

Apoptosis: Neuronal Death by Design

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Issue: *Neurons are equipped with the molecular machinery to kill themselves. The process is called apoptosis. Cellular suicide may be desirable for some neurons and the cause of psychiatric disorders in others.*

Dying is generally an undesired affair. In recent years, however, it has become clear that many cells, including neurons, are actively programmed to commit molecular hari-kari. Such a process is called apoptosis. This is not the messy affair associated with cellular poisoning or suffocation, known as necrosis. Necrotic cell death is characterized by a severe and sudden injury associated with an inflammatory response. By contrast, apoptosis is more subtle, akin to fading away. Apoptotic cells shrink, whereas necrotic cells explode. The original scientists who discovered apoptosis coined that term to rhyme with necrosis, and also to mean literally a "falling off," as the petals fall off a flower or the leaves fall from a tree. The cell death machinery is a set of genes which stand ever ready to self-destruct.

Normal brain development and neuronal apoptosis

Why should a neuron purposely slit its own throat and commit cellular suicide? For one thing, if a neuron (and especially its DNA) gets damaged by a virus or a toxin, apoptosis destroys and silently removes these sick genes, which may serve to protect surrounding healthy neurons. More impor-

tantly, apoptosis is a natural part of development of the immature central nervous system. One of the many wonders of the brain is the built-in redundancy of neurons early in development. These neurons compete vigorously to migrate, innervate target neurons, and drink trophic factors necessary to fuel this process. Apparently, there is survival of the fittest, because up to 50% of many types of neurons normally die in this time of brain maturation. Apoptosis is a natural mechanism to eliminate the unwanted neurons without making as big a molecular mess as doing it via necrosis.

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Mismanaged apoptosis and neurodevelopmental disorders

One can easily imagine scenarios where the wrong cells are eliminated

by faulty genetic programming, by in utero chemicals and toxins, or indeed by undesirable experiences. Perhaps schizophrenia is characterized by such aberrant neurodevelopmental processes. Normally, extra neurons are available in a brain bank until the wiring of the brain is completed, and then the extras are discarded by apoptosis. Failure to eliminate excess neurons may cause a tangled wiring of the brain's computer, and thus form the substrate for neurodevelopmental disorders.

Selective neuronal death and apoptosis in slow neurodegenerative disorders

A number of neurodegenerative conditions are characterized by a progressive fading away of neurons. Since there is often a lack of inflammation, researchers postulate that

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Take-Home Points About Apoptosis

- ◆ Desired apoptosis is programmed cell death, or death by design
- ◆ May be key for normal brain development to occur
- ◆ Apoptosis can also be triggered by diseases, thus causing neuronal murder
- ◆ Preventing apoptosis is a provocative new strategy for the treatment of neurodegenerative disorders, stroke, and epilepsy

the cells are exiting via apoptosis. Why would certain neurons suddenly decide to start leaving? Is their apoptosis machinery activated? In the case of Huntington's disease, neurons in the basal ganglia and cerebral cortex, which seem completely normal, all of a sudden start to degenerate. The abnormal inherited gene is evidently a ticking time bomb which doesn't go off for about 50 years. Why does the genetic program push the self-destruct button and why does it wait 50 years?

Similarly, cerebral cortical neurons (Alzheimer's), substantia nigra dopamine neurons (Parkinson's), and alpha motor neurons (amyotrophic lateral sclerosis; Lou Gehrig's disease) mysteriously check out of the nervous system after many years of apparently normal functioning. Is their demise programmed from within, or is their suicide somehow assisted? If the molecular events which activate apoptosis and which mediate cellular destruction can be harnessed, it is possible that neurodegenerative disorders might be interrupted. This is an amazing

therapeutic possibility, as until very recently it seemed conceptually impossible to ever rescue the dying brain.

Catastrophic neurodegeneration in stroke and epilepsy as a collaboration between necrosis and apoptosis

Neurons can be murdered by any number of assailants: three common culprits are poisons, strangulation (choking off oxygen in ischemia), and abusive overwork resulting in a type of "nervous breakdown" after exhaustion (such as in status epilepticus). In such situations, both necrosis and apoptosis may occur. For example, in stroke, necrosis may mediate the death of neurons at the scene of the crime, but apoptosis may be triggered in neuronal bystanders at considerable distance from the central core of ischemia. A great deal of the ultimate disability from stroke may be mediated by these bystanders

falling on their swords in an apoptotic mass suicide. As this process takes several days to be completed, there is the possibility that a squad of molecular rescue

workers could interrupt the delayed process and salvage bystanders. Such a possibility fuels efforts to find therapies which could prevent or reverse the damage of a stroke in progress, a radical concept inconceivable prior to the discovery of apoptosis. ◆

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