this stage and the need for them to communicate with one another is minimal. It is possible, however, that once blastomeres differentiate to give rise to the first two distinct cell types—inner cell mass cells and trophectoderm cells—these cells and the various cell types they give rise to become dependent on signals from other cells. If there are mammalian cells other than blastomeres that can survive without signals from other cells, lens cells and cartilage cells might be expected to be among them, as both lens and cartilage contain only a single cell type and are not innervated, vascularized, or penetrated by lymphatic vessels. Although neonatal rat lens epithelial cells can survive in vitro for many weeks in the absence of exogenous signaling molecules (or any exogenous proteins) if cultured at high density, they undergo programmed cell death if cultured in these conditions at low cell density (*45*). Culture medium from high-density cultures promotes the survival of cells in low-density cultures, suggesting that lens cells secrete survival signals for other lens cells (*45*). Similar results have been obtained with cartilage cells (chondrocytes) isolated from neonatal rats or embryonic chicks (*46, 47*). Thus, neither lens epithelial cells nor chondrocytes seem to need signals from other types of cells to survive in culture but do seem to require autocrine signals from other cells of the same kind. If lens and cartilage cells need signals from other cells to survive in culture, it seems likely that all mammalian cells (other than blastomeres) may also require signals, at least during development and possibly in the adult as well.

Survival Factors and the Control of Cell Numbers

Each hour, millions of our cells undergo programmed cell death. For the most part, for every cell that dies a cell divides to replace it, so that our tissues neither shrink nor grow. It remains a mystery how this balance between cell death and cell proliferation is maintained, but it seems likely that both cell survival and proliferation are controlled so that they occur only if stimulated by signals from other cells. Such "social controls" ensure that our cells normally survive only when and where they are needed and divide only when new cells are required. And just as cells can produce signals that either stimulate or repress cell proliferation, so they can produce signals that either stimulate or repress programmed cell death, although in this review we have focused on survival signals that suppress cell death and have ignored those that activate it.

In principle, one way that the balance between cell proliferation and cell death in an organ could be maintained is for the concentrations or amounts of survival factors for a specific cell type to be set such that only a certain number of the cells can be supported: If the number of cells increases above this value, more cells automatically die, whereas if the number falls below the value, fewer cells die (*39*). If such a mechanism operates, the challenge will be to discover how the levels of survival signals are determined.

There is experimental evidence that is consistent with such a mechanism. If adult rats are treated with a progestin or with phenobarbital, for example, hepatocytes are stimulated to proliferate, causing the liver to enlarge; when the drug treatment is stopped, the liver rapidly returns to its normal size because of a large increase in programmed cell death of hepatocytes (*48*). This result can be readily explained by the above model of cell survival control, as long as the hepatocytes themselves do not produce their own survival factors. Similar results are obtained when cell proliferation is experimentally induced in other organs, including the adrenal cortex (*30*), kidney (*49*), and pancreas (*50*).

The Ced-9–Bcl-2 Connection

Cells that die normally during development or as the result of purposeful survival factor deprivation have a number of morphological features in common (*30*): They tend to shrink, the nucleus condenses (Fig. 1B), and the nucleus and cells often fragment. In vivo the cells or fragments are rapidly phagocytosed before the integrity of the plasma membrane is lost, so that there is no leakage of cytoplasmic components and, hence, no inflammation. This form of cell death is often called apoptosis to distinguish it from cell necrosis, in which, as a result of acute injury, cells swell and lyse, releasing their contents and inducing an inflammatory response (*30*). Normal cell death is also referred to as programmed cell death (PCD), because the cell is thought to activate an intrinsic death program and kill itself (*30, 31*).

The mechanism of PCD is still a mystery. Important clues have come from genetic studies in *C. elegans*, which have identified two genes, *ced-3* and *ced-4*, that are required for PCD in the worm: If either gene is inactivated by mutation, the cell deaths that take place during normal worm development fail to occur (*31, 51*). The genes have been cloned and sequenced, but this information has not yet established how the proteins they encode contribute to cell death (*31*); it is still unknown, for example, whether the proteins are effectors or activators of the death program. A third gene, *ced-9*, normally acts as a brake on the death program: If it is inactivated by mutation, many cells that would normally live undergo *ced-3*– and *ced-4*–dependent PCD and the embryo dies early in development (*52*). It seems that most cells in a normal developing worm survive only because *ced-9* suppresses their death program.

Remarkably, *ced-9* is structurally (*53*) and functionally (*54*) homologous to the mammalian gene *bcl-2*, which was first identified as an oncogene in human follicular B cell lymphomas, where it is overexpressed because of a chromosomal translocation (*55*). The *bcl-2* gene not only suppresses PCD in many types of mammalian cells (*56*), but the human gene can also suppress PCD in *C. elegans* when it is put into the worm (*54*). These crucially important findings suggest that both PCD and some of the mechanisms that control it has been conserved in evolution from worms to humans, confirming that PCD is a fundamental feature of animal cells and that a normal function of *bcl-2* is to suppress PCD. The intracellular membrane-bound protein Bcl-2 is probably associated with the cytoplasmic surface of the nuclear envelope, endoplasmic reticulum, and mitochondria (*57, 58*), but its mode of action is unknown. Nonetheless, the identification of the proteins that interact with Bcl-2 (*59*) should make it eventually possible to define the proteins that mediate PCD. It is already clear that Bcl-2 is only one member of a family of related proteins, including Bax (*59*) and Bcl-X (*60*), that normally regulate PCD in mammalian cells.

Constitutive Expression of the Cell-Death Machinery

The first evidence that normal cell deaths in vertebrates reflect an intrinsic cell-death program came from experiments in which the death could be suppressed or postponed by inhibitors of RNA or protein synthesis (*42*, *61*), suggesting that a cell has to make new RNA and protein to die in this way. There are an increasing number of examples, however, in which RNA or protein synthesis inhibitors fail to suppress PCD and can even trigger it (*62*). A high concentration of the protein kinase inhibitor staurosporine, for example, induces PCD in many types of cells in culture including oligodendrocytes and their precursors (*63*), human fibroblast cell lines (*58*), lens epithelial cells (*45*), and chondrocytes (*47*); in all cases tested, RNA or protein synthesis inhibitors fail to block these deaths (*63*). Moreover, cells whose nuclei have been removed by treatment with cytochalasin and centrifugation still die with the characteristic features of PCD when either treated with staurosporine or deprived of survival factors (*64*). In addition, cytotoxic T lymphocytes can kill most types of mammalian cells as long as the cells express on their surface class I major histocompatibility complex proteins complexed with foreign antigenic peptides, usually derived from an intracellular microbe such as a virus. The cytotoxic cells seem to kill their target cells by inducing them to undergo PCD, but drugs that inhibit RNA or protein synthesis do not inhibit the killing (*65*). (Cytotoxic T cells presumably kill by inducing PCD, because this ensures that the dead target cells will be rapidly phagocytized before they leak and induce an inflammatory response.) Taken together, these findings suggest that most mammalian cells constitutively express all the protein components of the death program. When RNA or protein synthesis is required for PCD, this may be because these processes are needed to activate the program. Corticosteroids, for example, induce PCD in thymocytes (*65*). Because corticosteroid receptors are ligand-activated gene regulatory proteins, it is not surprising that inhibitors of RNA and protein synthesis block PCD. Thymocytes, however, can be induced to undergo PCD in the presence of such inhibitors by other forms of treatment—with mild hyperthermia (*66*) or a high concentration of staurosporine (*64*), for instance.

Generalizing from what was already known for some cell types, we argued that most and perhaps all mammalian cells (other than blastomeres) require signals from other cells to survive and that cells deprived of such survival signals kill themselves by activating their intrinsic death program (*39*). If the machinery for the death program is constitutively expressed, then at least one function of extracellular survival signals must be to suppress the machinery. As discussed above, in many cells in *C. elegans*, at least early in development, *ced-9* is required to suppress the *ced-3*– and *ced-4*–dependent death program (*52*), but it is not known whether the activity of *ced-9* depends on signals from other cells. In some mammalian cells, however, extracellular signals that promote cell survival stimulate the expression of *bcl-2* (*67*), and it seems likely that in other cases survival signals stimulate the expression of other genes that suppress PCD, including some related to *bcl-2* (*60*).

Survival Factors as Therapeutic Agents

The seminal paper by Kerr, Wyllie, and Currie distinguished between cell necrosis, which results from cell injury, and apoptosis, which occurs normally (*68*). However, it seems that injured cells, if they have time, can detect the injury and elect to die by PCD rather than by necrosis (*30*). This is the altruistic way for a cell to die, because it avoids inflammation and ensures that the cell is rapidly removed. DNA-damaging agents such as irradiation or DNA-intercalating drugs, for example, can induce PCD by a process that depends on the protein p53 (*69*). Programmed cell death can also occur in response to ischemia, trauma, and ATP depletion, for example. It seems likely, therefore, that even in situations in which most cells die by necrosis as a result of acute injury, some cells have time to die by PCD.

The discovery of neurotrophic factors and the emergence of the neurotrophic theory emphasized the importance of survival signals in vertebrate neural development. The theory, however, did not predict the surprising findings that the delivery of exogenous neurotrophic factors or other cytokines ameliorates the effects of many types of neuronal injury, including ischemia, hypoglycemia, excitotoxicity, oxidative damage (*70*), and even genetic defects (*71*) that cause neuronal death. It is still unclear whether these findings reflect the ability of high concentrations of survival factors to suppress PCD in injured cells or whether the high concentrations can protect cells from dying by necrosis or in other ways. In either case, the therapeutic use of survival factors could well revolutionize the treatment of conditions in which cells die, both in the nervous system and outside it, especially in situations in which cells die acutely.

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